(3 H, s), -0.02 (3 H, s), 0.026 (9 H, s), 0.034 (21 H, s), 0.04 (12 H, s), 0.05 (18 H, s), 0.07 (12 H, s), 0.076 (15 H, s), 0.084 (24 H, s), 0.095 (6 H, s), 0.103 (3 H, s), 0.11 (3 H, s), 0.80-1.03 (14 H, m), 0.82 (9 H, s), 0.84 (9 H, s), 0.86 (18 H, s), 0.87 (27 H, s), 0.88 (27 H, s), 0.886 (54 H, s), 0.899 (27 H, s), 0.94 (9 H, s), 0.97 (3 H, d, J = 7.2 Hz), 1.03-2.55 (74 H, m), 1.08 (3 H, d, J = 6.5 Hz), 1.17 (3 H, s), 1.35 (3 H, s), 1.38 (3 H, s), 1.51 (3 H, s), 1.81 (3 H, s), 1.90 (3 H, s), 1.95 (3 H, s), 1.99 (3 H, s), 2.00 (3 H, s), 2.66 (1 H, ddd, J = 16.0, 8.2, 8.2 Hz), 3.11-3.19 (1 H, m), 3.15 (3 H, s), 3.23 (1 H, d, J = 2.9 Hz), 3.33-3.38 (2 H, m), 3.41 (1 H, ddd, J = 13.9, 6.1, 2.9 Hz), 3.51 (1 H, br s), 3.54 (1 H, br s), 3.56-3.98 (28 H, m), 3.60 (3 H, s), 3.65 (3 H, s), 3.70 (3 H, s), 3.71 (3 H, s), 3.73 (12 H, s), 3.77 (3 H, s), 3.78 (3 H, s), 4.11-4.19 (5 H, m), 4.19 (1 H, d, J = 10.6 Hz), 4.21 (1 H, d, J = 11.4 Hz), 4.21-4.30 (6 H, m), 4.32-4.41 (2 H, m), 4.34 (1 H, d, J = 11.2 Hz), 4.36 (1 H, d, J = 11.4 Hz), 4.41 (1 H, d, J = 11.6 Hz), 4.42 (1 H, d, J = 11.5 Hz), 4.43-4.48 (1 H, m), 4.45 (1 H, d, J = 10.7 Hz), 4.48 (1 H, d, J = 11.7 Hz), 4.51 (1 H, d, J = 11.9 Hz), 4.52 (1 H, d, J = 11.3 Hz), 4.54-4.59 (1 H, m), 4.57 (1 H, d, J = 11.3 Hz), 4.59 (1 H, br, d, J = 9.7 Hz), 4.65 (1 H, d, J = 11.4 Hz), 4.66 (1 H, d, J = 10.2 Hz), 4.78 (1 H, d, J = 11.4 Hz), 4.79 (1 H, d, J = 11.6 Hz), 4.81 (1 H, d, J = 10.6 Hz), 4.88 (1 H, d, J = 11.1 Hz), 4.90 (1 H, s), 4.92 (1 H, d, J = 3.6 Hz), 4.95 (1 H, s), 4.99 (1 H, dd, J = 6.2, 6.0 Hz), 5.03 (1 H, dd, J = 6.6, 6.6 Hz), 5.21 (1 H, br m), 5.25-5.45 (6 H, m), 5.28 (1 H, dd, J = 10.7, 8.3 Hz), 5.50-5.75 (6 H, m), 5.78 (1 H, br s, J = 11.9 Hz), 5.95 (1 H, dd, J = 11.2, 10.9 Hz), 6.28 (1 H, dd, J = 10.6, 10.6 Hz), 6.48 (1 H, dd, J = 14.4, 11.6 Hz), 6.63-6.70 (6 H, m), 6.73 (2 H, d, J = 9.6 Hz), 6.75 (4 H, d, J = 8.4 Hz), 6.76 (2 H, d, J = 8.3 Hz), 6.79 (2 H, d, J = 8.5 Hz), 