



Absolute configuration of biologically active marine natural products
by David Ernest Barnekow

A thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in
Chemistry

Montana State University

© Copyright by David Ernest Barnekow (1989)

Abstract:

Investigation of the absolute configuration and biological activity of three nakafuran derivatives isolated from the marine sponge *Dysidea etheria* resulted in the determination of the absolute configuration of the secondary alcohol 5-hydroxynakafuran-8, 40, by means of a modified Korean's method. This modification was the substitution of 2-phenylbutanoyl chloride for 2-phenylbutanoic anhydride.

The stereochemistry of the other two nakafurans, 5-acetoxy-nakafuran-8, 41, and 5-ketonakafuran-8, 42, was assigned by chemical degradation of transformation to the lead compound 40. All three nakafurans were evaluated for their phytotoxicity, cytotoxicity, insecticidal and antimicrobial activity.

Investigation of the cytotoxic organic extract of the marine green alga *Neomeris annulata* resulted in the isolation of three novel metabolites, 2-bromo-5-hydroxy-cis-selin-6-ene, 114, 1R-bromo-ent-maaliol, 115, and neomeranol, 116, which possesses a previously unknown regular isoprenoid sesquiterpene carbon skeleton. In the brine shrimp toxicity assay compounds 114 and 115 were twice as toxic as 116, although all three were inactive in the KB in vitro assay. Neomeranol, 116, was the only compound to display phytotoxic activity against johnsongrass. All three compounds were also screened for insecticidal and antimicrobial activity. The absolute configuration of compound 115 was determined by chemical degradation and comparison to the natural product maaliol, 118. The absolute configuration of neomeranol, 116, was determined by the same modified Korean's method that was employed in the nakafuran work.

The breadth of application of the modified Korean's method was evaluated with nine secondary alcohols of varying steric hindrance. These alcohols were esterified with both the anhydride and acid halide. The results demonstrated that sterically hindered secondary alcohols gave higher optical yields when resolved with the acid halide and less hindered secondary alcohols gave better optical yields with the anhydride.

ABSOLUTE CONFIGURATION OF BIOLOGICALLY
ACTIVE MARINE NATURAL PRODUCTS

by

David Ernest Barnekow

A thesis submitted in partial fulfillment
of the requirements for the degree

of

Doctor of Philosophy

in

Chemistry

MONTANA STATE UNIVERSITY
Bozeman, Montana

April 1989

D378
B262

ii

APPROVAL

of a thesis submitted by

David Barnekow

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.

28 Apr 89
Date

John C. ...
Chairperson, Graduate Committee

Approved for the Major Department

April 28, 1989
Date

Edwin H. Abbott
Head, Major Department

Approved for the College of Graduate Studies

May 11, 1989
Date

Henry L. Parsons
Graduate Dean

STATEMENT OF PERMISSION TO USE

In presenting this thesis in partial fulfillment of the requirements for a doctoral degree at Montana State University, I agree that the Library shall make it available to borrowers under rules of the Library. I further agree that copying of this thesis is allowable only for scholarly purposes, consistent with "fair use" as prescribed in the U.S. Copyright Law. Requests for extensive copying or reproduction of this thesis should be referred to University Microfilms International, 300 North Zeeb Road, Ann Arbor, Michigan 48106, to whom I have granted "the exclusive right to reproduce and distribute copies of the dissertation in and from microfilm and the right to reproduce and distribute by abstract in any format."

Signature



Date

April 28, 1989

Sue

my best friend
wife
and the mother of our children

an encourager
a motivator
and a provider

Leah Marie, Jeremy Alan and Baby

for the special meaning of the word

Daddy

ACKNOWLEDGEMENT

I must first acknowledge my Lord and Savior, Jesus Christ and The Holy Spirit, for the guidance and strength they gave to me during the past 4½ years.

I would like to acknowledge all those individuals who have contributed to my development as a scientist and as a person during my educational experience at Montana State University. The following individuals I give recognition by name for their special contributions and assistance to my research: Dr. Joe Sears, Dr. Tom Livinghouse, Dr. Andrea Stierle, Dr. Brad Van Wagenen, Mike Raub, Rob Hendrickson, Rhonda Dillman, and Kate Graham. A special thanks is extended to Dr. Gary Martin for his assistance in obtaining the wonderful 2D NMR data, as well as the time he spent discussing 2D NMR techniques with me.

