TOPICS IN CURRENT CHEMISTRY 266

Volume Editors M. Larhed · K. Olofsson

Microwave Methods in Organic Synthesis

Springer

Microwave Methods in Organic Synthesis

Volume Editors: Mats Larhed · Kristofer Olofsson

With contributions by

P. Appukkuttan · K. Ersmark · E. Van der Eycken · C. O. Kappe
J. M. Kremsner · M. Larhed · I. Mutule · P. Nilsson · K. Olofsson
A. Stadler · C. R. Strauss · E. Suna · R. S. Varma · J. Wannberg
W. Zhang

Springer

The series *Topics in Current Chemistry* presents critical reviews of the present and future trends in modern chemical research. The scope of coverage includes all areas of chemical science including the interfaces with related disciplines such as biology, medicine and materials science. The goal of each thematic volume is to give the nonspecialist reader, whether at the university or in industry, a comprehensive overview of an area where new insights are emerging that are of interest to a larger scientific audience.

As a rule, contributions are specially commissioned. The editors and publishers will, however, always be pleased to receive suggestions and supplementary information. Papers are accepted for *Topics in Current Chemistry* in English.

In references *Topics in Current Chemistry* is abbreviated Top Curr Chem and is cited as a journal.

Visit the TCC content at springerlink.com

ISSN 0340-1022
ISBN-10 3-540-36757-8 Springer Berlin Heidelberg New York
ISBN-13 978-3-540-36757-4 Springer Berlin Heidelberg New York
DOI 10.1007/11535799

Springer is a part of Springer Science+Business Media

springer.com

Cover design: WMXDesign GmbH, Heidelberg
Typesetting and Production: LE-TEX Jelonek, Schmidt & Vöckler GbR, Leipzig

Printed on acid-free paper 02/3100 YL – 5 4 3 2 1 0

266
Topics in Current Chemistry

Topics in Current Chemistry

Recently Published and Forthcoming Volumes

Atomistic Approaches in Modern Biology
From Quantum Chemistry to Molecular Simulations
Volume Editor: Reiher, M.
Vol. 268, 2007

Glycopeptides and Glycoproteins
Synthesis, Structure, and Application
Volume Editor: Wittmann, V.
Vol. 267, 2007

Microwave Methods in Organic Synthesis
Volume Editors: Larhed, M., Olofsson, K.
Vol. 266, 2006

Supramolecular Chirality
Volume Editors: Crego-Calama, M., Reinhoudt, D. N.
Vol. 265, 2006

Radicals in Synthesis II
Complex Molecules
Volume Editor: Gansäuer, A.
Vol. 264, 2006

Radicals in Synthesis I
Methods and Mechanisms
Volume Editor: Gansäuer, A.
Vol. 263, 2006

Molecular Machines
Volume Editor: Kelly, T. R.
Vol. 262, 2006

Immobilisation of DNA on Chips II
Volume Editor: Wittmann, C.
Vol. 261, 2005

Immobilisation of DNA on Chips I
Volume Editor: Wittmann, C.
Vol. 260, 2005

Prebiotic Chemistry
From Simple Amphiphiles to Protocell Models
Volume Editor: Walde, P.
Vol. 259, 2005

Supramolecular Dye Chemistry
Volume Editor: Würthner, F.
Vol. 258, 2005

Molecular Wires
From Design to Properties
Volume Editor: De Cola, L.
Vol. 257, 2005

Low Molecular Mass Gelators
Design, Self-Assembly, Function
Volume Editor: Fages, F.
Vol. 256, 2005

Anion Sensing
Volume Editor: Stibor, I.
Vol. 255, 2005

Organic Solid State Reactions
Volume Editor: Toda, F.
Vol. 254, 2005

DNA Binders and Related Subjects
Volume Editors:Waring, M. J., Chaires, J. B.
Vol. 253, 2005

Contrast Agents III
Volume Editor: Krause,W.
Vol. 252, 2005

Chalcogenocarboxylic Acid Derivatives
Volume Editor: Kato, S.
Vol. 251, 2005

New Aspects in Phosphorus Chemistry V
Volume Editor: Majoral, J.-P.
Vol. 250, 2005

Volume Editors

Prof. Mats Larhed

Department of Medicinal Chemistry
Organic Pharmaceutical Chemistry; BMC
Uppsala University
Box 574
SE-75123 Uppsala, Sweden
mats@orgfarm.uu.se