6.82 (2 H, d, J = 8.5 Hz), 7.05 (2 H, d, J = 8.5 Hz), 7.09 (2 H, d, J = 7.6 Hz), 7.11 (2 H, d, J = 7.8 Hz), 7.12 (2 H, d, J = 8.2 Hz), 7.13 (2 H, d, J = 8.1 Hz), 7.15 (2 H, d, J = 7.8 Hz), 7.16 (2 H, d, J = 8.6 Hz), 7.17 (2 H, d, J = 8.8 Hz), 7.18 (2 H, d, J = 8.7 Hz), 7.22-7.30 (4 H, m), 7.39 (2 H, dd, J = 7.6, 7.6 Hz), 7.45 (1 H, dd, J = 7.3, 7.3 Hz), 7.48-7.59 (4 H, m), 7.62 (1 H, dd, J = 7.4, 7.4 Hz), 7.82 (2 H, d, J = 7.9 Hz), 7.89 (2 H, d, J = 7.8 Hz), 8.03 (2 H, d, J = 7.9 Hz), 8.31 (2 H, d, J = 7.7 Hz); ^{13}C NMR ($CDCl_3$) δ -5.06, -4.97, -4.88, -4.78, -4.63, -4.57, -4.50, -4.45, -4.33, -4.28, -4.14, -4.03, -3.99, -3.84, -3.76, -3.68, -3.63, -3.46, -3.19, -3.11, -2.82, -2.78, -1.50, 14.08, 14.52, 14.72, 14.98, 15.19, 17.05, 17.74, 17.91, 17.99, 18.06, 18.11, 18.20, 18.39, 18.44, 18.62, 20.35, 20.77, 20.94, 21.26, 21.48, 23.21, 24.30, 24.68, 25.73, 25.76, 25.85, 25.93, 25.99, 26.04, 26.07, 26.14, 26.19, 26.27, 26.32, 26.46, 26.92, 27.32, 27.43, 28.00, 28.70, 29.32, 29.66, 29.71, 30.28, 31.24, 31.55, 31.68, 32.86, 33.26, 33.94, 35.04, 36.15, 36.94, 37.66, 38.12, 38.26, 38.57, 38.68, 39.89, 39.97, 40.53, 41.05, 41.98, 44.74, 48.16, 51.94, 55.04, 55.12, 55.18, 55.22, 62.97, 65.09, 65.39, 67.29, 67.48, 68.44, 69.32, 70.58, 70.83, 71.42, 71.52, 71.69, 71.88, 72.01, 72.22, 72.34, 72.81, 72.93, 73.38, 73.67, 73.74, 73.94, 74.08, 74.21, 74.64, 74.78, 75.35, 75.68, 75.81, 76.01, 76.05, 76.63, 77.40, 77.61, 78.02, 78.16, 78.40, 78.73, 78.96, 79.19, 79.76, 80.29, 80.72, 80.99, 82.56, 83.29, 100.28, 107.77, 108.49, 112.51, 113.50, 113.61, 113.66, 113.70, 113.83, 127.43, 127.53, 128.23, 128.44, 128.58, 128.65, 128.98, 129.11, 129.26, 129.39, 129.43, 129.66, 129.81, 130.06, 130.21, 130.37, 130.44, 130.54, 130.64, 130.78, 130.92, 131.96, 132.86, 132.93, 133.04, 133.51, 133.87, 134.67, 145.07, 157.03, 158.76, 158.80, 158.84, 159.02, 159.08, 159.18, 165.00, 165.37, 165.73, 166.18, 169.54, 169.74, 169.84, 169.97, 170.06, 170.48.

