Tetrahedron Letters, Vol.22, No.29, pp 2781 - 2784, 1981
Printed in Great Britain

0040-4039/81/292781-04$02.00/0

FURTHER STUDIES ON PALYTOXIN. II. STRUCTURE OF PALYTOXIN[1]

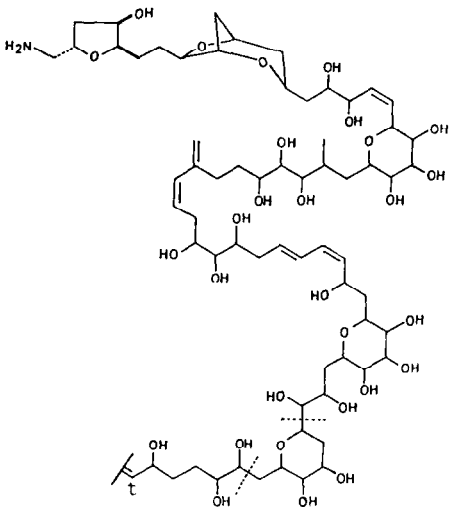
Daisuke UEMURA,[a] Katsuhiro UEDA,[b] and Yoshimasa HIRATA[c]
[a]Faculty of Liberal Arts, Shizuoka University, Ohya, Shizuoka 422, Japan
[b]Department of General Education, University of Ryukyus, Naha 903, Japan
[c]Faculty of Pharmacy, Meijo University, Tempaku, Nagoya 468, Japan
Hideo NAOKI and Takashi IWASHITA
Suntory Institute for Bioorganic Research, Shimamoto-cho, Mishima-gun, Osaka 618, Japan

Summary: The full structure of palytoxin, a potent coelenterate toxin, is reported.

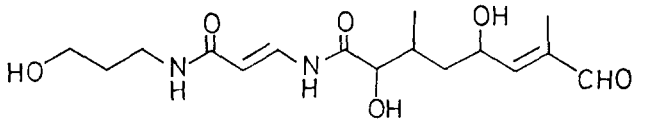
The structural elucidation of palytoxin has involved some complicated and difficult problems because it is a non-crystalline, water soluble, unstable and novel molecule.[2] However, we could ultimately elucidate its total structure by overcoming those problems. As we expected,[3] palytoxin falls under the category of the polyketides but not the polysaccharides or peptides. So long as we know, palytoxin is one of the most complicated and largest molecules except for the naturally occurring polymers. Now, we wish to report herein the full structure of palytoxin, isolated from Palythoa tuberculosa which has been collected in Ishigaki Island in the southern part of Japan.

In the previous report,[4] we described the partial structure (1) of palytoxin which was composed of 66 carbon atoms starting from the terminal amino group. The partial structure (1) and compound (2)[3] possess six double bonds and two double bonds, respectively. Since eight double bonds are present in palytoxin,[3] it is possible to determine the full structure of palytoxin by elucidating the structure of the segment between the terminal double bond (trans)[3,5] in 1 and the trisubstituted double bond in 2. Though the corresponding degradation product was unstable, the structure was assigned by the careful spectral analysis of the fragment itself and further degraded products. Complete ozonolysis of N-(p-bromobenzoyl)palytoxin followed by immediate and careful reduction with $NaBH_4$ was carried out to give a mixture of two epimeric polyols (3) [FDMS, m/e 1069 $(M+Na)^+$], which were not separated each other. Since a signal appeared at δ101.9 (s) in the ^{13}C-NMR spectrum of 3, the presence of the carbon bearing two oxygen atoms was suggested. This carbon may be assigned to the signal at δ100.3 (s) in palytoxin, which disappeared in the ^{13}C-NMR spectra of the products obtained from acetylation[5] of palytoxin or from treatment of palytoxin itself with various acids. In order to obtain the suitable derivatives for the ^1H-NMR analysis, we attempted the acetylation of 3 with Ac_2O/py. We obtained the α,β-unsaturated ketones (4) in low yield instead of polyacetates of 3. The partial structure