Dr. Kristofer Olofsson

Medicinal Chemistry
Biolipox AB
Berzelius Väg 3, plan 5
SE-17165 Solna, Sweden
kristofer.olofsson@biolipox.com

Editorial Board

Topics in Current Chemistry Also Available Electronically

For all customers who have a standing order to Topics in Current Chemistry, we offer the electronic version via SpringerLink free of charge. Please contact your librarian who can receive a password or free access to the full articles by registering at:

springerlink.com

If you do not have a subscription, you can still view the tables of contents of the volumes and the abstract of each article by going to the SpringerLink Homepage, clicking on "Browse by Online Libraries", then "Chemical Sciences", and finally choose Topics in Current Chemistry.

You will find information about the

- Editorial Board
- Aims and Scope
- Instructions for Authors
- Sample Contribution

at springer.com using the search function.

Preface

We are delighted to present this volume with contributions from some of the most renowned and experienced microwave chemists today.

The delivery and introduction of energy has been closely connected with the discovery and investigation of new chemistry. It is with pleasure that we have seen an increased use of microwave irradiation over the years and we hope that this volume will reflect the current interest in expanding the scope of microwave applications in both organic and medicinal chemistry. One important explanation behind the growth of microwave-enhanced chemistry has been the introduction of dedicated microwave reactors.

As a result of this development we are proud to present a diverse set of reviews. Apart from chapters spanning the scope that is usually associated with microwave methods, such as heterocyclic chemistry – an intriguing, but frustratingly diverse field that is excellently presented in one of the reviews – and transition metal-catalyzed reactions, we also present a review on microwave-assisted natural product chemistry, a topic that is of high interest and neither often nor widely covered. A contribution on microwave-accelerated synthesis of protease inhibitors underlines the usefulness of microwave heating in medicinal chemistry and a review of fluorous microwave chemistry highlights the importance of the combination of high-speed reactions and quick separations. Two separate chapters on scaled-up microwave reactions and green and sustainable chemistry give an overview of aspects of microwave chemistry that might be of great use in both industrial and small-scale applications.

We would like to take this opportunity to express our sincere gratitude to the contributors of this volume for their valuable time and efforts. We believe that the presented work will further promote the use of controlled microwave heating in both academia and industry.

Uppsala, September 2006 Mats Larhed and Kristofer Olofsson

Contents *Topics Heterocyclic Chemistry Vol. 1*

Microwave-Assisted Synthesis of Heterocycles

Volume Editors: Erik Van der Eycken · Oliver Kappe
ISBN: 3-540-30983-7

Contents

Top Curr Chem (2006) 266: 1–47
DOI 10.1007/128_051

Published online: 8 July 2006

Microwave-Assisted Natural Product Chemistry

Prasad Appukkuttan[1] · Erik Van der Eycken[2] (✉)

[1]Department of Medicinal Chemistry, Organic Pharmaceutical Chemistry, BMC, Uppsala University, P.O. Box. 574, SE 751 23 Uppsala, Sweden

[2]Department of Chemistry, University of Leuven, Celestijnenlaan 200F, B-3001 Leuven, Belgium
erik.vandereycken@chem.kuleuven.be

Abstract An overview of the application of microwave irradiation in natural product synthesis is presented, focusing on the developments in the last 5–10 years. This contribution covers the literature concerning the total synthesis of natural products and their analogues, the synthesis of alkaloids and the construction of building blocks of interest for natural product synthesis. As microwave irradiation appeared on the scene only recently, we are at an early stage of its application in natural product chemistry, even though some nice examples have been communicated recently. The application of dedicated microwave instruments as well as domestic microwave ovens is discussed, giving emphasis to the microwave-enhanced transformations.

