



Organic constituents of the marine sponge *Dysidea etheria*, the nudibranch *Hypselodoris zebra*, and the gorgonian soft coral *Briareum polyanthes*
by Stephen Howard Grode

A thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry
Montana State University
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Abstract:

This thesis comprises a report of research into the chemical constituents of the marine sponge *Dysidea etheria*, the gorgonian soft coral *Briareum polyanthes*, and the nudibranch *Hypselodoris zebra*. A total of eleven compounds were characterized, six of which were new molecules.

The compounds isolated and characterized from *D. etheria* were the sesquiterpenes furodysinins, 27, and the heretofore unreported furodysinins lactone, 56, and the ceramides α -hydroxy N-acylsphingosines, 60, and N-acylsphingosines, 61. The extraction and subsequent fractionation of *H. zebra* yielded the furanosesquiterpenes furodysinins, euryfurans, 34, 5-acetoxy nakafuran—8, 24, and 5-hydroxynakafuran, 59. *Briareum polyanthes* was the source of a series of novel, highly functionalized diterpenes which possessed the briaran carbon skeleton. These molecules were given the trivial names, brianthein X, 69, Y, 68, and Z, 67.

Characterization of all isolates was accomplished, predominantly, by analysis of NMR, MS, IR, and UV data on the purified compounds and their chemical derivatives. The structure of brianthein Y was confirmed by an X-ray diffraction analysis.

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March 1983

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APPROVAL

of a thesis submitted by

Stephen Howard Grode

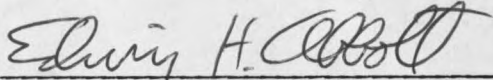
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11 March 1983

To my grandparents, whose foresight and fortitude brought them to the shores of this great nation.

To my parents, who allowed me the freedom to find my own way.

To my wife.

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Acknowledging all those responsible for my professional development at Montana State University would not be possible. I would, however, like to thank Thomas R. James, Jr., for the isolation of the brianthein series. Thanks are also due to Dr. Robert T. Orth for helpful discussions on mass spectrometry and Richard Taylor and Dr. Mark Waddington for helpful instruction on the NMR spectrometer. The assistance of William Grey in setting up the plant pathogenic antimicrobial assays is also gratefully acknowledged. Dr. Bradford P. Mundy, Dr. P.W. Jennings, and their respective research groups also deserve to be thanked for allowing me the occasional use of their chemicals and glassware.

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ABSTRACT

This thesis comprises a report of research into the chemical constituents of the marine sponge Dysidea etheria, the gorgonian soft coral Briareum polyanthes, and the nudibranch Hypselodoris zebra. A total of eleven compounds were characterized, six of which were new molecules.

The compounds isolated and characterized from D. etheria were the sesquiterpenes furodysin, **27**, and the heretofore unreported furodysin lactone, **56**, and the ceramides α -hydroxy N-acylsphingosines, **60**, and N-acylsphingosines, **61**. The extraction and subsequent fractionation of H. zebra yielded the furanosesquiterpenes furodysin, euryfuran, **34**, 5-acetoxy nakafuran-8, **24**, and 5-hydroxy nakafuran-8, **59**. Briareum polyanthes was the source of a series of novel, highly functionalized diterpenes which possessed the briaran carbon skeleton. These molecules were given the trivial names, brianthein X, **69**, Y, **68**, and Z, **67**.

