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A CONVERGENT SYNTHETIC STRATEGY FOR THE POLYENE MACROLIDE PIMARICIN

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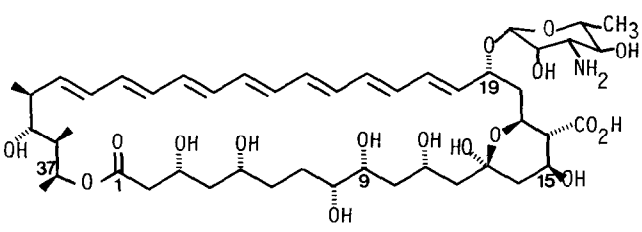
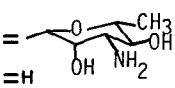
Summary: The synthesis of two chiral fragments representing C1-11 and C12-25 of the polyene macrolide pimaricin from dimethyl 3-hydroxyglutarate is described.

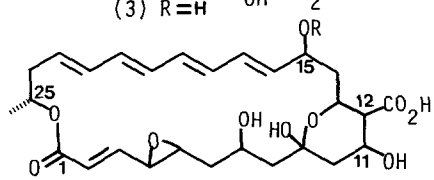
The polyene macrolide antibiotics are endowed with a unique structure composed of a highly functionalized macrocyclic lactone which incorporates opposed lipophilic polyene and hydrophilic polyol carbon units and in some cases contain a carboxyl group and an amino-glycosyl residue.[1] The most widely studied member is amphotericin B (1), whose absolute structure has been fully established by X-ray crystallography.[2] The structures of other members, such as pimaricin (2),[3] are based mainly on results of chemical degradation, MS and NMR spectral studies.[4] Amphotericin B is produced by microbial fermentation of various Streptomyces organisms and is used clinically for the treatment of systemic mycotic infections.[5] Increasing medicinal interest in polyene macrolides has been realized from studies describing biological activities involving complexation with steroids,[6] interactions with cell membranes,[7] and enhancement of antitumor drug activity.[8] To date, very few synthetic studies of this complex group of natural products have been reported.[9]

As part of our program in studing the chemistry of polyene macrolides, we are developing a convergent strategy for the total synthesis of the smaller member pimaricin (2), initially, and plan to extend the scheme to amphotericin B (1). We proceeded with the assumption that the polyene macrolides follow a consistent biosynthetic pattern, such that, the absolute configuration for pimaricin is the same as amphotericin B in complementary portions of the respective molecules. A key feature of our plan was to accomplish a mirror-image synthesis of two chiral fragments from dimethyl-3-hydroxyglutarate (4) which would be further elaborated and ultimately combined to provide the aglycone of pimaricin (3).