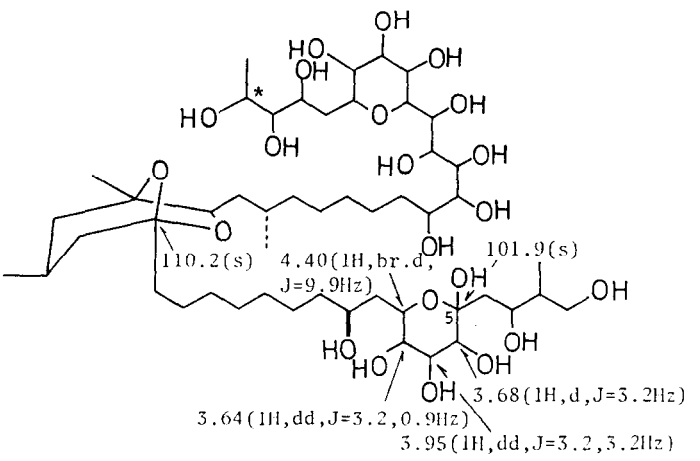
around the ketonic carbon of 4 was suggested by the assignment of each proton in the ^{1}H-NMR spectrum as shown in the figure (4).



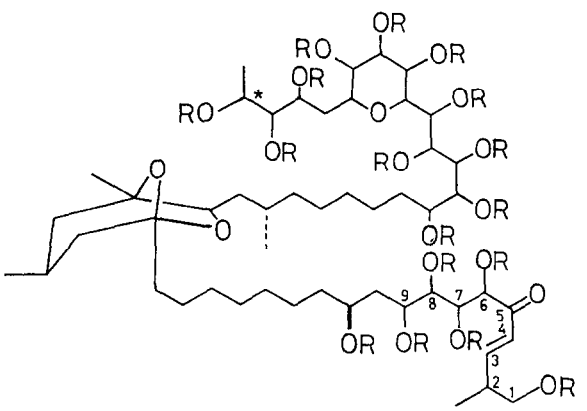
(1)



(2)

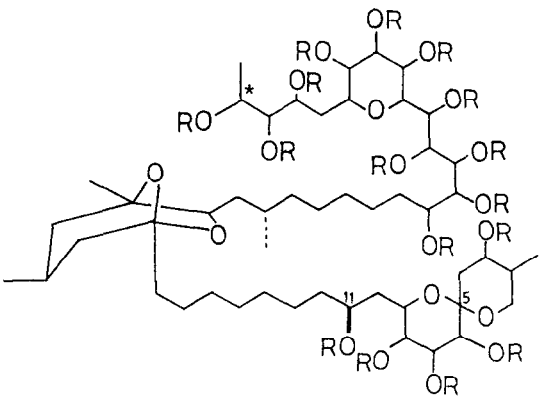


(3) *epimeric carbon



(4) R= $COCH_3$ [FDMS, $^{+}$m/e 1743 $(M+H)^{+}$]

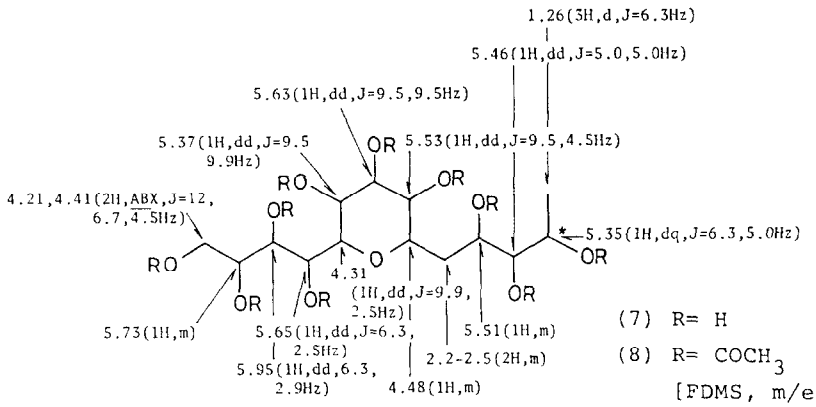
3.73(2H,d,J=6.8Hz,H-1), 2.28(1H,m,H-2), 0.66 (3H,d,J=6.8Hz,2-CH_3),6.92(1H,dd,J=15.3,7.6Hz, H-3),6.39(1H,dd,J=15.3,1.4Hz,H-4),6.34(1H,d, J=9.0Hz,H-6) and 6.10(1H,dd,J=9.0,15.9Hz,H-7).