Acknowledgment. We thank Mr. Higuchi, Mass Spectrometer Application Lab., JEOL USA, for measurements of FAB mass spectra. Financial assistance from the National Institutes of Health (NS-12108) and the National Science Foundation (CHE 89-09762) is gratefully acknowledged. We thank the National Institutes of Health for awarding Postdoctoral Fellowships to R.W.A. (GM-10813), M.J.M. (NS-07831), and J.B.W. (GM-09274), the French National Research Center to J.-M.B., and Merck Sharp & Dohme to W.J.C.

Supplementary Material Available: General experimental procedures and spectroscopic data of key coupling products (8 pages). Ordering information is given on any current masthead page.

Total Synthesis of Palytoxin Carboxylic Acid and Palytoxin Amide

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Abstract: The total synthesis of palytoxin carboxylic acid and palytoxin amide was achieved from the fully protected palytoxin carboxylic acid. The fully protected palytoxin carboxylic acid **1** contains eight different and 42 total protecting groups. All these protecting groups were successfully removed in five synthetic operations, i.e., (1) DDQ treatment, (2) aqueous $HClO_4$ hydrolysis, (3) aqueous LiOH hydrolysis, (4) $(n\text{-}Bu)_4NF$ treatment, and (5) aqueous AcOH hydrolysis. The completely deprotected palytoxin carboxylic acid was isolated in approximately 35% overall yield and identified with the authentic sample. An efficient method to convert palytoxin carboxylic acid **2** into palytoxin amide **3** was developed.

As seen from the fully protected palytoxin carboxylic acid **1**,[1] we chose to use several different protecting groups for this synthetic work. The suitability of these protecting groups for our purposes was demonstrated as soon as each building block became available. We would like to start by briefly reviewing the rationale behind these choices for the left half of molecule.

First, we chose the C.1 protecting group[2] primarily because of its ease of preparation. However, we met with some difficulties while attempting deprotection of this group under basic conditions. This problem was nicely solved by deprotecting the C.5 group first, resulting in the δ-lactone, which was smoothly hydrolyzed on brief

(1) Armstrong, R. W.; Beau, J.-M.; Cheon, S. H.; Christ, W. J.; Fujioka, H.; Ham, W.-H.; Hawkins, L. D.; Jin, H.; Kang, S. H.; Kishi, Y.; Martinelli, M. J.; McWhorter, W. W., Jr.; Mizuno, M.; Nakata, M.; Stutz, A. E.; Talamas, F. X.; Taniguchi, M.; Tino, J. A.; Ueda, K.; Uenishi, J.; White, J. B.; Yonaga, M. *J. Am. Chem. Soc.*, preceding article in this issue.

(2) For the numbering of palytoxin adopted in this paper, see structure **2**.

0002-7863/89/1511-7530$01.50/0

treatment with an aqueous base. Second, we chose the C.5 protecting group because of the maximum efficiency of the Ni(II)/Cr(II)-mediated coupling reaction in terms of the chemical yield and the stereoselectivity.[3] Third, we chose *p*-methoxyphenylmethyl (MPM) because of its stability under the variety of reaction conditions we used for the synthesis of the C.8–C.22 segment and also because of its ease of deprotection under the conditions developed by the late Dr. Oikawa.[4] However, the problem was its overall efficiency; even if the deprotection were achieved in 95% yield per group, the overall efficiency should be only 63% as there are nine MPM groups in the left half of molecule. We overcame this difficulty by extensive experimentation, defining the suitable conditions to achieve the deprotection in greater than 95% overall yield. Fourth, we originally planned to use a MPM group as the C.2 protecting group. However, during the DDQ deprotection study, we noticed that the rate of deprotection of the C.2 MPM group was considerably slower than the remaining MPM groups. Changing the electronic nature of this group to *o,p*-dimethoxyphenylmethyl (DMPM) provided an enhancement in the rate of deprotection, comparable with the deprotection rate of the remaining MPM groups. However, we later realized that the C.2 DMPM did not fulfill our needs completely. Namely, during the DDQ deprotection, a tetrahydrofuran ring formation was observed between the C.2 and C.5 positions.[5,6] For these reasons, an acetyl group was chosen for the C.2 protecting group. Finally, one might suspect the chemical stability of the C.47 hemiketal group, particularly under acidic conditions. Indeed, we observed the smooth spiroketalization involving the C.43 and C.51 hydroxyl groups during synthesis of the C.38–C.51 segment with MPM protecting groups. We hoped that this difficulty might be overcome via destabilization of the probable intermediate of the spiroketalization by introducing the electron-withdrawing group at the C.46 hydroxyl group. An acyl group such as a benzoate or an acetate matched our demand extremely well. The C.47 methoxy group now became stable even under acidic conditions. We could deprotect this group easily by hydrolyzing first the C.46 acyl group, followed by brief treatment with dilute aqueous acetic acid. The C.41, C.44, and C.45 acyl groups were used because of the convenience of synthesis of the C.38–C.51 segment. The choice of benzoates over acetates was not definitive except that benzoates were better behaved substrates, both in terms of stability and chromophore activity.

