Studies toward the total synthesis of scytophycin C : sythesis of the C(1)-C(18) fragment
by Michael John Harney

A thesis submitted in partial fulfillment Of the requirements for the degree of Master of Science
Chemistry
Montana State University

Abstract:
The goal of this investigation was to provide a synthetic route to the C(1) - C(18) fragment of scytophysin C 5 which would be amenable to large scale preparation of the target compound. To achieve this goal it would be necessary to circumvent the problems encountered in Grieco and Speakers aforementioned synthesis. These problems were namely the reduction of the nitrile at C(14) in the presence of the C(1) carboxymethyl group and the protecting group manipulations which were necessitated by the alternate homologation strategy which was employed.

Synthetic Strategy In order to avoid possible interference resulting from the presence of the C(I) carbomethoxy group during the reduction of the C(14) nitrile it was decided to delay introduction of the C(1) - C(6) portion of the molecule until the last steps of the synthesis. Therefore, it would be necessary to reduce the C(7) aldehyde product of the Ferrier rearrangement and subsequently protect the resultant alcohol. Provided the reduction of the C(14) nitrile was a success the C(15) - C(18) portion of the molecule could then be installed using Roush's (S,S) diisopropyltartrate-Z-crotylboronate. Finally, the C(1) - C(6) portion of the molecule could be elaborated by deprotection and oxidation of the C(7) alcohol to it's corresponding aldehyde followed by a vinylogous Muldyama type aldol reaction, Homer-Emmons olefmation, and protection of the C(7) alcohol as its tert-butyldimethylsilyl ether. It was thought that this route, if feasible, would result in a significantly shorter and more efficient synthesis of 5.

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APPROVAL

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Michael John Harney

This thesis has been read by each member of the thesis committee and has been found to be satisfactory regarding content, English usage, format, citations, bibliographic style, and consistency, and is ready for submission to the College of Graduate Studies.

Paul A. Grieco, Ph.D. _____ (Signature) 4-15-04 (Date)

Approved for the Department of Chemistry

Paul A. Grieco, Ph.D. _____ (Signature) 4-15-04 (Date)

Approved for the College of Graduate Studies

Bruce R. McLeod, Ph.D. Bruce R. McLeod (Signature) 4-19-04 (Date)

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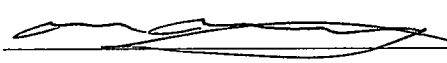
Signature 

Date 4-15-04

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LIST OF ABBREVATIONS

Ac	acetyl
AIBN	2,2-azobisisobutyronitrile
Bn	benzyl
n-Bu	*normal*-butyl
CI	chemical ionization
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL	diisobutylaluminum hydride
DMAP	N,N-dimethylaminopyridine
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
EI	electron impact
Et	ethyl
g	gram
h	hour
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry
Hz	hertz
Imid	imidizole
IR	infrared
J	coupling constant in hertz
LDA	lithium diisopropylamide
M	molarity

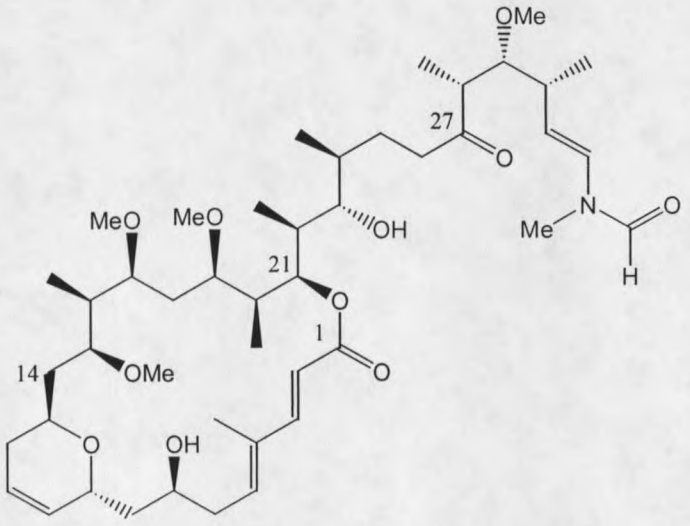
LIST OF ABBREVIATION CONTINUED

Me	methyl
mg	milligram
MHz	megahertz
min	minutes
mL	milliliter
μL	microliter
mmol	millimole
MS	mass spectrometry
NMR	nuclear magnetic resonance
Oac	acetoxy
OMe	methoxy
Ph	phenyl
Piv	pivaloyl
PMB	*para*-methoxybenzyl
ppm	parts per million
rt	room temperature
TBS	*tert*-butyldimethylsilyl
TBAF	tetrabutylammonium fluoride
TiPS	*tert*-butyldiisopropylsilyl
THF	tetrahydrofuran
Tf	*para*-toluenetrifluoromethanesulfonyl

INTRODUCTION

Background

In 1986 Moore *et al.* reported[1] the isolation of a series of five cytotoxic polyketide derived[2] macrolides from a culture of the terrestrial blue-green alga *Scytonema pseudohofmanni* Dubbed scytophycins A – E[3], these isolates were found to exhibit potent cytotoxicity toward a variety of human carcinoma cell lines as well as a broad spectrum of anti-fungal activity. By spectrographic and X-ray crystallographic analysis[3] of an acid degradation product of scytophycin C **1**, it was determined that the scytophycins are a series of novel polyoxygenated 22-membered macrolides possessing an N-methylvinylformamide terminal side chain at C(21).



