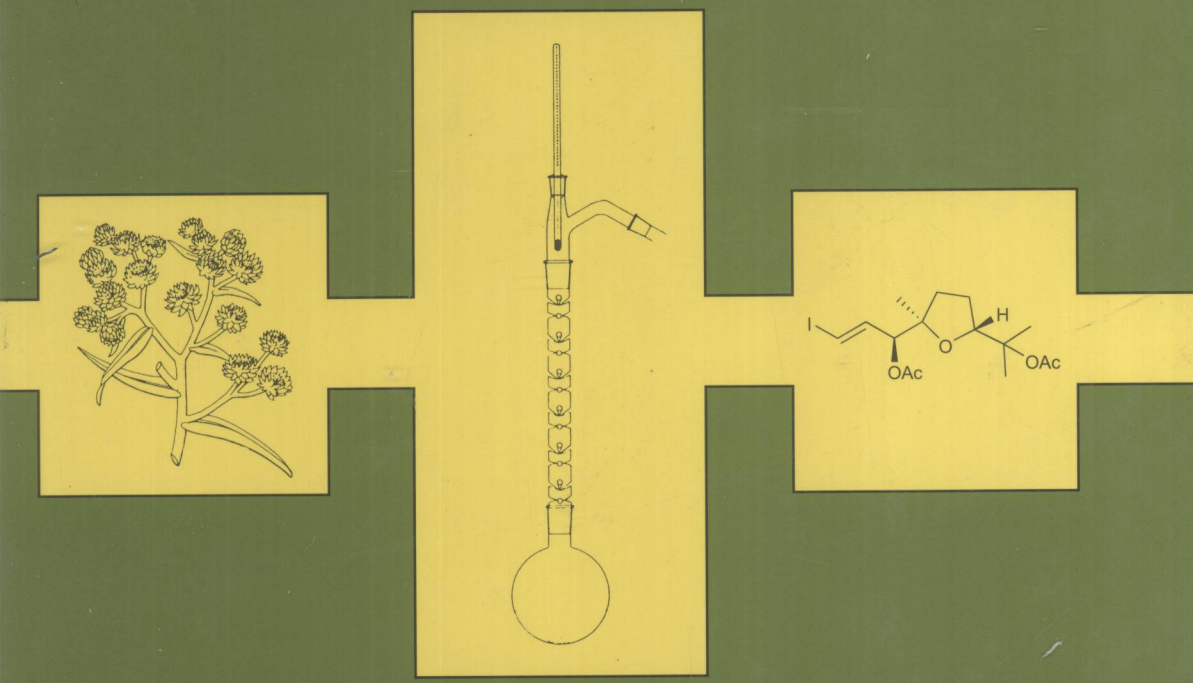
Studies in Natural Products Chemistry

Atta-ur-Rahman, FRS
Editor



Volume 35

Bioactive Natural Products (Part O)

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Edited by

Atta-ur-Rahman, FRS

International Center for Chemical and Biological Sciences,
(H.E.J. Research Institute of Chemistry),
University of Karachi, Karachi 75270, Pakistan

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PREFACE

This volume of "Studies in Natural Product Chemistry" represents the 35th of this series which I initiated, the first volume of which was published in 1988. It also represents the 14th volume devoted to bioactive natural products. The first seven reviews cover interesting recent developments in the field of bioactive marine natural products. The article by Little and coworker describes synthetic approaches to thyrsiferol and its analogues along with their biological activities. Marine invertebrates such as ascidians, sponges etc. are an important source of bioactive secondary metabolites. Ueda and coworker describe the isolation, structure elucidation, bioactivity and synthetic approaches to bioactive metabolites from marine invertebrates from Okinawan waters. Another article by Martinez and coworkers describes recent developments on antiviral products from marine sources, particularly from invertebrates such as sponges, tunicates, bryozoans and molluscs as well as from marine bacteria and cyanobacteria. Kalinin and coworkers present a comprehensive review on triterpene glycosides from sea cucumbers, including their functions and biological activities. The article by Liu and coworker focuses on new compounds with anti-tumor activity, enzyme inhibitors, anti-virus and other bioactive metabolites from marine microorganism including fungi, bacteria, actinomycetes and cyanobacteria reported between 2000 and 2005. The review by Maier is concerned with biological activities of sulfated glycosides from echinoderms. It particularly focuses on the structural characteristics and biological properties of saponins isolated from starfishes and sea cucumbers in the last five years with special reference to the structural elucidation and evaluation of antifungal, cytotoxic and antiviral properties. Another interesting review by Turk and coworkers is concerned with the synthesis, biological activity and potential uses of 3-akylpyridinium and 3-alkylpyridine compounds from marine sponges.