With respect to the right half of the molecule, there were two obvious options, MPM or *tert*-butyldimethylsilyl (TBS), to protect the hydroxyl groups. We did not prefer one over the other except that we felt, through model experiments, deprotection of TBS groups to be slightly cleaner. Second, neither the MPM nor the TBS group was found suitable as the C.73 protecting group. In the case of the MPM, under the DDQ-deprotection conditions, the MPM-protected *cis,trans*-dienol functionality around the C.73 position was smoothly and cleanly oxidized to the corresponding *cis,trans*-dienone. On the other hand, in the case of the TBS, the rate of the Suzuki coupling reaction was too sluggish for practical purposes.[7] In this connection, it is interesting to add that the Suzuki coupling using the *cis*-iodoolefin bearing a free hydroxy group at the C.73 position was not successful in a practical sense.[7] On the basis of these considerations, an acetyl group was chosen for the C.73 protecting group. Third, the C.100, C.101 acetonide group was chosen because this was the only protecting group,

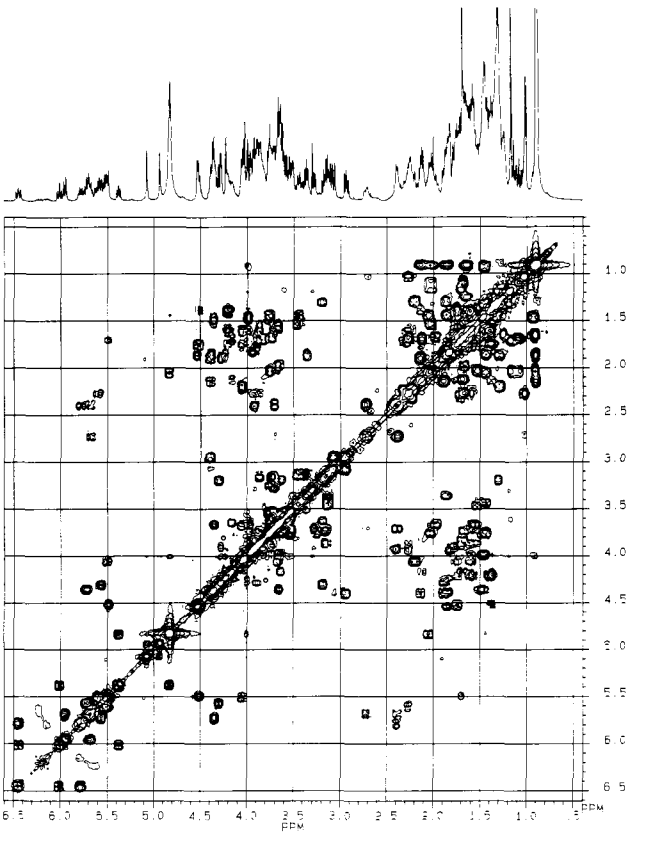


Figure 1. 2D COSY ^{1}H NMR spectrum (500 MHz) of palytoxin carboxylic acid **2** in 85:15 CD_3OD–D_2O. The small signals around 6.1–6.3 ppm are due to the C.74,C.76 *trans,trans*-diene isomer contaminated.

which gave satisfactory results in the Wittig olefination forming the C.98–C.99 bond in our hands. Last, the choice of the protecting group for the C.115 amino group was made because of its stability under the variety of reaction conditions used for the synthesis and also because of its ease of deprotection under the conditions required for the deprotection of TBS groups.

As mentioned in the preceding paper, the C.46 benzoate group was found to migrate readily onto the C.49 hydroxy group, which was further followed by scrambling of the remaining benzoate groups. To avoid this complication, it was necessary to protect the C.49 alcohol, which was cleanly achieved by acetylation at 0 °C.[8] The C.8 and C.53 acetate groups were used because of the experimental convenience.

The fully protected palytoxin carboxylic acid **1** contains eight different and 42 total protecting groups. We anticipated that all these protecting groups could be removed by five synthetic operations: (1) DDQ treatment to remove the MPM groups, (2) acid treatment to hydrolyze the acetonide group, (3) base treatment to hydrolyze the acetate and benzoate groups, (4) fluoride treatment to remove the TBS and urethane groups, and (5) aqueous acid treatment to hydrolyze the hemiketal group.[9] For specific reasons, including (1) the DDQ treatment must be before the base treatment otherwise the C.73 alcohol would be oxidized and (2) the base treatment must occur before the hydrolysis of the C.47 hemiketal, we found the order described above to be best.

