Synthesis of Palytoxin from Palytoxin Carboxylic Acid

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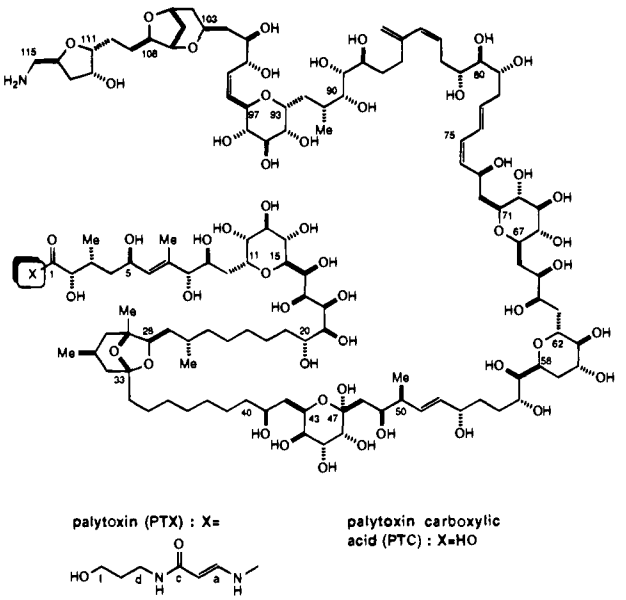
Palytoxin (PTX), an extraordinarily toxic natural product isolated from marine soft corals of the genus *Palythoa*, has commanded the attention of scientists for decades.[1] Our research efforts have resulted in elucidation of the complete structure of PTX,[2] the total synthesis of palytoxin carboxylic acid (PTC),[3] and the preferred solution conformation of PTC.[4]



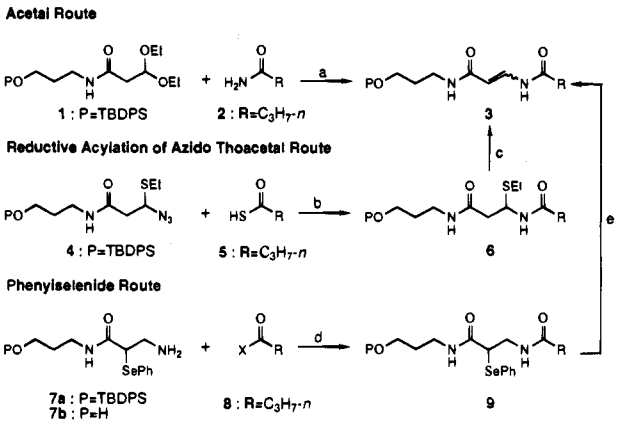
palytoxin (PTX) : X=

palytoxin carboxylic acid (PTC) : X=HO

In the synthetic frontier, we were interested in the chemical transformation of PTC to PTX to complete the total synthesis of PTX, which necessitated the functional group transformation of the C-1 carboxylic acid to the corresponding *N*-acyl vinylogous urea.[5] In this communication, we report three syntheses of *N*-acyl vinylogous ureas from carboxylic acids or carboxylic acid derivatives, their chemical properties and reactivities, and the successful synthesis of PTX from PTC without use of protecting groups.

The chemistry of *N*-acyl vinylogous ureas, especially their synthesis, was not well explored. Several syntheses of *N*-acyl vinylogous ureas were recorded in the literature,[6] but none was general enough to solve our problem. Therefore, we began to pursue a flexible synthesis of this functionality, and this yielded three methods (Scheme 1). The first method (acetal route) gave the desired coupling product in the presence of camphorsulfonic acid (CSA) in 70−80% yield. In all the cases studied,[7] the product was exclusively cis. The second method (reductive acylation of azido thioacetal route) involved reductive coupling of an azido thioacetal with a thiocarboxylic acid in the presence of triphenylphosphine, followed by Hg^{2+}- or base-induced elimination. The overall yield of this route was good (70−80%), and the stereochemistry of product was exclusively cis ($HgCl_2/CH_2Cl_2$) or predominantly cis (10:1 ratio with *t*-BuOK/MeOH). The third method (phenylselenide route) also consisted of two steps: coupling and elimination. It is worth noting that: (1) the amino group in **7** reacted with a wide variety of electrophiles including lactones (*vide infra*), (2) elimination of the phenylselenide was readily effected under oxidative conditions, (3) the overall yield was good (70−80%), and (4) the cis:trans ratio depends on the solvents for the oxidative elimination step; for example, trans:cis = 4:1 for MCPBA in aqueous THF and 1:1 in CH_2Cl_2; 1:1 for Davis' (camphorsulfonyl)oxaziridine[8] in THF and 0:1 in CH_2Cl_2).

