Stereochemistry of Palytoxin. 1. C85–C115 Segment†

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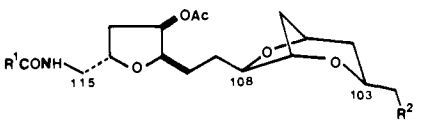
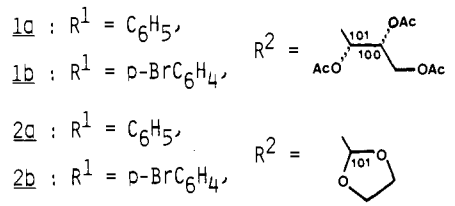
Palytoxin, the toxic principle isolated from marine soft corals of the genus *Palythoa*, is the most poisonous substance known to date except for a few polypeptides and proteins found in bacteria and plants. Pioneering investigations by the Hawaii group[1] and by the Nagoya group[2] have recently led them independently to suggest the gross structure of palytoxin.[3] In this series of papers, we will describe the complete assignment of the stereochemistry of palytoxin[4] primarily on the basis of organic synthesis.

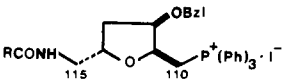
We chose to study degradation product **1a**[2d,1a] as our first target.

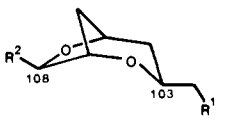


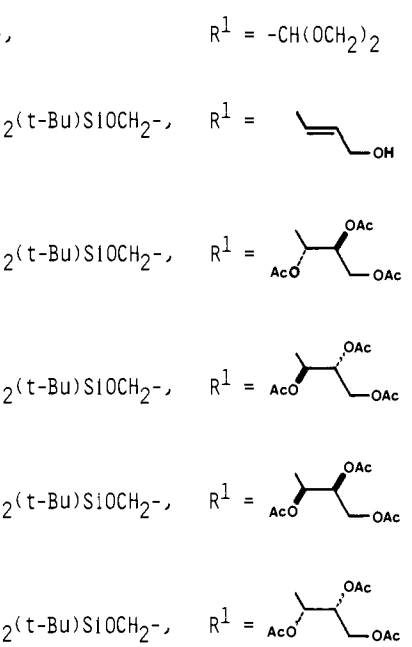


The structure, including the absolute configuration, of acetal **2b**, which is a more advanced degradation product of **1b**, was determined by Hirata, Uemura, and their co-workers using X-ray analysis.[2a,c] A stereospecific, practical synthesis of **2a** via **3** and **4** was recently achieved in our laboratory.[5] We next turned our attention to the degradation product **1a**, which had two unassigned

Chart I







asymmetric centers. In order to determine the configuration of these asymmetric centers unambiguously, we decided to synthesize all the possible stereoisomers of **1a** or its equivalent. Using the carbohydrate chain-extension method developed in our laboratory,[6] we synthesized the two erythro isomers **6**[7] and **7** (Chart I) from trans-allylic alcohol **5**, which was obtained from **4**. The assignment of the absolute configuration of these compounds depended upon Sharpless' asymmetric epoxidation,[8] which is reliable for trans-allylic alcohols.[9] Since the stereochemical outcome of Sharpless' asymmetric epoxidation of cis-allylic alcohols is not always predictable,[9] the two threo alcohols **8** and **9** were prepared from the intermediates used in the transformation of **5** into **6** and **7**.[10] The chemical shifts and spin–spin coupling constants for the C99, C100, and C101 protons of only isomer **9** were found to closely resemble those of **1a**, suggesting that **9** possesses the natural

† 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.

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§ National Science Foundation Predoctoral Fellow, 1978–1981; Monsanto Chemical Co. Fellow at Harvard University, 1981–1982.

‖ Studienstiftung des Deutschen Volkes Fellow, 1980–1981.