The reaction conditions specified were carefully optimized for each step. In this connection, it is worthwhile to note the fact that the C.100, C.101 acetonide group was found to be much more acid-stable than we originally anticipated, and its hydrolysis required rather strong conditions. Among many acidic conditions examined, perchloric acid in aqueous THF at 25 °C for 8 days

(3) We found that the chemical yield and the stereoselectivity delicately depended on the C.5 protecting group. A silyl protecting group improved both the chemical yield and the stereoselectivity significantly. This observation, an improvement of the chemical yield and the stereoselectivity with substrates with silyl protecting groups, was found true for many cases tested in our laboratories.

(4) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885, 889.

(5) This was first demonstrated by using the model compound bearing the C.1–C.16 portion of palytoxin.

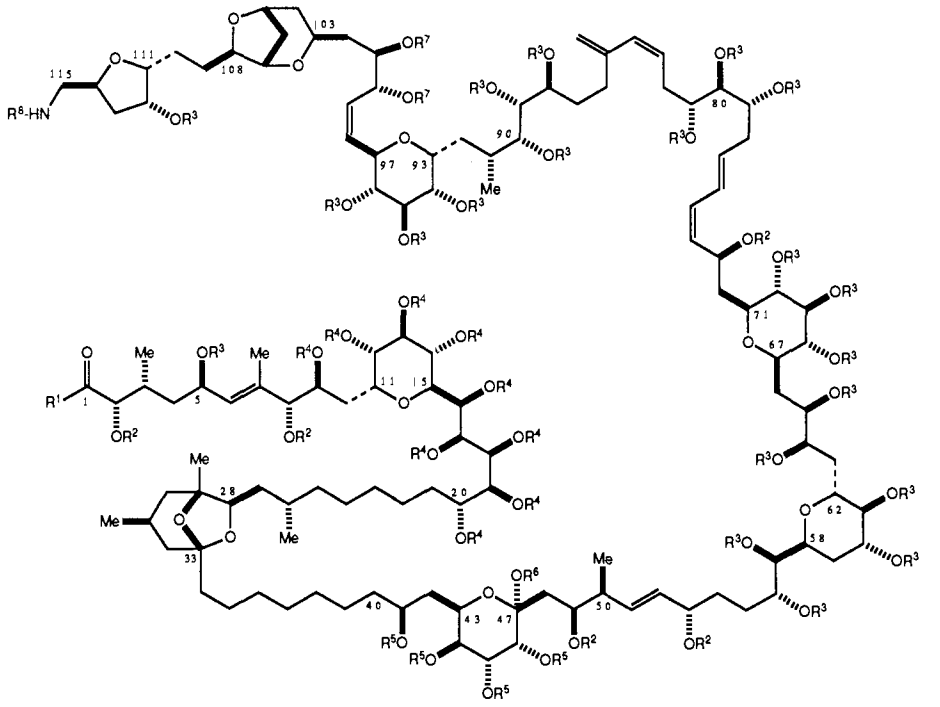
(6) Palytoxin carboxylic acid was isolated as a minor product from the attempted deprotection of the fully protected palytoxin carboxylic acid with C.2 DMPM protecting group.

(7) Uenishi, J.; Beau, J.-M.; Armstrong, R. W.; Kishi, Y. *J. Am. Chem. Soc.* **1987**, *109*, 4756.

(8) A migration of the C.46 benzoate group onto the C.49 hydroxyl group was not observed at 0 °C but was at room temperature.

(9) It was likely that the C.5 protecting group was removed at the $HClO_4$ step to form the δ-lactone, which was hydrolyzed at the LiOH step.

