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 **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

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Received July 19, 1982

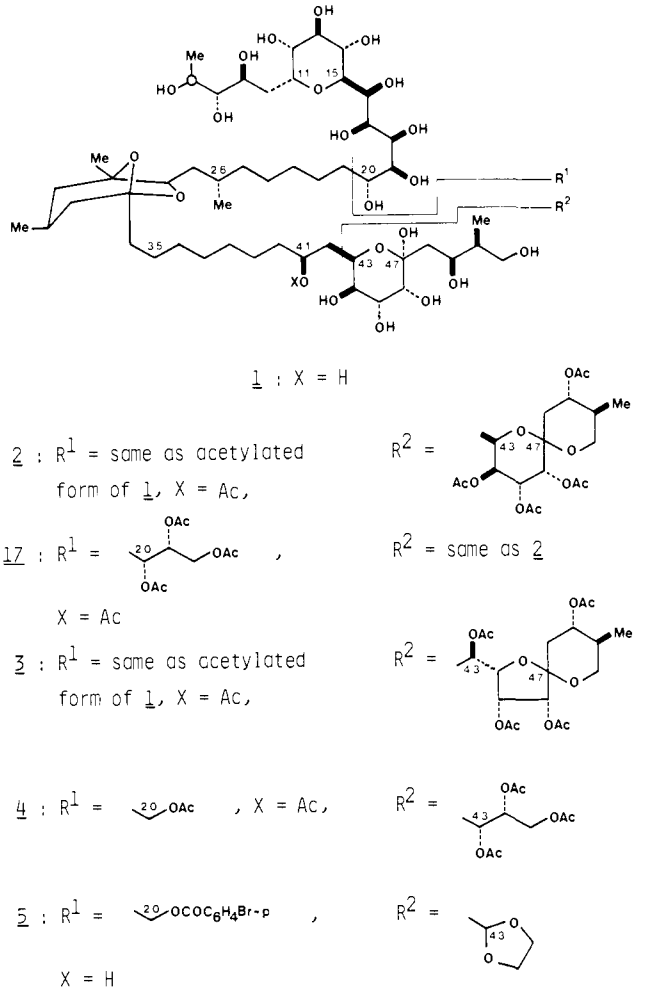
For investigation of the configuration of C7–C51 of palytoxin,[2] degradation products **1–5** (Chart I) were available.[3] Of these, **5** deserves special comment. Hirata, Uemura, and their co-workers established its structure, including the absolute configuration, by X-ray analysis.[4] We have recently 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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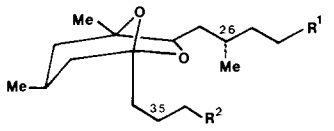
Chart II

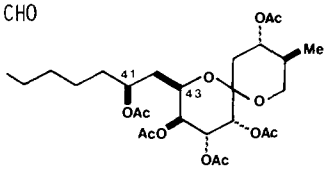


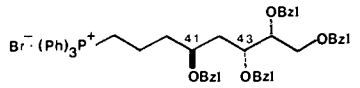
6 : $R^1 = CH_2OH$, $R^2 = CH(OMe)_2$

7 : $R^1 = (CH_2)_4OAc$, $R^2 = CHO$

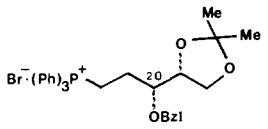
14 : $R^1 = CH_2OCH_2OBzl$, $R^2 = CH_2P^+(Ph)_3, I^-$

