Studies towards the synthesis of the C(8)-C(15) fragment of tedanolide
by David James Cole

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in Chemistry
Montana State University
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Abstract:
Tedanolide is a 18-membered macrolide of marine origin which displays antitumor activity and presents a synthetic challenge. To date, the total synthesis of tedanolide has not been reported however the synthesis of 13-deoxytedanolide, another closely related macrolide isolated from a different sea sponge, was recently accomplished.

Progress towards the synthesis of tedanolide is described with specific attention given to the synthesis of the C(8)-C(15) portion of the molecule. The approach involves the use of rigid bicyclic ring systems to control the stereocenters found in the natural product. The approach contained herein has not yet led to the total synthesis of tedanolide but has led to a precursor of the 18-membered ring.

STUDIES TOWARDS THE SYNTHESIS OF THE C(8)-C(15) FRAGMENT OF TEDANOLIDE

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APPROVAL

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David James Cole

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.

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Signature David Cole

Date 8/9/04

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LIST OF ABBREVIATIONS

Ac	acetyl
Bn	benzyl
br	broad
Bu	butyl or normal-butyl
n-Bu	normal–butyl
tBu	tert-butyl
c	concentration
cat	catalytic
COSY	correlated spectroscopy
cm^{-1}	wavenumber
CSA	camphorsulfonic acid
°C	degrees Celsius
CI	chemical ionization
d	doublet
dd	doublet of doublets
ddd	doublet of doublet of doublets
DEIPS	diethylisopropylsilyl
DIBAH	diisobutylaluminium hydride
DMAP	N,N-dimethylaminopyridine
DMF	N,N-dimethylformamide

LIST OF ABBREVIATIONS - CONTINUED

DMP	dimethyoxyphenol
DMPM	3,4-dimethyoxybenzyl or dimethoxyphenylmethyl
dt	doublet of triplets
ee	enatiomeric excess
EI	electron impact
equiv	equivalents
Et	ethyl
g	gram
h	hour
HRMS	high resolution mass spectrometry
Hz	hertz
Ipc	isopinocamphenyl
IR	infrared
J	coupling constant in hertz
kg	kilogram
KHMDS	potassium hexamethyl disilazide
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
m	multiplet
M	molarity

LIST OF ABBREVIATIONS - CONTINUED

M^+	parent ion peak
mCPBA	meta-chloroperbenzoic acid
Me	methyl
M/e	mass to charge ratio
mg	milligram
MHz	megahertz
min	minutes
mL	milliliter
μg	microgram
μL	microliter
μm	micrometer
mmol	millimole
MOM	methoxymethyl
MP	methoxyphenol
Ms	methanesulfonyl
MS	mass spectrum or molecular sieves
NMR	nuclear magnetic resonance
OAc	acetyloxy
PCC	pyridinium chlorochromate
Ph	phenyl

LIST OF ABBREVIATIONS - CONTINUED

Piv	pivaloyl
PMB	4-methyoxybenzyl
i-Pr	iso-propyl
ppm	parts per million
PPTS	pyridinium para-toluenesulfonate
py	pyridine
Rf	retention or retardation factor
rt	room temperature
s	singlet
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBS	tert-butyldimethylsilyl
TBDPS	tert-butyldiphenylsilyl
TES	triethylsilyl
Tf	Triflate
THF	tetrahydrofuran
TIPS	tert-butyldiisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
p-Ts	para-toluenesulfonyl

ABSTRACT

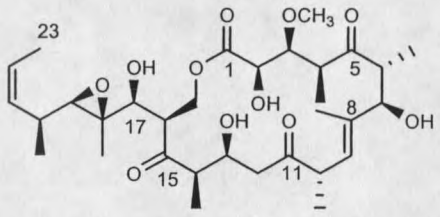
Tedanolide is a 18-membered macrolide of marine origin which displays antitumor activity and presents a synthetic challenge. To date, the total synthesis of tedanolide has not been reported however the synthesis of 13-deoxytedanolide, another closely related macrolide isolated from a different sea sponge, was recently accomplished.

Progress towards the synthesis of tedanolide is described with specific attention given to the synthesis of the C(8)-C(15) portion of the molecule. The approach involves the use of rigid bicyclic ring systems to control the stereocenters found in the natural product. The approach contained herein has not yet led to the total synthesis of tedanolide but has led to a precursor of the 18-membered ring.