Keywords Alkaloids · Microwave irradiation · Natural products · Steroids · Total synthesis

Abbreviations

Boc	*tert*-butoxycarbonyl
CNS	central nervous system
m-CPBA	*m*-chloroperbenzoic acid
CTH	catalytic transfer hydrogenation
o-DCB	*o*-dichlorobenzene

DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
HIV	human immunodeficiency virus
IEDDA	inverse electron-demand Diels–Alder
PEA	phenethylamine
PMB	*p*-methoxybenzyl
PTSA	*p*-toluene sulfonic acid
RCAM	ring-closing alkyne metathesis
RCM	ring-closing metathesis
TBAF	*N*,*N*,*N*,*N*-tetrabutylammonium fluoride
TBDMS	*tert*-butyl dimethyl silyl
THF	tetrahydrofuran

1 Introduction

For many years the (total) synthesis of natural products has inspired many chemists to develop synthetic approaches that many times are conceptually real beauties. Nature is an inexhaustible source of diverse chemical compounds and many of them possess interesting biological activities. That is exactly what makes natural products so important for mankind: they represent a nearly unlimited reservoir of precious starting compounds for the development of new medicines by combinatorial chemistry, high throughput screening and medicinal chemistry. Taxol and penicillin are two of the striking examples of what nature is offering us.

In contrast with the enormous effort directed at natural product synthesis, the application of microwave irradiation in this field is rather scarcely investigated, and a systematic use of this technique for most of the conversions in a (total) synthesis sequence is still a challenging target. We have just reached dawn in the development of microwave-assisted natural product synthesis, although unquestionably, some beautiful examples have already been described.

We attempted to give an overview of the last 5–10 years and via different searches we tried to retrieve the relevant literature, which was not an obvious task. Nevertheless, we hope that we have covered as much as possible of the published research, although obviously some work will be missing. For the sake of clarity we divided the collected literature into five subsections: (1) Total synthesis of various classes of natural products; (2) Synthesis of alkaloids, as this is a clear and well-defined subcategory of natural products; (3) Modifications of natural products (i.e. synthesis starting from natural products); (4) Synthesis of unnatural analogues of natural products (i.e. synthesis not starting from natural products) and finally; (5) Synthesis of interesting building blocks for natural product synthesis. We decided not to

incorporate peptide chemistry and related topics in this work, as we judged that this belongs to a separate field from natural product chemistry. Moreover, the literature dealing with the application of microwave irradiation in peptide synthesis is, to date, relatively scarce.

As dedicated microwave instruments appeared rather recently on the market and several interesting applications of microwave irradiation for natural product synthesis were described applying domestic microwave ovens, we decided to include also research performed with domestic ovens, although one could argue that some of these experiments lack reproducibility. On the other hand, the development of safe and reproducible synthetic routes for domestic instruments, which are cheap and at the disposal of every research lab all over the world, is a challenge worth the task as this should tremendously speed up the introduction of microwave irradiation in organic synthesis in general.

2 Total Synthesis of Various Classes of Natural Products

Natural products are undoubtedly the most challenging class of compounds for total synthesis, due to their structural diversity and complexity as well as the interesting biological activity inherent in many of them. During the last decades many examples of beautifully designed synthetic approaches have been published, using the plethora of available reagents and methods of the time. However, as microwave irradiation appeared on the scene only recently, its application has not been used in full strength for natural product synthesis, although some attractive examples have appeared in the recent literature.

Turrianes [1] are naturally occurring cyclophane derivatives (Fig. 1). These compounds are of particular interest as they are proven to be potent DNA cleaving agents under oxidative conditions [2–4] when administered in the presence of copper ions. An ingenious total synthesis has been elaborated by A. Fürstner et al. [5], applying a Ring Closing Metathesis (RCM) [6–10] or a Ring Closing Alkyne Metathesis (RCAM) [11–14].

The sequence starts with the synthesis of the sterically hindered biaryl entity, formed by the Grignard reaction, followed by further conversions