I must also express many thanks to Dr. John H. Cardellina II, my advisor, for challenging me to always perform up to my potential and for encouraging me when my performance was not up to my potential.

TABLE OF CONTENTS

	<u>Page</u>
INTRODUCTION.	1
KNOWN CHEMISTRY OF THE SPONGE GENUS <u>Dysidea</u>	4
INVESTIGATION OF THE OXYGENATED NAKAFURAN-8 DERIVATIVES ISOLATED FROM <u>Dysidea etheria</u>	18
KNOWN CHEMISTRY OF MARINE GREEN ALGAE	42
INVESTIGATION OF THE SECONDARY METABOLITES FROM <u>Neomeris annulata</u>	62
THE HOREAU'S METHOD FOR DETERMINING THE ABSOLUTE STEREOCHEMISTRY OF CHIRAL SECONDARY ALCOHOLS.	133
INVESTIGATION OF THE APPLICATION OF THE MODIFIED HOREAU'S METHOD.	139
CONCLUSION.	149
EXPERIMENTAL.	157
General.	157
NMR.	158
Homonuclear 2D-NMR Experiments	
Autocorrelated Proton (COSY) 2D-NMR.	159
Proton Zero Quantum Coherence 2D- NMR (ZQCOSY)	159
Proton Double Quantum Coherence 2D-NMR (DQCOSY).	160
Heteronuclear 2D-NMR Experiments (HETCOR)	
Heteronuclear Chemical Shift Correlation (HETCOR) <u>via</u> $^1J_{CH}$ with Selective Vicinal Proton Decoupling.	161
Long Range Heteronuclear Chemical Shift Correlation with One Bond Modulation Decoupling	162

Table of Contents-continued

	<u>Page</u>
Reverse (Proton) Detected Long Range Heteronuclear Chemical Shift Correlation via Heteronuclear Multiple Quantum Coherence (HMBC).	162
Biological Activity Testing.	163
Cytotoxicity.	163
Phytotoxicity	164
Insecticidal Screening.	166
Tobacco Hornworm Assay	166
Grasshopper Assay.	166
Differential DNA Repair Assay	167
<u>Dysidea etheria</u>	168
Isolation of 5-Acetoxy na kafuran-8, 41 and 5-Hydroxy na kafuran-8, 40	168
Hydrolysis of 5-Acetoxy na kafuran-8.	171
Attempted Esterification of 5-Hydroxy- na kafuran-8, 40, with 2-Phenylbutyric Anhydride, 44.	171
Attempted Esterification of 5-Hydroxy- na kafuran-8, 40, with 2-Phenylbutyric Acid Chloride, 47.	172
Preparation of 5-(2-Phenylbutyryl)- na kafuran-8, 46.	173
Attempted Acid Hydrolysis of 5-(2-Phenyl- butyryl)- na kafuran-8, 46	174
Attempted Basic Hydrolysis of 5-(2- Phenylbutyryl)- na kafuran-8, 46, Using Barium Hydroxide	174
Attempted Basic Hydrolysis of 5-(2- Phenylbutyryl)- na kafuran-8, 46, Using Potassium Hydroxide.	174
Attempted Reduction of 5-(2-Phenyl- butyryl)- na kafuran-8, 46, Using Lithium Aluminum Hydride	175
Oxidation of 5-Hydroxy na kafuran-8, 40, to 5-Keto na kafuran-8, 42	175
Preparation of 5-mesylnakafuran-8, 48	176
Attempted Iodine Replacement of 5-Mesylnakafuran-8, 48	177
Attempted Thiocyano Replacement of the Mesylate of 5-Hydroxy na kafuran-8, 48	177