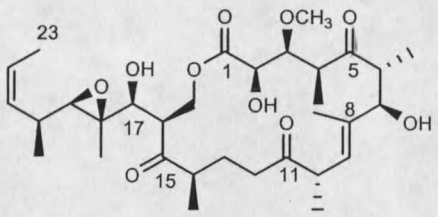
INTRODUCTION

Background

Tedanolide **1** was first isolated in 1984 by Schmitz and co-workers[1] from the sea sponge *Tedania ignis* also known as the fire sponge because of the burning sensation caused upon exposure to skin. The extracts from this sponge are of interest because they exhibited cytotoxicity as well as in vivo tumor inhibition. Tedanolide, which was believed to be a metabolite due to its presence in small amounts, was found in sponge specimens collected off the coast of Florida. Tedanolide was isolated using a series of methanol and chloroform extractions. Schmitz and co-workers found that tedanolide increased the lifespan of mice implanted with lymphocytic leukemia cells 23% at 1.56 μg/kg.[2] In 1991, Fusetani and co-workers isolated 13-deoxytedanolide **2** from the sea sponge *Mycale adhairens* collected off the coast of Hiburi, a small island southwest of Tokyo.[3] 13-Deoxytedanolide was also a remarkably cytotoxic metabolite.[3]



1
Tedanolide



2
13-Deoxytedanolide

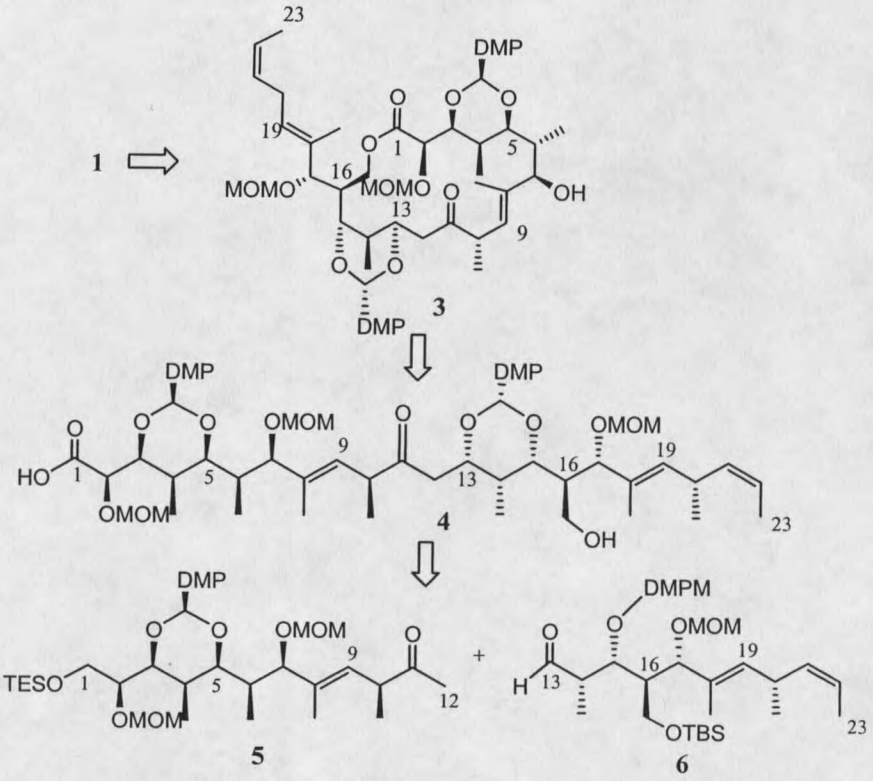
The structures of tedanolide and 13-deoxytedanolide differ from other macrolides in that the 18-membered lactone is constructed using a primary (instead of the usual

secondary) hydroxyl group.[4] Structural features which make this molecule synthetically challenging are the six readily epimerizable centers and the high degree of functionality on the carbon backbone.[5]

Due to the interesting and highly functionalized structure of the tedanolides, many research groups have taken up the synthetic challenge these molecules present.[2,4-8] To date, there has been no reported total synthesis of tedanolide and only one successful synthesis of 13-deoxytedanolide.[5] Most groups, including those of Roush, Yonemitsu, and Taylor, have envisioned the C(12)-C(13) bond being formed from an aldol reaction.[2,4,6-8] All the groups working on the tedanolides have planned to use a Yamaguchi macrolactonization[9] in order to form the 18-membered lactone.[2,4-8]