Novel Domino reactions involving acid-catalyzed intermolecular cyclization have been used as a viable synthetic tool for the stereospecific formation of different classes of polycyclic natural products. This is discussed in the review by Bhar and coworker by using these reactions for the synthesis of bioactive diterpenoids and alkaloids. About 1/3rd of all the diseases worldwide are due to infectious diseases. There have been therefore constant efforts to discover new anti-microbial compounds that have a broad range of activities especially against multidrug-resistant strains of microbes. The article by Mahady and coworkers focuses on medicinal plants and phytochemicals active against a wide range of gram-positive and gram-negative bacteria. The potential of medicinal plants of the Anthemideae tribe, both as potential antimicrobial crude drugs as well as sources for natural compounds that act as new anti-infectious agents, is described in the review by Martinez and coworkers. The article by Maurya reviews compounds with antiosteoporotic activity. Rodrigues and coworkers have presented an interesting review of plants with possible anxiolytic and/or hypnotic effects.

Another article by Daffre and coworkers reviews recent developments in the field of bioactive natural peptides including their characterization and biological activities. Many cyclic lipopeptide antibiotics have been discovered, mainly from microorganisms, algae and plants that often exhibit interesting and useful biological activities. The article by Hashizume and coworker describes the chemistry, biological activities and pharmacology of natural cyclic lipopeptides. A large number of *Salvia* diterpenoids have exhibited interesting biological activities e.g. anti-tuberculous, antitumor, antimicrobial, antibacterial, antileishmanial and antispasmolytic activities. This is discussed in the review by

Kabouche and coworkers. Finally Rezanka and coauthor present a comprehensive review on biologically active compounds of semi-metals such as boron, silicon, arsenic, selenium and tellurium.

It is hoped that this volume will be another useful addition to this Series and be of considerable interest to a large number of scientists working on bioactive compounds with potential use in medicine.

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Atta-ur-Rahman, *FRS*
Federal Minister/Chairman
Higher Education Commission/
Director, International Center for Chemical Sciences
Karachi, Pakistan

CONTRIBUTORS

Dmitry L. Aminin	Pacific Institute of Bioorganic Chemistry, Far East Division, Russian Academy of Sciences, 690022, Vladivostok, Russia
Sergey A. Avilov	Pacific Institute of Bioorganic Chemistry, Far East Division, Russian Academy of Sciences, 690022, Vladivostok, Russia
Paulina Bermejo Benito	Department of Pharmacology, Faculty of Pharmacy, University Complutense, 28040, Madrid, Spain
Shanta S. Bhar	Department of Chemistry, University of Mumbai, Santacruz(E), Mumbai-400098, India
Philippe Bulet	TIMC-IMAG, UMR UJF CNRS 5525, Team BioVie & Santé, France
Wing Lai Chan	Open Laboratory of Chirotechnology of the Institute of Molecular Technology for Drug Discovery and Synthesis and Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hong Kong, China
Sirlei Daffre	Department of Parasitology, ICB, University of São Paulo, São Paulo, SP, Brazil
Brian J. Doyle	Departments of Pharmacy Practice, and Medicinal Chemistry and Pharmacognosy, UIC PAHO/WHO Collaborating Centre for Traditional Medicine, University of Illinois at Chicago, College of Pharmacy, 833 South Wood St., Chicago, IL 60612, USA
Laurence Ehret-Sabatier	Institut Pluridisciplinaire Hubert Curien, Department of Analytical Sciences, ECPM-25 rue Becquerel, F-67087 Strasbourg Cedex 2, France
José Carlos F. Galduróz	Department of Psychobiology, Universidade Federal de São Paulo, Rua Botucatu, 862 – 1° andar Edificio Biomédicas CEP 04023-062, São Paulo, S.P., Brazil
Graziano Guella	Laboratory of Bioorganic Chemistry, Department of Physics, University of Trento, I-38050 Povo, Italy
Hideki Hashizume	Microbial Chemistry Research Center, 3-14-23, Kamiosaki, Shinagawa-ku, Tokyo, Japan

