Total Synthesis of a Fully Protected Palytoxin Carboxylic Acid

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Abstract: The total synthesis of a fully protected palytoxin carboxylic acid was achieved from eight building blocks **1**, **2**, **4**, **6**, **8**, **9**, **11**, and **13**. The C.22–C.23 and C.37–C.38 bonds were formed via Wittig olefination, followed by hydrogenation. The Ni(II)/Cr(II)-mediated coupling reaction was utilized for formation of the C.7–C.8 and C.84–C.85 bonds. The TlOH-accelerated diene synthesis was applied for formation of the C.75–C.76 bond. The C.98–C.99 olefinic bond was introduced by a Wittig reaction, whereas the C.51–C.52 olefinic bond was introduced by a Horner–Emmons reaction, followed by stereoselective $LiBH_4/EuCl_3$ reduction.

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 naturally occurring proteins found in bacteria and plants.[1] The gross structure of palytoxin was elucidated in 1981 by two groups independently.[2a,b] Hence, it immediately became evident that palytoxin is uniquely distinct from molecules with which organic chemists have previously dealt, both in terms of magnitude of molecular size and of structural complexity, and we decided to undertake the investigation of this extraordinary natural product. Our interests were primarily twofold: chemical synthesis and conformational analysis. However, we realized that the information given by the gross structure was not sufficient enough to address our questions properly. For this reason, the very first phase of our research was to establish unambiguously the complete structure of palytoxin. On the basis of extensive efforts for approximately 2 years, we succeeded in elucidating the complete structure of palytoxin in 1982, primarily by organic synthesis.[3] In this and the following paper,[4] we would like to report the total synthesis of palytoxin carboxylic acid and palytoxin amide.

By the summer of 1985, we had developed the efficient and practical syntheses of the eight key building blocks[5] and began to focus on the convergent coupling of these moieties. Some of the couplings were conducted in a straightforward manner. For example, the C.22–C.23 and C.37–C.38 bonds[6] were formed via Wittig olefination, followed by hydrogenation. Thus, the ylide generated from the phosphonium salt **2** was reacted with the aldehyde, prepared from the alcohol **1** under the Swern conditions,[7] to give a mixture of *cis*- and *trans*-olefins in 88% overall yield from **1**. Hydrogenation of this olefin mixture, followed by treatment with $(n\text{-Bu})_4NF$, yielded the primary alcohol **3** in 95% overall yield.[8] After the necessary functionalization of the C.37 position to the phosphonium surrogate, the primary alcohol **4** was oxidized to the aldehyde and once again subjected to the Wittig olefination and subsequent hydrogenation, to yield the desired product in 62% overall yield. The required adjustment of the C.8 protecting group was performed in two steps in 81% yield, to furnish the primary alcohol **5**.

Using model compounds, we evaluated the feasibility and applicability of various bond-forming reactions and found the Ni(II)/Cr(II)-mediated coupling reaction[9] to be the best by far for the C.7–C.8 bond formation.[10] Thus, the iodoolefin **6** and the aldehyde prepared from **5** under the Swern conditions were treated with $CrCl_2$ containing a small amount of $NiCl_2$ in a DMSO–THF mixture, to yield the desired allylic alcohol (C.8 α-OH, 64% yield) along with the undesired allylic alcohol (C.8 β-OH, 18% yield). The minor undesired allylic alcohol could be converted into the desired allylic alcohol via oxidation/reduction in 91% overall yield with a stereoselectivity of 8:1. After acetylation, the desired allylic acetate was treated with pyridinium *p*-toluenesulfonate (PPTS),[11] to furnish the complete left half **7** in 97% overall yield. The C.8 stereochemistry introduced at the Ni(II)/Cr(II)-mediated coupling reaction was established based on degradation work.[12]

The C.98–C.99 olefinic bond was stereoselectively introduced by a Wittig reaction. One problem encountered in this coupling was the C.97 epimerization via a ring opening/closing process.[13,14] Fortunately, however, we were able to identify the conditions to

(1) For review on palytoxin, see: (a) Moore, R. E. *Prog. Chem. Org. Nat. Prod.*; Springer-Verlag: New York, 1985; Vol. 48, p 81ff, and reviews cited therein. (b) Hirata, Y.; Uemura, D.; Ohizumi, Y. *Handbook of Natural Toxins*; Tu, A. T., Ed. Marcell Dekker: New York, 1988; Vol. 3, p 241ff.

(2) For the gross structure of palytoxin, see: (a) Uemura, D.; Ueda, K.; Hirata, Y.; Naoki, H.; Iwashita, T. *Tetrahedron Lett.* **1981**, *22*, 2781, and references cited therein. (b) Moore, R. E.; Bartolini, G. *J. Am. Chem. Soc.* **1981**, *103*, 2491, and references cited therein.

(3) (a) For the stereochemistry assignment primarily based on organic synthesis, see: Cha, J. K.; Christ, W. J.; Finan, J. M.; Fujioka, H.; Kishi, Y.; Klein, L. L.; Ko, S. S.; Leder, J.; McWhorter, W. W., Jr., Pfaff, K.-P.; Yonaga, M.; Uemura, D.; Hirata, Y. *J. Am. Chem. Soc.* **1982**, *104*, 7369, and preceding papers. (b) For the stereochemistry assignment primarily based on spectroscopic methods, see: Moore, R. E.; Bartolini, G.; Barchi, J.; Bothner-By, A. A.; Dadok, J.; Ford, J. *J. Am. Chem. Soc.* **1982**, *104*, 3776.