Table of Contents-continued

	<u>Page</u>
Attempted Reduction of 5-Mesylnaka- furan-8, 48.	178
Attempted Reduction of 5-Hydroxynaka- furan-8, 40, <u>via</u> Triakysilanes and Trifluoroacetic Acid	178
<u>Neomeris annulata</u>	179
Collection and Extraction	179
2-Bromo-5-hydroxy-cis-selin-6-ene, 114.	181
1R-Bromo-ent-maaliol, 115	181
Neomeranol, 116	181
Oxidation of Neomeranol, 116.	182
Debromination of 1R-Bromo-ent- maaliol, 115	182
Preparation of the 2-phenylbutyryl Ester of Neomeranol.	183
Modified Horeau's Method for Determining Absolute Configuration of Hindered Secon- dary Alcohols.	184
Preparation of Racemic 2-Phenyl-butyric Anhydride, 44.	184
Preparation of Racemic 2-Phenylbutyryl Chloride, 47	184
Reaction of 2R-Butanol, 131, with Racemic 2-Phenylbutyric Anhydride, 44.	185
Reaction of 2R-Butanol, 131, with Racemic 2-Phenylbutyryl Chloride, 47	185
Reaction of Stigmasterol, 132, with Racemic 2-Phenylbutyric Anhydride, 44.	186
Reaction of Stigmasterol, 132, with Racemic 2-Phenylbutyryl Chloride, 47	186
Reaction of 1R-Phenylethanol, 133, with Racemic 2-Phenylbutyric Anhydride, 44.	187
Reaction of 1R-Phenylethanol, 133, with Racemic 2-Phenylbutyryl Chloride, 47	188
Reaction of 2S-Octanol, 134, with Racemic 2-Phenylbutyric Anhydride, 44.	188
Reaction of 2S-Octanol, 134, with Racemic 2-Phenylbutyryl Chloride, 47	189
Reaction of (-)-Menthol, 135, with Racemic 2-Phenylbutyric Anhydride, 44.	189
Reaction of (-)-Menthol, 135, with Racemic 2-Phenylbutyryl Chloride, 47	190

Table of Contents-continued

	<u>Page</u>
Reaction of [1S-Endo]-Borneol, 136, with Racemic 2-Phenylbutyric Anhydride, 44. . .	191
Reaction of [1S-Endo]-Borneol, 136, with Racemic 2-Phenylbutyryl Chloride, 47 . . .	191
Reaction of Brianthein X, 137, with Racemic 2-Phenylbutyric Anhydride, 44. . .	192
Reaction of Brianthein X, 137, with Racemic 2-Phenylbutyryl Chloride, 47 . . .	192
Reaction of Yohimbine, 138, with Racemic 2-Phenylbutyric Anhydride, 44. . .	193
Reaction of Yohimbine, 138, with Racemic 2-Phenylbutyryl Chloride, 47 . . .	193
Reaction of 5-Hydroxynakafuran-8, 40, with Racemic 2-Phenylbutyryl Chloride, 47	194
Preparation of (-)-2R-Phenylbutyryl Chloride, 139.	194
Reaction of (-)-2R-Phenylbutyryl Chloride, 139, with Pyridine and 4-dimethylaminopyridine at Room Temperature.	195
Reaction of (-)-2R-Phenylbutyryl Chloride, 139, with Pyridine and 4-Dimethylaminopyridine at 60°	195
Reaction of (-)-2R-Phenylbutyryl Chloride, 139, with Pyridine at Room Temperature.	196
Reaction of (-)-2R-Phenylbutyryl Chloride, 139, with Pyridine at 60°	196
Reaction of 2S-Octanol, 134, with (-)-2R-Phenylbutyryl Chloride.	197
REFERENCES CITED.	198

LIST OF TABLES

<u>Table</u>		<u>Page</u>
1.	Differential DNA Repair and Brine Shrimp Assay Data41
2.	NMR Data, 2-Bromo-5-hydroxy-cis-selin-6-ene, 11484
3.	NMR Data, 1R-Bromo-ent-maaliol, 115.92
4.	NMR Data, Neomeranol, 116.	114
5.	Summary, Comparison of Optical Yields, Acid Anhydride vs Chloride.	142
6.	Racemization of (-)-2R-Phenylbutyryl Chloride, 139.	146
7.	Characteristics of Repair Deficient Strains.	169