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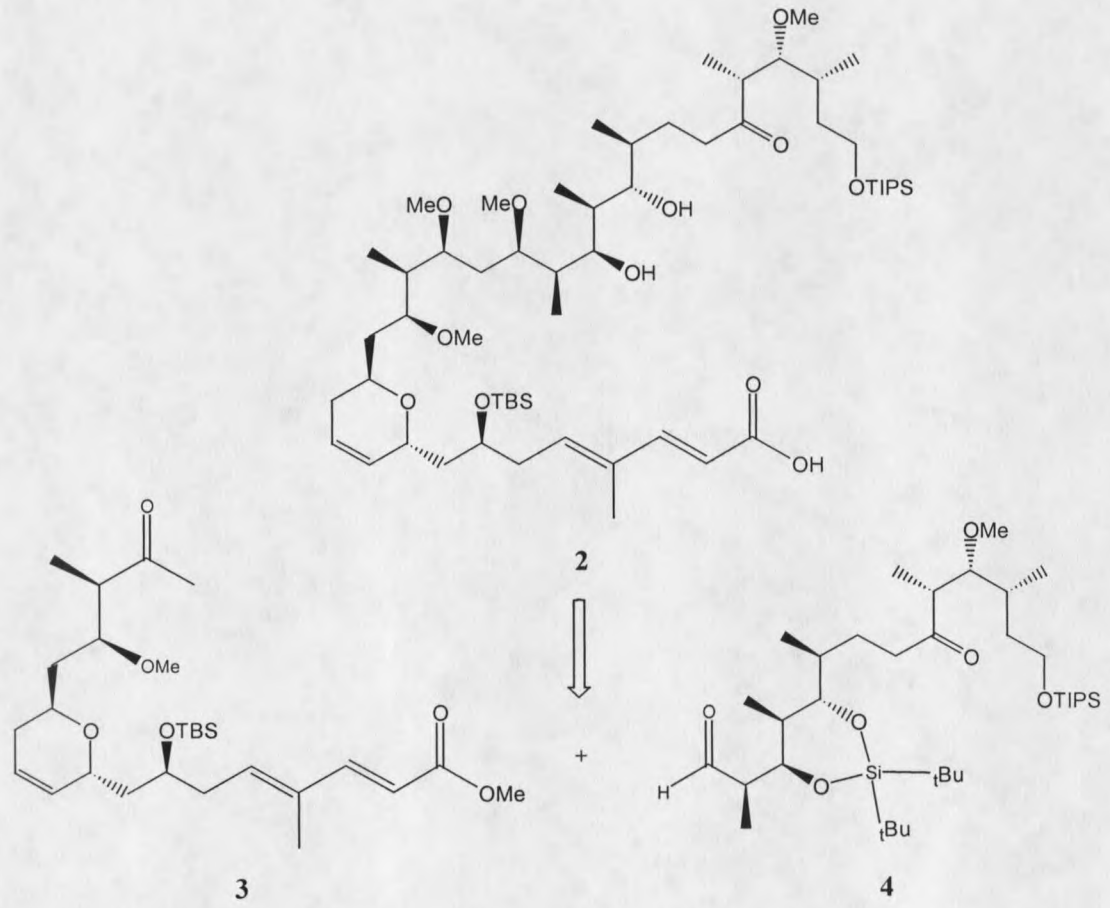
The five members of the scytophycin series, although possessing the same carbon framework, differ in substitution at C(6), C(16), and C(27). The scytophycins have garnered interest[4,7] within the organic synthesis community due to their interesting mode

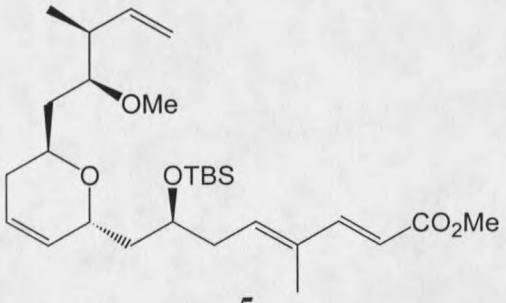
of action as well as the synthetic challenge they present. In 1993 it was reported that the scytophycins act as microtubulin depolymerizers[5], leading to their broad-spectrum cytotoxicity. At the same time it was reported that they circumvent P-glycoprotein mediated mutidrug resistance in tumor cells[6], making them potentially useful as therapeutics in cancer chemotherapy patients.