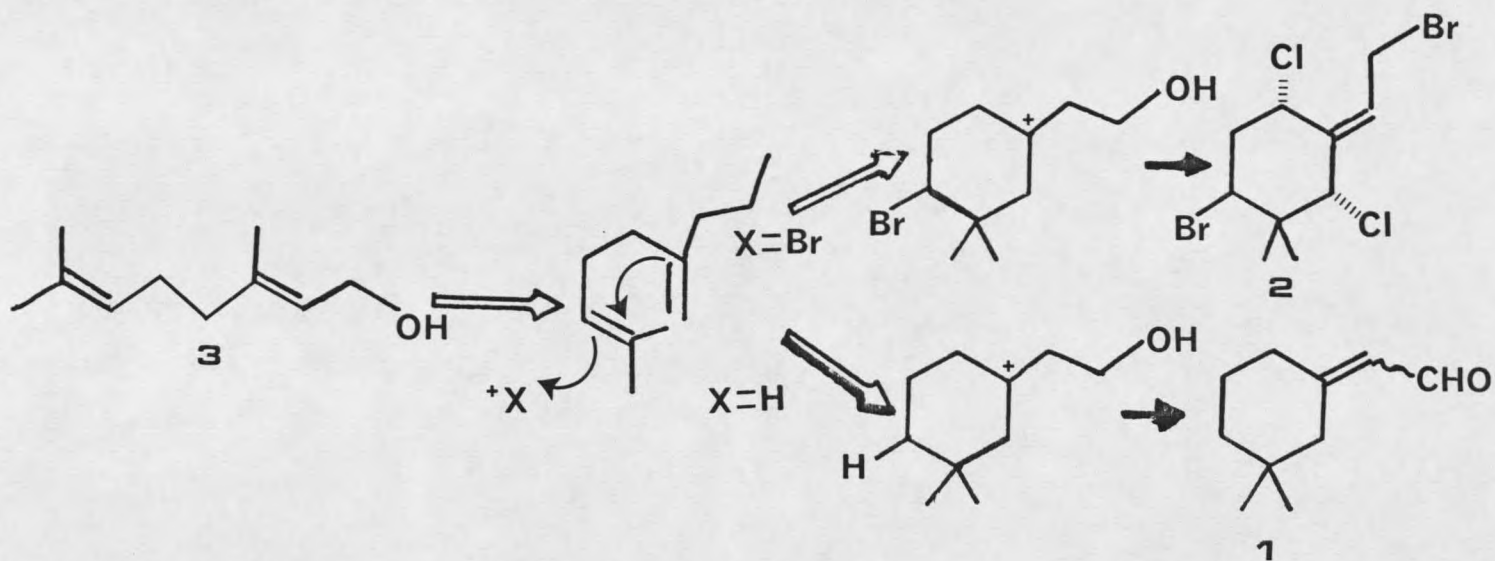
Characterization of all isolates was accomplished, predominantly, by analysis of NMR, MS, IR, and UV data on the purified compounds and their chemical derivatives. The structure of brianthein Y was confirmed by an X-ray diffraction analysis.

INTRODUCTION

The natural products chemist is primarily motivated by the search for new and unique compounds. From a biological perspective, the uniqueness might be inherent in biological activity (e.g., antibiotic, antimicrobial, antiviral, or antineoplastic), a role in chemical communication, or use as a taxonomic marker. From a chemical perspective, the uniqueness would be inherent in novel structure.

It is quite reasonable to suspect that the high ionic content of the ocean would be conducive to formation of unique compounds; that is, it would be possible to form biogenetic intermediates in the marine environment that would be unstable or highly unlikely in the terrestrial environment. An example of the differing intermediates formed in the marine and terrestrial environments, as presented in Scheme I, is the biosynthesis of cis and trans-3,3 dimethyl- $\Delta^{1,\alpha}$ -cyclohexaneacetaldehyde, **1**, a sex pheromone from the male boll weevil Anthonomus grandis (1), and ochtodene, **2**, isolated from tropical red seaweeds of the family Rhizophyllidaceae (2). Starting from the same precursor, geraniol, **3**, the first step in the terrestrial environment is proton induced cyclization, whereas the first step in the marine environment is presumed to be bromonium ion induced cyclization. The next step in both is proton loss to form the alkene. Ochtodene is then further halogenated.

The intense interest in marine natural products began about fifteen years ago and was spurred by the aforementioned search for



2

Scheme I. Proposed Biosynthetic Pathways from Geraniol in the Marine and Terrestrial Environments.

novel structures. Systematic studies have been directed toward a particular phylum, such as sponges (3), toward a particular class of compounds (4-8), or toward a class of compounds in a phylum (9-13). Since many of these novel structures demonstrated biological activity, three major pharmaceutical firms, Hoffman La Roche in Australia, Roussel in Brazil, and Suntory in Japan, as well as independent researchers (14,15), have undertaken systematic screening of marine organisms for biological activity.

