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SYNTHETIC STUDIES ON PALYTOXIN.
STEREOCONTROLLED, PRACTICAL SYNTHESIS OF THE C.101-C.115 SEGMENT[1]

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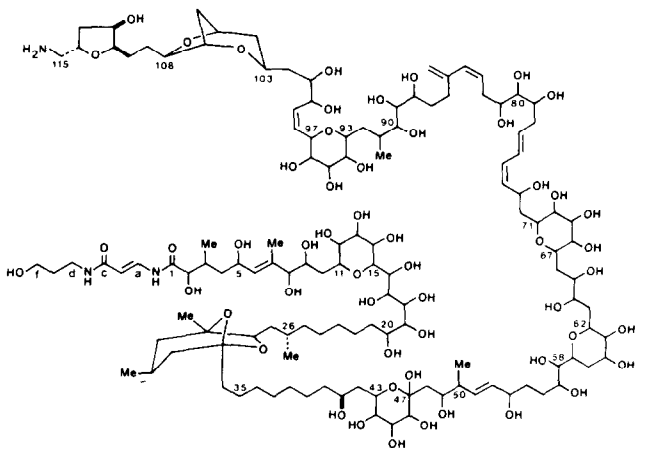
Abstract: A stereocontrolled and practical synthetic route to the acetal 2a, a degradation product of palytoxin, in optically active form is described.

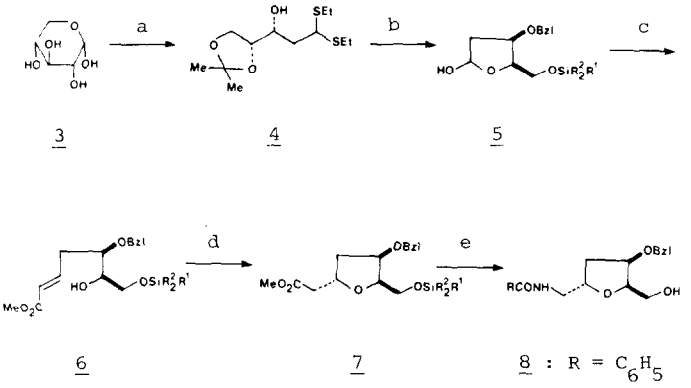
Palytoxin, the toxic principle isolated from marine soft corals of the genus Palythoa, is the most poisonous substance known to date, except for a few polypeptides and proteins found in bacteria and plants. Pioneering investigations by the Hawaii group[2] and by the Nagoya group[3] recently led them independently to suggest the gross structure 1 for palytoxin.[4] Related to our interest in the stereochemistry assignment and total synthesis of palytoxin, we needed to establish a synthetic route to the acetal 2a, a degradation product of palytoxin, with the indicated absolute configuration.[3c] In this communication we report a practical synthesis of 2a.



1: palytoxin

The synthesis of the left half (8) of 2a is summarized in Scheme 1. The acetonide 4, prepared from D-xylose (3) in 4 steps according to Gray's procedure,[5] was converted into the α,β-unsaturated ester 6[6] as an 8:1 mixture of trans and cis isomers in 5 steps. As expected, treatment of 6 with Triton B yielded exclusively the saturated ester 7, which was further transformed to the amide 8[7] by routine synthetic operations. This 11-step synthesis is not only completely stereoselective but also very practical (about 60% overall yield from 4) and suitable for a large scale experiment.

