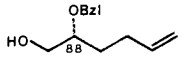
The stereochemistry of alcohols **21** and **22** was established by the following experiments. Benzylation of the major alcohol **22** followed by aqueous acid hydrolysis, periodate oxidation, and sodium borohydride reduction afforded 2-(benzyloxy)hex-5-en-1-ol (**23**). The α_D value of **23** was found to be -9.4°. The specific



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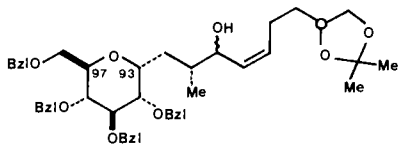

24

rotations of (*R*)- and (*S*)-2-(benzyloxy)hex-5-en-1-ols, prepared from D- and L-glyceraldehyde ketals,[23] were found to be -11.7 and +10.4°, respectively. Thus, C88 has the *S* configuration in the minor alcohol **21**. This conclusion was further confirmed by comparison of the ^{1}H NMR spectra of MTPA[25] esters of **23** obtained from the above-mentioned sources.

The experiments summarized above allowed us to assign the stereochemistry of degradation product **10** as indicated. Since this assignment of the relative stereochemistry between C90 and C91 was based solely on the results of Sharpless' asymmetric epoxidation[8] of **15**, we felt it was desirable to have additional evidence.[26] For this reason, the stereochemistry assignment at C88, C89, and C90 was performed by an alternative method. Thus, cis-allylic alcohols **24** were prepared from **14**[24] and subjected to OsO_4 oxidation, aqueous acid hydrolysis, debenzylation, and acetylation to yield a mixture of nonaacetates corresponding to **10**. However, none of these nonaacetates was identical with degradation product **10**, establishing the relative stereochemistry at C88 and C89 as threo. This information, along with knowledge of the relative stereochemistry between C89 and C90 and of the absolute stereochemistry at C88 and C91 (vide supra), excluded all possible structures for degradation product **10** except the one shown.

Acknowledgment. Financial assistance from the National Institutes of Health (NS-12108) and the National Science Foundation (CHE 78-06296) to the Harvard group is gratefully acknowledged. The Nagoya group is grateful to the Foundation for the Promotion of Research on Medical Resources and the Ministry of Education, Japanese Government (Grants-in-Aid 411704 and 56540320) for financial support. Appreciation is also expressed for the use of the 500-MHz NMR instrument at the NMR Facility for Biomolecular Research located at the F. Bitter National Magnet Laboratory, MIT. The NMR facility is supported by Grant RR00995 from the Division of Research Resources of the NIH and by the National Science Foundation under Contract C-670.

Supplementary Material Available: Spectroscopic data for compounds **1a**, **10** (two diastereomers), and **11** and details of some synthetic sequences (2 pages). Ordering information is given on any current masthead page.

(23) D-Glyceraldehyde acetonide was prepared according to the method reported in the following: Fischer, H. O. L.; Baer, E. *Helv. Chim. Acta* **1934**, *17*, 622). With the procedure reported for the D-series (Zinner, H.; Milbradt, J. *Carbohydr. Res.* **1966**, *2*, 470), L-glyceraldehyde cyclohexanone ketal was prepared from L-arabinose. Transformation of glyceraldehyde ketals into **23** was achieved in eight steps.[24]

(24) Details of this synthesis are given in the supplementary material.

(25) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543. Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *Ibid.* **1973**, *38*, 2143.

(26) Chemical correlation of optically active epoxides prepared by asymmetric epoxidation has been performed in many cases; for example, see footnotes 6, 8, and 9.