One of the most intensely studied invertebrate phyla is Porifera, with a steady stream of publications dating back to the late eighteen hundreds (16). Sponges are among the lowest and simplest forms of animal life. They are primitive multicellular animals that are more complicated than the protozoa and less complicated than the typical coelenterate. Some of the more interesting species, from a chemical standpoint, belong to the genus Dysidea. There are three classes in the phylum Porifera; Dysidea belongs to the class Demospongiae, order Dictyoceratida and family Disideidae. About one hundred different species of the class Demospongiae have been examined, yielding about two hundred new molecules, many of them novel and not observed in the terrestrial environment (12).

Most natural products chemists concentrate their search on secondary metabolites (e.g., terpenes, sterols, carotenoids, tyrosine derived bromo compounds, and bromopyrrole derivatives) leaving the primary metabolites (amino acids, carbohydrates, and

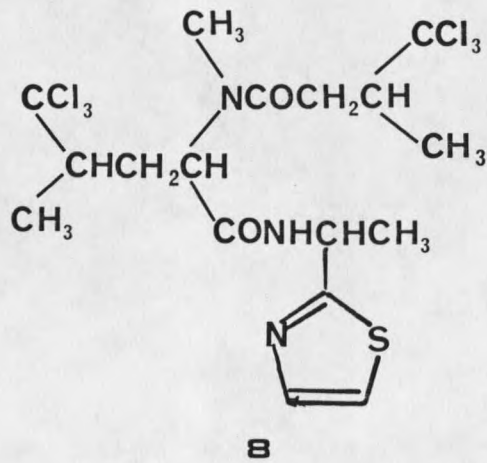
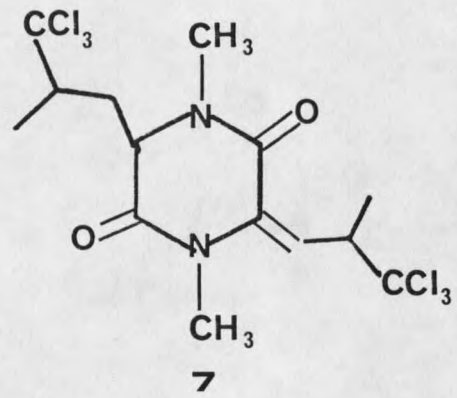
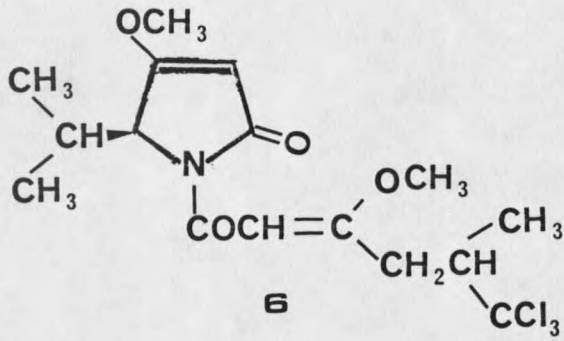
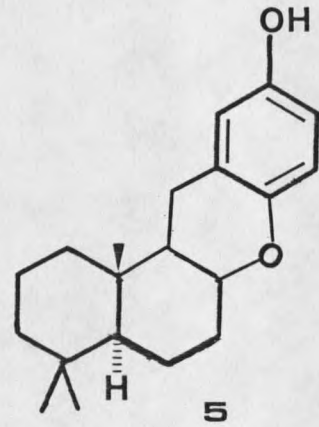
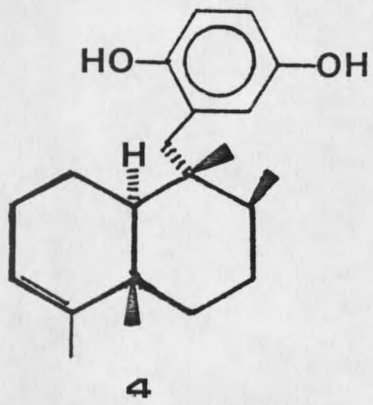
proteins) to the biochemists. Consequently, the following review of natural products will concentrate solely on secondary metabolites.