LIST OF FIGURES

<u>Figure</u>	<u>Page</u>
1. Biosynthetic Pathway A, Proposing the Formation of Furanosesquiterpenes From <u>Dysidea</u>13
2. Biosynthetic Pathway B, Proposing the Formation of Furanosesquiterpenes From <u>Dysidea</u>14
3. Atrolatic Acid Synthesis With 5-Hydroxynakafuran-8, 4016
4. Fischer Projection for a Levorotatory Acid20
5. Fischer Projection for a Dextrorotatory Acid21
6. Illustrated Absolute Configuration of a Secondary Alcohol From a Levorotatory Acid21
7. Esterfication of the Alcohol 40 with the Anhydride 44 in Pyridine24
8. Esterfication of the Alcohol 40 with the Acid Chloride 47 in Pyridine With DMAP.26
9. 250 MHz ^1H NMR Spectrum of 5-Hydroxynakafuran-8, 40 , in CDCl_328
10. 250 MHz ^1H NMR Spectrum of 5-(2-Phenylbutanoyl)-Nakafuran-8, 46 , in CDCl_329
11. 250 MHz ^1H NMR Spectrum of 5-Acetoxynakafuran-8, 41 , in CDCl_330
12. Low Resolution EI Mass Spectrum of 5-(2-Phenylbutanoyl)-Nakafuran-8, 4631
13. 250 MHz ^1H NMR Spectrum of 2-Phenylbutanoic Acid, 45 , in CDCl_332
14. Illustrated Absolute Configuration Denoted by the Modified Horeau's Method for 5-Hydroxynakafuran-8, 4033
15. Hydrolysis of the Acetate 41 to the Alcohol 4036
16. Oxidation of the Alcohol 40 to the Ketone 4237

LIST OF FIGURES-continued

<u>Figure</u>	<u>Page</u>
17. 250 MHz ^1H NMR Spectrum of 5-Ketonakafuran-8, 41 , in CDCl_338
18. Classification of the Class Bryopsidophyceae From the Phylum Chlorophyta.43
19. HPLC Chromatography of 114 , 115 and 116 . Beckman Altex Ultrasphere CN (25 x 1 cm); hexane-methylene chloride (4:1); 3 mL/min; RI; 2 mm/min.64
20. 250 MHz ^1H NMR Spectrum of 2-Bromo-5-Hydroxy-cis- Selin-6-ene, 114 , in CDCl_365
21. 250 MHz ^1H NMR Spectrum of $1R$ -Bromo-ent- Maaliol, 115 , in CDCl_366
22. 250 MHz ^1H NMR Spectrum of Neomeranol, 116 , in CDCl_367
23. Low Resolution EI Mass Spectrum of 2-Bromo-5- Hydroxy-cis-Selin-6-ene, 11469
24. Infrared Spectrum of 2-Bromo-5-Hydroxy-cis-Selin- 6-ene, 11470
25. 300 MHz ^{13}C NMR Spectrum of 2-Bromo-5-Hydroxy-cis- Selin-6-ene, 114 , in C_6D_671
26. 250 MHz ^1H NMR Spectrum of 2-Bromo-5-Hydroxy-cis- Selin-6-ene, 114 , in C_6D_672
27. Zero Quantum Coherence Pulse Sequence Employed by Martin ¹⁰⁸74
28. Double Quantum Coherence Pulse Sequence Employed by Martin ¹⁰⁹75
29. 300 MHz ^1H ZQCOSY Spectrum of 2-Bromo-5-Hydroxy- cis-Selin-6-ene, 114 , in C_6D_678
30. 300 MHz ^1H DQCOSY Spectrum of 2-Bromo-5-Hydroxy- cis-Selin-6-ene, 114 , in C_6D_680

