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SYNTHETIC STUDIES ON PALYTOXIN[1]
STEREOCONTROLLED PRACTICAL SYNTHESIS OF THE C.85 - C.98 SEGMENT

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Abstract: A stereocontrolled 12-step synthesis of the C.85-C.98 segment of palytoxin is described.

Recent work in this laboratory has established the complete structure and laid a solid foundation for the chemical synthesis of the structurally novel and highly physiologically active marine natural product palytoxin.[2,3] Our synthetic plan calls for construction of the toxin from a series of segments containing multiple chiral centers which were chosen by key bond disconnections of the carbon backbone. For this communication, we would like to report a highly stereoselective and efficient synthesis of the C.85-C.98 segment.[4]

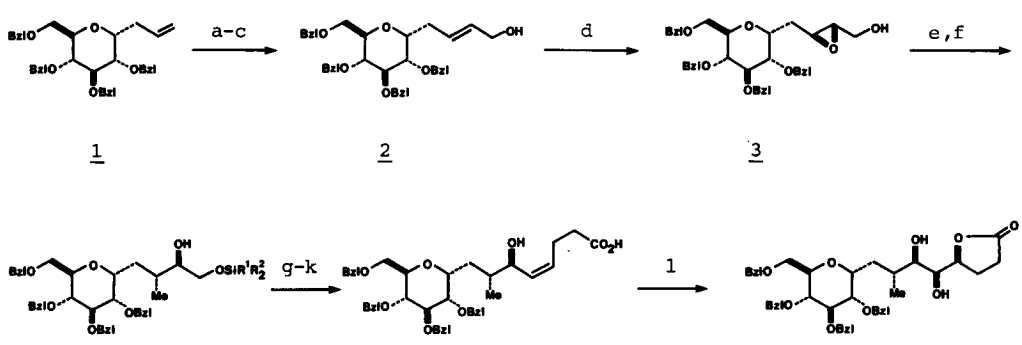
The synthesis began with the α-allylpyranose 1, which was readily available from 2,3,4,6-tetra-O-benzyl-D-glucopyranose in large quantities.[5] Ozonolysis of 1, followed by Wittig reaction using $(i\text{-PrO})_2P(O)CH_2CO_2Et$ in the presence of t-BuOK,[6] gave the expected trans-ester[7] contaminated with less than 2% of the corresponding cis-ester. Diisobutylaluminum hydride (DIBAL) reduction of the ester yielded the trans-allylic alcohol 2 [α_D +44.2° (c 1.56, $CHCl_3$)] in 78% overall yield from 1. The trans stereochemistry of the olefinic bond was concluded from the spin-spin coupling constant (J = 15.5 Hz) for the olefinic protons of the trans-ester. Sharpless' asymmetric epoxidation of 2 using L-(+)-diethyl tartrate[8] yielded the expected epoxide 3 [α_D +25.8° (c 1.16, $CHCl_3$)] in 90% yield along with about 2% of a by-product.[9]

After protection, 3 was subjected to the epoxide ring-opening reaction with lithium dimethylcuprate, to yield the desired alcohol 4 [^{1}H-NMR ($CDCl_3$) 0.07 ppm (6H, s), 0.85 (3H, d, J = 6.6 Hz), 0.89 (9H, s); α_D +26.5° (c 1.38, $CHCl_3$)] in 88% overall yield. In addition to spectroscopic evidence, the fact that the major product reacted smoothly with sodium periodate to yield an aldehyde while the minor product did not react with sodium periodate supported the structural assignments. This epoxide ring-opening process was stereospecific and highly regioselective (the regioselectivity: about 20:1). The remarkable regioselectivity observed seems to be due primarily to complexation of the nucleophile with the substrate.[10,11]

After adjustment of the protecting groups of 4, the resulting primary alcohol was subjected to Swern oxidation,[12] followed by a Wittig reaction with $(C_6H_5)_3P^+(CH_2)_3CO_2H.Br^-$ and then treat-

ment with aqueous acetic acid, to furnish an 8:1 mixture of the cis-olefin alcohol 5 [^{1}H-NMR ($CDCl_3$) 0.85 ppm (3H, d, J = 6.6 Hz), 5.4-5.5 (2H, m); α_D +31.3° (c 2.48, $CHCl_3$)] and the corresponding trans-olefin in about 80% combined overall yield.[13] The stereochemistry of 5 was concluded from the spin-spin coupling constant (J = 10.4 Hz) for the olefinic protons of one of the diastereomeric THP derivatives of 5.