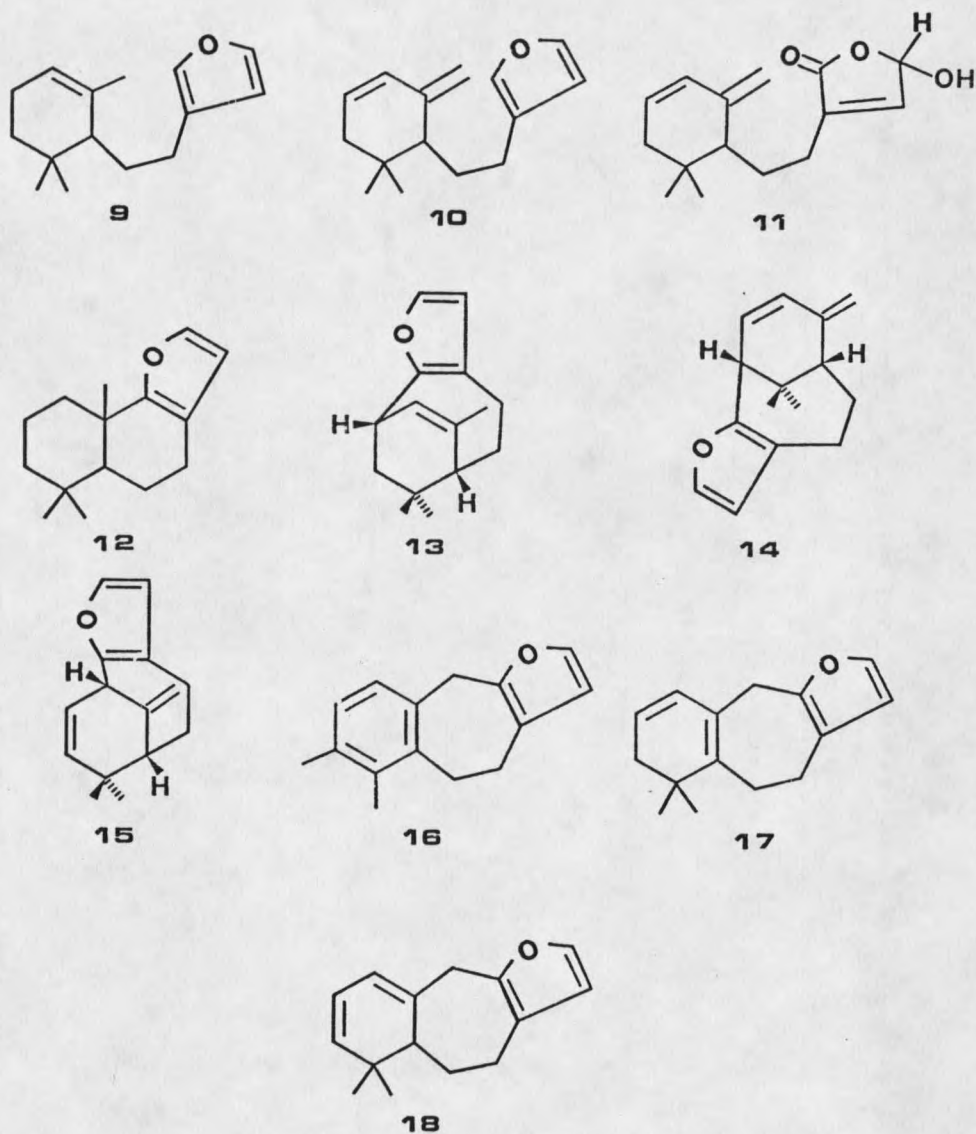
The secondary metabolites reported from species of Dysidea can be separated into three main classes: phenolic compounds, polychlorinated amino acid derived metabolites, and the terpenes. Avarol, 4, is a sesquiterpenoid hydroquinone isolated from Dysidea avara and has been shown to inhibit cell division in sea urchin eggs (17). The (+) enantiomer of chromazonarol, 5, was isolated from D. pallescens (18). Chromazonarol was originally isolated from Dictyopteris undulata, a brown seaweed (19).

Several polychlorinated amino acid derived metabolites were all isolated from Dysidea herbacea; however, they may actually be products of symbiotic blue-green algae or bacteria (20). The structure of dysidin (21), 6, was determined by single crystal X-ray analysis, while the diketopiperazine (22), 7, and dysidenin (23), 8, were identified by NMR, IR, UV, and MS studies.