16 : $R^1 = CHO$

$R^2 =$ 



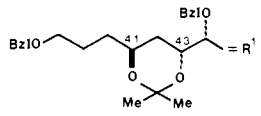
8

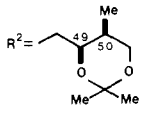


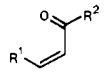
18

19 : antipode of 18

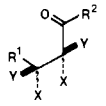
Chart III





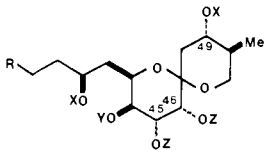


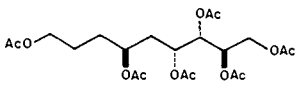
9



12a : X = OH, Y = H

12b : X = H, Y = OH





13

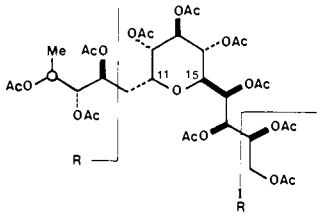
10a,b : R = CH_2OBzl, Y = Bzl
X = H, C,45-C,46 is
a double bond instead
of OZ and OZ

11 : R = CH_2OBzl, X = Z = Ac,
Y = Bzl

15 : R = CHO, X = Y = Z = Ac

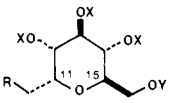
ketone **9**. Osmium tetroxide oxidation of **9** *prior* to spiroketalization led to a 2:1 mixture of two erythro diols, **12a** and **12b**. Acetic acid treatment of the major diol **12a** followed by acetylation

Chart IV

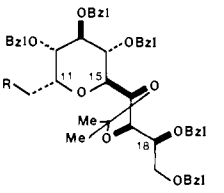


20

21 : R = CH_2OAc



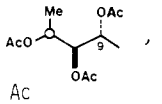
23 : R = CH_2=CH-, X = Bzl,
Y = H



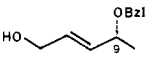
24 : R = $HOCH_2$-

25 : R = $MeCOCH^{c}$=CH-

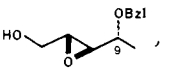
26 : R = $MeCOCH^{t}$=CH-

27 : R = 

X = Y = Ac

28 : R = 

X = Y = Bzl

29 : R = 

X = Y = Bzl

yielded a 1:2 mixture of spiro-6,6-ketal tetraacetates. The minor product was identical with **11**, while the major product was identical with the corresponding spiro-6,6-ketal tetraacetate derived from **10b**, establishing that **12a** had the same relative stereochemistry between C44 and C45 as did **11**, and consequently **12b** had the opposite. The stereochemistry at C44 and C45 of **12b** was, in turn, proven by its successful transformation to **13**[10] and correlation with 2-deoxy-D-glucose.[9]

Having determined the stereochemistry of **11**, we studied the coupling of the spiroketal segment with the bicyclic segment. The bicyclic segment **6** was converted to phosphonium salt **14**[9] and reacted with aldehyde **15**, derived from **11**,[9] under standard Wittig reaction conditions. Subsequent hydrogenation–hydrogenolysis and Swern oxidation[11] yielded aldehyde **16**. In order to establish the stereochemistry at C19 and C20, we had originally planned to couple **16** with a suitable segment to synthesize degradation product **2**. However, further efforts fortunately led to the isolation of a new degradation product, the gross structure of which was shown to be **17**.[12]

Wittig reaction of aldehyde **16** with phosphonium salt **18**, prepared from D-xylose,[9] followed by hydrogenation–hydrogenolysis, deacetonization, and acetylation, furnished octaacetate **17** [^{1}H NMR (C_6D_6) δ 0.87 (3 H, d, J = 6.6 Hz), 0.93 (3 H, d, J = 7.3 Hz), 1.08 (3 H, d, J = 6.6 Hz), 1.17 (3 H, s), 1.66 (3 H,

(10) Transformation of **12b** into **13** was performed in the following seven steps: (1) CH_2=C(OMe)Me/camphorsulfonic acid (CSA); (2) MCPBA/$CHCl_3$; (3) $LiAlH_4$/THF; (4) Ac_2O/py; (5) H_2/Pd–C/AcOEt; (6) aqueous AcOH; (7) Ac_2O/py.

(11) See ref 18 in part 1 of this series.