Scheme 1



[a] Reagents and reaction conditions: (a) CSA (catalytic)/reflux in toluene, room temperature in dioxane, or room temperature in nitromethane. (b) **4** + **5**/PPh_3/CH_2Cl_2/room temperature. (c) $HgCl_2/K_2CO_3/CH_2Cl_2$ or KOBu-*t*/MeOH/room temperature. (d) RCOCl/NEt_3/CH_2Cl_2/room temperature or lactone/py/room temperature. (e) MCPBA/aqueous THF or CH_2Cl_2/room temperature or Davis's oxaziridine/py or CH_2Cl_2/room temperature.

With sufficient quantities of the *N*-acyl vinlogous urea in hand, we studied the cis ↔ trans isomerization in the presence of an acid. Upon treatment with CSA in toluene or chloroform at room temperature, the *trans*-isomer completely isomerized to the *cis*-isomer. On the other hand, no isomerization was observed in polar solvents (CSA/MeOD or MeCN/room temperature, D_2SO_4/MeOD, DCl/D_2O or DMSO/room temperature).[9] Importantly, no deuterium incorporation at C-b was observed under these conditions. However, facile isomerization of the *cis*-isomer to the *trans*-isomer could be achieved by passing gaseous HCl in polar solvents; the trans:cis ratio observed in MeOH, DMF, MeCN, and DMSO was 1:0, 1:0, 1:0, and 3:1, respectively.[9] The thermodynamic preference for the *cis*-isomer in nonpolar solvents apparently is due to the intramolecular hydrogen-bond stabilization, cf. **A**. In this connection, it is worth noting that: (1) the ethyl propenoate derivative **B** did not show an exclusive preference for the *cis*-olefin isomer, (2) the hydroxamic acid dervivative **C** showed

(1) For a review on PTX, for example, see: Moore, R. E. *Prog. Chem. Org. Nat. Prod.* **1985**, *48*, 81.

(2) 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 the preceding papers.

(3) 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.; Talmas, F. X.; Taniguchi, M.; Tino, J. A.; Ueda, K.; Uenishi, J.-i.; White, J. B.; Yonaga, M. *J. Am. Chem. Soc.* **1989**, *111*, 7530 and the preceding paper.

(4) Kishi, Y. *Pure Appl. Chem.* **1993**, *65*, 771.

(5) The PTX numbering system is used throughout this paper.

(6) For example, see: (a) Sodum, R. S.; Klein, R. S.; Otter, B. A. *J. Heterocycl. Chem.* **1986**, *23*, 1239. (b) Moore, R. E.; Dietrich, R. F.; Hatton, B.; Higa, T.; Scheuer, P. J. *J. Org. Chem.* **1975**, *40*, 540.

(7) Although Scheme 1 shows only one specific *N*-acyl vinylogous urea, these methods were tested for a wide variety of substrates.

(8) Davis, F. A.; Towson, J. C.; Weismiller, M. C.; Lal, S.; Carroll, P. J. *J. Am. Chem. Soc.* **1988**, *110*, 8477. For recent reviews on this class of chiral reagents, see: (a) Davis, F. A.; Chen, B.-C. *Chem. Rev.* **1992**, *92*, 919. (b) Davis, F. A. *Pure Appl. Chem.* **1993**, *65*, 633. For oxidation of selenides by Davis's oxaziridine, see: Davis, F. A.; Stringer, O. D.; Billmers, J. M. *Tetrahedron Lett.* **1983**, *24*, 1213.