LIST OF FIGURES-continued

<u>Figure</u>	<u>Page</u>
31. Expanded 300 MHz ^1H DQCOSY Spectrum of 2-Bromo-5-Hydroxy-cis-Selin-6-ene, 114, in C_6D_681
32. 300 MHz ^1H - ^{13}C HETCOR Spectrum of 2-Bromo-5-Hydroxy-cis-Selin-6-ene, 114, in C_6D_685
33. Deep Slice of a 300 MHz Long Range ^1H - ^{13}C HETCOR Spectrum of 2-Bromo-5-Hydroxy-cis-Selin-6-ene, 114, in C_6D_686
34. Shallow Slice of a 300 MHz Long Range ^1H - ^{13}C HETCOR Spectrum of 2-Bromo-5-Hydroxy-cis-Selin-6-ene, 114, in C_6D_687
35. Expansion of the 300 MHz Long Range ^1H - ^{13}C HETCOR Spectrum of 2-Bromo-5-Hydroxy-cis-Selin-6-ene, 114, in C_6D_688
36. Mass Spectral Fragmentations of 2-Bromo-5-Hydroxyl-cis-Selin-6-ene, 114.89
37. Observed nOe Correlations for 2-Bromo-5-Hydroxy-cis-Selin-6-ene, 11490
38. 300 MHz ^1H - ^{13}C HETCOR Spectrum of 1R-Bromo-ent-Maaliol, 115, in C_6D_691
39. Low Resolution EI Mass Spectrum of 1R-Bromo-ent-Maaliol, 11594
40. 300 MHz ^{13}C NMR Spectrum of 1R-Bromo-ent-Maaliol, 115, in C_6D_695
41. Infrared Spectrum of 1R-Bromo-ent-Maaliol, 115, in CDCl_396
42. 300 MHz ^1H ZQCOSY Spectrum of 1R-Bromo-ent-Maaliol, 115, in C_6D_697
43. 250 MHz ^1H NMR Spectrum of 1R-Bromo-Ent-Maaliol, 115, in C_6D_698
44. 300 MHz ^1H COSY Spectrum of 1R-Bromo-ent-Maaliol, 115, in C_6D_6	100

LIST OF FIGURES-continued

<u>Figure</u>	<u>Page</u>
45. 300 MHz ^1H Expanded ZQCOSY Spectrum of <u>1R</u> -Bromo-ent-maaliol, 115 , in C_6D_6	102
46. 300 MHz Long Range ^1H - ^{13}C HETCOR Spectrum of <u>1R</u> -Bromo-ent-Maaliol, 115 , in C_6D_6	104
47. Mass Spectral Fragmentations of <u>1R</u> -Bromo-ent-Maaliol, 115	105
48. Observed nOe Correlations for <u>1R</u> -Bromo-ent-Maaliol, 115 ,	106
49. Debromination of <u>1R</u> -Bromo-ent-Maaliol, 115 , to Compound 119	108
50. 250 MHz ^1H NMR Spectrum of (-)-Maaliol, 119 , in C_6D_6	109
51. 300 MHz ^{13}C NMR Spectrum of (-)-Maaliol, 119 , in C_6D_6	110
52. Low Resolution EI Mass Spectrum of Neomeranol, 116	112
53. 300 MHz Long Range ^1H - ^{13}C HETCOR Spectrum of Neomeranol, 116 , in C_6D_6	113
54. 300 MHz ^{13}C NMR Spectrum of Neomeranol, 116 , in C_6D_6	115
55. Infrared Spectrum of Neomeranol, 116 , in CDCl_3	116
56. 250 MHz ^1H NMR Spectrum of Neomeranol, 116 , in C_6D_6	117
57. 300 MHz ^1H ZQCOSY Spectrum of Neomeranol, 116 , in C_6D_6	118
58. 250 MHz ^1H NMR Spectrum of compound 120 in C_6D_6	120
59. 250 MHz ^{13}C NMR Spectrum of compound 120 in C_6D_6	121
60. Infrared Spectrum of compound 120 in CDCl_3	122

LIST OF FIGURES-continued

<u>Figure</u>	<u>Page</u>
61. Expansion of the 300 MHz Long Range ^1H - ^{13}C HMBC Spectrum of Neomeranol, 116, in C_6D_6	125
62. 300 MHz Long Range ^1H - ^{13}C HMBC Spectrum of Neomeranol, 116, in C_6D_6	126
63. Mass Spectral Fragmentation of Neomeranol, 116	128
64. Observed nOe Correlations for Neomeranol, 116.	129
65. Proposed Biosynthetic Rationale for the Formation of the <u>Neomeris</u> Sesquiterpenes	132

