

# “Metathesis in Natural Product Synthesis”

Edited by Janine Cossy, Stelios Arseniyadis and Christophe Meyer (ESPCI, Paris, France), Wiley-VCH, Weinheim, Germany, 2010, 412 pages, ISBN: 978-3-527-32440-8, £115, €144, US\$205 (Print version); e-ISBN: 9783527629626, doi:10.1002/9783527629626 (Online version)

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“Metathesis in Natural Product Synthesis” subtitled ‘Strategies, Substrates and Catalysts’ benefits from a foreword by Robert H. Grubbs, joint recipient of the 2005 Nobel Prize in Chemistry for his work on the development of the metathesis method in organic synthesis. This timely publication focuses on developments in the synthesis of natural products which use as a key step the versatile metathesis reaction catalysed by transition metal complexes, especially ruthenium. While reference to metathetic pathways in obtaining natural products or their mimics is encountered sporadically in many books and articles which primarily deal with metathesis as a catalytic process, to the best of our knowledge this is the first monograph devoted entirely to a systematic treatment of metathesis applications in natural product synthesis. The field has direct relevance for the drug industry, and currently receives a great deal of attention due to the pharmacological activity found in many natural compounds. Therefore, this volume promises to be a very helpful resource.

## Total Synthesis of Natural Compounds

Taking full advantage of the wide range of synthetic possibilities offered by alkene and alkyne metathesis, the book illustrates how a great variety of natural compounds with small, medium or macrocycles can now be routinely obtained through considerably shorter and more efficient protocols than in the past. A major problem in total synthesis of natural compounds is the numerous reaction steps needed, resulting in a modest overall yield and proceeding only with moderate to low product selectivity. The ability of metathesis to selectively lead to a desired biologically active stereoisomer or enantiomer makes it an efficient approach which can considerably improve the outcome of otherwise difficult natural product syntheses. The advances showcased in the book have been stimulated by the parallel introduction of a

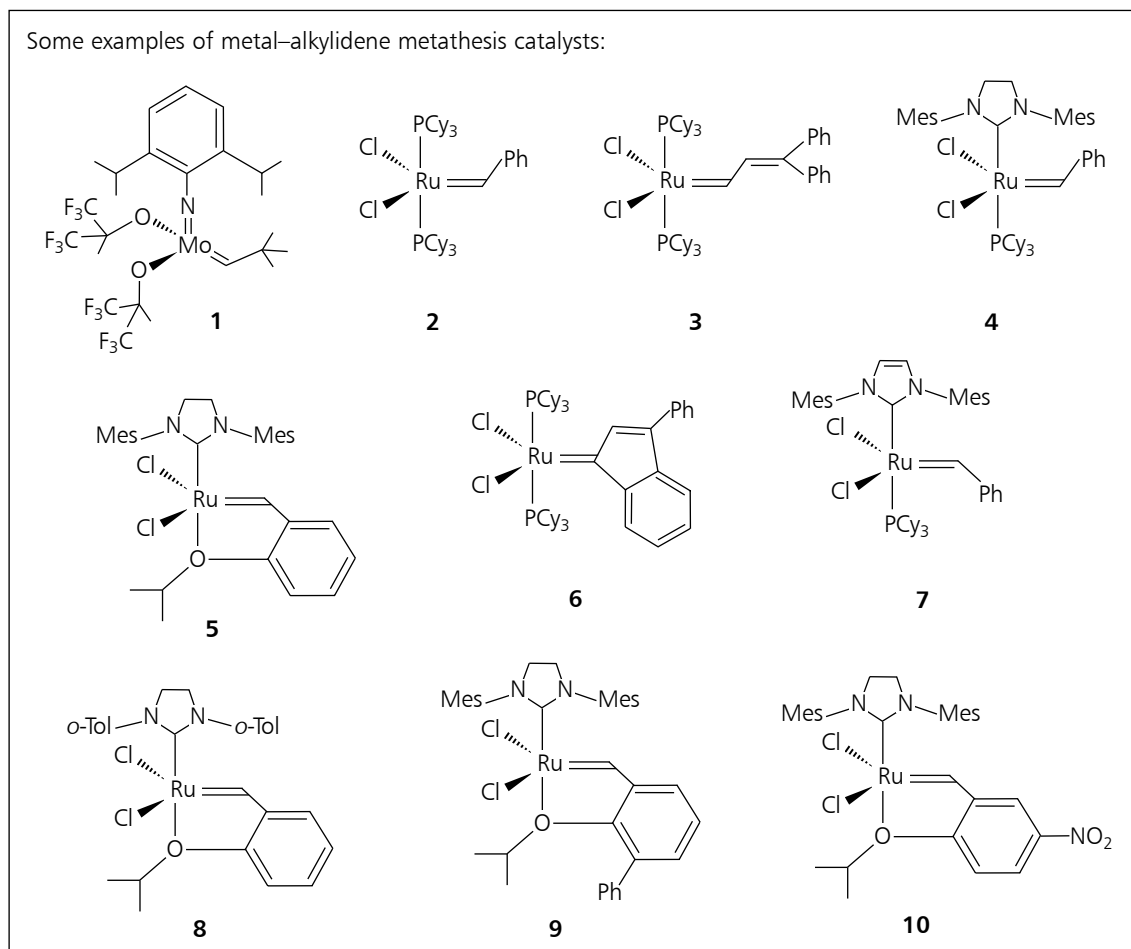
wide variety of well-defined metathesis catalysts (1–10), many of which are ruthenium-based systems which tolerate a range of functional groups and reaction conditions.