Stereochemistry of Palytoxin. 2.[1] C1-C6, C47-C74, and C77-C83 Segments†

S. S. Ko, J. M. Finan, M. Yonaga, and Y. Kishi*

Department of Chemistry, Harvard University Cambridge, Massachusetts 02138

D. Uemura

Faculty of Liberal Arts, Shizuoka University Ohya, Shizuoka 422, Japan

Y. Hirata

Faculty of Pharmacy, Meijo University Tempaku, Nagoya 468, Japan

Received July 19, 1982

Continuing from the preceding communication, we will describe the stereochemistry assignment of the C1-C6, C47-C74, and C77-C83 portions of the marine natural product palytoxin.[2]

The lactone diacetate **1** (Chart I), containing C1-C6, is a known degradation product of palytoxin. The ^{1}H NMR spectrum of **1** suggested that the relative stereochemistry at C2, C3, and C5 was as indicated in **1**, but the absolute stereochemistry was unknown.[3] By use of the carbohydrate chain-extension method,[4] tetraacetate **2**[5] [^{1}H NMR ($CDCl_3$) δ 0.97 (3 H, d, J = 6.9 Hz), 2.05 (3 H, s), 2.06 (3 H, s), 2.07 (3 H, s), 2.09 (3 H, s); α_D +17.0° (*c* 0.17, $CHCl_3$)] was synthesized from (*S*)-(+)-3-hydroxy-2-methylpropionic acid.[6,7] Upon comparison of spectroscopic data and optical rotations, tetraacetate **2** was found to be identical with the tetraacetate prepared from the degradation product,[8] establishing the absolute stereochemistry of C2, C3, and C5.

The tetraacetate **3**, containing C47-C56, was isolated as a degradation product of palytoxin.[9] By use of the carbohydrate chain-extension method,[4] triacetate **4** [^{1}H NMR ($CDCl_3$) δ 0.95 (3 H, d, J = 7.4 Hz), 2.02 (3 H, s), 2.03 (3 H, s), 2.04 (3 H, s); α_D -14.2° (*c* 0.73, CH_2Cl_2)] and its C49 diastereomer were synthesized from (*S*)-(+)-3-hydroxy-2-methylpropionic acid.[6,7] On comparison of spectroscopic data and optical rotations, triacetate **4** was found to be identical with advanced degradation product **4**.[10] Wittig reaction of aldehyde **6**[7] with phosphonium salt **5**[7] followed by debenzylation and acetylation gave trans-olefin **3** [^{1}H NMR ($CDCl_3$) δ 1.01 (3 H, d, J = 7.0 Hz), 2.03 (3 H, s), 2.04 (3 H, s), 2.05 (6 H, s)]. Starting with **5** and the antipode[7] of **6**, the C53 diastereomer of **3** was also prepared. Upon comparison of ^{1}H NMR data, synthetic tetraacetate **3** was found to be identical with degradation product **3**, establishing the stereochemistry at C49, C50, and C53.

The pentaacetate **7**, which contains C77-C83, is a degradation product of palytoxin. The relative stereochemistry of **7** was found

† This work was presented by Y. Kishi as part of a lecture at the symposium honoring the memory of Dr. Willy Leimgruber on March 26, 1982, at Rutgers University, Newark, NJ.

(1) Part 1 of this series: *J. Am. Chem. Soc.* preceding paper in this issue.

(2) For the structure and numbering of palytoxin, see part 4 of this series.

(3) This assignment was made based on the spin-spin coupling constants $J_{2,3}$ = 11.6 Hz and $J_{4,5}$ = 12.0 and 3.5 Hz, given in the supplementary material for ref 1a of the preceding paper.

(4) See ref 6 in the preceding paper.

(5) Satisfactory spectroscopic data were obtained for all new compounds in this paper.

(6) We are indebted to Dr. Cohen, Hoffmann-La Roche Inc., for a generous gift of this acid.

(7) Details of this synthesis are given in the supplementary material.

(8) This substance was prepared from the degradation product reported as compound **1** in ref 2f of the preceding paper in four steps: (1) O_3/MeOH/-78 °C, followed by $NaBH_4$ workup; (2) Ac_2O/py; (3) $LiAlH_4$/THF/0 °C; (4) Ac_2O/py.

(9) See ref 2f and 2d in the preceding paper.

(10) This substance was prepared from the degradation product reported as compound **21** in ref 1a of the preceding paper in three steps: (1) NaOH/MeOH/room temperature; (2) $NaIO_4/H_2O$/0 °C, followed by $NaBH_4$ workup: (3) Ac_2O/py, followed by TLC separation.