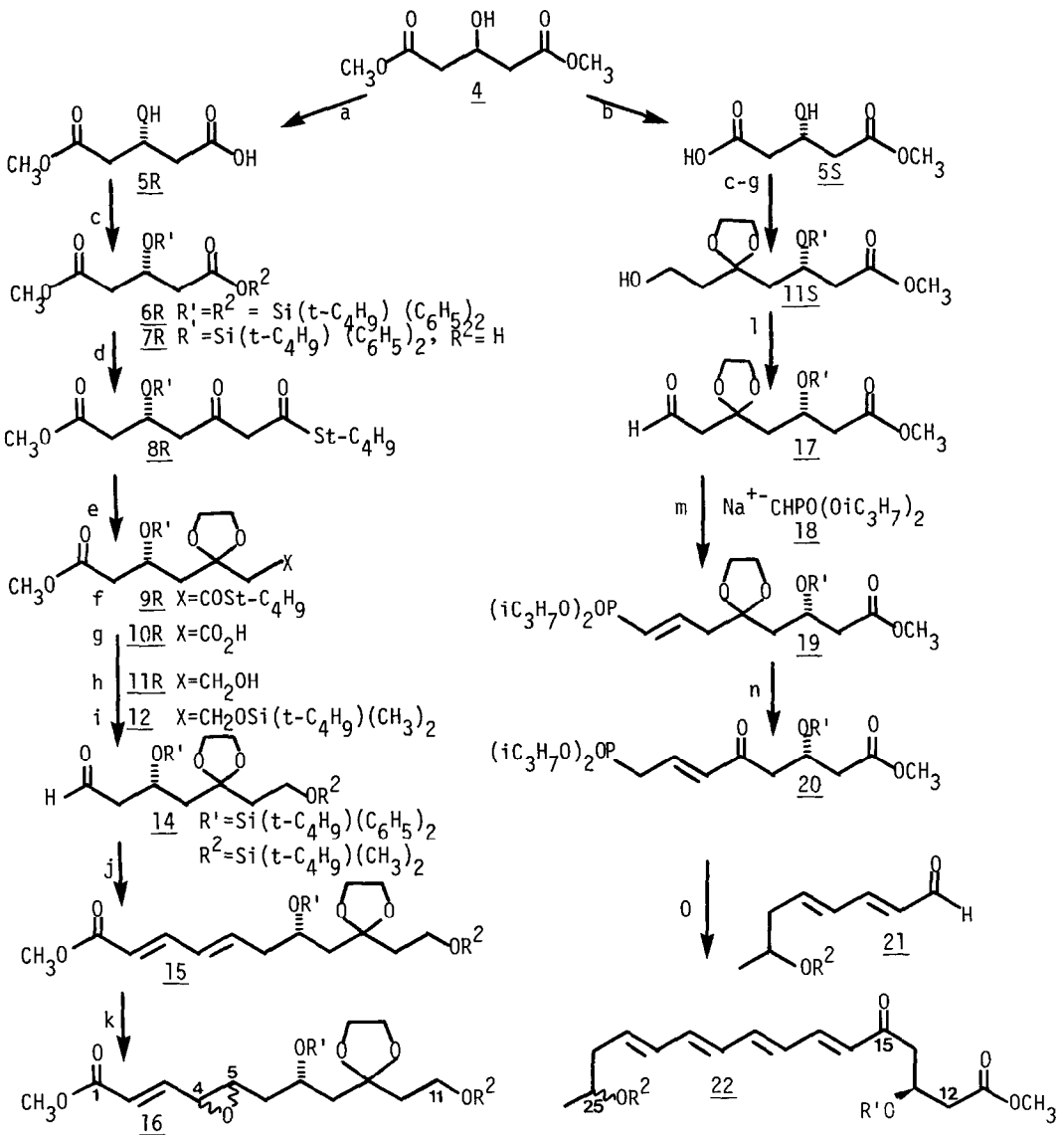
amphotericin (1)



pimaricin(2) R= 
(3) R=H



Scheme 1


4
a
b
5R
5S
c
c-g
6R R'=R2 = Si(t-C4H9)(C6H5)2
7R R'=Si(t-C4H9)(C6H5)2, R2= H
11S
d
l
8R
17
e
m
Na+-CHPO(OiC3H7)2
18
f
9R X=COSt-C4H9
g
10R X=CO2H
h
11R X=CH2OH
i
12 X=CH2OSi(t-C4H9)(CH3)2
19
n
20
14 R'=Si(t-C4H9)(C6H5)2
R2=Si(t-C4H9)(CH3)2
j
o
21
15
k
16
22