Scheme 1



1 2 3

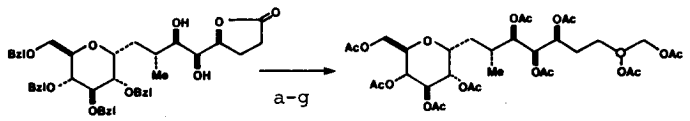
4 5 6

Reagents: a. O_3/NaOAc/MeOH-CH_2Cl_2 (1:1)/-78°C, followed by $(CH_3)_2S$ work-up (-78°C -> RT). b. $(i\text{-PrO})_2P(O)CH_2CO_2Et$/t-BuOK/THF/-78°C -> 0°C.[6] c. DIBAL/CH_2Cl_2/0°C. d. t-BuO_2H/$Ti(i\text{-PrO})_4$/L-(+)-diethyl tartrate/CH_2Cl_2/-30° ± 5°C/6 hr.[8] e. $(Me)_2(t\text{-Bu})SiCl$/imidazole/DMF/35°C. f. $LiCu(Me)_2/Et_2O$/-23°C. g. DHP/p-TSA·Py/CH_2Cl_2/RT. h. $(n\text{-Bu})_4N^+F^-$/THF/RT. i. Swern oxidation.[12] j. $(C_6H_5)_3P^+(CH_2)_3CO_2H\cdot Br^-$/n-BuLi/THF-HMPA/-65°C -> RT or Na^+DMSO^-/DMSO/RT. k. AcOH-H_2O (4:1)/THF/45°C. l. MCPBA/CH_2Cl_2/0°C, followed by treatment with acetic acid at 75°C.

Based on a consideration of the preferred conformation of sp^3-sp^2 carbon-carbon single bond systems,[14] coupled with the well-known directing effect of a hydroxy group,[15] it was hoped that peracid-epoxidation of 5 would yield the desired epoxide. Indeed, m-chloroperbenzoic acid oxidation of 5, followed by treatment with acetic acid, afforded the desired lactone 6 as the major product. The lactone 6 [α_D +34.8° (c 0.95, $CHCl_3$)] was isolated by silica gel chromatography in 52% overall yield from the alcohol 4.[16] The stereoselectivity of this epoxidation was at least 13:1. The stereochemistry of 6 was unambiguously established by its successful transformation into the nonaacetate 7, a degradation product of palytoxin[2,3] (Scheme 2).

The overall yield of 6 from 1 in this 12-step sequence was about 32% and suitable for the preparation of multi-gram quantities.

Scheme 2



6 7

Reagents: a. $CH_3C(OCH_3)_2CH_3$/CSA/RT. b. DIBAL/CH_2Cl_2/-78°C. c. $(C_6H_5)_3P^+CH_3 \cdot Br^-$/ Na^+DMSO^-/DMSO/RT. d. OsO_4/Py/THF/RT. e. AcOH-H_2O (4:1)/50°C. f. H_2/Pd-C/ AcOH/MeOH/RT. g. Ac_2O/Py/RT.

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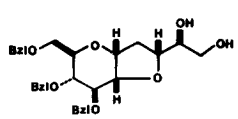
References and Footnotes