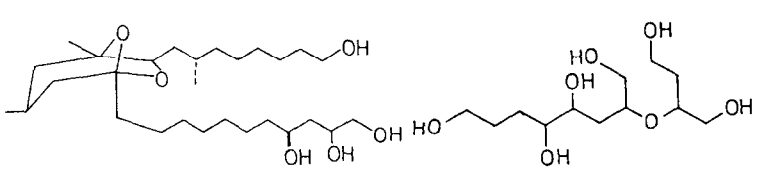


(5) R= H

(6) R= $COCH_3$ [FDMS, $^{+}$m/e 1701 $(M+H)^{+}$]

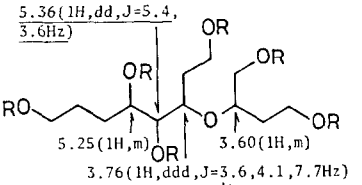
5.34,4.20(2H,ABX,J=10.8,0.5,2.7Hz,H-1), 0.90(3H,d,J=7.7Hz,2-CH_3),4.81(1H,m,H-3), 5.23(1H,d,J=3.6Hz,H-6),5.71(1H,dd,J=2.7, 3.6Hz,H-7),5.19(1H,dd,J=2.7,1.8Hz,H-8), 4.57(1H,ddd,J=9.9,2.3,1.8Hz,H-9),1.6-2.0 (2H,m,H-10) and 5.11(1H,m,H-11).





(9)

(10)



(11) R= $COCH_3$

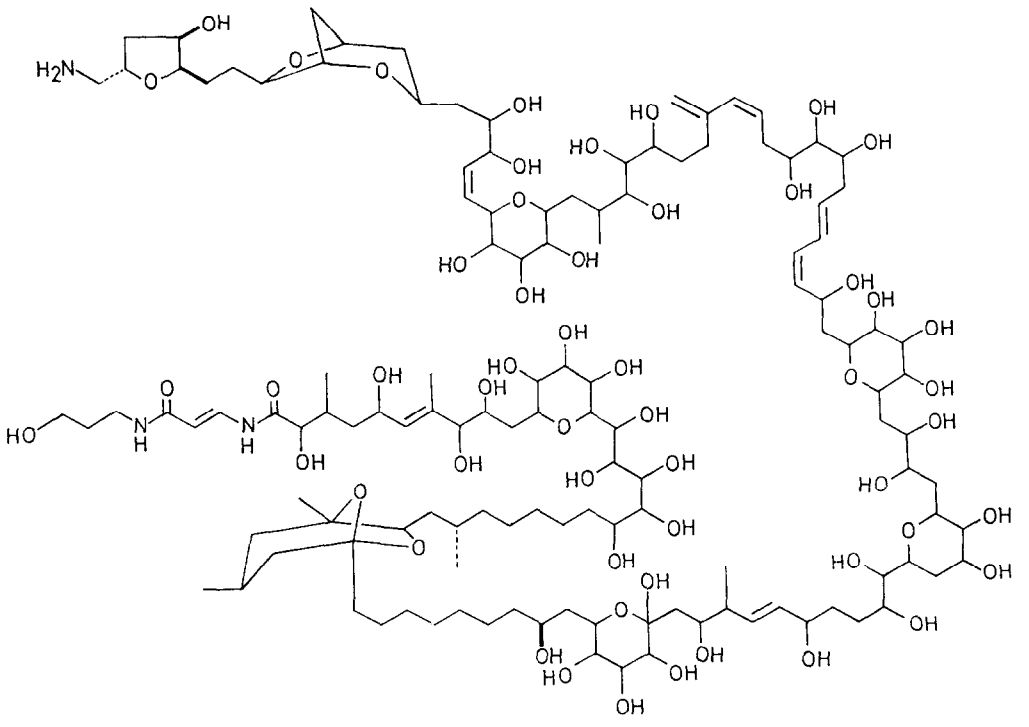


Fig.1. The structure of palytoxin, $C_{129}H_{223}N_3O_{54}$, including the absolute configuration in part.[3,7]