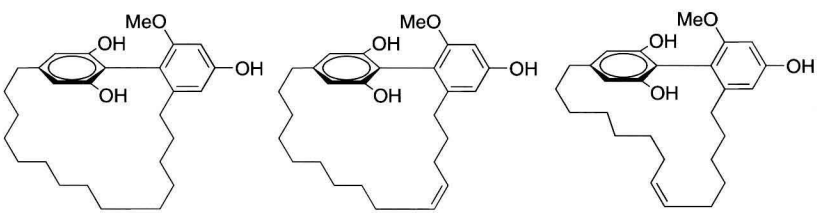
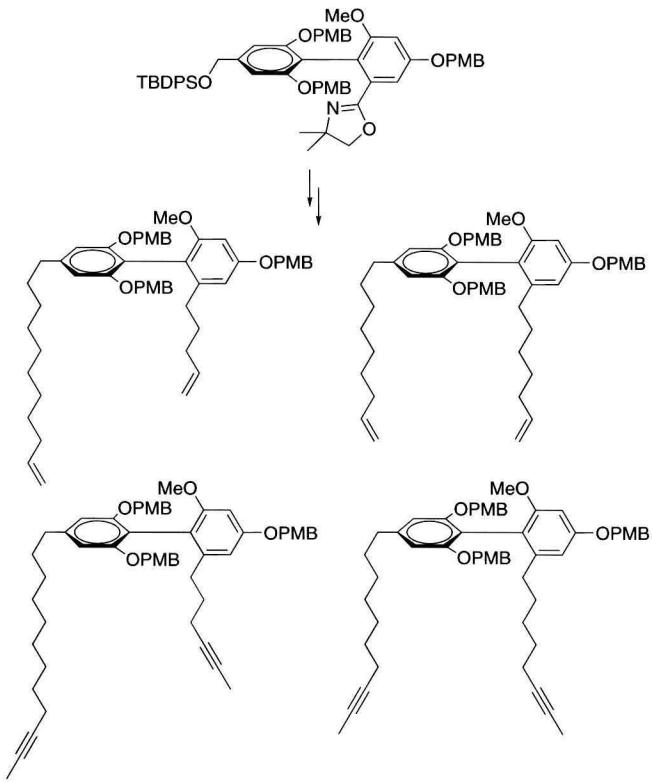


Fig. 1 Naturally occurring cyclophane derivatives belonging to the Turriane family

allowing the introduction of two different unsaturated tethers for macrocyclization (Scheme 1). PMB-ethers (PMB = *p*-methoxybenzyl) were found to be compatible protective groups with the diverse reaction conditions *en route* to the final natural compounds. Macrocyclization was investigated via RCM starting from the alkene-tethered substrates applying the Grubbs catalyst or a phenylindenylidene analogue in refluxing CH_2Cl_2. As expected, these compounds cyclize smoothly to the corresponding 20-membered rings, although unfortunately in a mixture of both stereoisomers with the undesired (*E*)-alkene prevailing (Fig. 2).

This problem could be circumvented when RCAM was applied starting from the acetylene-tethered compounds, as the initially formed cycloalkynes could be stereoselectively reduced to the *Z*-alkenes using Lindlar hydrogenation (Fig. 2). For the RCAM two different catalyst systems were evaluated: *t*-$(BuO)_3W \equiv CCMe_3$ in toluene at 80 °C for 16 h and $Mo(CO)_6/F_3CC_6H_4OH$ in chlorobenzene at 135 °C for 4–6 h, resulting in good yields of the cyclized products. However, the reaction times were rather long and, as in the



Scheme 1 Synthesis of the biaryl precursors for RCM and RCAM

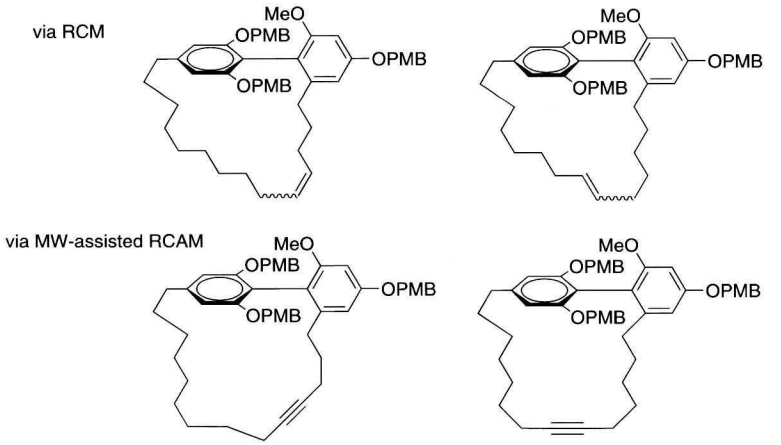
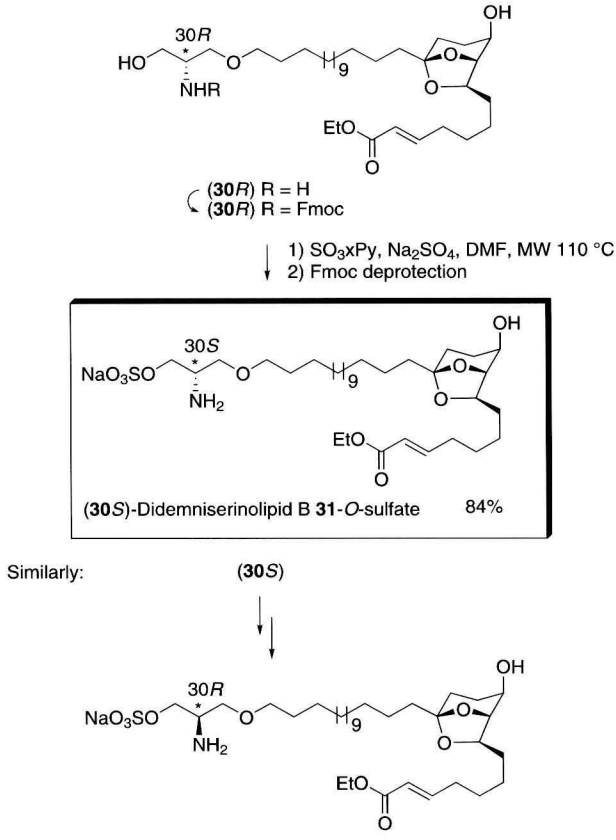