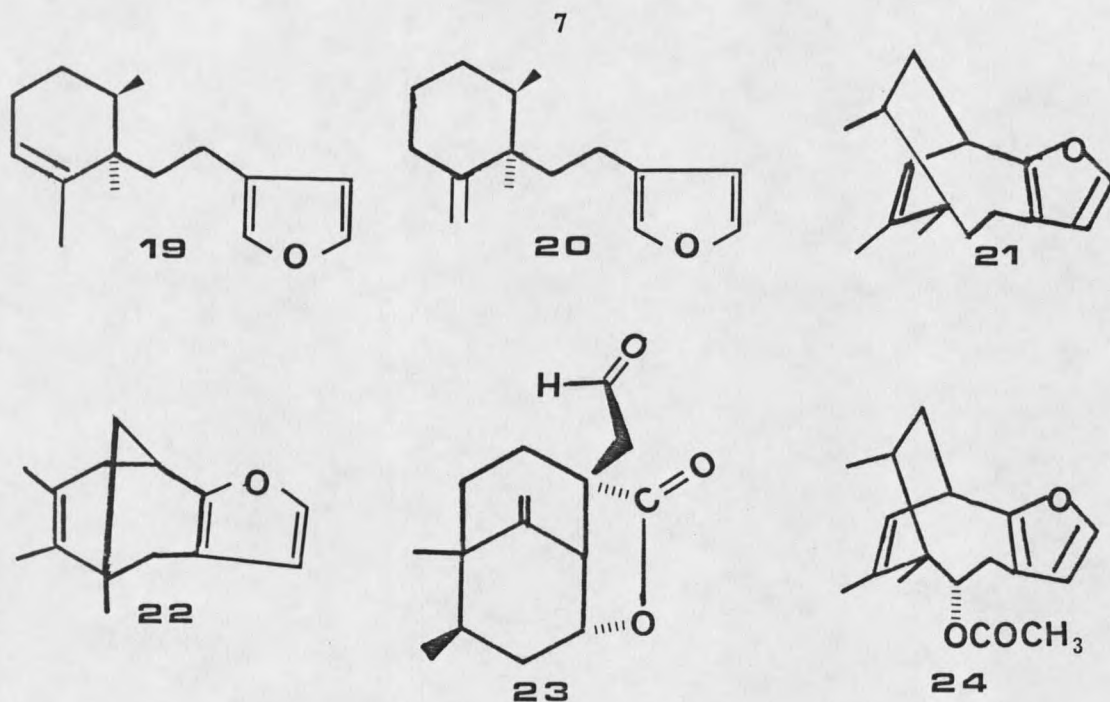
Terpenes are the most abundant secondary metabolites to be isolated from sponges. Most of these have been isolated from the order Dictyoceratida, to which Dysidea belongs. Sesquiterpenes are the most abundant terpenoids to be isolated from Dysidea species and all but one have a furan or oxidized furan ring.

A series of sesquiterpenes have been isolated from D. pallescens. Identification was made by chemical degradations, spectral data, biogenetic considerations, and establishment of the





interrelationship amongst them. Pallescensin-1, 9, -2, 10, and -3, 11, are of the known monocyclofarnesane type (24) while pallescensin A, 12, B, 13, C, 14, D, 15, E, 16, F, 17, and G, 18, are of previously unknown skeletons (25,26). Isolates from *D. fragilis* include, microcionin-2, 19, and -4, 20, (27) (originally isolated from *Microciona toxystila* (28)), nakafuran-8, 21, and -9, 22, (29)