(9) Cleavage of the TBDPS group was observed under strong acidic conditions.

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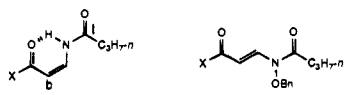


A : X=NH-(CH2)3-OTBDPS
B : X=OEt
C : X=NH-(CH2)3-OTBDPS

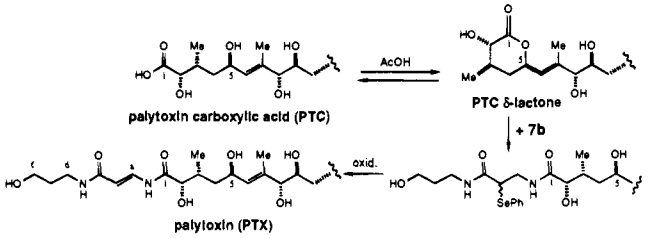
an exclusive preference for the *trans*-isomer in nonpolar solvents, and (3) *cis*-isomers are more soluble in organic solvents and less polar on thin layer chromatography (TLC) than the corresponding *trans*-isomer. Interestingly, *trans*-isomers studied were highly crystalline, whereas their *cis*-isomers were oils.[10]

The cis ↔ trans isomerization was also induced under photochemical conditions in a solvent-dependent manner; approximately a 6.5:1 ratio of the *trans*- and *cis*-isomers was obtained at the photostationary states in DMF, whereas approximately a 2.4:1 ratio in water or a 1.7:1 in methanol was observed. The optimum wavelength for the isomerization was around 300 nm and independent of concentration. Interestingly, the λ_{max} values for both the cis and trans isomers were identical in both protic and aprotic solvents, but their extinction coefficients were significantly different,[11] which might offer a reason for the difference in the photostationary states for the two isomers in various solvents.

Moore observed the *N*-acyl vinylogous urea present in PTX to be readily hydrolyzed under mild acidic and basic conditions.[6b,12] Interestingly, *N*-acyl vinylogous urea **3** was found amazingly stable under acidic and basic conditions. These observations suggested that the facile hydrolysis of this group in PTX was related to a unique arrangement of functional groups. Through our synthetic work, we speculated that this specific reactivity was due to the δ-hydroxyl group.[3] Indeed, *N*-acyl vinylogous ureas bearing such a hydroxyl group at the γ- or δ-position were found to be labile under mild acidic and basic conditions.[13]

Having learned the chemistry of *N*-acyl vinylogous ureas, we focused on the chemical transformation of PTC to PTX. In this connection, it should be noted that: (1) the method of activating the C-1 carboxylic acid of PTC via δ-lactone and its synthetic potential had been explored[3] and (2) PTX had been known to be rather fragile under acidic and basic conditions. These suggested that the phenylselenide approach, followed by photochemically induced cis ↔ trans isomerization, was most promising. Thus, we first demonstrated that: (1) **7a,b** added smoothly to both γ- and δ-lactones and, upon oxidation, yielded the desired *N*-acyl vinylogous ureas in excellent overall yields, (2) the amine **7b**, bearing a free alcohol, gave no complications for this transformation, and (3) Davis' (camphorsulfonyl)-oxaziridine[8] proved to be effective for the oxidation step. This oxidant was particularly appealing because of its selective reactivity toward sulfides over amines, suggesting a possibility that the desired transformation could be achieved without protecting the C-115 amine.