Yue Huang	Departments of Pharmacy Practice, and Medicinal Chemistry and Pharmacognosy, UIC PAHO/WHO Collaborating Centre for Traditional Medicine, University of Illinois at Chicago, College of Pharmacy, 833 South Wood St., Chicago, IL 60612, USA
Ahmed Kabouche	Laboratory of Therapeutic Substances, Faculty of Sciences, University of Mentouri-Constantine, 25000 Constantine, Algeria
Zahia Kabouche	Laboratory of Therapeutic Substances, Faculty of Sciences, University of Mentouri-Constantine, 25000 Constantine, Algeria
Vladimir I. Kalinin	Pacific Institute of Bioorganic Chemistry, Far East Division, Russian Academy of Sciences, 690022, Vladivostok, Russia
Rubén Martín Lazaro	Department of Pharmacology, Faculty of Pharmacy, University Complutense, 28040, Madrid, Spain
Yongcheng Lin	Department of Applied Chemistry and Department of Pharmacy, Zhongshan University, Guangzhou, P.R. China
R. Daniel Little	Department of Chemistry and Biochemistry, University of California, Santa Barbara, CA 93106, USA
Xiaohong Liu	Department of Applied Chemistry and Department of Pharmacy, Zhongshan University, Guangzhou, P.R. China
Tracie Locklear	Departments of Pharmacy Practice, and Medicinal Chemistry and Pharmacognosy, UIC PAHO/WHO Collaborating Centre for Traditional Medicine, University of Illinois at Chicago, College of Pharmacy, 833 South Wood St., Chicago, IL 60612, USA
Gail B. Mahady	Departments of Pharmacy Practice, and Medicinal Chemistry and Pharmacognosy, UIC PAHO/WHO Collaborating Centre for Traditional Medicine, University of Illinois at Chicago, College of Pharmacy, 833 South Wood St., Chicago, IL 60612, USA
Marta S. Maier	Departamento de Química Orgánica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Pabellón 2, Ciudad, Universitaria, (1428) Buenos Aires, Argentina
Ines Mancini	Laboratory of Bioorganic Chemistry, Department of Physics, University of Trento, I-38050 Povo, Italy

Maria Jose Abad Martinez	Department of Pharmacology, Faculty of Pharmacy, University Complutense, 28040, Madrid, Spain
Rakesh Maurya	Medicinal and Process Chemistry Division, Central Drug Research Institute, Chattar Manzil Palace, Lucknow-226001, India
Giuseppina Negri	Department of Psychobiology, Universidade Federal de São Paulo, Rua Botucatu, 862 – 1° andar Edificio Biomédicas CEP 04023-062, São Paulo, S.P., Brazil
Gisele A. Nishiguchi	Department of Chemistry and Biochemistry, University of California, Santa Barbara, CA 93106, USA
Yoshio Nishimura	Microbial Chemistry Research Center, 3-14-23, Kamiosaki, Shinagawa-ku, Tokyo, Japan
Luis Miguel Bedoya Del Olmo	Department of Pharmacology, Faculty of Pharmacy, University Complutense, 28040, Madrid, Spain
M.M.V. Ramana	Department of Chemistry, University of Mumbai, Santacruz(E), Mumbai-400098, India
T. Řezanka	Institute of Microbiology, Vídeňská 1083, Prague 142 20, Czech Republic
Eliana Rodrigues	Department of Psychobiology, Universidade Federal de São Paulo, Rua Botucatu, 862 – 1° andar Edificio Biomédicas CEP 04023-062, São Paulo, S.P., Brazil
Eliane G. Rodrigues	Experimental Oncology Unit, Federal University of São Paulo, São Paulo, SP, Brazil
Kristina Sepčic	Department of Biology, University of Ljubljana, SI-1000 Ljubljana, Slovenia
Changlun Shao	Department of Applied Chemistry and Department of Pharmacy, Zhongshan University, Guangzhou, P.R. China
Zhigang She	Department of Applied Chemistry and Department of Pharmacy, Zhongshan University, Guangzhou, P.R. China
K. Sigler	Institute of Microbiology, Vídeňská 1083, Prague 142 20, Czech Republic
Alexandra S. Silchenko	Pacific Institute of Bioorganic Chemistry, Far East Division, Russian Academy of Sciences, 690022, Vladivostok, Russia