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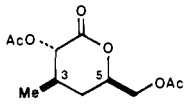
Chart I



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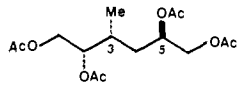

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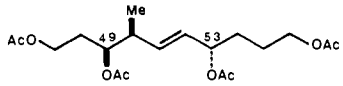

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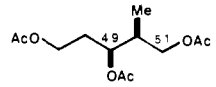

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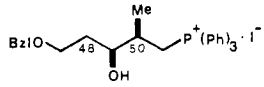

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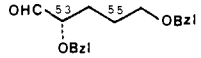

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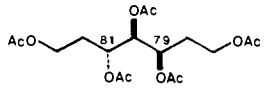
Chart II



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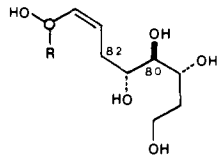
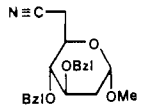


9 : R = C.86-C.115 segment



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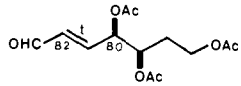

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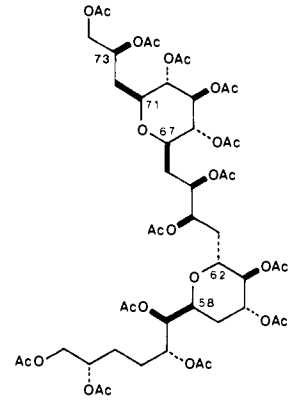
Chart III



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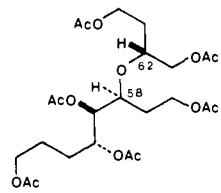

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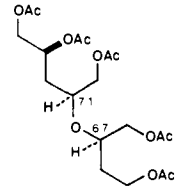
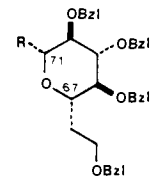
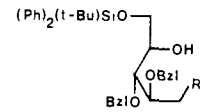


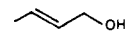
13

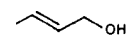
16 : antipode of 13

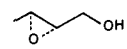
Chart IV

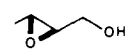




14 : R = 

17 : R = 

15 : R = 

18 : R = 

by NMR experiments to be as indicated, but the absolute stereochemistry remained unknown.[11] Synthesis of pentaacetate **7** from 2-deoxy-D-glucose via nitrile **8** was performed straightforwardly.[7] Upon comparison of α_D values, synthetic pentaacetate **7** [^{1}H-NMR ($CDCl_3$) δ 2.04 (6 H, s), 2.05 (3 H, s), 2.06 (3 H, s), 2.15 (3 H, s); α_D +53.4° (*c* 0.46, $CHCl_3$)] was found to be identical with degradation product **7** (Chart II). To determine the connectivity of **7** with the remaining portions of the palytoxin structure, we performed a stepwise degradation reaction. Palytoxin was partially degraded to **9**,[11] which was then ozonized and treated with acetic anhydride/pyridine to yield trans-α,β-unsaturated aldehyde **10**. Synthesis of the two possible diastereomers, i.e., **10** [^{1}H NMR ($CDCl_3$) δ 2.05 (3 H, s), 2.07 (3 H, s), 2.18 (3 H, s), 6.22 (1 H, ddd, J = 16, 7.6, 1.5 Hz), 6.72 (1 H, dd, J = 16, 4.6), 9.57 (1 H, d, J = 7.6)] and its C80 diastereomer, was achieved from **8**.[7] Upon comparison of the ^{1}H NMR spectra, synthetic **10** was found to be identical with degradation product **10**, establishing the stereochemistry of C79, C80, and C81 as shown in **9**.

We then turned our attention to degradation product **11** (Chart III), containing the C52–C74 carbon backbone of palytoxin.[11] The ^{1}H NMR spectrum of **11** provided valuable information on the relative stereochemistry of the cyclic portions,[12] indicating it to be as shown in **11**. In addition, two more advanced degradation products **12**[13] and **13**[14] were useful in this study.