(1) (a) Moore, R. E.; Bartolini, G. *J. Am. Chem. Soc.* **1981**, *103*, 2491. (b) Moore, R. E.; Woolard, F. X.; Bartolini, G. *Ibid.* **1980**, *102*, 7370. (c) Moore, R. E.; Woolard, F. X.; Sheikh, M. Y.; Scheuer, P. J. *Ibid.* **1978**, *100*, 7758. (d) Moore, R. E.; Dietrich, R. E.; Hatton, B.; Higa, T.; Scheuer, P. J. *J. Org. Chem.* **1975**, *40*, 540. (e) Moore, R. E.; Scheuer, P. J. *Science (Washington, D.C.)* **1971**, *172*, 495.

(2) (a) Uemura, D.; Ueda, K.; Hirata, Y.; Naoki, H.; Iwashita, T. *Tetrahedron Lett.* **1981**, *22*, 2781. (b) Uemura, D.; Ueda, K.; Hirata, Y.; Naoki, H.; Iwashita, T. *Ibid.* **1981**, *22*, 1909. (c) Uemura, D.; Ueda, K.; Hirata, Y.; Katayama, C.; Tanaka, J. *Ibid.* **1980**, *21*, 4861. (d) Uemura, D.; Ueda, K.; Hirata, Y.; Katayama, C.; Tanaka, J. *Ibid.* **1980**, *21*, 4857. (e) Macfarlane, R. D.; Uemura, D.; Ueda, K.; Hirata, Y. *J. Am. Chem. Soc.* **1980**, *102*, 875. (f) Hirata, Y.; Uemura, D.; Ueda, K.; Takano, S. *Pure Appl. Chem.* **1979**, *51*, 1875.

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

(4) Palytoxin used in this study was extracted from Okinawan *Palythoa tuberculosa*. See ref 2 and also part 4 of this series.

(5) Ko, S. S.; Klein, L. L.; Pfaff, K.-P.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 4415.

(6) Minami, N.; Ko, S. S.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 1109. Finan, J. M.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2719. Similar methods were also reported by Corey (Corey, E. J.; Hopkins, P. B.; Munroe, J. E.; Marfat, A.; Hashimoto, S. *J. Am. Chem. Soc.* **1980**, *102*, 7986), Roush (Roush, W. R.; Brown, R. J. *J. Org. Chem.* **1982**, *47*, 1371), and Masamune and Sharpless (Katsuki, T.; Lee, A. W. M.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. *Ibid.* **1982**, *47*, 1373. Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Viti, S. M. *Ibid.* **1982**, *47*, 1378. Lee, A. W. M.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Walker, F. J. *J. Am. Chem. Soc.* **1982**, *104*, 3515).

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

(8) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. The latest publication on this subject from the Sharpless group is given in the following: Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *Ibid.* **1981**, *103*, 6237.

(9) For examples, see: Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873. See also the references cited in footnote 6.

(10) This was performed by the following steps: (1) Swern oxidation of five-membered carbonate alcohols (cf. compound **18** in our *J. Am. Chem. Soc.* publication cited under footnote 6); (2) $NaBH_4$ or $Zn(BH_4)_2$ reduction; (3) TLC separation; (4) aqueous base hydrolysis. For an alternative solution, see the last Masumune–Sharpless publication cited under ref 6.

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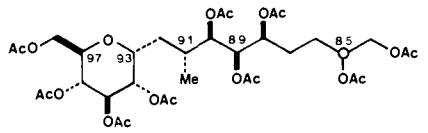
configuration at these asymmetric centers. Indeed, the tetraacetate **1a** [^{1}H NMR ($CDCl_3$) δ 2.03 (3 H, s), 2.07 (3 H, s), 2.09 (3 H, s), 2.10 (3 H, s); α_D + 68.8° (*c* 0.52, $CHCl_3$)], synthesized from **3** and a derivative of **9**,[11] was found to be identical with degradation product **1a**[12] on comparison of spectroscopic data, establishing the stereochemistry of palytoxin at C100 and C101 as shown in **1a**.