Geetu Singh	Medicinal and Process Chemistry Division, Central Drug Research Institute, Chattar Manzil Palace, Lucknow-226001, India
Alberto Spisni	Department of Experimental Medicine, University of Parma, Parma, Italy
Valentin A. Stonik	Pacific Institute of Bioorganic Chemistry, Far East Division, Russian Academy of Sciences, 690022, Vladivostok, Russia
Ricardo Tabach	Department of Psychobiology, Universidade Federal de São Paulo, Rua Botucatu, 862 – 1° andar Edificio Biomédicas CEP 04023-062, São Paulo, S.P., Brazil
Luiz R. Travassos	Experimental Oncology Unit, Federal University of São Paulo, São Paulo, SP, Brazil
Tom Turk	Department of Biology, University of Ljubljana, SI-1000 Ljubljana, Slovenia
Katsuhiro Ueda	Department of Chemistry, Biology and Marine Sciences, University of the Ryukyus, Nishihara-cho, Okinawa 903-0213, Japan
Daisuke Uemura	Department of Chemistry, Graduate School of Science, Nagoya University Furo-cho, Chikusa, Nagoya 464-8602, Japan
Fang Xu	Department of Applied Chemistry and Department of Pharmacy, Zhongshan University, Guangzhou, P.R. China
Prem P. Yadav	Medicinal and Process Chemistry Division, Central Drug Research Institute, Chattar Manzil Palace, Lucknow-226001, India

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SYNTHETIC EFFORTS TOWARD, AND BIOLOGICAL ACTIVITY OF, THYRSIFEROL AND STRUCTURALLY-RELATED ANALOGUES

R. DANIEL LITTLE* AND GISELE A. NISHIGUCHI

Department of Chemistry and Biochemistry, University of California, Santa Barbara, Santa Barbara, CA 93106, USA

ABSTRACT: Marine natural products have played an important role in the discovery of novel biologically active compounds. Thyrsiferol was originally isolated off the coast of New Zealand from a marine red algae of the genus *Laurencia*. Several analogues having similar structural features have been identified and their biological properties investigated and identified. The array of activities is significant and includes: cytotoxic, anti-viral, and anti-tumor activity, the specific inhibition of protein serine/threonine phosphatase 2A, and apoptotic cell death in human leukemic T- and B-cell lines. Therefore, it is of interest to design and develop methods that would make these compounds accessible in the laboratory through synthetic organic chemistry. This review will discuss the biological properties and synthetic endeavors that have been used to access thyrsiferol and related analogues.

THYRSIFEROL AND ANALOGUES

Introduction

The marine ecosystem has revealed a multitude of bioactive natural products [1]. These marine-derived compounds are found primarily among soft corals, sponges, algae, and bacteria. Their therapeutic properties include significant activities in antitumor, anti-inflammatory, analgesia, allergy, and anti-viral assays. Although there is no single marine-derived natural product that has become a pharmaceutical drug as of 2004, a large number of compounds of marine origin are currently undergoing clinical trials. Bryostatin I (phase II), ecteinascidin 743 (phase II/III), and discodermolide (phase I), for example, are currently under clinical investigation for the treatment of cancer [2].

Hence, marine natural products represent a valuable foundation for the discovery of novel biologically active compounds. The potential therapeutic applications provided by these molecules along with their unique structural features have encouraged substantial scientific interest and investigations.

Squalene-derived polyethers encompass a unique class of marine natural products displaying a broad array of bioactivities [3]. These triterpenoids have been isolated primarily from *Laurencia*, a red alga found in several geographic locations. The next section of this chapter will serve to introduce the reader to the isolation, characterization, structural features, and pharmacological profiles of marine polyoxygenated triterpenoid ethers isolated from *Laurencia*.

Isolation and Characterization of Triterpenoids from *Laurencia*

Thyrsiferol [**1**, Fig. (**1**)] was isolated from the red algae *Laurencia thyrsifera* that was collected off the coast of New Zealand. It constitutes the first example of a triterpenoid squalene-derived polyether of marine origin containing a dioxabicyclo[4.4.0]decane B-C framework. The unique framework of thyrsiferol consists of a central *trans*-fused pyranopyran unit, an appended cyclic bromo ether and an aliphatic side chain connecting the central unit to a *trans*-tetrahydrofuran ring. Isolation and spectroscopic characterization of thyrsiferol was first carried out by Munro *et al* in 1978 [4]. An x-ray crystallographic analysis of its C_{18}-acetate derivative established its chemical structure and assigned each of the relative stereocenters. The absolute stereochemistry was not determined at the time of the isolation, but it was elucidated a few years later when venustatriol (**2**) was characterized [5].

The X-ray crystallographic analysis of thyrsiferol 18-acetate (**5**) revealed a strained tetrahydropyran ring C in a twist-boat conformation so as to avoid 1,3-diaxial interactions between the methyl groups at C_{10} and C_{15}. Initial biological studies of the natural product by Munro *et al* did not reveal any significant pharmacological activity [4].