(4) 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.*, following article in this issue.

(5) The details of these syntheses will be published in a full account.

(6) For the numbering of palytoxin adopted in this paper, see structure **15**.

(7) (a) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651. (b) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(8) All the new compounds reported in this paper gave satisfactory spectroscopic data, including ^1H and ^{13}C NMR, IR, and MS.

(9) (a) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644. (b) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Uchimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048.

(10) We studied couplings of C.7 methyl ketone with ketophosphonates or acetylenes to form, directly or indirectly, α,β-unsaturated ketones. Some of these attempts yielded interesting solutions to this problem, but their overall efficiency was not comparable to that of the Ni(II)/Cr(II)-coupling route.

(11) Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.

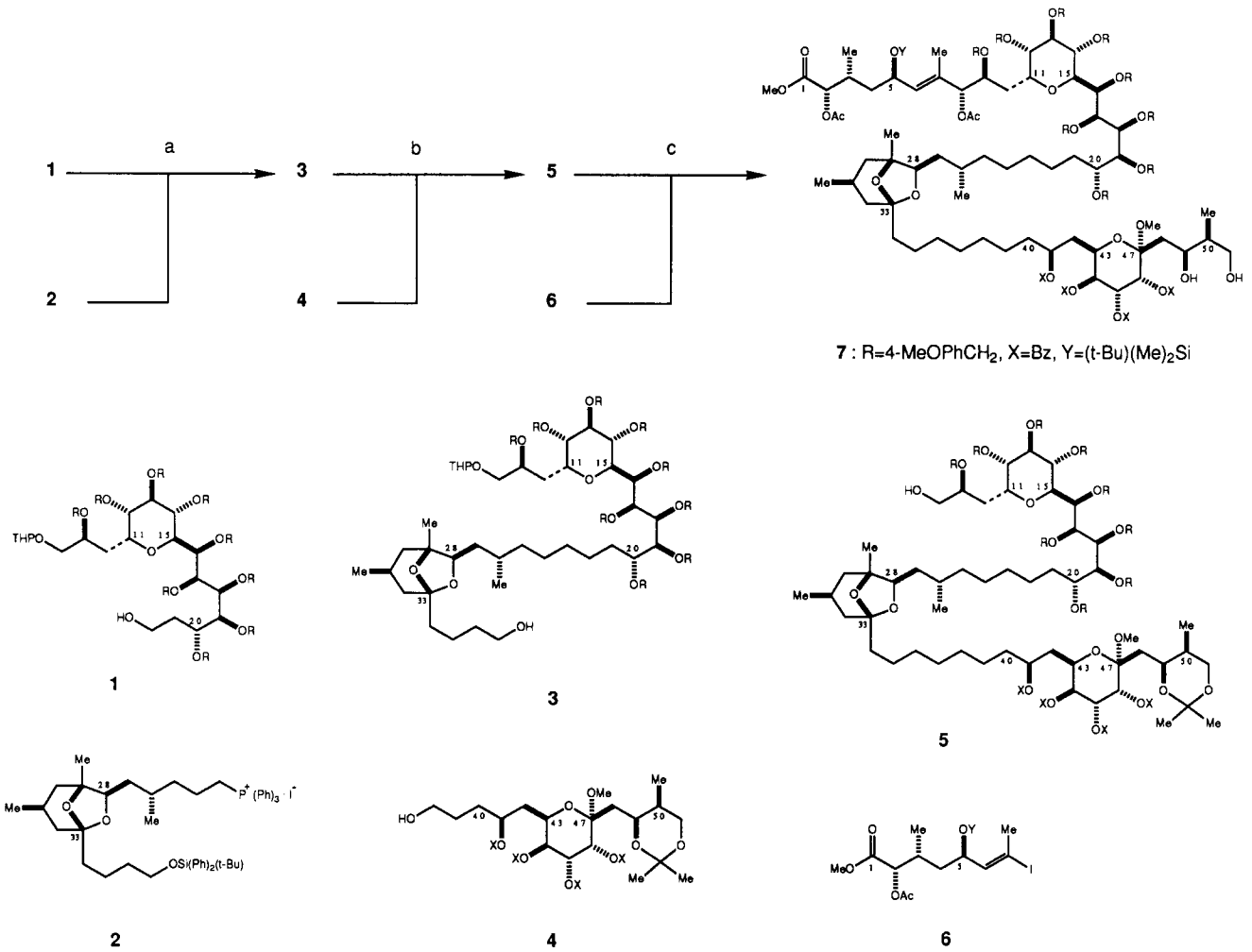
(12) The Ni(II)/Cr(II)-mediated coupling was also conducted by using the C.8 aldehyde bearing a $OSi(Ph)_2(t\text{-Bu})$ group at the C.22 position. The C.8 configuration of the major diastereomer (the stereoselectivity was approximately 8:1 for this case) was established via degradation work: ozonization and $NaBH_4$ reduction, to yield the C.7–C.22 segment, which was compared with an authentic sample available in our laboratories in connection with the stereochemistry assignment of palytoxin. By using a sequence of reactions similar to the one described in the text, the major diastereomer obtained in the Ni(II)/Cr(II) coupling was converted into the left half of palytoxin, which was confirmed to be identical with **7**.

