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3 β -Hydroxy-4 β -hydroxymethylfusida-17(20)[16, 21-cis], 24-diene の単離

佐藤良博

Isolation of 3β -Hydroxy- 4β -hydroxymethylfusida-17(20)-[16,21-cis],24-diene*¹ Yoshihiro Sato

Recently the intact incorporation of the squalene chain into the fusidane skeleton was demonstrated and 3β -hydroxy- 4β -methylfusida-17(20)[16,21-cis],24-diene (II) was proposed as the precursor of fusidic acid (III)¹). In this communication we wish to report the isolation of one of the precursors of helvolic acid (IV) whose structure is assigned to be 3β -hydroxy- 4β -hydroxymethylfusida-17(20)[16,20-cis],24-diene (V).

After a great part of IV of the metabolites mixture extracted from the mycelia of *Cephalo-sporium caerulens* was removed by recrystallization, the components of the mother liquor were chromatographed on silical gel column. Recrystallization of the eluate between ergosterol and IV afforded a diol^{*2} (V), m.p. 143°, $C_{30}H_{50}O_2^{*3}$ M⁺ 442, $[\alpha]_p^{20}$ +19.1°, IR (CCl₄, C=0.0026 M. the calibration standard: indene) 3628 ± 1 (sharp, nonbonded OH), 3567 ± 1 cm⁻¹ (broad, bonded OH), diacetate (VI), m.p. 96°, $C_{34}H_{54}O_4$, M⁺ 526, $[\alpha]_p^{20}$ +32.6°.

As shown in Table I, the NMR spectra indicate the existence of three methyls on the double bond, four tertiary methyls, and the partial structures CH-OR and $-C-CH_2OR$ (R=H or Ac).

These NMR spectral date, the molecular formula, and the origin of this diol strongly suggested that this must be one of the precursors of IV in which a secondary and a primary hydroxy groups are most probably located at C_3 -position and at one of the two C_4 -methyls. To confirm this assumption, 2.0 mg of the diol ³H-labeled by the Wilzbach method²) (2.61×10⁷ dpm/mg) was fed into a culture of *C. caerulens* (100 ml), preincubated for 2 days and continued cultivation for further 5 days. The usual work up followed by silica gel column chromatography and one recrystallization furnished IV, m.p. 214—5°, 14.45 mg. After dilution with 73.20 mg of cold IV, seven recrystallizations gave the specific activity 1.03×10^4 dpm/mg. This incorporation (1.71%) demonstrated that this compound is one of the intermediates in the main biogenetic path of IV and consequently the

^{*1)} 本報告は S. Okuda, Y. Sato, T. Hattori, H. Igarashi, T. Tsuchiya, N. Wasada, *Tetrahedron letters*, 4769 (1968) に発表.

^{*2)} This diol was kindly identified with the sample isolated from the culture of *Fusidium coccineum* (a private communication from Dr. W.O. Godtfredsen).

^{*3)} The compound whose molecular formula is cited gave satisfactory analytical data. Unless otherwise stated, NMR (δ) and $[\alpha]_D$ were taken in CDCl₃ and CHCl₃ respectively.

¹⁾ W.O. Godtfredsen, H. Lorck, E.E. van Tamelen, J.D. Willett, R.B. Clayton, J. Am. Chem. Soc., 90, 208 (1968).

²⁾ K.E. Wilzbach, J. Am. Chem. Soc., 79, 1013 (1957).

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TABLE I

	OR -Ċ- <u>H</u>	H C=C	$-\overset{l}{\overset{l}{\underset{1}{\subset}}}-C\underline{H}_{2}OR$	>C=C< _{CH3}	$-\overset{!}{\underset{l}{\operatorname{C-CH}}}$	О -О•С-С <u>Н</u> 3
V (R=H)	3.43^{a} diffused t. J=ca 8	5.10 (m)	3.26 slightly diffused d, $J=11.0^{b}$ 4.21 d, $J=11.0^{b}$	$1.57 \\ 1.58 \\ 1.67$	$0.73 \\ 0.88 \\ 1.11 \\ 1.20$	
VI(R=Ac)	$\begin{array}{c} 4.60 \\ \text{diffused t.} \\ J = \text{ca 8} \end{array}$	5.10 (m)	4.16 d, J=12.0 4.29 d, J=12.0	$ 1.59 \\ 1.60 \\ 1.67 $	$\begin{array}{c} 0.76 \\ 0.97 \\ 1.02 \\ 1.14 \end{array}$	2.03 2.05

a) The values obtained under addition of D_2O .

b) These signals were analyzed by the measurement under addition of D_2O utilizing spin-spin decoupling technique.

structure V can be assigned to it except the stereochemistry of C_3 -OH and C_4 -CH₂OH, which was elucidated as described below.

This proposed structure can rationalize the mass spectral data of this diol. The high resolution mass spectrum showed the peaks [CnHmO₂: 442(M), 373(a), 250(b-2), 237(c-1), 223(d-1), 101(e-1). CnHmO₁: 411(f), $355(a-H_2O)$. CnHm: 394(g), 218(h), 189(i-1), 69(j)].

The orientation of 3β -OH and 4β -CH₂OH could be assigned by the IR- and NMRspectral studies. The IR-spectrum of the diol in the diluted CCl₄ solution exhibited only the absorption due to a nonbonded secondary OH of equatorial type at 3628 cm⁻¹ but a nonbonded axial secondary (3637-3639 cm⁻¹) or a nonbonded primary OH (3640-3642 cm⁻¹) could not be observed. This fact cleary demonstrates that this compound possesses the partial structure (A: 3β -OH, 4β -CH₂OH, the preferred form of the axial primary OH away from the axial 10-methyl group), since the absorption due to a non-

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bonded primary OH should exist in all the other cases, (B: 3β -OH, 4β -CH₂OH, the equilibrium mixture of two forms), (C: 3α -OH, 4α -CH₂OH, the equilibrium mixture of two forms) and (D: 3α -OH, 4β -CH₂OH, no hydrogen bonding)³).

In the NMR spectrum of diacetate the shape of the signal due to C_3 -H (a slightly diffused triplet, J=ca 8 cps) is in accordance with that of the 3α -H (axial type, t., J=8, W/2=17) of the similar compound such as isoaescigenin pentacetate epoxide⁴). On the other hand the average value ($\frac{\text{Ha}+\text{Hb}}{2}$ =4.42) of the chemical shifts of C_4 -CHaHbOAc of the diacetate is very similar to that (4.08-4.30), reported in the case of C_4 -CH₂OAc of axial type but different from that (ca 3.84) of the equatorial type.⁵) Thus the stereochemistry of 3β -OH and 4β -CH₂OH in the diol was also proved from the NMR-spectral data.

Consequently this diol, expected to be the first oxidation product of II, is assigned as 3β -hydroxy- 4β -hydroxymethylfusida-17(20)[16,21-cis],24-diene (V).

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³⁾ A.R.H. Cole and G.T.A. Müller, J. Chem. Soc., 1224 (1959).

⁴⁾ J.B. Thomson, Tetrahedron Letters, 2229 (1965).

⁵⁾ A. Gaudemer, J. Polensky and E. Wenkert, Bull. Soc. Chim. France, 407 (1964).