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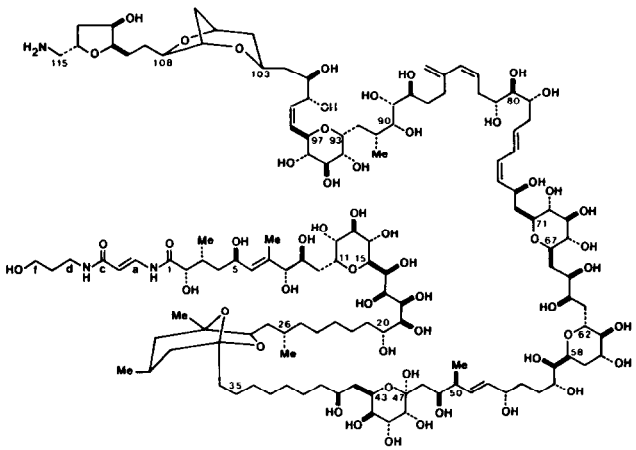
SYNTHETIC STUDIES ON PALYTOXIN[1]

STEREOCONTROLLED PRACTICAL SYNTHESIS OF THE C.23 - C.37 SEGMENT

J. Leder, H. Fujioka and Y. Kishi*
Department of Chemistry, Harvard University
12 Oxford Street, Cambridge, Massachusetts 02138, U.S.A.

Abstract: An 8-step synthesis of the bicyclic ketal 2 from l-(+)-citronellal is described.

Ongoing investigations in these laboratories concerning the stereochemistry of the marine natural product palytoxin[2] have recently led us to conclude its complete structure to be 1.[3a-d,4] In the course of these studies, it was necessary to develop an efficient synthesis of the bicyclic ketal 2, which played a central role in determining the stereochemistry at the C.19-C.50 portion of palytoxin.[3c] In this communication, we would like to report a practical synthesis suitable for the preparation of multi-gram quantities of 2 in optically active form.[5]

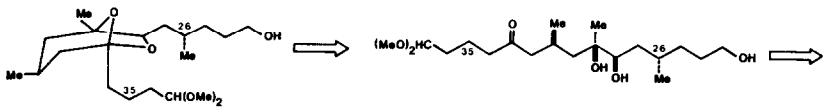


1 : palytoxin

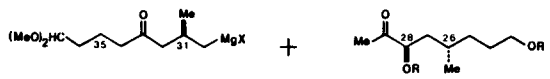
Our synthetic plan is outlined in Scheme 1. The bicyclic ketal 2 was considered to be equivalent with the acyclic keto-triol 3, which was further simplified to the Grignard reagent 4 and the α-alkoxy methyl ketone 5. According to the cyclic model for Cram's rule, the major product of the reaction of 5 with 4 should have the desired stereochemistry, and based on numerous known examples, the stereoselectivity of the proposed reaction was expected to be excellent.[6] Thus, the problem was reduced to synthesis of key intermediates 4 and 5 or their equivalents.

The synthesis of methyl ketone 5 is summarized in Scheme 2. l-(+)-Citronellal (6) was reacted with lithium acetylide[7], followed by in situ oxidation with Jones reagent, to give the acetylenic ketone 7[8] (bp 91-94°C at 5.4 mm) in 74% overall yield after distillation. Selective

Scheme 1



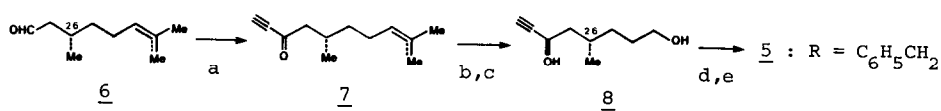
2 3



4 5

ozonolysis of 7, followed by $(Me)_2S$ work-up and reduction of the crude keto-aldehyde with lithium aluminum hydride/(+)-Darvon alcohol complex,[9] allowed cleavage of the olefinic bond and introduction of the C.28 hydroxy group to yield a 7:2 mixture of the diol 8 and its C.28 diastereomer,[10] which was used for the next step without separation. After being protected as the dibenzyl ethers, this crude product was subjected to a hydration reaction to yield the required methyl ketone 5 as a 7:2 mixture of 5 and its C.28 diastereomer. Since the commercially available l-(+)-citronellal (6) is contaminated by about 17% of its double-bond isomer (cf. the dotted double bond in structure 6), the crude methyl ketone 5 thus obtained contained its homologue in addition to the C.28 diastereomer. However, neither side product caused a practical problem, since a single silica gel chromatogram[11] allowed clean separation of these products to give the desired methyl ketone 5 [colorless oil; ^{1}H-NMR ($CDCl_3$) 0.83 ppm (3H, d, J = 6.3 Hz), 2.16 (3H, s), 3.44 (2H, t, J = 6.6), 3.82 (1H, dd, J = 9.7, 3.5); α_D +38.0° (c 2.35, $CHCl_3$); IR 1712 cm^{-1}] in 43% overall yield from 7.[12]

Scheme 2



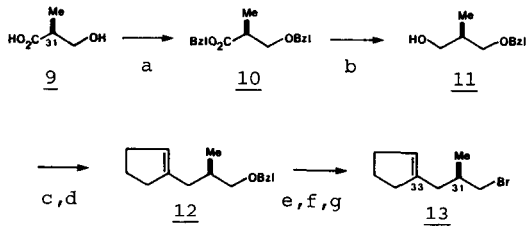
6 7 8

Reagents: a. $LiC{\equiv}CH$/THF/-78°C[7], followed by Jones oxidation. b. O_3/1.5 eq. MeOH/Sudan Red 7B/CH_2Cl_2/-78°C,[13,14] followed by treatment with $(Me)_2S$/-78°C -> RT. c. $LiAlH_4$/(+)-Darvon alcohol/Et_2O/-78°C. d. $C_6H_5CH_2Br$/NaH/THF-DMF(4:1)/0°C -> RT. e. $HgCl_2/H_2O$-MeOH (1:250)/60°C.