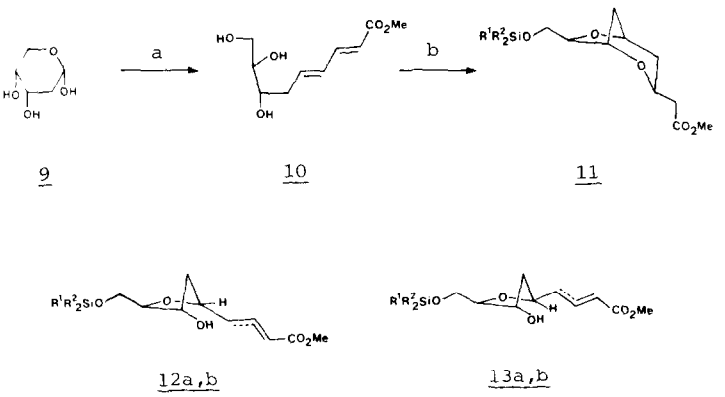
Scheme 1



Reagents: a. See reference 5. b. 1. $C_6H_5CH_2Br/NaH/THF-DMF(4-1)/RT$. 2. 75% aq. AcOH/50°C. 3. $(C_6H_5)_2(t\text{-Bu})SiCl/imidazole/DMF/RT$. 4. $HgO/HgCl_2/99\%$ aq. acetone/60°C. c. $(C_6H_5)_3P{=}CHCO_2Me/C_6H_6/reflux$. d. $C_6H_5CH_2N(Me)_3OMe/MeOH/RT$. e. 1. $NH_2NH_2{\cdot}H_2O/MeOH/RT$. 2. $NOCl/CH_2Cl_2/-50°C$. 3. $C_6H_6/reflux$. 4. 10% HCl/dioxane/70°C. 5. $C_6H_5COCl/1$ N NaOH/$Et_2O/0°C$.

The synthesis of the right half (11) of 2a is summarized in Scheme 2. Wittig reaction of 2-deoxy-D-ribose (9)[8] afforded the diene ester 10. After the primary alcohol was protected, 10 was treated with potassium t-butoxide under carefully controlled conditions to give the desired bicyclic ester 11[9] in about 50% yield in addition to a mixture of four monocyclic esters, i.e. 12a,b and 13a,b, in about 35% yield. As expected, an equilibrium between 12, 13 and 11 was

Scheme 2

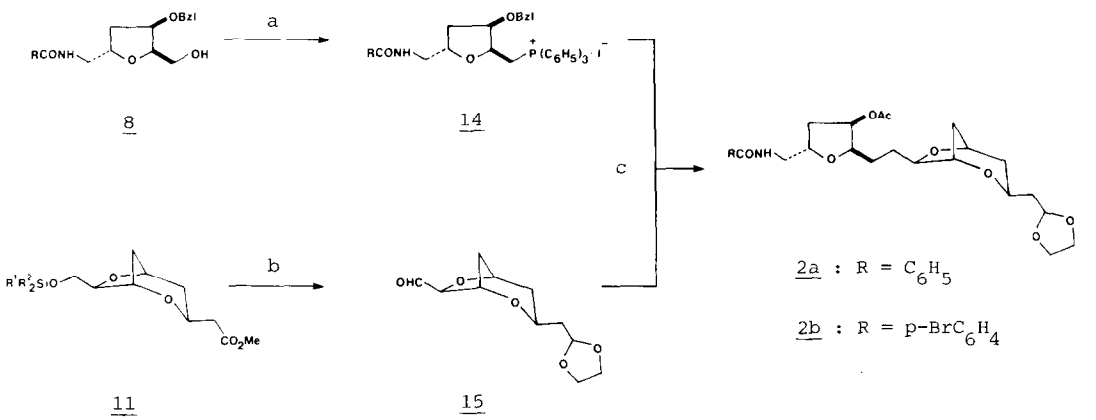


Reagents: a. $(C_6H_5)_3P{=}CH{-}CH{=}CHCO_2Me/C_6H_6/reflux$.[13] b. 1. $(C_6H_5)_2(t\text{-Bu})SiCl/imidazole/DMF/RT$. 2. t-BuOK (0.3 eq.; 1M in t-BuOH)/C_6H_6/RT.

established via the diene ester. Thus the monocyclic esters could be recycled for the preparation of 11, if desired. The composition of the equilibrium mixture delicately depended on the base and solvent used; the best conditions were 0.3 equivalents of t-BuOK in a mixture of t-BuOH and C_6H_6. Isolation of 10 was easily performed by chromatography using a short silica gel column. The bicyclic ester 10 was stereochemically pure, and confirmed, as anticipated, to be desired -- note the serious steric compression in the transition state to the undesired product. Not surprisingly, this three-step synthesis is very practical (about 35% overall yield from 9 without recycling) and suitable for a large scale experiment.