After an inspiring foreword by Grubbs, a detailed table of contents and the concise preface by the editors, the book begins with a list of structures of the main catalysts involved in the synthetic work, which is fully cross-referenced with the book's index. Then, in thirteen chapters and roughly 400 pages, it progresses to an in-depth look at synthetic strategies which use metathesis reactions as crucial steps in sequential and cascade sequences applied to natural product synthesis. The information is up to date and is organised by the editors according to carbocycle size, the nature of the heteroatom incorporated into the heterocyclic moiety of the targeted compounds, the type of metathesis reaction (ring-closing

metathesis (RCM), cross-metathesis (CM), ring-opening metathesis (ROM), etc.) and the techniques used. The first chapters report on RCM as the first, and still most widely used, type of metathesis reaction for natural product synthesis.

In Chapter 1, Nicolas Blanchard and Jacques Eustache (Université de Haute Alsace, France) depict the synthesis of naturally occurring molecules focusing on the construction by RCM of medium-sized carbocycles (five- to ten-membered rings) and complex spiro-, bicyclic or polycyclic structures. In this chapter the reader quickly becomes acquainted with a plethora of natural compounds having diverse pharmacological properties that can be accessed easily by RCM. Novel reaction sequences such as [3,3]-sigmatropic rearrangement/RCM and RCM/fragmentation are also discussed as efficient routes to natural compounds.

Some examples of metal-alkylidene metathesis catalysts:



### Biologically Active Compounds

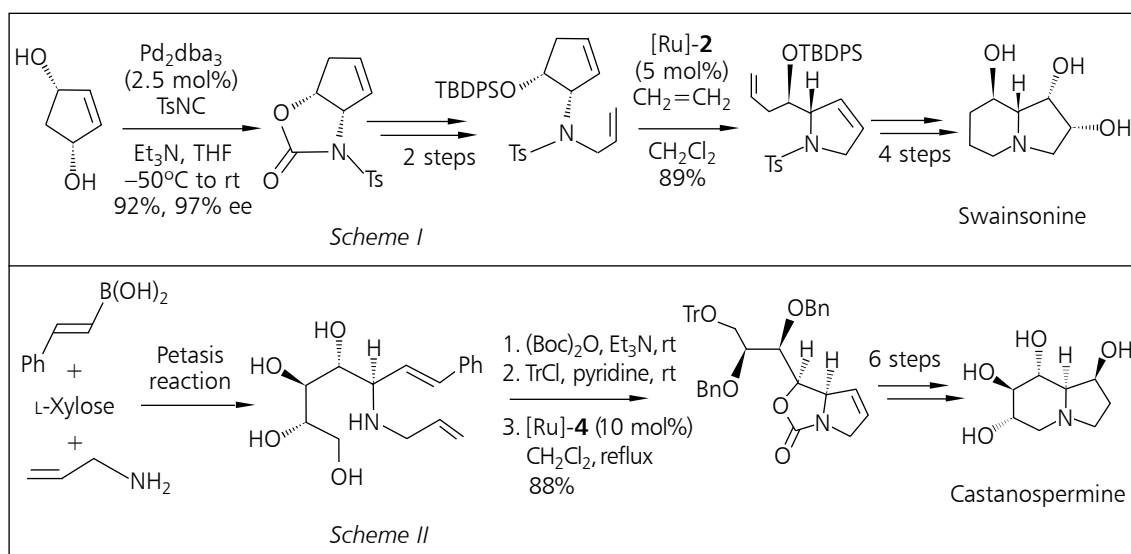
An impressive array of products with five- and six-membered nitrogen heterocycles is illustrated in the next chapter, by the well-known group of authors Sebastiaan (Bas) A. M. W. van den Broek, Silvie A. Meeuwissen, Floris L. van Delft and Floris P. J. T. Rutjes (Radboud Universiteit Nijmegen, The Netherlands). Several important alkaloid families (pyrrolidine, pyrrolizidine, piperidine, indolizidine and quinolizidine), many of them recognised for their potent and versatile biological activity are shown to become available by efficient ruthenium-catalysed RCM, carried on appropriate diene substrates, to yield the five- and six-membered heterocyclic units incorporated into their respective molecules. See for instance swainsonine (**Scheme I**) and castanospermine (**Scheme II**). The less frequently encountered cyclisation by RCM to seven- and eight-membered *N*-heterocycles, as in balanol and manzamine A, respectively, is also highlighted.