For the synthesis of an equivalent of 4 (Scheme 3), we chose the cyclopentenyl group as a convenient protected form of the 1,5-dicarbonyl moiety. Use of O-benzyl trichloroacetimide[15] allowed direct dibenzylation of (S)-(-)-3-hydroxy-2-methylpropionic acid (9), and subsequent reduction with lithium aluminum hydride afforded alcohol 11 [α_D +16.4° (c 4.50, $CHCl_3$)] in 65% overall yield after distillation.[16] Treatment of the p-toluenesulfonate of 11 with the Grignard reagent formed from 1-bromocyclopentene[17] in the presence of Li_2CuCl_4[18] yielded the cyclopentenyl compound 12 [bp 98-100°C at 0.4 mm; ^{1}H-NMR ($CDCl_3$) 0.91 ppm (3H, d, J = 6.3 Hz), 3.26 (1H, ABX, J = 8.9,6.6), 3.35 (1H, ABX, J = 8.9,5.6) 5.33 (1H, broad s); α_D -1.40° (c 1.29, $CHCl_3$)] in

90-95% yield after distillation. This compound was then converted to the required bromide 13 [bp 80-82°C at 6.2 mm; ^{1}H-NMR ($CDCl_3$) 1.01 ppm (3H, d, J = 6.3 Hz), 3.30 (1H, ABX, J = 9.7,5.8), 3.40 (1H, ABX, J = 9.7,4.5) 5.40 (1H, broad s); α_D -12.9° (c 1.40 $CHCl_3$)] in the usual manner.

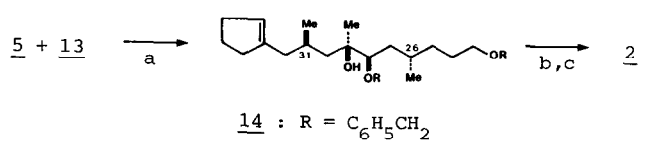
Scheme 3



Reagents: a. $C_6H_5CH_2OC(=NH)CCl_3/CF_3SO_2OH/c\text{-}C_6H_{12}\text{-}CH_2Cl_2$ (2:1)/RT.[15] b. $LiAlH_4$/Et_2O/0°C -> RT. c. TsCl/py/0°C -> RT. d. RMgBr/Li_2CuCl_4[18]/THF/RT/2.5 days. e. Li/liq. NH_3/THF. f. MsCl/py/0°C -> RT. g. LiBr/DMF/60°C.

The two halves of the molecule were then joined together (Scheme 4) by treatment of the methyl ketone 5 with 2 equivalents of the Grignard reagent prepared from 13 to yield the coupled product 14 [oil; ^{1}H-NMR ($CDCl_3$) 0.94 ppm (3H, d, J = 6.6 Hz), 0.97 (3H, d, J = 6.3), 1.11 (3H, s), 3.34 (1H, dd, J = 9.5, 1.8), 3.44 (2H, t, J = 6.6), 4.49 (2H, s), 4.65 (1H, AB, J = 11.3), 4.69 (1H, AB, J = 11.3), 5.33 (1H, broad s); α_D -5.25° (c 2.44, $CHCl_3$)] as a 10:1 mixture of diastereomers at the newly formed center (63% direct yield; 85% yield based on 5 consumed), which was readily separated by silica gel chromatography. Deprotection of the triol, followed by ozonolysis in methanol and work-up with dimethyl sulfide in methanol containing a small amount of camphorsulfonic acid, led to cleavage of the double bond and smooth cyclization to give the desired bicyclic ketal 2 [oil; ^{1}H-NMR ($CDCl_3$) 0.90 ppm (3H, d, J = 5.6 Hz), 0.93 (3H, d, J = 5.9), 1.19 (3H, s), 3.29 (3H, s), 3.30 (5H, s), 3.63 (2H, m), 3.92 (1H, broad d, J = 10.2), 4.39 (1H, t, J = 5.4); α_D +74.5° (c 1.88, $CHCl_3$)].[19]

Scheme 4



Reagents: a. Bromide 13/Mg/I_2/THF/reflux, followed by its addition to ketone 5 at -78°C. b. Li/liq. NH_3/THF. c. O_3/MeOH/-78°C, followed by treatment with camphorsulfonic acid/$(Me)_2S$/-78°C -> RT.

The overall yield of 2 from l-(+)-citronellal in this 8-step sequence was about 21%.

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References and Footnotes

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(10) This ratio was determined by HPLC analysis of the mono-silyl ether prepared from the crude product by treatment with $(Ph)_2(t\text{-}Bu)SiCl$/imidazole/DMF/RT.
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(12) If desired, recycling of the C.28 epimer is possible, i.e. (1) NaOMe/MeOH/RT, and (2) chromatographic separation.
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