We next turned our attention to nonaacetate **10**,[13] a degradation



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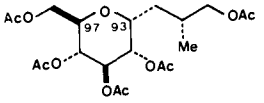

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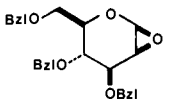
product known to contain the C84–C98 carbon backbone.[2d,1a] The ^{1}H NMR spectrum of **10** suggested that the relative stereochemistry of the tetrahydropyran portion was as indicated in the structure.[1a,2d] However, the relative stereochemistry of the acyclic portion remained unknown. To determine the relative and absolute sterochemistry of **10** efficiently, we initially studied the more advanced degradation product **11**.[14]

3,4,6-Tribenzyl-D-mannose 1,2-epoxide (**12**)[15] was reacted with



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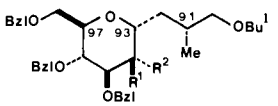
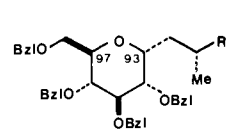


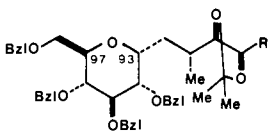
13 : R^1 = OH, R^2 = H

14 : R^1 = H, R^2 = OH

the Grignard reagent prepared from (*S*)-(+)-3-*tert*-butoxy-2-methyl-1-bromopropane[16] in the presence of Li_2CuCl_4[17] to yield stereoselectively alcohol **13**. Swern oxidation[18] of **13** followed by diborane reduction[19] furnished an 8:1 mixture of alcohols **14** and **13**. Debutylation of **14** followed by debenzylation and acetylation gave pentaacetate **11** [^{1}H NMR ($CDCl_3$) δ 0.96 (3 H, d, J = 7 Hz), 2.03 (3 H, s), 2.04 (3 H, s), 2.06 (3 H, s), 2.08 (6 H, s); α_D +64.7° (*c* 0.65, $CHCl_3$)]. Starting with **12** and (*R*)-(−)-3-*tert*-butoxy-2-methyl-1-bromopropane,[16] the same sequence of reactions produced the C91 diastereomer of **11**. On comparison of the spectroscopic data and optical rotations, synthetic pentaacetate **11** was found to be identical with degradation product **11**, establishing the stereochemistry at C91, C93, C94, C95, C96, and C97.

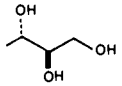
Chart II

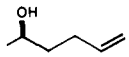


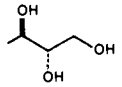


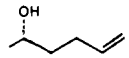
15 : R = 

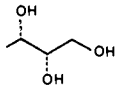
20 : R = $-CH_2OH$

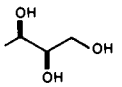
16 : R = 

21 : R = 

17 : R = 

22 : R = 

18 : R = 

19 : R = 

In order to study the stereochemistry at C88, C89, and C90, we converted **14** to trans-allylic alcohol **15** (Chart II) and then subjected it to the carbohydrate chain-extension method[6] in a manner identical with that used for allylic alcohol **5**. The triols **16–19** resulted. The threo relationship of triols **18** and **19**, and consequently the erythro relationship of triols **16** and **17**, was further confirmed by the fact that OsO_4 oxidation of the *tert*-butyldiphenylsilyl ether of trans-allylic alcohol **15** followed by $(n\text{-Bu})_4NF$ treatment furnished a 1:1 mixture of triols **18** and **19**.

The acetonide alcohol **20**, prepared from a derivative of threo-triol **19**,[20] was subjected to Swern oxidation[18] followed by addition of 3-butenylmagnesium bromide to the resulting aldehyde to yield approximately a 1:2 mixture of alcohols **21** and **22**.[21] Osmium tetroxide oxidation of the minor alcohol **21** followed by aqueous acid hydrolysis, debenzylation, and acetylation furnished nonaacetate **10**. The same sequence of reactions on **22** gave the corresponding nonaacetate. On comparison of the spectroscopic data, synthetic nonaacetate **10**[22] was found to be identical with degradation product **10**,[22] while the nonaacetate derived from **22** was different. The corresponding nonaacetates were likewise synthesized from derivatives of the remaining triols **16–18**, and none was found to be identical with degradation product **10**.