Using computer modeling, the Yonemitsu strategy first involved finding a suitable seco-acid to undergo lactonization. Trying to keep the conformation as close as possible to the desired lactone, Yonemitsu found that the seco-acid **4** should undergo macrolactonization and give rise to intermediate **3** (Scheme 1). The seco-acid was seen to come from a Felkin controlled aldol reaction between the C(1)-C(12) and the C(13)-C(23) fragments, **5** and **6** respectively. Unfortunately the aldol reaction gave rise to a mixture of the desired Felkin aldol product **4** and the C(13) epimer. The resulting ratios varied from 1:1.2-1:1.9 with the undesired C(13) epimer as the major product.[4a]

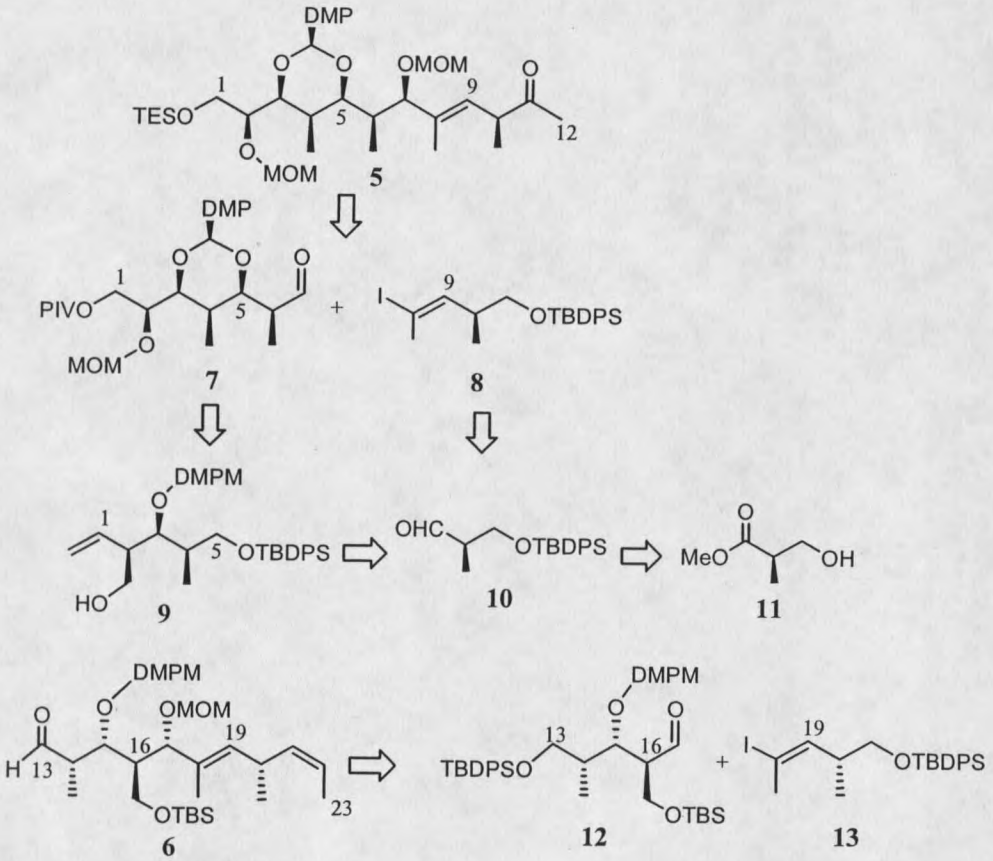
Scheme 1. Later Steps in Yonemitsu's Synthetic Strategy



Yonemitsu prepared the C(1)-C(12) fragment **5** by tert-butyl lithium mediated reaction of vinyl iodide **8** with aldehyde **7.** The desired C(13) stereocenter is expected on the basis of Felkin-Ahn control (Scheme 2). Indeed the desired alcohol was the major product.[4a] Both the C(1)-C(7) **7** and the C(8)-C(11) **8** fragments used in this coupling were generated from chiral aldehyde **10** which was derived from (R)-3-hydroxy-2-methylpropionate **11**.[4a] The C(13)-C(23) fragment **6** was formed via tert-butyl lithium mediated addition of vinyl iodide **13** to aldehyde **12** giving rise to the undesired cram product. The resulting alcohol was oxidized and reduced thus giving rise to the desired alcohol.[4c] Yonemitsu prepared the vinyl iodides **8** and **13** by reaction of the

corresponding alkyne, generated using the Corey-Fuchs procedure,[11c] with Schwartz reagent.[10,4]