Interesting applications of RCM in synthesis of natural products containing medium-sized *O*-heterocycles are introduced by Jon D. Rainier (University of Utah, USA) in Chapter 3. Supported by beautiful graphic representation of intricate chemical structures, the illustrated compounds include members of the polycyclic ether family (brevetoxins, ciguatoxins, etc.), the laurencins, and heliannuol A, along with representatives from the eunicellin diterpene family. Typical specimens for eight-membered ring lactones

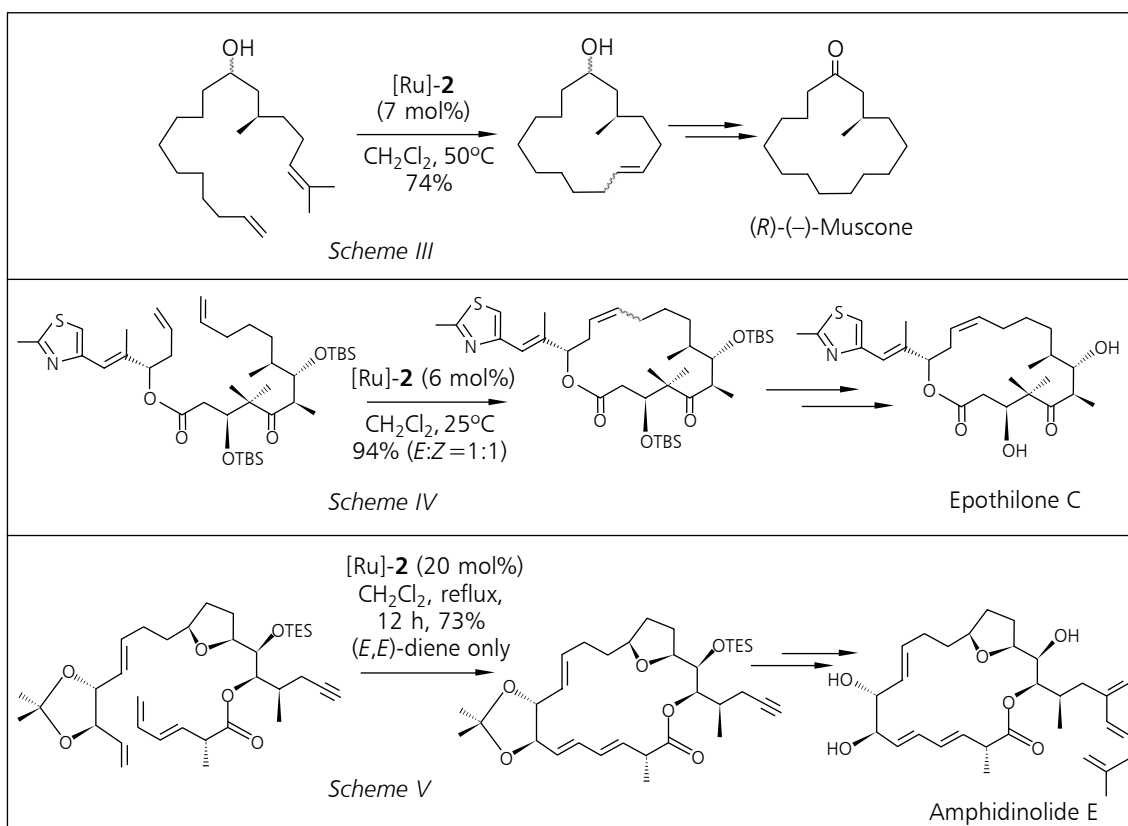
(octalactin A) and ten-membered ring lactones (microcarpalide and herbarumin III) are presented as well. Additionally, data on the related carbonyl-olefination cyclisation using a stoichiometric titanium reagent are included.