Scheme I[a]



1 : R^1=OMe, R^2=Ac, R^3=(t-Bu)(Me)$_2$Si, R^4=4-MeOPhCH$_2$, R^5=Bz, R^6=Me, R^7=acetonide, R^8=(Me)$_3$SiCH$_2$CH$_2$OCO

a

2 : Palytoxin Carboxylic Acid : R^1=OH, R^2=R^3=R^4=R^5=R^6=R^7=R^8=H

b

3 : Palytoxin Amide : R^1=NH_2, R^2=R^3=R^4=R^5=R^6=R^7=R^8=H

[a] Reagents and Reaction Conditions: (a) (1) DDQ/*t*-BuOH–CH_2Cl_2–phosphate buffer (pH 7.0) (1:8:1), sonicator, room temperature, 4.5 h, followed by acetylation (Ac_2O–DMAP/pyridine room temperature).[14] (2) $HClO_4$ [1.18 N, prepared by mixing 9 mL of H_2O–THF (3:7) and 1 mL of concentrated $HClO_4$]–THF (1:12), 25 °C, 8 days. (3) 0.08 N LiOH/H_2O–MeOH–THF (1:2:8), 25 °C, 20 h. (4) (*n*-Bu)$_4$NF in THF, 22 °C, 18 h and then in THF–DMF (1:1), 22 °C, 72 h. (5) AcOH–H_2O (1:350), 22 °C, 36 h. (b) (1) AcOH–H_2O (1:9), room temperature, 12 h. (2) NH_3/pyridine, room temperature, 10 min.

was the best. Under the more forcing conditions, a significant degree of isomerization of the *cis,trans*-diene around the C.74 position into the corresponding *trans,trans*-diene was observed.[10] In this connection, it is interesting to note that the corresponding isomerization was much more facile in palytoxin than in the current case; this remarkable reactivity difference is apparently due to the effect of the electron-withdrawing C.73 acetate in the fully protected series.

The completely deprotected product was isolated in approximately 35% overall yield by using a TSK G3000S polystyrene gel column in pure form. On comparison of biological activity, chromatographic behavior, and spectroscopic data [MS, 1D and 2D (Figure 1) ^{1}H NMR, ^{13}C NMR], the synthetic material was found identical with naturally occurring palytoxin carboxylic acid **2**.[11] Identification of the synthetic palytoxin carboxylic acid with the authentic sample was further demonstrated by spectroscopic and chromatographic comparison of the corresponding *N*-benzoate.[12]

As described before, during the hydrolysis of the methyl ester, we observed the δ-lactone formation, which immediately suggested an interesting possibility that selective functionalization of the carboxylic group of palytoxin carboxylic acid might be feasible.[5] Indeed, by ^{1}H NMR spectroscopy, we could demonstrate that palytoxin carboxylic acid cyclizes to the δ-lactone on treatment with an aqueous acetic acid solution and it is smoothly hydrolyzed back to palytoxin carboxylic acid on brief aqueous base. It was also possible to open the δ-lactone with ammonia to yield palytoxin amide **3** in excellent yield. The spectroscopic data (1D and 2D ^{1}H NMR) of this product were fully consistent with the amide structure assigned. It was further confirmed by degradation work; the C.8–C.9 bond was cleaved by periodate oxidation, to yield the C.1–C.8 amide aldehyde. The reactivity observed on palytoxin carboxylic acid would, we believe, provide an important clue for converting palytoxin carboxylic acid into palytoxin. In addition, it is interesting to note that one of the palytoxins recently isolated from sea weeds was suggested to have the structure of palytoxin amide.[13]

Experimental Section

General Experimental Procedures. See the supplemental material of the preceding paper.[1]

Palytoxin Carboxylic Acid. DDQ (37.0 mg, 163 μmol) was added to a suspension of fully protected palytoxin carboxylic acid **1** (40.8 mg, 6.03 μmol), *tert*-butyl alcohol (0.65 mL), and a phosphate buffer solution (pH 7.0, 0.65 mL) in dichloromethane (5.1 mL). The two-phase reaction mixture was stirred vigorously and sonicated every 10 min. After 3.5 h, additional DDQ (12.0 mg, 52.9 μmol) was added, and after 4.5 h, the reaction was quenched by diluting with dichloromethane and saturated $NaHCO_3$. The mixture was stirred for 20 min, and the aqueous phase

(10) Details of this observation will be published elsewhere.

(11) We are indebted to Professors Hirata and Uemura for a sample of natural palytoxin carboxylic acid and palytoxin.

(12) *N*-Benzoate was prepared under the conditions described for the preparation of the corresponding *N*-*p*-bromobenzoate: Uemura, D.; Ueda, K.; Hirata, Y.; Katayama, C.; Tanaka, J. *Tetrahedron Lett.* **1980**, *21*, 4857.