The synthesis of **16** (the antipode of **13**) was next accomplished. The trans-allylic alcohol **14** (Chart IV), synthesized from D-glucose,[7] was subjected to Sharpless' asymmetric epoxidation[15] by using L(+)-diethyl tartrate to yield the expected epoxide **15**. Regioselective reductive epoxide opening of **15**[4] followed by acetylation, debenzylation, periodate oxidation, borohydride reduction, and acetylation furnished pentaacetate **16** [^{1}H NMR C_6D_6) δ 1.72 (3 H, s), 1.74 (3 H, s), 1.76 (3 H, s), 1.81 (3 H, s), 1.83 (3 H, s); α_D +9.8° (*c* 0.05, $CHCl_3$)]. The C73 epimer of **16** was also synthesized from **14** by treatment with the same sequence of reagents except for D(−)-diethyl tartrate in the asymmetric epoxidation.[15] Upon comparison of spectroscopic data and optical rotations, **16** was found to be the antipode of degradation product **13** [α_D −8.9° (*c* 0.09, $CHCl_3$)], establishing the stereochemistry at C67, C71, and C73. The stereochemistry C68, C69, and C70 was not determined directly by this synthesis but

(11) See ref 2b and 1a in the preceding paper.

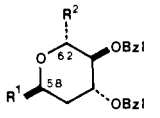
(12) This was concluded based on the values of $J_{60,61}$, $J_{61,62}$, $J_{67,68}$, $J_{68,69}$, $J_{69,70}$, and $J_{70,71}$ reported for **11**: see ref 2b, 2a, and 1a in the preceding paper.

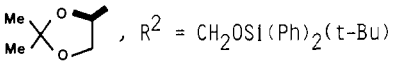
(13) See ref 2b and 2a in the preceding paper.

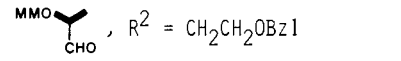
(14) This substance was prepared from the degradation product reported as compound **12** in ref 2b of the preceding paper in two steps: (1) O_3/MeOH/−78 °C, followed by $NaBH_4$ workup; (2) Ac_2O/py.

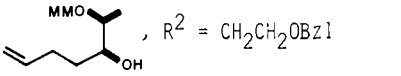
(15) See ref 8 in the preceding paper.

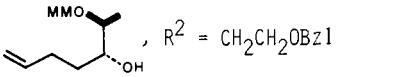
Chart V

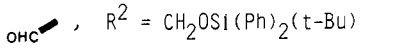


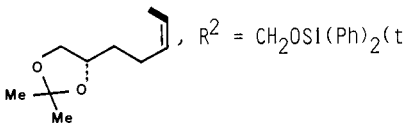












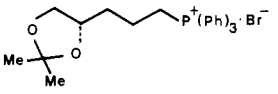


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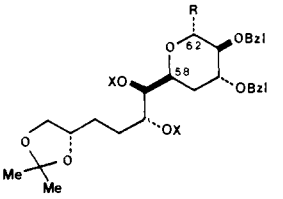
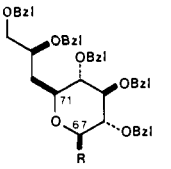
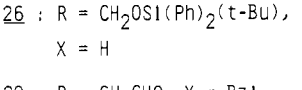
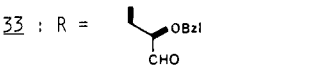
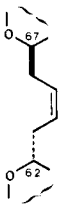
Chart VI











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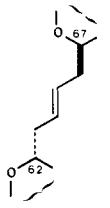

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was concluded with reasonable confidence from the aforementioned ^{1}H NMR data and was later confirmed by synthesis (vide infra).