ABSTRACT

Investigation of the absolute configuration and biological activity of three nakafuran derivatives isolated from the marine sponge Dysidea etheria resulted in the determination of the absolute configuration of the secondary alcohol 5-hydroxynakafuran-8, 40, by means of a modified Horeau's method. This modification was the substitution of 2-phenylbutanoyl chloride for 2-phenylbutanoic anhydride. The stereochemistry of the other two nakafurans, 5-acetoxynakafuran-8, 41, and 5-ketonakafuran-8, 42, was assigned by chemical degradation of transformation to the lead compound 40. All three nakafurans were evaluated for their phytotoxicity, cytotoxicity, insecticidal and antimicrobial activity.

Investigation of the cytotoxic organic extract of the marine green alga Neomeris annulata resulted in the isolation of three novel metabolites, 2-bromo-5-hydroxy-cis-selin-6-ene, 114, 1R-bromo-ent-maaliol, 115, and neomeranol, 116, which possesses a previously unknown regular isoprenoid sesquiterpene carbon skeleton. In the brine shrimp toxicity assay compounds 114 and 115 were twice as toxic as 116, although all three were inactive in the KB in vitro assay. Neomeranol, 116, was the only compound to display phytotoxic activity against johnsongrass. All three compounds were also screened for insecticidal and antimicrobial activity. The absolute configuration of compound 115 was determined by chemical degradation and comparison to the natural product maaliol, 118. The absolute configuration of neomeranol, 116, was determined by the same modified Horeau's method that was employed in the nakafuran work.

The breadth of application of the modified Horeau's method was evaluated with nine secondary alcohols of varying steric hindrance. These alcohols were esterified with both the anhydride and acid halide. The results demonstrated that sterically hindered secondary alcohols gave higher optical yields when resolved with the acid halide and less hindered secondary alcohols gave better optical yields with the anhydride.

INTRODUCTION

The concept of stereoisomerism of organic molecules was first recognized in 1815 by a French physicist, Jean Baptiste Biot¹. While working with the oils of laurel and lemon and a solution of camphor in alcohol, he observed that these solutions would rotate plane polarized light. Thus the term optically active compound was developed.

The French scientist Louis Pasteur² was the first to recognize that the optical activity was caused by an asymmetric grouping of atoms in the molecule (chiral molecules). Pasteur was famous for his work with (+)-tartaric acid, but it was not until 1951 that the Dutch scientist J.M. Bijvoet determined the absolute configuration of (+)-tartaric acid via a special x-ray technique.³

With the rapid evolution of this new field, stereochemistry, in organic chemistry, a general method for designating the absolute structure of a stereoisomer was needed. The R - S convention for defining the absolute configuration of an asymmetric carbon was developed by two English scientists, R.S. Cahn and C.K. Ingold, and a Swiss scientist, V. Prelog.⁴

scientist, V. Prelog.⁴

Although enantiomers have the same physical properties, their biological activities are often very different. R and S carvone were shown to have different odors; R-carvone had a spearmint odor while S-carvone was the source of a caraway odor.² In an undergraduate organic text⁵, the importance of knowing which enantiomer displayed a particular biological activity was emphasized by the following examples. When grown on a diet of racemic tartaric acid, the mold Penicillium glaucum was shown to consume only the (+)-tartaric acid while leaving the (-)-tartaric acid. The hormone (-)-adrenaline was demonstrated to be many times greater in activity than the enantiomer (+)-adrenaline. Only one of the stereoisomers of chloromycetin shows antibiotic activity. In the case of (-)-ephedrine, which was used as a drug, there was actually interference with its activity by the other enantiomer, (+)-ephedrine. Among amino acids only one of the stereoisomers of asparagine and leucine was sweet, and only one of the stereoisomers of glutamic acid enhanced the flavor of foods.