A satisfactory method to couple the left and right halves is shown in Scheme 3. A Wittig reaction using β-alkoxy phosphonium salt is often known to cause complications due to elimination of the alcohol.[10] We overcame this problem by titrating a mixture of the phosphonium salt 14, prepared from 8 in 3 steps, and the aldehyde 15, prepared from 11 in 4 steps, with LDA. In this way the desired olefin was obtained in 70-75% yield. It is interesting to note that the alternative combination, i.e. the phosphonium salt on the bicyclic side and the aldehyde on the monocyclic side, gave less satisfactory results in terms of yield. The olefin was converted to 2a[11] in 3 steps with 70% overall yield. On comparison of spectroscopic data (^{1}H-MNR, IR, MS, α_D), the synthetic substance was found to be identical with the degradation product 2a.[12]

Scheme 3



Reagents: a. 1. $(CF_3CO)_2O$/Py/-20°C ∿ -10°C. 2. $(n\text{-}Bu)_4NI/CH_2Cl_2$/reflux.[14] 3. $P(C_6H_5)_3$/MeCN/120°C. b. 1. DIBAL/CH_2Cl_2/-78°C. 2. $(CH_2OH)_2$/p-TSA/C_6H_6/reflux. 3. $(n\text{-}Bu)_4NF$/THF/RT. 4. Swern oxidation.[15] c. 1. LDA/DMF-THF (2-1)/-78°C -> RT. 2. HN=NH/dioxane/RT. 3. H_2/Pd-C/AcOH-MeOH (1-20)/RT. 4. Ac_2O/Py-DMAP/RT.

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References and Footnotes

(1) 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, New Jersey.

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(4) Palytoxin studied by the Hawaii group was extracted from Hawaiian Palythoa toxica or a Tahitian Palythoa species, whereas palytoxin studied by the Nagoya group was extracted from Okinawan Palythoa tuberculosa. Although, to our knowledge, direct comparison of Okinawan palytoxin with Hawaiian or Tahitian palytoxin has not yet been made, it seems from ^{13}C-NMR spectra of palytoxin and ^{1}H-NMR spectra of degradation products that they are identical.[2,3]

(5) Wong, M. Y. H.; Gray, G. R. J. Am. Chem. Soc. 1978 100, 3548.

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

(7) Spectroscopic data of 8: ^{1}H-NMR ($CDCl_3$) 1.78 ppm (1H, ddd, J = 13.5, 9.2, 4.9 Hz), 2.27 (1H, ddd, J = 13.5, 5.9, 1.7), 2.57 (1H, br s), 3.48 (1H, ddd, J = 14.2, 5.9, 5.9), 3.77 (1H, ddd, J = 14.2, 4.6, 3.3), 3.82 (1H, dd, J = 12.0, 4.6), 3.90 (1H, dd, J = 12.0, 5.0), 4.10 (1H, dt, J = 4.9, 4.6), 4.26 (1H, dt, J = 4.9, 1.7), 4.41 (1H, d, J = 11.9), 4.45 (1H, m), 4.63 (1H, d, J = 11.9), 6.70 (1H, br t), 7.26-7.80 (10H, m); α_D -36.9° (c 1.06, $CHCl_3$).

(8) We are indebted to Dr. Rachlin, Hoffmann-La Roche Company, for a generous gift of 2-deoxy-D-ribose.

(9) Spectroscopic data of 11: ^{1}H-NMR ($CDCl_3$) 1.04 ppm (9H, s), 1.68-1.90 (2H, m), 2.44 (1H, dd, J = 14.8, 5.3 Hz), 2.55 (1H, dd, J = 14.8, 7.3), 3.42 (1H, dd, J = 10.9, 6.6), 3.66 (1H, dd, J = 10.9, 4.3), 3.69 (3H, s), 4.35-4.52 (4H, m), 7.35-7.66 (10H, m); α_D +24.7° (c 3.29, $CHCl_3$).

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(11) Spectroscopic data of 2a: ^{1}H-NMR ($CDCl_3$) 1.25-2.20 ppm (12H, m), 2.09 (3H, s), 3.37 (1H, ddd, J = 14.2, 6.9, 4.6 Hz), 3.80 (1H, ddd, J = 14.2, 6.6, 3.0), 3.83 (2H, br s), 3.84 (1H, m), 3.90-4.05 (3H, m), 4.17 (2H, br s), 4.26 (1H, dd, J = 7.7, 5.4), 4.36 (1H, m), 4.49 (1H, t, J = 4.8), 4.96 (1H, t, J = 4.9), 5.33 (1H, t, J = 3.8), 7.47 (3H, m), 7.78 (2H, d, J = 6.9); α_D +56.0° (c 1.26, $CHCl_3$).

(12) We are indebted to Professors Hirata and Uemura for a sample of degradation product 2b, which was transformed to 2a under standard hydrogenolysis conditions.

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