(13) (a) Schweizer, E. E.; Creasy, W. S.; Light, K. K.; Shaffer, E. T. *J. Org. Chem.* **1969**, *34*, 212. (b) Secrist, J. A., III; Barnes, K. D. *J. Org. Chem.* **1980**, *45*, 4526, and references cited therein.

(14) McWhorter, W. W., Jr. Harvard Thesis, 1984.

0002-7863/89/1511-7525$01.50/0

Scheme I[a]



[a] Reagents and Reaction Conditions: (a) (1) The aldehyde, prepared from **1** under the Swern conditions, was treated at −78 to 0 °C with the ylide generated (*n*-BuLi/THF −78 °C) from **2**. (2) H_2 (1 atm)−10% Pd on C/MeOH−Et_2O (1:2), room temperature. (3) $(n\text{-Bu})_4NF$/THF, room temperature. (b) (1) **3**/MsCl−$(Et)_3N/CH_2Cl_2$, 0 °C. (2) NaI/2-butanone, 60 °C. (3) $P(Ph)_3$/DMF, 110 °C. (4) The aldehyde, prepared from **4** under the Swern conditions, was treated at −78 to 0 °C with the ylide generated from the phosphonium salt (*n*-BuLi/THF, −78 °C). (5) H_2 (1 atm)−10% Pd on C/MeOH−Et_2O (2:1), room temperature. (6) PPTS/MeOH−Et_2O (3:1), 42 °C. (7) PPTS/acetone, room temperature. (c) (1) **6** and the aldehyde prepared from **5** under the Swern conditions/$CrCl_2$ containing 0.11% $NiCl_2$/DMSO−THF (1:3), 32 °C. (2) Ac_2O−DMAP/pyridine, room temperature. (3) PPTS/MeOH−Et_2O (3:1), 40 °C. For the conversion of the minor allylic alcohol into the major allylic alcohol: (1) Swern oxidation. (2) $Zn(BH_4)_2/Et_2O$, 0 °C.

realize the cis-olefination without significant epimerization at the C.97 position. Under these conditions, the desired *cis*-olefin **10** was isolated in 60–80% overall yield from the primary alcohol **8** along with a small amount of the corresponding *trans*-olefin (cis/trans stereoselectivity, ≥8:1). It was interesting to note that the C.97 epimerization was also observed even in the isolation and purification process of the phosphonium salt **9**. This technical difficulty was overcome by using a TSK G3000S polystyrene gel column.[15]

After oxidative hydrolysis of the thioacetal group, we subjected **10** to a Ni(II)/Cr(II)-mediated coupling with the *cis*-iodoolefin **11** in a DMSO−THF mixture at room temperature, to yield the desired allylic alcohols as a 3:2 diastereomeric mixture. This mixture was oxidized to the corresponding cis-α,β-unsaturated ketone by pyridinium dichromate (PDC),[16] which was then converted into the desired diene by using a Wittig reaction. It is worthwhile to note that this olefination was extremely sluggish in THF, but facile in a mixture of hexanes and THF. The overall yield of the desired diene from the thioacetal **10** was 70–75% yield.

The Pd(0)-catalyzed diene synthesis, developed by Suzuki and co-workers,[17] seemed to ideally meet our requirement for the C.75–C.76 bond formation. Indeed, by using a model compound, we could show that the desired *cis,trans*-diene was stereospecifically formed in fairly good yield in THF as well as in aqueous THF. However, with the increase in the molecular size of substrates, we observed a sharp decrease in chemical yield. In some cases no desired diene formation was detected, which clearly suggested that an improvement should be made to apply this process successfully to our work. For this reason, we studied possible ways to enhance the rate of the Suzuki coupling reaction and discovered that TlOH has a pronounced effect.[18]

Vinylboronic acids[19] required for the Suzuki diene synthesis are usually available via catechol hydroboration of acetylenes. However, we observed that catecholborane attacked the C.115 urethane group existing in the upper half of palytoxin faster than the terminal acetylene. This problem was solved by using the reagent developed by Matteson.[20] The aldehyde prepared from

(15) TSK G3000S polystyrene gel was a generous gift from Professor Hirata, Meijo University, Nagoya, Japan.