(12) Aqueous base hydrolysis [10% aqueous NaOH–MeOH(1:1)/room temperature] of **2** gave the corresponding polyalcohol, which was subjected to $NaIO_4$ oxidation (10 wt. % $NaIO_4/H_2O$/0 °C/2 min) followed by $NaBH_4$ workup, acetylation, and TLC separation to yield **17**.

s), 1.69 (3 H, s), 1.75 (3 H, s), 1.76 (3 H, s), 1.78 (3 H, s), 1.79 (3 H, s), 1.87 (3 H, s), 2.19 (3 H, s); α_D +112° (*c* 0.18, $CHCl_3$)]. The same sequence of reactions was performed with phosphonium salt **19** (the antipode of **18**), prepared from L-xylose,[9] to yield the C19 and C20 diastereomer of **17**.[13] Upon comparison of the spectroscopic data, synthetic octaacetate **17** was found to be identical with degradation product **17**, establishing the stereochemistry at C19, C20, C45, and C46.

The acetates **20–22** (Chart IV) were known to be more advanced degradation products of **1**.[14] The ^1H NMR spectrum of **20** suggested that the relative stereochemistry of the tetrahydropyran ring was as indicated in the structure.[14] The stereochemistry of the acyclic portions remained unknown. Synthesis of **22** [^1H NMR ($CDCl_3$) δ 2.06 (3 H, s), 2.08 (3 H, s), 2.09 (6 H, s); α_D +34.0° (*c* 0.11, $CHCl_3$)] was achieved in six steps from alcohol **23**,[9] which was synthesized from 2,3,4-tribenzyl-1,6-anhydro-D-glucopyranose.[15] Upon comparison of spectroscopic data and optical rotations, synthetic triacetate **22** was found to be identical with degradation product **22**, establishing the absolute configuration at C11 and C15.

Since the stereochemistry of the tetrahydropyran ring was known from the ^1H NMR data, only four diastereomers remained as structural possibilities for degradation product **21**. By use of the carbohydrate chain-extension method,[16] all four diastereomeric heptaacetates were synthesized from alcohol **23**.[17] Upon comparison of ^1H NMR spectra, synthetic threo heptaacetate **21** [^1H NMR (C_6D_6) δ 1.61 (3 H, s), 1.73 (6 H, s), 1.78 (6 H, s), 1.85 (3 H, s), 1.87 (3 H, s)] was found to be identical with degradation product **21**, establishing the stereochemistry at C12, C13, C14, C16, and C17. With use of similar methods, alcohol **24** and its C18 diastereomer were synthesized. The stereochemistry at C18 of **24** was unambiguously established by synthesis of one of the intermediates from L-glyceraldehyde.[17] In order to study the stereochemistry at C8, C9, and C18, we transformed **24** into cis- and trans-α,β-unsaturated ketones **25** and **26** via routine synthetic operations. Osmium tetroxide oxidation of cis-α,β-unsaturated ketone **25**, followed by separation of isomers, borohydride reduction, deacetonization, debenzylation, and acetylation, furnished two pairs of decaacetates with an erythro relationship between C8 and C9. Likewise, two pairs of decaacetates with a threo relationship between C8 and C9 were obtained from trans-α,β-unsaturated ketone **26**. Upon comparison of ^1H NMR spectra, one pair of the erythro decaacetates was found to be identical with degradation product **20**,[18] establishing the relative stereochemistry between C8 and C9 and the absolute stereochemistry at C18.

The absolute configuration at C8 was concluded by the following experiments. The erythro diol with the unnatural configuration at C8 and C9, obtained by OsO_4 oxidation of **25** (vide supra), was transformed into heptaacetate **27**.[19] The absolute configuration of **27** was determined as follows. Trans-allylic alcohol **28**[20] was subjected to Sharpless' asymmetric epoxidation[21] by using D(−)-diethyl tartrate to yield the expected epoxide **29**,[22] which was then converted to heptaacetate **27**.[23] Heptaacetate **27** thus prepared was found to be identical with heptaacetate **27** derived from **25**, establishing the absolute stereochemistry at C8 and consequently at C9.