The stereochemistry of degradation product **12** was established by the following synthesis. Trans-allylic alcohol **17**, prepared from 2-deoxy-D-glucose,[7] was subjected to asymmetric epoxidation[15] using D(−)-diethyl tartrate to yield the expected epoxide **18** as the major product. Camphorsulfonic acid treatment of **18** in acetone at room temperature gave acetonide **19** (Chart V) as the sole product. Grignard reaction of aldehyde **20**, prepared from **19**,[7] with 3-butenylmagnesium bromide in ether gave a 6:1 mixture of alcohols **21** and **22**.[16] Upon comparison of spectroscopic data and optical rotations, hexaacetate **12** [^{1}H NMR (C_6D_6) δ 1.71 (3 H, s), 1.79 (12 H, s), 1.81 (3 H, s); α_D +7.8° (*c* 0.16, $CHCl_3$)], obtained from the minor alcohol **22**,[7] was found to be identical with degradation product **12** while the corresponding hexaacetate derived from the major alcohol **21** was different, establishing the stereochemistry at C57, C58, and C62. The relative stereochemistry between C56 and C57, which was not confirmed by this synthesis, was found to be erythro as follows. Wittig reaction of aldehyde **23**[7] with phosphonium salt **24**[7] yielded cis-olefin **25** ($J_{56,57}$ = 11.0 Hz). After modification of the R^2 side chain, **25** was subjected to osmium tetroxide oxidation to furnish a 7:1 mixture of the two possible erythro diols. Upon comparison of spectroscopic data, hexaacetate **12** derived from the major erythro diol[7] was found to be identical with degradation product **12**.

The relative stereochemistry between C64 and C65 was determined as follows. Wittig reaction of phosphonium salt **28**, prepared from **27**,[7] with aldehyde **29**, prepared from **26**,[7] gave cis-olefin **30** (Chart VI). The stereochemistry of the olefinic bond was established by the spin–spin coupling constant ($J_{64,65}$ = 11.4 Hz) of the olefinic protons. Osmium tetroxide oxidation of **30** followed by acetylation, aqueous acid hydrolysis, debenzylation, and acetylation yielded a 1:1 mixture of two erythro acetates. Neither was found to be identical with degradation product **11** upon comparison of spectroscopic data. Photochemically induced double-bond isomerization of **30** gave a mixture of trans-olefin **31** ($J_{64,65}$ = 15.5 Hz) and cis-olefin **30**. Osmium tetroxide oxidation of **31** followed by conversion to the polyacetates as before yielded a 2:1 mixture of threo-acetate **11** [^{1}H NMR (C_6D_6) δ 1.68 (3 H, s), 1.70 (3 H, s), 1.75 (6 H, s), 1.78 (3 H, s), 1.79 (3 H, s), 1.80 (3 H, s), 1.81 (3 H, s), 1.84 (3 H, s), 1.86 (3 H, s), 1.88 (3 H, s), 1.93 (3 H, s), 2.02 (3 H, s); α_D +18.4° (*c* 0.69, $CHCl_3$)] and its C64–C65 diastereomer. Upon comparison of spectroscopic data and optical rotations, one of the threo isomers was found to be identical with degradation product **11**.

The absolute configuration at C65 was established as follows. Wittig reaction of phosphonium salt **32**, prepared from **26**,[7] with aldehyde **33**, prepared from **27**,[7] produced a cis olefin, which was sequentially subjected to hydroboration, aqueous acid hydrolysis, debenzylation, and acetylation to yield a mixture of acetates. Upon comparison of spectroscopic data, one of these acetates was found to be identical with degradation product **11**. Assignment of the absolute configurations at C65 and C73 was based on Sharpless' asymmetric epoxidation[15] used in the course of the synthesis of **33**. This assignment was further supported by the fact that the heptaacetate prepared from **33**[17] was a meso compound—note the symmetry of this substance. Since the relative stereochemistry between C64 and C65 was shown to be threo (vide supra), the absolute stereochemistry of C64 was now known. Thus, the stereochemistry of the degradation product **11** is as shown in the structure.

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(16) The stereochemistry outcome of this reaction is not surprising; for example, see: Still, W. C.; McDonald, J. H., III *Tetrahedron Lett.* **1980**, *21*, 1031 and references cited therein. Also see ref 21 in the preceding paper.

(17) The following sequence of reactions was applied to **33** to prepare the heptaacetate: (1) $NaBH_4$/MeOH/0 °C, (2) aqueous HCl/room temperature; (3) H_2/Pd–C/MeOH; (4) Ac_2O/py/room temperature.

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Supplementary Material Available: Spectroscopic data for compounds **2–4**, **7**, and **10–13** and details of some synthetic sequences (6 pages). Ordering information is given on any current masthead page.