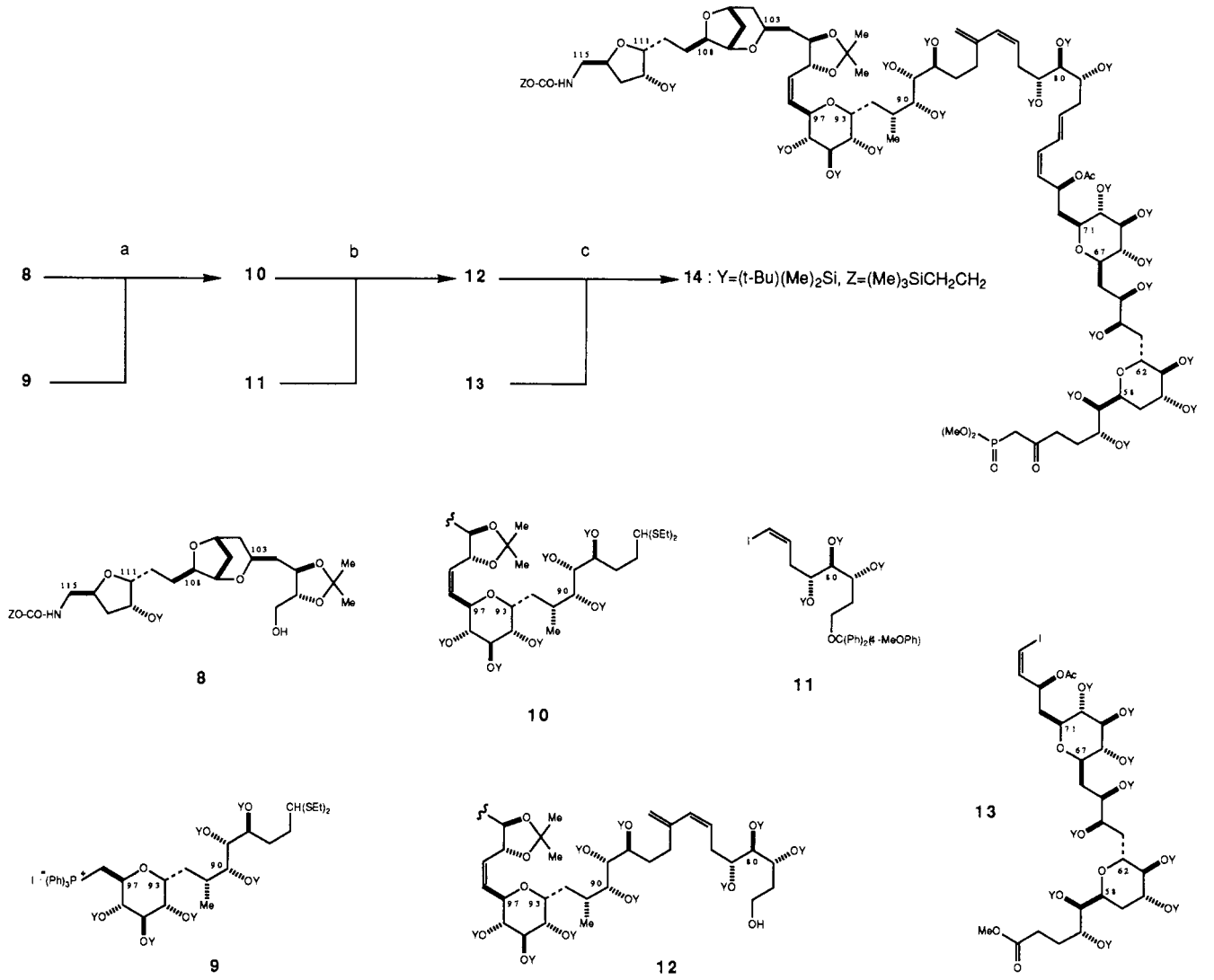
(16) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399. In order to have clean and facile oxidation, it was important to use PDC recrystallized from distilled water.

(17) Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972, and references cited therein.

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

(19) The coupling reactions using boronic acids gave cleaner results than the ones using the corresponding boronates in our hands.

Scheme II[a]



[a] Reagents and Reaction Conditions: (a) A mixture of the aldehyde, prepared from **8** under the Swern conditions, and **9** was titrated by dropwise addition of LDA (0.4 M in THF) in THF–HMPA (5:1) at room temperature. (b) (1) I_2–$NaHCO_3$/acetone–water (19:1), 0 °C. (2) The aldehyde and **11**/$CrCl_2$ containing 0.11% $NiCl_2$/DMSO–THF (3:1), room temperature. (3) PDC–DMF, 0 °C. (4) The α,β-unsaturated ketone and $H_2C{=}P(Ph)_3$/hexanes–THF (2:1), 0 °C. (5) PPTS/MeOH–CH_2Cl_2 (1:5), room temperature. (c) (1) Swern oxidation. (2) The aldehyde and $LiCH[B(OCH_2CH_2CH_2O)]_2$–TMEDA/THF, 0 °C, followed by workup with EtOAc–brine containing 1 N HCl. (3) The vinylboronic acid/TlOH (10% aqueous solution)–hexanes, room temperature, followed by addition of **13** and $Pd[P(Ph)_3]_4$ at room temperature. (4) The methyl ester and $LiCH_2P(O)(OMe)_2$ (30 equiv)/THF, −78 °C.

12 under the Swern conditions was coupled with $LiCH[B(OCH_2CH_2CH_2O)]_2$ and followed by brief acid workup to yield the expected vinylboronic acid with an 8–10:1 stereoselectivity, favoring the desired *trans*-vinylboronic acid. Without purification, the vinylboronic acid was treated with the cis-iodide **13** in hexanes in the presence of $Pd[P(Ph)_3]_4$ and TlOH, to give the desired *cis,trans*-diene in 70% overall yield from the primary alcohol **12**. As the coupling rate to form *cis,cis*-diene was much slower than the one to form *cis,trans*-diene,[18] the product isolated from this reaction was stereochemically pure even though an ca. 8:1 mixture of *trans*- and *cis*-vinylboronic acids was used. By use of the standard procedure, the methyl ester was then converted into the ketophosphonate **14** in nearly quantitative yield.