(13) Maeda, M.; Kodama, T.; Tanaka, T.; Yoshizumi, H.; Nomoto, K.; Takemoto, T.; Fujita, T. Thirtieth Symposium on the Chemistry of Natural Products, Abstracts; Fukuoka, Japan, 1988; p 616ff.

(14) This acetylation was performed because of convenience of isolation.

was separated and extracted with dichloromethane (3×). The organic layers were combined, washed with saturated $NaHCO_3$, H_2O, and brine, and dried over Na_2SO_4. The solution was concentrated to dryness, and the residue was purified by flash chromatography (5% followed by 10% methanol/dichloromethane) to afford the polyol as a colorless oil (30.3 mg, 88.4% yield).

A solution of partially protected palytoxin carboxylic acid (30.3 mg), acetic anhydride (100 μL), and DMAP (1.0 mg) in pyridine (1.0 mL) was allowed to stand at room temperature for 10 h. The reaction mixture was concentrated under vacuum and azeotroped with toluene (2×). The residue was passed through a short pad of silica gel (1:1 ethyl acetate–hexanes) to give the polyacetate as a colorless oil (31.6 mg).

$HClO_4$ (1.18 N, prepared by mixing 9.0 mL of 3:7 H_2O–THF and 1.0 mL of concentrated $HClO_4$; 0.55 mL) was added to a solution of the acetonide (31.6 mg) in THF (6.25 mL; the overall concentration of $HClO_4$ was 0.095 M). The flask was placed in a constant temperature bath at 25 °C for 8 days. The reaction was quenched with 1 N $NaHCO_3$ (0.72 mL), stirred for 20 min, and decanted. The solution was concentrated to ~1 mL, diluted with dichloromethane and benzene, and evaporated to ~1 mL (2×). The residue was diluted in dichloromethane, dried over Na_2SO_4, filtered, and concentrated to dryness to give an oil.

A 1 N LiOH aqueous solution (0.62 mL) was added to a solution of the crude product in 1:4 methanol–THF (7.4 mL). The reaction mixture was allowed to stand at 25 °C for 20 h and then concentrated to dryness. The product was mixed with TSK G3000S polystyrene gel/H_2O, and the mixture, was applied on top of a polystyrene gel column [3 × 0.9 (i.d.) cm; the column was equilibrated with H_2O before use]. The column was washed with H_2O (100 mL) to remove the salts and then with THF to recover the organic material. Removal of the solvent afforded the crude product as an oil (23.3 mg).

A solution of the crude product (23.3 mg) and $(n\text{-}Bu)_4NF{\cdot}3H_2O$ (95 mg, 0.30 mmol) in THF (4.0 mL) was allowed to stand at 22 °C for 18 h. The reaction mixture was diluted with DMF (4.0 mL) and stirred for an additional 72 h. The solution was concentrated to dryness, and the residue was charged on a TSK G3000S polystyrene gel column in H_2O (2 mL) [4 × 1.5 (i.d.) cm; the column was equilibrated with H_2O before use]. Monitoring with an UV detector at 233 nm, the product was eluted by passing H_2O (150 mL), 10%, 20%, and 30% EtOH/H_2O (150 mL each), 40%, 50%, 60%, 70%, and 80% EtOH/H_2O (100 mL each), and EtOH (200 mL). Palytoxin carboxylic acid methyl ketal (5.5 mg) was present mainly in the fractions of 50% EtOH/H_2O.

A solution of palytoxin carboxylic acid methyl ketal (5.5 mg) and acetic acid (5.7 μL) in H_2O (2.0 mL) was allowed to stand at 22 °C for 36 h. The solution was concentrated to ~1 mL, diluted with H_2O, and concentrated to give palytoxin carboxylic acid as an oil. The product was dissolved in a solution of 0.02 M NaH_2PO_4 (1.0 mL) and desalted in a short column of TSK G3000S polystyrene gel column. The product was eluted by 1:3 water–ethanol. Removal of the solvent furnished synthetic palytoxin carboxylic acid **2** (5.5 mg, 35.7% overall yield from **1**), which was identical with natural palytoxin carboxylic acid by TLC (E. Merck HPTLC NH_2 F_{254} precoated no. 15647, 9:8:6 pyridine–H_2O–*n*-AmOH; E. Merck HPTLC silica gel 60 F_{254} no. 13727, 7:7:6 *n*-AmOH–pyridine–H_2O). For the 2D COSY NMR spectrum, see Figure 1. For 1D ^1H NMR and FAB MS spectra, see the supplementary material.