(11) The triol corresponding to triacetate **9**, i.e., R^1 = CH(OH)CH(OH)CH_2OH in structure **9**, was first converted to the pivaloyl acetonide [(1) $(Me)_3CCOCl$/py and (2) $MeC(OMe)_2Me$/acetone/*p*-TSA] and then subjected to the following sequence of reactions: (1) $(n\text{-Bu})_4NF$/THF; (2) Swern oxidation; (3) Wittig reaction with **3** (LDA/DMF–THF); (4) HN=NH; (5) H_2/Pd–C/MeOH; (6) aqueous NaOH; (7) aqueous AcOH; (8) Ac_2O/py.

(12) Degradation product **1a** was prepared by hydrogenolysis (Pd–C/AcOH–MeOH) of **1b**.[2d,1a]

(13) This substance was a diastereomeric mixture at C85. In this series of papers a small circle such as the one in structure **10** indicates that a degradation product (or its related compound) is a diastereomeric mixture due to the asymmetric center introduced during degradation reactions.

(14) This substances was prepared from **10** in three steps: (1) aqueous NaOH; (2) $NaIO_4$/MeOH, followed by $NaBH_4$ workup; (3) Ac_2O/py, followed by silica gel TLC separation.

(15) Sondheimer, S. J.; Yamaguchi, H.; Schuerch, C. *Carbohydr. Res.* **1979**, *74*, 327.

(16) This substance was prepared from (*S*)-(+)-3-hydroxy-2-methylpropionic acid according to the Cohen–Saucy procedure (Cohen, N.; Eichel, W. F.; Lopresti, R. J.; Neukom, C.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3505). We are indebted to Dr. Cohen for a generous gift of the acid.

(17) Tamura, M.; Kochi, J. *Synthesis* **1971**, 303.

(18) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

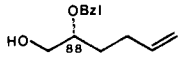
(19) Garegg, P. J.; Maron, L. *Acta Chem. Scand., Ser. B* **1979**, *33B*, 453.

(20) The acetonide alcohol **20** was synthesized from **19** in three steps: (1) $(Me)_3CCOCl$/py; (2) $MeC(OMe)_2Me$/acetone/*p*-TSA; (3) $LiAlH_4$/THF.

(21) The stereochemistry outcome of this reaction is not necessarily surprising; for examples see: Suzuki, K.; Yuki, Y.; Mukaiyama, T. *Chem. Lett.* **1981**, 1529 and references cited therein. Bernardi, R.; Fuganti, C.; Grasselli, P. *Tetrahedron Lett.* **1981**, *22*, 4021 and references cited therein. Danishefsky, S.; Kobayashi, S.; Kerwin, J. F., Jr. *J. Org. Chem.* **1982**, *47*, 1981 and references cited therein.

(22) This substance was a diastereomeric mixture due to the C85 position. Separation of the diastereomers was possible by preparative silica gel TLC (Merck silica gel 5769; solvent system 5:1 ether–hexane). The less polar nonaacetate **10** had the following spectroscopic data: ^{1}H NMR ($CDCl_3$) δ 0.93 (3 H, d, J = 7 Hz), 2.02 (6 H, s), 2.07 (3 H, s), 2.08 (3 H, s), 2.09 (3 H, s), 2.09 (6 H, s), 2.10 (3 H, s), 2.11 (3 H, s); α_D +36.2° (*c* 0.41, $CHCl_3$). The more polar nonaacetate **10** had the following: ^{1}H NMR ($CDCl_3$) δ 0.93 (3 H, d, J = 7 Hz), 2.03 (3 H, s), 2.04 (3 H, s), 2.06 (3 H, s), 2.07 (6 H, s), 2.09 (6 H, s), 2.10 (3 H, s), 2.14 (3 H, s); α_D +31.1° (*c* 0.13, $CHCl_3$).

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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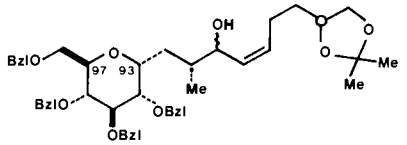

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rotations of (*R*)- and (*S*)-2-(benzyloxy)hex-5-en-1-ols, prepared from D- and L-glyceraldehyde ketals,[23] were found to be −11.7 and +10.4°, respectively. Thus, C88 has the *S* configuration in the minor alcohol **21**. This conclusion was further 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.

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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†

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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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