Using suitable model compounds, we evaluated the feasibility and applicability of various olefin-forming reactions for the C.51–C.52 case.[21] Among them, the ketophosphonate route yielded the most satisfactory results; the aldehyde, prepared by oxidation of **7** with $RuCl_2[P(Ph)_3]_3$,[22] was coupled with the anion, generated from the ketophosphonate **14**, to yield exclusively the desired trans-α,β-unsaturated ketone in 75–80% yield. As one might expect, the starting material as well as the product showed interesting but undesired reactivities, particularly against basic reagents.[23] These undesired side reactions were avoided by generating the anion from 2.0 equiv of ketophosphonate **14** and approximately 2 equiv of NaH in THF, followed by coupling with 1.0 equiv of the aldehyde. The potential drawback of this procedure was that the reaction was performed at the expense of 1.0 equiv of the ketophosphonate. Fortunately, however, the excess ketophosphonate could easily be recovered by silica gel chromatography almost quantitatively. The entire carbon skeleton could be assembled by using the inverse order of the two crucial bond-forming reactions, i.e., the C.51–C.52 bond formation

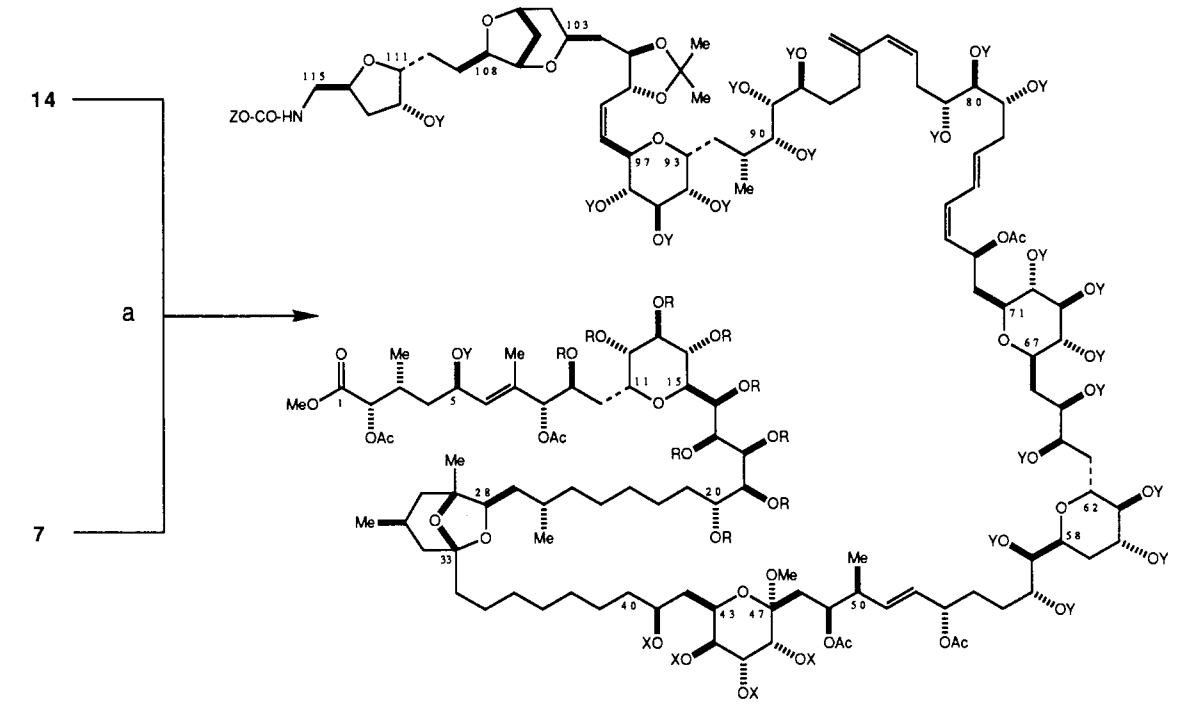
(20) Matteson, D. S.; Moody, R. J. *Organometallics* **1982**, *1*, 20.

(21) We studied several different approaches including Julia olefination and Ni(II)/Cr(II)-mediated coupling with some success. However, the Horner–Emmons route described in the text was far superior to any one of these in terms of the overall efficiency.

(22) Tomioka, H.; Takai, K.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 1605.

(23) The side reactions observed included a benzoate group migration from the C.46 to the C.49 position, followed by scrambling of the remaining benzoate groups, the dehydration of the C.49 alcohol, the epimerization of the C.50 methyl, and the retro-aldol condensation.

Scheme III[a]



15 : R=4-MeOPhCH$_2$, X=Bz, Y=(t-Bu)(Me)$_2$Si, Z=(Me)$_3$SiCH$_2$CH$_2$

[a] Reagents and Reaction Conditions: (a) (1) **14**/NaH/THF room temperature, followed by an addition of the aldehyde, prepared from **7** [$RuCl_2[P(Ph)_3]/C_6H_6$, room temperature], at 0 °C to room temperature. (2) $LiBH_4$–$EuCl_3$/MeOH–Et_2O (1:1), −45 °C. (3) Ac_2O–DMAP/pyridine, 0 °C.

followed by the C.75–C.76 bond formation. However, with respect to the overall efficiency, the first route had the clear edge over the second.