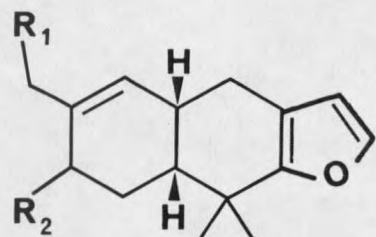


and upial, **23**, (**30**). All were identified by analysis of spectral data and chemical degradations. The 5-acetoxy nakafuran-8, **24**, was isolated from *D. etheria* and was also identified by spectral data and chemical degradations (31-33). Another series of sesquiterpenes has been characterized from *D. herbacea* (**20**). They are furodysin, **25**, thiolfurodysin, **26**, furodysin, **27**, and thiolfurodysin, **28**, (previously reported from an unidentified *Dysidea* species (34)), (4a^{S*},7R^{*},8aR^{*})-6,9,9-trimethyl-4,4a,7,8,8a,9-hexahydronaphtho[2,3-b]furan-7-ol, **29**, (4aR^{*},6R^{*},8aS^{*})-4,4,7-trimethyl-4,4a,5,6,8a,9-hexahydronaphtho[2,3-b]furan-6-ol, **30**, (4aR^{*},7R^{*},8aS^{*})-4,4,7-trimethyl-4,4a,5,6,8a,9-hexahydronaphtho[2,3-b]furan-6-ol, **31**, 4,4-dimethyl-7-methylene-cis-4,4a,5,6,7,8,8a,9-octahydronaphtho[2,3-b]furan, **32**, (2Z,4E,6E)-3-(4,8-dimethylnona-2,4,6-trienyl)furan, **33**, and euryfuran, **34**. All were identified using spectral data only. The probable precursor of furodysin and furodysin is spirodysin,

35, also isolated from D. herbacea (35). Furodysin and furodysinin were obtained by exposure of spirodysin to boron trifluoride etherate or heat (35).

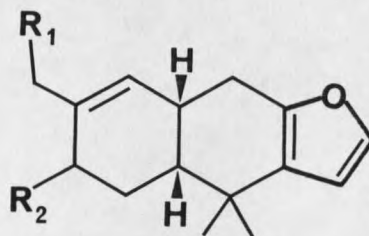
Until a few years ago, diterpenes isolated from the marine environment were quite rare. Recently, however, compounds have been identified from seaweeds (36-38), coelenterates of the orders Alcyonacea (39-43) and Gorgonacea (44-50) and from a few sponges (51). A series of diterpenes have been isolated from Dysidea amblia (52). Ambliol A, 36, dehydroambliol A, 37, ambliolide, 38, ambliofuran, 39, and ambliol B, 40, were identified by spectral data and chemical degradation. The sponge was steeped in methanol for two weeks at 0°C, homogenized, and then Soxhlet extracted with fresh methanol for two days. Ambliolide, therefore, was probably formed by air oxidation of ambliol A in the methanolic solution.

Sesterterpenes are very rare in terrestrial fauna and flora but are more common in the marine environment, especially in sponges. Disidein, 41, isolated from D. pallescens is a pentacyclic sesterterpene, whose identification was accomplished primarily by the mass spectral fragmentation pattern of the diester degradation product (53). Its biogenesis, as presented in Scheme II, is probably the proton catalyzed cyclization of the linear phenolic sesterterpene, 42. Furospogolide, 43, is a twenty one carbon terpene isolated from D. herbacea collected in the Red Sea (54). Tetranorsesterterpenes are among the most unusual terpenoid

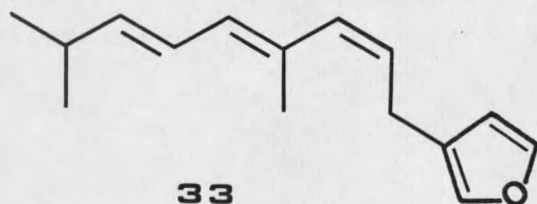


	$\underline{R_1}$	$\underline{R_2}$
25	H	H
26	SAc	H
29	H	βOH

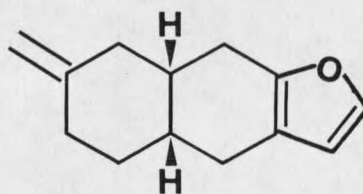
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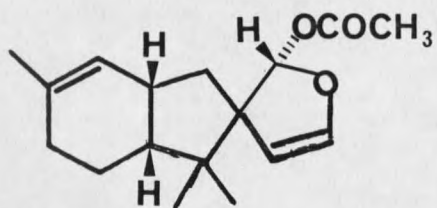
	$\underline{R_1}$	$\underline{R_2}$
27	H	H
28	SAc	H
30	H	βOH
31	H	αOH



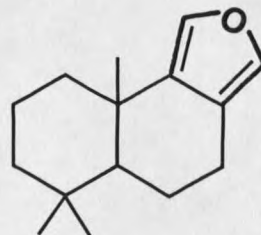
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