***N*-Benzoyl Palytoxin Carboxylic Acid.** *p*-Nitrophenyl benzoate (7.9 mg, 32 μmol) was added to a solution of palytoxin carboxylic acid (8.3 mg, 3.2 μmol) in pyridine (1.2 mL). After being stirred for 10 h at room temperature, the reaction mixture was diluted with H_2O (1.2 mL), filtered through a glass frit, and concentrated. The resultant residue was purified by preparative HPTLC (E. Merck NH_2 F_{254} precoated no. 15647 9:8:7 pyridine–H_2O–*n*-AmOH) and then column chromatography (Sephadex LH-20, 4:1 MeOH–H_2O) to give *N*-benzoyl palytoxin carboxylic acid (7.6 mg, 88% yield).

For 1D and 2D ^1H NMR and FAB mass spectra, see the supplementary material.

Palytoxin Amide. Acetic acid (250 μL) was added to a solution of palytoxin carboxylic acid **2** (7.2 mg, 2.8 μmol) in H_2O (2.3 mL). After being stirred for 12 h at room temperature, the reaction mixture was concentrated to dryness. The resulting residue was dissolved in pyridine (3.0 mL), and NH_3 was bubbled through the solution for 10 min. After removal of the solvent, the residue was purified by preparative HPTLC (E. Merck NH_2 F_{254} precoated no. 15647, 9:8:7 pyridine–H_2O–*n*-AmOH) and then column chromatography (Sephadex LH-20, 4:1 MeOH–H_2O) to give palytoxin amide **3** (2.5 mg, 64% yield based on the consumed starting material) and recovered palytoxin carboxylic acid **2** (3.3 mg). For 1D and 2D ^1H NMR spectra, see the supplementary material.

Degradation of Palytoxin Amide. Palytoxin amide **3** (0.9 mg, 0.4 μmol) was charged on a TSK G3000S polystyrene gel column [4 × 1 (i.d.) cm], which was washed well with EtOH and then H_2O. An aqueous $NaIO_4$ solution (8.0 mg, 37 μmol, 0.8 mL) was applied to this column. After washing with H_2O, 50% aqueous EtOH was passed through the column. The solution was concentrated, and the resulting residue was purified by preparative TLC (15:85 MeOH–CH_2Cl_2) to give amide aldehyde: ^1H NMR (D_2O) δ 0.81 (3 H, d, J = 5.0 Hz), 1.41 (1 H, ddd, J = 10.1, 6.7, 3.2 Hz), 1.64 (3 H, s), 1.71 (1 H, ddd, J = 10.1, 6.9, 3.7 Hz), 2.03–2.08 (1 H, m), 3.99 (1 H, d, J = 1.7 Hz), 4.67–4.72 (1 H, m), 6.15 (1 H, d, J = 4.1 Hz), 9.25 (1 H, s); HRMS (FAB, glycerol) calcd for $C_{10}H_{17}NO_4$ 238.1055, 216.1236, 198.1130; found 238.1045 $(M + Na)^+$, 216.1234 $(M + H)^+$, 198.1148 $(M - H_2O + H)^+$.

Acknowledgment. We thank Mr. Higuchi, Mass Spectrometer Application Lab., JEOL USA, for measurements of FAB mass spectra. Financial assistance from the National Institutes of Health (NS-12108) and the National Science Foundation (CHE 89-09762) is gratefully acknowledged. We thank the National Institutes of Health for awarding Postdoctoral Fellowships to R.W.A. (GM-10813), M.J.M. (NS-07831), and J.B.W. (GM-09274), the French National Research Center to J.-M.B., and Merck Sharp & Dohme to W.J.C.

Supplementary Material Available: ^1H NMR, 2D COSY ^1H NMR, and FAB MS spectroscopic data for palytoxin carboxylic acid, its *N*-benzoate, and palytoxin amide (10 pages). Ordering information is given on any current masthead page.