The C.53 ketone was reduced to the desired alcohol by using $LiBH_4/EuCl_3$[24] in methanol–ether to furnish an at least 5:1 mixture of the expected allylic alcohols quantitatively. The stereochemistry of the major product was established by chemical degradation: ozonization and reduction of the major allylic alcohol yielded the triol of the C.52–C.74 segment, which was then compared with the authentic sample available in our laboratories in connection with the structural study of palytoxin.[3]

Finally, acetylation of the major allylic alcohol under the standard conditions furnished the fully protected palytoxin carboxylic acid **15** in 90% yield. The successful deprotection of this substance into palytoxin carboxylic acid and its transformation into palytoxin amide will be reported in the following paper.[4]

Experimental Section

C.22–C.23 Bond Formation. To a solution of oxalyl chloride (414 μL, 4.75 mmol) in dichloromethane (28 mL) was added DMSO (603 μL, 8.50 mmol) at −78 °C under Ar. The mixture was stirred for 15 min, and then the alcohol **1** (952 mg, 607 μmol) in dichloromethane (11 mL) was added dropwise. After stirring for 25 min, triethylamine (1.69 mL, 12.1 mmol) was added, and the mixture was stirred for 15 min at −78 °C and 30 min at 0 °C. The reaction mixture was diluted with 1:2 ether–benzene and washed with saturated NH_4Cl, water, and brine. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residual oil was purified by flash chromatography (2:3 ethyl acetate–hexanes) to give the aldehyde (919 mg, 96.7% yield) as a colorless oil.

To a solution of phosphonium salt **2** (550 mg, 595 μmol) in THF (14.8 mL) at −78 °C was added *n*-BuLi (1.87 M in hexanes; 286 μL, 535 μmol), and the resultant solution was stirred for 5 min under Ar. To this ylide solution was added a solution of the aldehyde (417 mg, 266 μmol) in THF (5.2 mL) at −78 °C dropwise. The mixture was stirred for 10 min at the same temperature and 10 min at 0 °C. The reaction was quenched with methanol (50 μL) and powdered NH_4Cl and diluted with ethyl acetate and saturated NH_4Cl. The organic layer was washed with water and brine, dried over $MgSO_4$, and evaporated. The oily residue was purified by flash chromatography (2:3 ethyl acetate–hexanes) to give a mixture of olefins (504 mg, 90.8% yield) as a colorless oil. The cis/trans ratio was not clear by ^1H NMR.

To a solution of the olefins (1.43 g, 686 μmol) in methanol (60 mL) and ether (120 mL) was added 10% palladium on charcoal (1.37 g), and the mixture was stirred under 1 atm H_2 for 12 h. The reaction mixture was filtered through Celite 545, and the residue was washed with dichloromethane. The filtrates were combined and concentrated under reduced pressure to give the desired product (1.43 g, quantitative yield) as an oil. The product thus obtained was sufficiently pure for use in the subsequent reaction. An analytical sample[25] was prepared by preparative TLC (2:3 ethyl acetate–hexanes).

C.37–C.38 Bond Formation. Oxidation of **4** was conducted in the same manner as described above. Accordingly, **4** (120 mg, 145 μmol) was converted to the corresponding aldehyde (120 mg, quantitative yield) as a colorless oil.

To a stirred solution of the phosphonium salt (360 mg, 162 μmol) in THF (4.0 mL) was added *n*-BuLi (1.87 M in hexanes; 84.5 mL, 158 μmol) dropwise at −78 °C under Ar. After the addition, the reaction mixture was stirred for 8 min, and then a solution of the aldehyde (120 mg, 146 μmol) in THF (2.3 mL) was added slowly at the same temperature. The reaction mixture was kept at −78 °C for 10 min and then at 0 °C for 5 min. This mixture was directly charged on a short silica gel column and eluted with ether, ethyl acetate, and 5:95 methanol–ethyl acetate. The fractions containing the desired product were collected and concentrated. Further purification by flash chromatography (2:3 ethyl acetate–hexanes) afforded the desired olefins (309 mg, 80.3% yield) as a colorless oil. Elution with 1:9 methanol–ethyl acetate gave the unreacted phosphonium salt (69.0 mg).

Palladium on charcoal (10%; 234 mg) was added to a solution of the olefins (309 mg, 117 μmol) in 1:2 ether–methanol (30 mL). After being stirred for 8 h under 1 atm H_2 at room temperature, the reaction mixture

(24) By using the C.23–C.82 segment as a model compound, we examined the stereoselectivity of reduction. The reagents tested included achiral hydrides [$NaBH_4$, $Zn(BH_4)_2$, etc.] and chiral hydrides [BH_3/(*S*)- or (*R*)-oxazaborolidine, $NaBH_4$/glucofuranoside–isovaleric acid, etc.]. Among them, the best stereoselectivity (>8:1) was observed under the conditions of $LiBH_4/EuCl_3$.

(25) The spectroscopic data of this product are included in supplementary material.

was diluted with ethyl acetate (150 mL) and filtered through a pad of Celite 545. Evaporation of the solvent and purification by flash chromatography (2:3 ethyl acetate–hexanes) gave the desired product[25] (279 mg, 90.2% yield) as a colorless oil.

C.7–C.8 Bond Formation. A mixture of the iodo olefin **6** (249 mg, 514 μmol) and the aldehyde (prepared from 63.0 mg of **5** in the same manner as described before; 60.0 mg, 23.5 μmol) was azeotroped from benzene (3×) and dried in vacuo for 2 h prior to use. In a glovebox, this mixture was dissolved in 1:3 DMSO–THF (1.26 mL) under N_2. To this solution was added $CrCl_2$ containing 0.11% $NiCl_2$ [prepared by mixing 14.3 g of $CrCl_2$ (Cerac, 99.9%) and 15.7 mg of $NiCl_2$ (Alfa, 99%) and then drying at 120 °C under high vacuum for 3 days; ca. 60 mg], and the resulting "paste" was stirred vigorously for 24 h at 32 °C. At this point some starting material was present, and more 0.11% $NiCl_2/CrCl_2$ (ca. 30 mg) was added. After 40 h (total reaction time), the mixture was diluted with ethyl acetate and saturated NH_4Cl (2.0 mL) and stirred for 30 min. The aqueous layer was exhaustively extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to dryness. Purification by flash chromatography (1:8 ethyl acetate–benzene) separated the allylic alcohols from the iodo olefin **6**. Separation of the C.8 epimeric alcohols was performed on preparative TLC (1:7 ethyl acetate–benzene) to afford the desired *R* alcohol[25] (43.8 mg, 64.0% yield) and *S* alcohol (12.4 mg, 18.1% yield) in pure form. The yield ranged from 68 to 82%.