(18) **Note Added in Proof**: The absolute configuration at C64 and C65 was further confirmed as follows. Hexa-1,3,4,6-tetraol 3,4-acetonide 1,6-diacetate [^{1}H NMR ($CDCl_3$) 1.38 ppm (6 H, s), 2.06 (6 H, s); α_D +44° (*c* 0.02, $CHCl_3$)] was successfully obtained from degradation product **11** in 7 steps [(1) NaOMe/MeOH/room temperature, (2) $MeC(OMe)_2Me$/Dowex-50X8-400/room temperature, (3) $Pb(OAc)_4/C_6H_6$–CH_2Cl_2/room temperature, followed by addition of MeMgI at room temperature, (4) Swern oxidation, (5) MCPBA/Na_2HPO_4/CH_2Cl_2/room temperature, (6) $LiAlH_4$/THF/room temperature, (7) Ac_2O/Py] and also from the major product of osmium tetroxide oxidation of **31** in 8 steps [(1) $MeC(OMe)_2Me$/Dowex-50X8-400/room temperature, (2) H_2/Pd-C/AcOH–MeOH/room temperature, (3–8) same as steps 2–7 described above). The absolute configuration of this substance was confirmed to be 3*R*,4*R* on comparison of the optical rotation with that of the authentic sample (α_D +44.5° (*c* 0.44, $CHCl_3$)) prepared from (−)-diethyl D-tartrate in 8 steps [(1) $MeC(OMe)_2Me$/*p*-TSA/C_6H_6, (2) $LiAlH_4/Et_2O$, (3) TsCl/Py, (4) 2 N HCl/MeOH, followed by KOH workup, (5) CH_2=$CHMgBr$/CuI/Et_2O, (6) $MeC(OMe)_2Me$/*p*-TSA/acetone, (7) O_3/MeOH, followed by $NaBH_4$ workup, (8) Ac_2O/Py].

Stereochemistry of Palytoxin. 3.[1] C7–C51 Segment

H. Fujioka, W. J. Christ, J. K. Cha, J. Leder,† and Y. Kishi*

Department of Chemistry, Harvard University Cambridge, Massachusetts 02138

D. Uemura

Faculty of Liberal Arts, Shizuoka University Ohya, Shizuoka 422, Japan

Y. Hirata

Faculty of Pharmacy, Meijo University Tempaku, Nagoya 468, Japan

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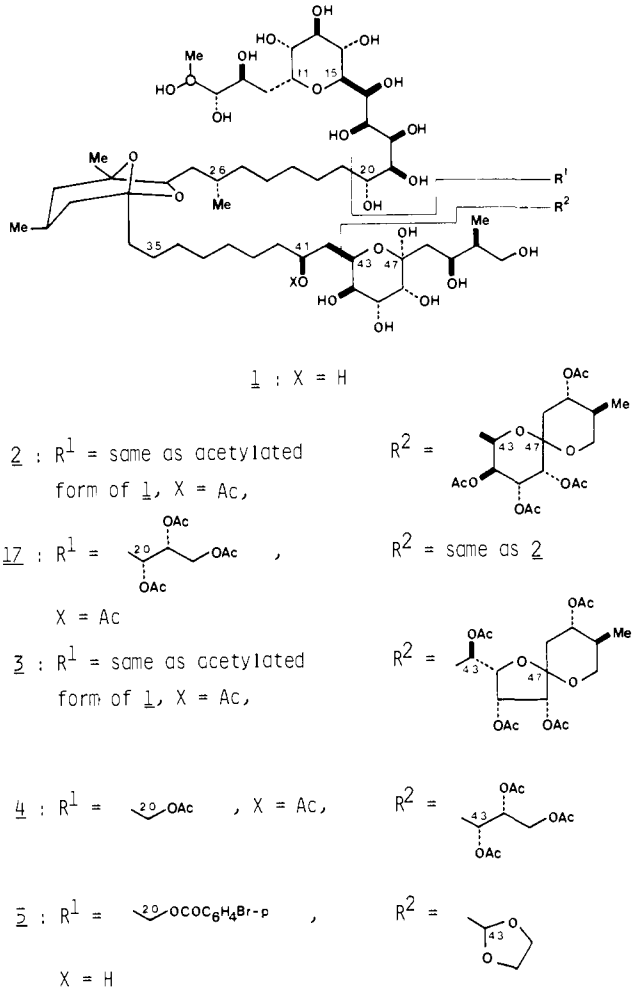
For investigation of the configuration of C7–C51 of palytoxin,[2] degradation products **1–5** (Chart I) were available.[3] Of these, **5** deserves special comment. Hirata, Uemura, and their co-workers established its structure, including the absolute configuration, by X-ray analysis.[4] We have recently developed a practical, stereoselective synthetic route from (*S*)-(−)-citronellal to the optically active bicyclic acetal alcohol **6**,[5,6] which provided a solid foundation to study the stereochemistry of C18–C51.