In order to prepare derivatives with C-5 bearing geminal two oxygen atoms which was originally present in 3, compounds (3) were treated with 50% acetic acid. The resulting spiro acetals (5) were immediately and smoothly acetylated to give the corresponding acetates (6). The analysis of the ^{1}H-NMR spectra of 6 with the aid of decoupling procedure suggested the partial structure around the spiro moiety in 6. The presence of six-membered hemiacetal in the original compounds (3) was indicated by the following evidence. In the ^{1}H-NMR spectrum of 3 the signal at δ4.40 was observed as a broad doublet (J=9.9Hz). Irradiation at δ1.86 (-C$\underline{H}_2$-) caused this broad doublet to collapse into a broad singlet. Furthermore, irradiation at δ3.64 (-C$\underline{H}$OH-) simplified the broad doublet at δ4.40 into a double doublet. The chemical shifts and coupling constants of each proton in the hemiacetal moiety were shown in the figure (3). However, all protons could not be assigned in the ^{1}H-NMR spectra of 3, 4 and 6 because the existence of two epimers in those compounds was recognized. This problem was solved by gentle treatment of 3 with $NaIO_4$ followed by rapid reduction with $NaBH_4$. Compounds (7) were obtained as a mixture of two epimers with respect to the carbon bearing the terminal methyl group. Each proton of these acetates (8) which were derived from 7 with Ac_2O/py was assigned in the ^{1}H-NMR spectrum by means of decoupling procedure. The chemical shifts and coupling constants of each proton of one epimer (8) were shown in the picture (8). Periodate oxidation of 3 followed by reduction with $NaBH_4$ gave the tetraol (9), the structure of which was unambiguously established previously.[3] From the aforementioned results, it is suggested that the structure of 3 is visualized as shown in 3, $C_{50}H_{94}O_{22}$. This molecular formula agreed with the result obtained by FDMS analysis of 3. On the other hand, we found that the previously reported structure (10)[4] of a periodate oxidation product was not correct. After reinvestigation[6] of this degradation product, we now regard its acetate as compound (11). Dotted lines in 1 indicate the moiety which is revised on the basis of this fact. Therefore, the full structure of palytoxin is pictured as shown in Fig.1, including the absolute configuration in part.[7] The molecular formula [$C_{129}H_{223}N_3O_{54}$ (MW, 2680.168)] of palytoxin was consistent with results from elementary analysis of N-(p-bromobenzoyl)palytoxin and with the molecular weight determined by ^{252}Cf PDMS measurements.[8]

Acknowlegdements: The authors are grateful to the Foundation for the Promotion of Research on Medical Resources, and the Ministry of Education, Japanese Government (Grant-in-aid, No.411704), for financial support. We are indebted to Professor T.Miyazawa, The University of Tokyo, for the NMR measurements, and to Dr.Y.Naya, Suntory Institute for Bioorganic Research, for the valuable suggestion.

REFERENCES AND NOTES: 1)This work was presented at the 43rd Annual Meeting of the Chemical Society of Japan,Tokyo,Japan,April 2,1981. 2)R.E.Moore and P.J.Scheuer,Science,172,495(1971),and S.Kimura and Y.Hashimoto, Publ.Seto.Mar.Bio.Lab.,20,713(1973). 3)D.Uemura,K.Ueda,Y.Hirata,C.Katayama,and J.Tanaka, Tetrahedron Lett.,21,4857 and 4861(1980). 4)D.Uemura,K.Ueda,Y.Hirata,H.Naoki,and T.Iwashita, Tetrahedron Lett., in press(1981). 5)Y.Hirata,D.Uemura,K.Ueda,and S.Takano, Pure Appl. Chem.,51,1875(1979). 6)We wish to thank Professor T.Matsumoto,Hokkaido University, for his valuable suggestion. 7)The details concerning the X-ray analysis will be reported in the near future. 8)R.D.Macfarlane,D.Uemura,K.Ueda,and Y.Hirata, J.Am.Chem.Soc.,102,875(1980).

(Received in Japan 13 April 1981)