Fig. 2 Macrocycles formed via RCM or microwave-assisted RCAM

latter case a high temperature was required, the authors tried out focused microwave irradiation in chlorobenzene at 150 °C.

This resulted in a dramatic decrease of the reaction time to a mere 5 min with comparable yields. The sequence was accomplished upon full (H_2/Pd – C) or partial and stereoselective reduction (Lindlar catalyst) of the double bond and cleavage of the PMB-ethers.

Another interesting class of natural products is the Serinol marine compounds isolated from Tunicate *Didemnum* sp. (Scheme 2). These structures shows promising biological activity as for example HIV-1 integrase inhibitors [15]. All these Serinolipids possess a unique serinol component and a 6,8-dioxabicyclo[3.2.1]octane core structure, which make them attractive targets for synthesis. S.V. Ley et al. [16] developed a multistep sequence starting from D-(or L-) serinol and a known butanediacetal (BDA)-protected chiral building block [17] to prove by synthesis the absolute and relative stereochemistry of (+)-Didemniserinolipid B [18]. After the accomplishment of the sequence, comparison of the ^{1}H NMR spectra of the synthesized compound with that of the natural product revealed that the peaks associated with the Serinol unit of the molecule were shifted significantly up field. In view of the fact that related natural products were sulfated on the Serinol unit, the authors believed that the structure should be reassigned as the monosulfated one. This was supported by re-measurements of the HR-FAB-MS spectrum. Therefore, the authors started to synthesize the monosulfate derivative (Scheme 2). To achieve monosulfation, the amino group was protected as the fluorenylmethoxycarbonyl (Fmoc) group. However, standard sulfation conditions (SO_3 × Py or SO_3 × NMe_3 in DMF, 1,4-dioxane and/or pyridine at 20–100 °C) failed to derivatize the diol and only starting material was obtained. On the contrary, when the reaction was performed with the aid



Scheme 2 Microwave-assisted synthesis of (30*R*)- and (30*S*)-Didemniserinolipid B 31-*O*-sulfate

of a dedicated microwave instrument, treatment of the diol (30*R*) with 1 equiv SO_3 × Py at 110 °C for 1 h provided the desired 31-*O*-sulfate as the major product. Deprotection of the Fmoc group under mild conditions (piperidine in DMF, rt) furnished 31-*O*-sulfate (30*S*). Similarly the (30*R*) diastereomer was synthesized for spectral comparison. It was shown that the spectroscopic data as well as the specific rotation of the (30*S*) diastereomer were in full agreement with those of the natural product, establishing a final proof for the structure of the natural product.

The two novel chromane derivatives rhododaurichromanic acids A and B [19] as well as the known Daurichromenic acid [20] are members of a new interesting class of anti-HIV agents and are therefore attractive synthetic targets (Scheme 3). These compounds were successfully synthesized by Z. Jin et al. [21] in good overall yields, applying a microwave-assisted tandem condensation and intramolecular S_N2'-type cyclization to form the