First, we worked with degradation product **4**. The ^{1}H NMR data suggested that the relative stereochemistry between C43 and C44 was as shown in **4**.[7] Routine synthetic operations allowed the transformation of **6** (Chart II) into aldehyde acetate **7**.[8,9] Wittig reaction of **7** with phosphonium salt **8**,[9] followed by hydrogenation–hydrogenolysis and acetylation, gave pentaacetate **4** [^{1}H NMR (C_6D_6) δ 0.88 (3 H, d, J = 6.5 Hz), 1.08 (3 H, d, J = 6.8), 1.17 (3 H, s), 1.72 (3 H, s), 1.77 (6 H, s), 1.84 (3 H, s), 1.89 (3 H, s); α_D +54° (*c* 0.85, $CHCl_3$)]. Upon comparison of the spectroscopic data and optical rotations, the synthetic substance was found to be identical with degradation product **4**, establishing the stereochemistry at C43 and C44.

Having already determined the stereochemistry at C49 and C50,[1] we next studied the configuration at C45 and C46. NMR studies on degradation products **2** and **3** suggested that the stereochemistry at these centers was most likely as shown in **1**.[7] This assignment was confirmed by the following experiments.

Aqueous acetic acid treatment of cis-α,β-unsaturated ketone **9**[9] (Chart III) resulted in the formation of a 3:2 mixture of two unsaturated spiro-6,6-ketals, **10a**, and **10b**, whose structures differed only in their configurations at the spiro center. Acetylation of the major isomer **10a** followed by OsO_4 oxidation and acetylation yielded a single tetraacetate. Since one face of the olefinic bond of acetylated **10a** was more sterically hindered, structure **11** was tentatively assigned to this product. This assignment was confirmed by further experiments utilizing cis-α,β-unsaturated

Chart I



†National Institutes of Health trainee at Harvard University, 1978 to present.

(1) Part 2 of this series: *J. Am. Chem. Soc.*, preceding paper in this issue.

(2) For the structure and numbering of palytoxin, see part 4 of this series.

(3) For degradation products **1**, **2**, **4**, and **5**, see ref 2a, 2c, and 1a in part 1 of this series. Hydrochloric acid treatment (3.5% HCl/room temperature/5 min) of **1**, followed by acetylation, yielded an approximately 1:1 mixture of two major products, **2** and **3**, along with small amounts of their stereoisomers with respect to the spiroketal center.

(4) See ref 2c in part 1 of this series.

(5) Leder, J.; Fujioka, H.; Kishi, Y., manuscript in preparation.

(6) For synthetic work related to this segment, see: Still, W. C.; Galynker, I. *J. Am. Chem. Soc.* **1982**, *104*, 1774.

(7) The approximately 5% NOE observed between the C44 and C45 protons and also between the C45 and C46 protons of **3** suggested that these three protons were cis oriented on the five-membered ring. The spin-spin coupling constants $J_{43,44}$ = 2.0 Hz, $J_{44,45}$ = 3.6 Hz, and $J_{45,46}$ = 4.0 Hz observed for **2** are consistent with this assignment. We are indebted to Drs. Naoki and Iwashita, Suntory Institute for Bioorganic Research, Osaka, Japan, for the NOE experiments.

(8) Satisfactory spectroscopic data were obtained for all new compounds in this paper.

(9) Details of this synthesis are given in the supplementary material.

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