1. For the preceding paper in this series, see J. Leder, H. Fujioka and Y. Kishi, Tetrahedron Lett., in press.
2. For the stereochemistry of palytoxin, see J. K. Cha, W. J. Christ, J. M. Finan, H. Fujioka, Y. Kishi, L. L. Klein, S. S. Ko, J. Leder, W. W. McWhorter, Jr., K.-P. Pfaff, M. Yonaga, D. Uemura and Y. Hirata, J. Am. Chem. Soc., 104, 7369 (1982) and preceding papers. Also, see R. E. Moore, G. Bartolini, J. Barchi, A. A. Bothner-By, J. Dadok, and J. Ford, J. Am. Chem. Soc., 104, 3776 (1982).
3. For the gross structure of palytoxin, see a. D. Uemura, K. Ueda, Y. Hirata, H. Naoki and T. Iwashita, Tetrahedron Lett., 22, 2781 (1981) and references cited therein. b. R. E. Moore and G. Bartolini, J. Am. Chem. Soc., 103, 2491 (1981) and references cited therein.
4. For the complete structure and numbering of palytoxin, see reference 2.
5. M. D. Lewis, J. K. Cha and Y. Kishi, J. Am. Chem. Soc., 104, 4976 (1982).
6. H. Nagaoka and Y. Kishi, Tetrahedron, 37, 3873 (1981).
7. Satisfactory spectroscopic data were obtained for all the new compounds in this paper.
8. T. Katsuki and K. B. Sharpless, J. Am. Chem. Soc., 102, 5974 (1980).
9. The spectroscopic data clearly suggested structure 8 for the by-product, which obviously arose via the epoxide ring-opening by the C.94 benzyloxy group. Reaction temperature and time were found to be critical to keep the amount of this by-product to a minimum.



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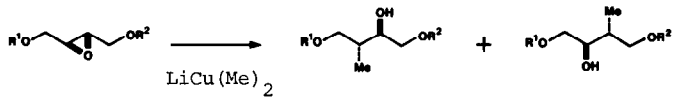
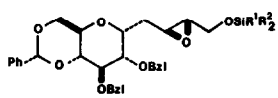
10. Examples shown below seem to support this explanation. It is interesting to note that the epoxide ring-opening of 3 under the same conditions yielded a 55:45 mixture of 1,2- and 1,3-diols and also that the epoxide ring-opening of 15 yielded a 2:1 mixture of 1,2- and 1,3-diols after deprotection.



		Ratio	
9 : R^1 = $CH_2OCH_2C_6H_5$, R^2 = Si(t-Bu)(Me)$_2$	10	3 : 2	11
12 : R^1 = $CH_2OCH_2C_6H_5$, R^2 = H	13	1 : 4	14



15 : R^1 = t-Bu, R^2 = Me

11. For the epoxide ring-opening of similar systems, see a. M. R. Johnson, T. Nakata and Y. Kishi, Tetrahedron Lett., 4343 (1979). b. T. Suzuki, H. Saimoto, H. Tomioka, K. Oshima and H. Nozaki, Tetrahedron Lett., 23, 3597 (1982). Although the pattern of epoxide-ring opening by Nozaki's method is the one desired for this work, treatment of 3 with $(CH_3)_3Al$ yielded exclusively 8, as expected.[9]
12. A. J. Mancuso, S.-L. Huang and D. Swern, J. Org. Chem., 43, 2480 (1978).
13. The ratio of cis- and trans-olefins was determined by HLC [Waters analytical μ-porasil; hexanes-chloroform-ether (2:1:1)] of the corresponding methyl esters. For preparative purposes, an 8:1 mixture of cis- and trans-olefins was carried forward, and the pure substance was chromatographically isolated at the stage of lactone 6.
14. For a review on the conformation of sp^3-sp^2 carbon-carbon single bond systems, see G. J. Karabatsos and D. J. Fenoglio, "Topics in Stereochemistry", E. L. Eliel and N. L. Allinger, eds., Vol. 5, p. 167 ff., Wiley-Interscience, New York, 1970. For work related to this case, see M. R. Johnson and Y. Kishi, Tetrahedron Lett., 4347 (1979).
15. H. B. Henbest and R. A. L. Wilson, J. Chem. Soc., 1958 (1957).
16. The acetonide [^{1}H-NMR ($CDCl_3$) 0.92 ppm (3 H, d, J = 6.9 Hz), 1.33 (3 H, s), 1.35 (3 H, s), 4.46 (1H, AB, J = 10.5), 4.47 (1H, AB, J = 11.7), 4.58 (1H, AB, J = 12.0), 4.59 (1H, AB, J = 12.0), 4.71 (1H, AB, J = 11.7), 4.81 (1H, AB, J = 10.9), 4.82 (1H, AB, J = 10.5), 4.95 (1H, AB, J = 10.9); α_D +37.0° (c 1.63, $CHCl_3$)], prepared from 6 [$CH_3C(OCH_3)_2CH_3$/CSA/RT], was useful for isolation, characterization and identification purposes.

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