C.98–C.99 Bond Formation. Oxidation of **8** was conducted in the same manner as described before. Accordingly, **8** (78.6 mg, 119 μmol) was converted to the corresponding aldehyde. The crude aldehyde was used immediately in the subsequent reaction after azeotroping with benzene (3×).

A THF solution (1.95 mL) of the crude aldehyde was added to a solution of phosphonium salt **9** (dried under vacuum in the presence of P_2O_5; 196 mg, 129 μmol) in HMPA (390 μL). To this solution was added dropwise a solution of LDA (0.4 M in THF; 371 μL, 148 μmol) at room temperature under Ar. After 30 min, the reaction was quenched by the addition of saturated NH_4Cl, followed by dilution with ethyl acetate. The aqueous layer was extracted with ethyl acetate (3×), and the combined organic layers were washed with brine and dried over Na_2SO_4. After filtration and concentration under reduced pressure, the residue was purified by flash chromatography (1:6 ethyl acetate–hexanes) to give *cis*-olefin **10**[25] (132 mg, 62.7% yield, based on **8**) as a white foam and a mixture including the corresponding *trans*-olefin contaminated with epimeric materials at lower R_f values. The yield of this Wittig reaction ranged from 60 to 80% with a cis/trans ratio of 8:1 as assayed by ^1H NMR analysis.

C.84–C.85 Bond Formation. To a vigorously stirring suspension of thioacetal **10** (204 mg, 115 μmol) and $NaHCO_3$ (58.2 mg, 693 μmol) in acetone (7.8 mL) and water (410 μL) at 0 °C was added iodine (87.8 mg, 346 μmol) portionwise. After 45 min, the reaction mixture was quenched by the addition of a 10% $Na_2S_2O_4$ solution. After the aqueous layer was extracted with ether, the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (1:4 ethyl acetate–hexanes) to give the aldehyde (187 mg, 97.5% yield) as a colorless oil.

A mixture of the aldehyde (204 mg, 123 μmol) and *cis*-iodoolefin **11** (347 mg, 378 μmol) was azeotroped with toluene (3×) under reduced pressure and placed in a glovebox under N_2. The mixture was dissolved in THF (560 μL) and DMSO (1.67 mL), and then 0.11% $NiCl_2/CrCl_2$ (prepared as described before; ca. 90 mg) was added. The green suspension was stirred at room temperature for 17 h. The reaction mixture was diluted with ethyl acetate followed by saturated NH_4Cl and stirred for 30 min. The aqueous layer was extracted with ethyl acetate (3×), and the combined organic layers were washed with brine and dried over Na_2SO_4. After filtration and concentration under reduced pressure, the residue was purified by flash chromatography (1:4 ethyl acetate–hexanes) to give the desired allylic alcohol (272 mg, 90.3% yield as a 3:2 mixture of allylic isomers).

To a solution of the allylic alcohols (172 mg, 70.1 μmol) in DMF (4.3 mL) at 0 °C was added PDC (recrystallized from water; 395 mg, 1.05 mmol). The solution was stirred at room temperature for 5 h, diluted with ether, and followed by the addition of Florisil. After being stirred for 20 min, the ethereal solution was passed through Florisil, eluted with ether, and concentrated under reduced pressure. The resultant residue was purified by flash chromatography (1:4 ethyl acetate–hexanes) to give the ketone (171 mg, 99.5% yield) as a colorless syrup.

To a suspension of methyltriphenylphosphonium bromide (2.15 g, 6.02 mmol) in THF (21.6 mL) at 0 °C under Ar was added *n*-BuLi (2.44 M in hexanes; 2.26 mL, 5.51 mmol). After stirring at room temperature for 40 min, a portion of the resultant orange solution (5.65 mL, 1.31 mmol) was transferred and added to the unsaturated ketone (121 mg, 49.4 μmol) in hexanes (11.3 mL) at 0 °C under Ar. After 45 min at 0 °C, the reaction was quenched with saturated NH_4Cl then diluted with ether. The aqueous layer was extracted with ether (3×), and the combined organic layers were washed with brine and dried over Na_2SO_4. After filtration and concentration under reduced pressure, the residue was purified by flash chromatography (1:4 ethyl acetate–hexanes) to yield the desired *exo*-diene[25] (97.6 mg, 80.7% yield) as a colorless oil.