There are many examples of biochemicals, agrochemicals, and pharmaceuticals in which only one of the isomers displays a particular activity. Knowing which enantiomer of a compound displayed the desired activity would be crucial to the commercial development of that

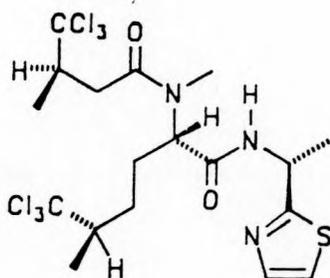
compound as a drug or agrochemical. Therefore, the complete characterization of a new biologically active, chiral natural product would conclude with the determination of the absolute configuration possessed by that compound.

The goals of the research presented herein were to isolate, fully characterize and then evaluate novel marine natural products with various bioassays to determine their biological activities. The complete characterization would involve the determination of the gross structure and relative stereochemistry via spectral techniques and the absolute configuration by chemical methods. Screening of biological activities of these marine natural products would utilize the following in house assays: brine shrimp toxicity, cut-leaf assay (phytotoxicity), tobacco hornworm and grasshopper assays (insecticidal) and differential DNA repair. The KB assay for cytotoxicity was performed at the National Cancer Institute.

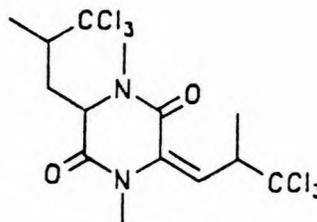
KNOWN CHEMISTRY OF THE SPONGE GENUS Dysidea

The sponge Dysidea has been one of the most chemically studied genera of sponges. The study of this genus has led to the isolation of a wide variety of secondary metabolites representing totally unrelated structural classes. These classes were represented by the following structural types; polyhalogenated nitrogenous metabolites, diphenyl ethers, phenols, and terpenoids.

Hexachloro-amino acid derivatives like isodysidenin 1, were isolated from Dysidea herbacea.^{6,7,8,9,10,11} The absolute configuration for isodysidenin was established by x-ray diffraction⁸. D. herbacea also produces the diketopiperazine 2.¹² The isolation of a large number of closely related amino acid metabolites from blue-green algae, as well as the discovery of the presence of blue-



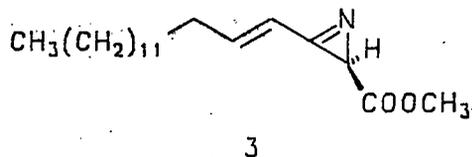
1



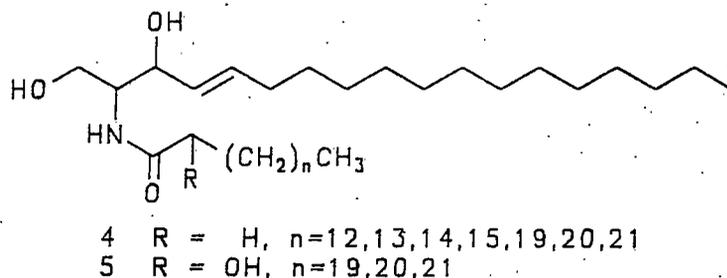
2

green algae in the sponge tissue, which at times represents half the cellular weight of the collection, has led to the belief that these metabolites were from the blue-green algae.¹³

From D. fragilis, an interesting cytotoxic and antimicrobial active azacyclopropene, dysidazirine, **3**, was isolated.¹⁴ The absolute configuration of **3** was determined after hydrolysis of the ester by circular dichroic spectral analysis the of p-bromobenzamide derivative.

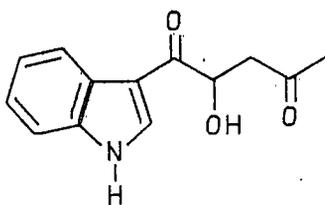


Sphingosine derivatives **4** and **5** were isolated from D. etheria,¹⁵ with predominantly C₂₂ or larger fatty acids comprising the amides. The fully saturated acids in **4**



displayed only weak antimicrobial activity by inhibiting Corynebacterium michiganense.¹⁶ Absolute configuration was determined by comparison of optical rotations for the methyl ester derivatives of the fatty acids to literature values for the corresponding fatty acid derivatives, and comparison of the spectral properties of the sphingosine triacetate to those reported in the literature.