Successful assignment of the stereochemistry of degradation products **17** and **20** allows us to define the stereochemistry of degradation product **1** as shown in the structure.[24]

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 **4**, **17**, **21**, **22**, and **27** (two diastereomers) and details of some synthetic sequences (4 pages). Ordering information is given on any current masthead page.

(13) ^1H NMR signals due to the C18–C21 portion of **17** were found to correspond exceptionally well to those of *threo*-nonane-1,2,3-triol triacetate but not to those of *erythro*-nonane-1,2,3-triol triacetate.

(14) For acetates **20** and **22**, see ref 2a and 1a, respectively, of part 1 of this series. Acetate **21** was isolated as a minor product of periodate oxidation of **1**.

(15) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976.

(16) See ref 6 in part 1 of this series.

(17) Details of these syntheses will be published elsewhere: Christ, W. J.; Cha, J. K.; Kishi, Y., manuscript in preparation.

(18) This substance was a diastereomeric mixture due to the C7 positon. Separation of the diastereomers was possible by analytical silica gel TLC (Merck HP-TLC silica gel 60F-254 5642; solvent system 1:1 hexane–AcOEt; four developments). ^1H NMR of the less polar decaacetate (500 MHz, C_6D_6) δ 1.26 (3 H, d, *J* = 6.6 Hz), 1.68 (3 H, s), 1.70 (3 H, s), 1.71 (3 H, s), 1.72 (3 H, s), 1.74 (3 H, s), 1.79 (3 H, s), 1.80 (3 H, s), 1.85 (3 H, s), 1.91 (6 H, s). ^1H NMR of the more polar decaacetate (500 MHz, C_6D_6) δ 1.09 (3 H, d, *J* = 6.6 Hz), 1.67 (3 H, s), 1.68 (3 H, s), 1.72 (3 H, s), 1.78 (3 H, s), 1.79 (3 H, s), 1.80 (3 H, s), 1.81 (3 H, s), 1.86 (3 H, s), 1.87 (3 H, s), 1.90 (3 H, s).

(19) This transformation was performed in the following six steps: (1) $NaBH_4$; (2) $C_6H_5CH_2Br/NaH$; (3) aqueous AcOH; (4) $NaIO_4$, followed by $NaBH_4$ workup; (5) H_2/Pd–C; (6) Ac_2O/py.

(20) This substance was prepared from **23** in seven steps: (1) $C_6H_5CH_2Br/NaH$; (2) O_3/MeOH/-78 °C; (3) $CH_2{=}CHMgBr/Et_2O$; (4) $C_6H_5CH_2Br/NaH$, followed by TLC separation; (5) O_3/MeOH/-78 °C; (6) $(i\text{-}PrO)_2P(O)CH_2CO_2Et/t\text{-}BuOK/THF$; (7) $DIBAL/CH_2Cl_2$–C_6H_6. The stereochemistry at C9 of **28** was not determined by this synthesis, but the fact that heptaacetate **27** had an erythro relationship between C8 and C9 permitted the conclusion of the C9 stereochemistry.

(21) See ref 8 in part 1 of this series.

(22) Asymmetric epoxidation using L(+)-diethyl tartrate yielded a diastereomeric epoxide of **29**.

(23) This transformation was performed in the following nine steps: (1) $C_6H_5CH_2OCOCl$/py; (2) $AlCl_3$; (3) $MeOCH_2Br/(i\text{-}Pr)_2(Et)N$; (4) aqueous NaOH; (5) $NaIO_4$; (6) MeMgI, followed by TLC separation; (7) concentrated HCl/MeOH; (8) H_2/Pd–C; (9) Ac_2O/py.

(24) For the stereochemistry at C47, see part 4 of this series.

Stereochemistry of Palytoxin. 4.[1] Complete Structure

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Received July 19, 1982

In the preceding communications we have disclosed the stereochemistry of key degradation products of the marine natural product palytoxin. It is important to note that *all* of the asymmetric centers existing in palytoxin are found intact[2] in these

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(1) Part 3 of this series: *J. Am. Chem. Soc.*, preceding paper in this issue.

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