C.75–C.76 Bond Formation. 2,2,6,6-Tetramethylpiperidine (distilled from CaH_2; 712 μL, 4.22 mmol) in THF (10.0 mL) at 0 °C under Ar was treated dropwise with a solution of *n*-BuLi (2.2 M in hexanes; 1.60 mL, 3.52 mmol). The solution was stirred for 15 min at 0 °C and 15 min at room temperature. The LTMP solution was then cooled to −78 °C and treated dropwise with propanediol methanediboronate (776 mg, 4.22 mmol) in THF (4.0 mL) and after 5 min with *N,N,N',N'*-tetramethylethylenediamine (distilled from CaH_2; 640 μL, 4.24 mmol). The resulting solution was stirred at −78 °C for 40 min, after which the cooling bath was changed to an ice bath. Within 5 min, the reaction mixture had become very thick with white precipitates containing several large clumps of the lithio salt. Stirring was continued at 0 °C for 30 min, followed by the addition of the aldehyde (prepared from 170 mg of **12** in the same manner as described before; 166 mg, 76.3 μmol) in THF (5.0 mL). Stirring was continued for another 15 min at 0 °C and then 10 min at room temperature. The reaction mixture was diluted with brine and then ethyl acetate, washed with 1:9 1 N HCl–brine, H_2O, saturated $NaHCO_3$, and brine, and dried over Na_2SO_4. After removal of the solvent in vacuo at room temperature, the residue was dried very briefly on the high vacuum line to give the vinylboronic acid (170 mg) which was used immediately in the next reaction.

To the freshly prepared vinylboronic acid (170 mg) in hexanes (distilled from Na and degassed under Ar; 7.6 mL) was added 10% aqueous TlOH (725 μL, 312 μmol) at room temperature. After the reaction mixture was stirred for 1 min under Ar, the iodoolefin **13** (154 mg, 88.0 μmol) in hexanes (5.6 mL) was added, which was immediately followed by addition of a THF solution of tetrakis(triphenylphosphine)palladium-(0) (33.9 mg, 29.3 μmol, 1.0 mL). The heterogeneous reaction mixture was stirred at room temperature under Ar for approximately 1 h, diluted with 1:1 ether–hexanes, followed by the addition of $MgSO_4$. The mixture was stirred for 10 min and then filtered through Celite 545 eluting with ether. The filtrate was concentrated and purified by flash chromatography (1:6 ethyl acetate–hexanes) providing the desired diene[25] (207 mg, 69.8%, three steps overall yield from the alcohol **12**). The overall yield of this reaction ranged from 63 to 70%.

C.51–C.52 Bond Formation. The diol **7** (44.4 mg, 15.2 μmol) in benzene (820 μL) was treated with $RuCl_2[P(Ph)_3]_3$ (29.2 mg, 30.5 μmol) at room temperature under Ar. After 1.5 h and again after 1 h, more $RuCl_2[P(Ph)_3]_3$ (15.0 mg, 15.6 μmol and 7.5 mg, 7.8 μmol) was added. The reaction mixture was diluted with ether after 3.5 h of the first addition of $RuCl_2[P(Ph)_3]_3$, applied on a small pad of SiO_2, and eluted with ethyl acetate. The solvent was removed, and the green oily residue was purified on preparative TLC (1:1 ethyl acetate–hexanes) to give the corresponding aldehyde (34.0 mg, 76.6% yield). The yield of this reaction ranged from 72 to 81%.

The ketophosphonate **14** (88.8 mg, 22.8 μmol) in THF (1.2 mL) was added to a suspension of NaH (5.1% in mineral oil prepared by diluting 60% NaH in mineral oil with mineral oil; 11.9 mg, 25.3 μmol) in THF (400 μL). The resultant mixture was stirred for 35 min at room temperature under Ar. The reaction was cooled in an ice bath, and the aldehyde (34.0 mg, 11.7 μmol) in THF (1.0 mL) was added dropwise. After being stirred for 50 min at 0 °C and 10 min at room temperature, the reaction mixture was diluted with ether, applied to a short pad of SiO_2, and eluted with ethyl acetate. The solvent was removed, and the residue was purified on preparative TLC (35:65 ethyl acetate–hexanes) to obtain the desired enone[25] (59.0 mg, 75.2%, yields varied from 75 to 80%) and ketophosphonate **14** (48.3 mg).

Fully Protected Palytoxin Carboxylic Acid. A solution of the enone (59.0 mg, 8.79 μmol) and $EuCl_3 \cdot 6H_2O$ (5.0 mg) in 1:1 methanol–ether (3.0 mL) was cooled to −45 °C, and an excess of lithium borohydride was added. The solution was stirred for 1 h and diluted with ethyl acetate and saturated NH_4Cl. The mixture was brought to room temperature, and the organic phase was washed with saturated NH_4Cl, H_2O, and brine. The solution was dried over $MgSO_4$ and concentrated to give the diol as an oil (58.0 mg, 98.3% yield).

A solution of the diol (58.0 mg, 8.63 μmol), acetic anhydride (80 μL), and DMAP (8.8 mg) in pyridine (525 μL) was allowed to stand at 0 °C for 22 h under Ar. The reagents were removed in vacuo and azeotroped with toluene (2×). The remaining residue was purified by preparative TLC (2:3 ethyl acetate–hexanes) to give fully protected palytoxin carboxylic acid **15** as a colorless oil (53.5 mg, 91.7% yield): $[\alpha]_D$ +18.4° (*c* 0.89, $CHCl_3$); FAB MS (*p*-nitrobenzyl alcohol) 6782 $(M + 5 + Na)^+$, 6797 $(M + 4 + K)^+$, 6889 $(M + 2 + Cs)^+$; ^1H NMR ($CDCl_3$) δ −0.08

(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.

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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**.

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