Scheme 1 : Reaction Conditions a. chymotrypsin as described in ref. 11; b. porcine liver esterase 10mg, 20 ml 0.1M Na_2HPO_4, 1.0g 4, rt, 12h, 80% conversion; c. 1.0M in CH_2Cl_2, add 2.5 eq imidazole, 0.1eq DMAP, 2.4 eq t-butyldiphenylsilyl chloride, rt, 6h, 95%; d. 1M in tert-butanol, add 1.1eq 1M KOH, 50° C, 2h, 80%; e. 2 M in THF, add 1.1eq carbonyldiimidazole, rt, 3h, add 1.2eq $Mg(OOCCH_2COSt\text{-}C_4H_9)_2$, 12h, rt, 90%; f. 0.1 M in THF, add 3 eq $Hg(OOCCF_3)_2$, rt, 24h, 80%; g. 0.1M in THF, add 2eq BH_3THF, rt, 4h, 65%; h. 0.5M in CH_2Cl_2, add 2eq NaOAc, 1.3eq PCC, rt, 6h, 85%; 1.0M in CH_2Cl_2, add 1.5 eq imidazole, 0.1 eq DMAP, 1.2 eq t-butyldimethylsilyl chloride, rt, 3h, 95%; i. 0.1M in THF, add excess $LiBH_4$, reflux, 6h, aqueous workup, then oxidation with PCC by condition h., 80%; j. 2eq NaH, 2eq $CH_3OOCCH=CHCH_2PO(OiC_3H_7)_2$, rt, 3h, 60%; k. 0.5M in CH_2Cl_2, add 1eq MCPBA, rt, 6h, 80%; l. oxidation with PCC by condition h., 85%; m. 2eq NaH, 2eq $CH_2(PO(OiC_3H_7)_2)_2$, rt, 5min, 99%; n. 0.5M in CH_3OH/H_2O 1:1, 10eq pyridinium p-toluenesulfonate, reflux, 16h, 60%; o. 1eq LDA , add 20, 0° C, 15min, add 21, rt, 16 h, 20%.

The synthesis of two chiral fragments representing C1-11 and C12-25 of 3 from the common precursor 4 is outlined in Scheme 1 and decribed as follows.[10] Chymotrypsin catalysed hydrolysis of 4 provided the R-hydroxymonoacid 5R.[11] A silylation sequence followed by selective deprotection of the silylester gave the acid 7R which was C-acylated to provide the two carbon extended unit 8R.[12] The carbonyl group was protected as an ethylene acetal and the thiol ester was then selectively reduced to provide the alcohol 11R, which represents a chiral C5-11 unit for 3 (or a C9-15 unit for 1). We discovered that a different hydrolase enzyme, esterase from porcine liver, catalyzed the hydrolysis of 4 to give the S-hydroxymonoacid 5S. This result is complementary to the chymotrypsin result and thus we had a convenient source of both enantiomers by asymmetric hydrolysis of a common prochiral precursor 4. The identical sequence of reactions described previously for the preparation of 11R was performed on the enantiomer 5S to provide 11S which represents a chiral C12-17 unit for 3 (or a C16-21 unit for 1).

Fragment 11R was further elaborated to provide a carbon unit 16 representing C1-11 of 3. Protection of the hydroxy group in 11R as a tert-butyldimethylsilyl ether and reduction of the ester group followed by oxidation gave the aldehyde 14. A standard Wadsworth-Emmons-Horner modified Wittig procedure[13] was used to prepare the diene ester 15. Regioselective epoxidation at C4,5 gave two diastereomeric epoxides 16.[14]

Fragment 11S was further elaborated to provide a carbon unit 22 representing C12-25 of 3. Oxidation of 11S gave the aldehyde 17 which was treated with the anion of methylenediphosphonate 18[15] to provide the vinylphosphonate 19. Hydrolysis of the ethylene acetal resulted in the formation of the enonephosphonate 20. Condensation of the anion of phosphonate 20 with the racemic dienal 21[16] provided a mixture of diastereomeric tetraenes 22.

This work demonstrates an efficient convergent strategy to prepare two chiral precursors representing the two halves of the aglycone of pimaricin (3) and highlights the application of hydrolase enzymes to effect prochiral distinctions thereby providing chiral precursors such as 5R and 5S which are aptly suited as starting materials for the synthesis of

polyketide derived natural products. Further work to complete the total synthesis of pimaricin and compare the chiral synthetic units described in this report with the corresponding fragments derived by selective degradation of natural polyene macrolides for structural verification are in progress.

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10. The structure of each synthetic intermediate was established by spectroscopic analysis including 470 MHz ^{1}H NMR and MS.

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