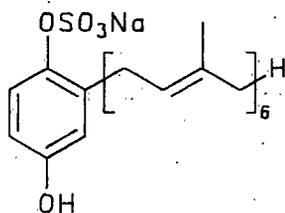
The first plant growth regulator from a sponge, 4-hydroxy-5-(indole-3-yl)-5-oxo-pentan-2-one (6), was isolated from D. etheria.¹⁷ This novel indole induced root length extensions of 15% over controls at a maximum effective concentration of 10^{-8} M.^{16,18}



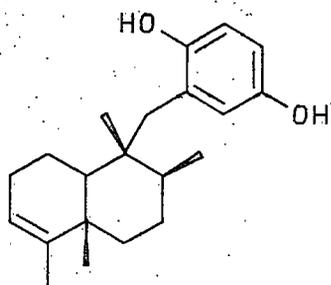
6

From an unidentified species of Dysidea¹⁹ was isolated the hexaprenylhydroquinone sulfate 7, was shown to inhibit H,K-ATPase with an IC_{50} of 4.6×10^{-6} M and phospholipase A_2 with an IC_{50} of 1.8×10^{-6} M. Another series of quinones, derived from avarol, 8, was isolated from D. avara.^{20,21,22} These compounds are represented by the sesquiterpenoid amino-quinone 9 and were shown to inhibit

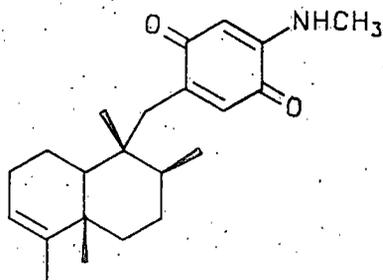
cell cleavage of the fertilized eggs from the sea urchin Sphaerechinus granularis. The absolute configuration of avarol was determined by spectroscopic and chemical methods.



7



8

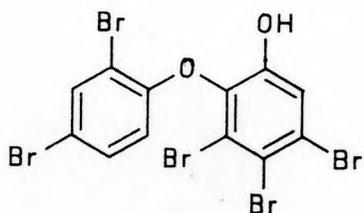


9

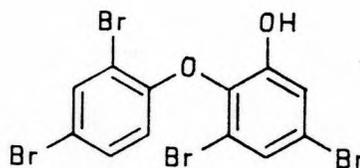
From D. herbacea^{23, 24, 25} ten polybrominated diphenyl ethers have been isolated. These compounds can be placed into two classes- pentabrominated 2-phenoxyphenols such as 10, and tetrabrominated 2-phenoxyphenols such as 11; they inhibit the growth of both Gram-negative and Gram-positive microorganisms.

This genus of sponge makes a great number of

biosynthetically unrelated terpenoid compounds. These

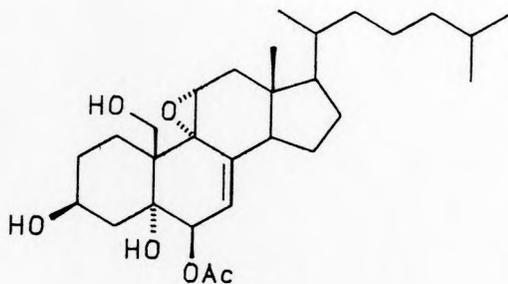


10

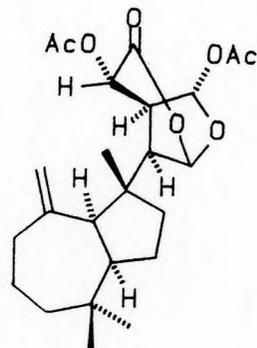


11

terpenoids include polyhydroxylated sterols^{26,27,28,29,30}, exemplified by the compound first reported, 9 α ,11 α -epoxycholest-7-ene-3 β ,5 α ,6 β ,19-tetrol, 12.²⁶ This compound was found to be slightly cytotoxic, ED₅₀ in PS³¹ of 4.9 μ g/mL.²⁶ Other polyhydroxylated sterols isolated from Dysidea have displayed the following activities; ichthyotoxicity²⁷, antimicrobial activity^{27,29}, and brine shrimp toxicity.²⁹



12



13