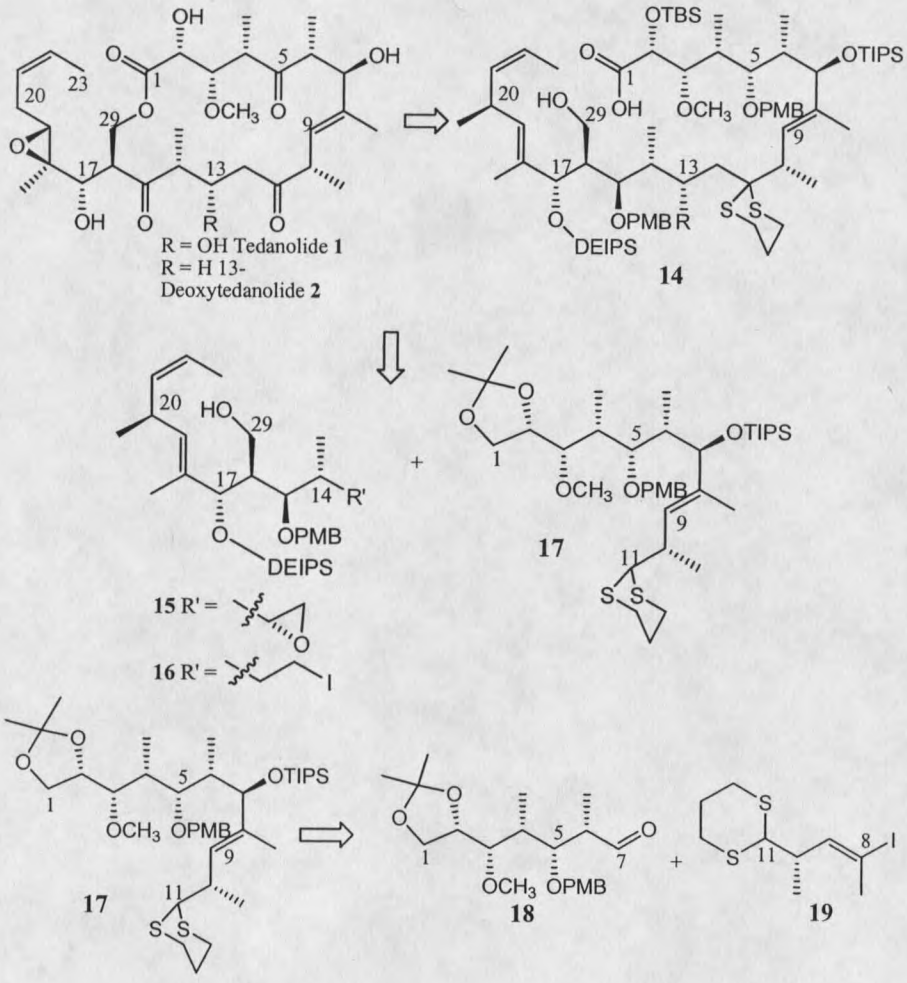
Scheme 2. Early Steps in Yonemitsu's Synthetic Strategy



In the successful synthesis of 13-deoxytedanolide **2,** the Smith group employed dithiane **17** and iodide **16** (Scheme 3). For the synthesis of tedanolide it was envisioned that the C(13) hydroxyl of tedanolide would be formed from nucleophilic ring opening of an epoxide at C(12) and C(13) (see compound **15**).[5] The C(1)-C(11) fragment was generated from tert-butyl lithium mediated addition of the C(8)-C(11) portion **19** to

aldehyde **18**. The correct stereochemistry at C(7) was expected on the basis of Felkin-Ahn control. Both the C(1)-C(7) fragment **18** and the C(13)-C(23) fragment **15** were obtained from iterative Evans aldol condensations.[5]

Scheme 3. The Smith Synthetic Strategy



Roush envisioned forming tedanolide from seco-acid **20** which was to be prepared from the corresponding C(5)-C(21) fragment (Scheme 4). The seco-acid was prepared by a Felkin-Ahn controlled aldol reaction to form the C(13) hydroxyl group