Scheme 1



Ian Paterson and his group at Cambridge reported the first total sythesis of scytophycin C **1** in 1997[7]. This synthesis involved the assembly of the complete carbon backbone of the molecule while providing for the necessary late introduction of the

highly acid sensitive[1] N-methylvinylformamide group. Paterson foresaw that preparation of the protected seco acid intermediate **2** (Scheme 1) could allow for the introduction of this sensitive moiety to be delayed until the endgame of the synthesis. The seco acid intermediate **2** was prepared by a Felkin-Anh controlled aldol coupling of the previously prepared C_1 - C_{18} ketone **3**[8] and C_{19} – C_{32} aldehyde **4**[9].



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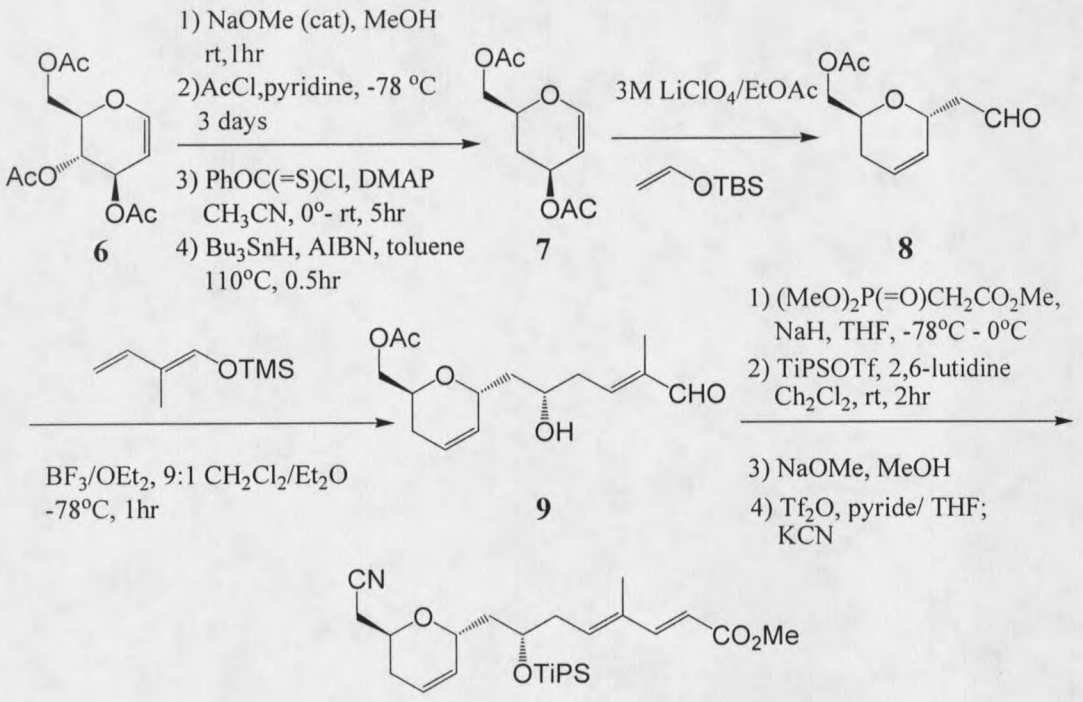
In 1997 Grieco and Speake reported[10] the synthesis of a precursor to the C_1 - C_{18} ketone of Paterson **5**, which featured a highly stereoselective carbon Ferrier type rearrangement[11] performed in polar media (Scheme 2). The synthesis commenced with the commercially available tri-O-acetoxy-D-glucal **6**. Protecting group manipulation followed by Barton deoxygenation[12] provided the protected 4-deoxy-gulcal **7** which was treated with *tert*-butyldimethylsilyl vinyl ether[13] in the presence of 3M $LiClO_4$ in ethyl acetate to effect the above mentioned carbon Ferrier type rearrangement. The reaction proceeds in 90% yield to afford aldehyde **8** as a single diastereomer. Treatment of aldehyde **8** with the trimethylsilylenol ether of tiglic aldehyde[14] in the presence of BF_3/ Et_2O using the conditions of Mukiyama[15] provided aldehyde **9** in 48% yield. Horner-Wadsworth-Emmons type olefination followed by protection of the C(7) alcohol as its triisopropylsilyl ether, deprotection of the C(12) alcohol by hydrolysis of the acetate

group, and one carbon homologation by displacement of the C(12) derived triflate with KCN led to nitrile **10.**

Scheme 2



Unfortunately all attempts to reduce the C(12) cyano group in the presence of the C(1) carboxymethyl group failed and it was deemed necessary to undertake a series of protecting group manipulations (Scheme 3) to circumvent this difficulty.

Scheme 3