Scheme 2



Thus, aqueous acetic acid treatment of PTC gave a mixture of PTC and PTC δ-lactone,[3] which was reacted with the amine **7b** in pyridine at room temperature to yield the phenylselenide in 36% direct yield or 62% yield based on the recovered PTC (Scheme 2). The phenylselenide was then oxidized with (2*S*,-8a*R*)-(−)- or (2*R*,8a*S*)-(+)-(camphorsulfonyl)oxaziridine[8,14] in pyridine for 30 min at room temperature, and the product (43% yield) was isolated by TSK G3000S column chromatography. The ^{1}H NMR spectrum [CD_3OH (85%)−D_2O (15%)] established that the product was a 3:2 mixture of *trans*- and *cis*-*N*-acyl vinylogous ureas[15,16] and that the major product was identical with natural PTX.[17] Meanwhile, using natural PTX, we demonstrated that the photochemically induced cis ↔ trans isomerization of the *N*-acyl vinylogous urea was effective and selective; PTX was dissolved in DMF, submersed in a stannous chloride filter solution,[18] and irradiated at 300 nm in a Rayonet reactor for 4 h at 37 °C. The ^{1}H NMR spectrum [CD_3OH (85%)−D_2O (15%)] revealed that the product (~100% yield) isolated by HPTLC, followed by a short column of LH-20 Sephadex, was approximately a 6:1 mixture[19] of C-a *trans*- and *cis*-PTXs.

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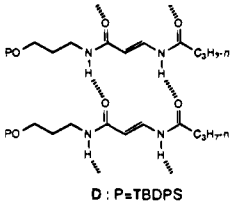
Supplementary Material Available: Synthetic schemes of **1**, **4**, and **7b**; spectroscopic data of **1**, **3** (cis and trans), **4**, and **7b**; photoisomerization of *cis*- to *trans*-*N*-acyl vinylogous urea; transformation of PTC into PTX; ^{1}H NMR of PTC phenylselenide and of 3:2 and 6:1 mixtures of C-a *trans*- and *cis*-PTXs (7 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(10) The crystalline nature of *trans*-isomers might be due to favorable intermolecular hydrogen bonds, which could form an array like a β-sheet, cf. **D**. This arrangement could also be reinforced through π-stacking of the extended conjugated system.



D : P=TBDPS

(11) For example, the *cis*-isomer of **3** exhibited a λ_{max} = 270 nm (ϵ = 28 800, DMF), whereas the corresponding *trans*-isomer had a λ_{max} = 270 nm (ϵ = 17 000, DMF).

(12) Moore, R. E.; Woolard, F. X.; Sheikh, M. Y.; Scheuer, P. J. *J. Am. Chem. Soc.* **1978**, *100*, 7758.

(13) With this knowledge, we developed a selective method to hydrolyze PTX into PTC, which was identified with PTC directly isolated from the natural sources: Suh, E. M.; Mizuno, M.; Kishi, Y., unpublished results.

(14) Davis' (camphorsulfonyl)oxaziridine gave an advantage over simpler Davis' oxaziridines for this work; for the case with this oxidant, separation of the product from the reagent-derived material was readily achieved by TSK G3000S polystyrene column chromatography.

(15) We attempted to separate the olefin isomers by using CM Sephadex, HPTLC, TSK G3000S polystyrene, and HPLC methods, but without success. The C-a olefinic proton of the trans isomer resonated at 7.77 ppm, whereas that of the cis isomer resonated at 7.23 ppm. Intriguingly, a weak but distinctive signal corresponding to the cis isomer was detectable in the ^{1}H NMR spectrum of homopalytoxin and bishomopalytoxin; see Figure 4 in the following: Uemura, D.; Hirata, Y.; Iwashita, T.; Naoki, H. *Tetrahedron* **1985**, *41*, 1007.

(16) The same trans:cis ratio was obtained from the selenoxide(s) prepared by (−)- and (+)-*N*-(phenylsulfonyl)(3,3-dichlorocamphoryl)-oxaziridines: Davis, F. A.; Reddy, R. T.; Han, W.; Carroll, P. J. *J. Am. Chem. Soc.* **1992**, *114*, 1428. We thank Professor Davis for a gift of the chiral oxaziridines.

(17) We are indebted to Professors Hirata and Uemura for samples of PTX and PTC.

(18) Without this filter [Zimmerman, H. E. *Mol. Photochem.* **1971**, *3*, 281], the C-74−C-76 cis−trans diene was also affected.

(19) This ratio was remarkably close to the trans:cis ratio observed for the model compound at the photostationary states in DMF.