In Chapter 4, Christopher D. Thomas and Paul R. Hanson (University of Kansas, USA) demonstrate the role played by RCM in the construction of sultone and phosphate heterocycles, thus providing an effective method in which both sulfur and phosphorus serve as temporary tethers to mediate several selective transformations. The sultone motif has been applied by Janine Cossy and coworkers in the synthesis of the originally proposed structure of ( $\pm$ )-mycothiazole to access 1,3-dienols possessing an internal *Z*-olefin. Further, Hanson *et al.* used phosphate tethers in the construction of asymmetric 1,3-*anti*-diols to build the C<sub>1</sub>–C<sub>14</sub> and C<sub>15</sub>–C<sub>30</sub> subunits of dolabelide.

The next chapter, coauthored by Ana Gradillas and Javier Pérez-Castells (Universidad CEU San Pablo, Spain), presents the RCM-based synthesis of natural products containing macrocyclic cores. Following the biogenetic classification, the authors address the synthesis of biologically important macrolactones, as divided into the main family groups: resorcinylic, salicylates, other antibiotic macrolides, macrocyclic musks (**Scheme III**), epothilones (**Scheme IV**), amphidinolides (**Scheme V**), other polyketides and natural cyclophanes, and then terpenoids, followed by the macrocycles resulting from amino acid



Schemes I and II. Ruthenium-based ring-closing metathesis in synthesis of swainsonine and castanospermine



Schemes III–V. Macrocycle access by ruthenium-based ring-closing metathesis strategy

metabolism (lactams, depsipeptides and alkaloids); and finally the macrocyclic glycolipids. Examples of macrolactone synthesis are described, revealing important aspects concerning control of the RCM process; in doing so, novel insights into factors affecting RCM, such as the influence of the catalyst, solvent, temperature and reactant concentrations are provided.

#### Development of Novel Synthetic Strategies

Extension of ene-yne metathesis to the synthesis of various natural products is concisely outlined by Miwako Mori (Hokkaido University, Japan) in Chapter 6. Starting from the first application of ene-yne RCM to the total synthesis of (–)-stemoamide, the author describes the development of this delicate strategy for production of a broad range of important natural compounds such as (–)-longithorone A, allocolchicine, (–)-galanthamine, (+)-anthramycin, lancifodilactone G, etc. Next, the alternative formation of 1,3-dienes from alkyne and ethylene using

cross-metathesis is demonstrated for the synthesis of anolignans, vitamin D receptor antagonists and amphidinolide E. Finally, transition metal-catalysed, in particular ruthenium-, palladium- and platinum-catalysed, skeletal rearrangements and reorganisations are illustrated for the formal total synthesis of streptorubin B, metacycloprodigosin, roseophilin and related compounds.

The following chapter, by Paul W. Davies (University of Birmingham, UK) examines the meaningful application of ring-closing alkyne metathesis (RCAM) in natural product synthesis. After introductory remarks on RCAM, the author overviews the catalyst systems, emphasising the potential of RCAM-based strategies for obtaining many biologically relevant molecular targets, in particular diaminosuberic acid derivatives, oligopeptides, glycophanes, cyclic  $\beta$ -turn mimics, lantibiotic nisin Z mimics and alkyne-linked glycoamino acids. The author describes two major strategic routes using RCAM macrocyclisation: (a) RCAM/hydrogenation protocols for the synthesis of macro-

cyclic musks, prostaglandin lactones, sophorolipid lactones, epothilone A, cruentaren A, latrunculins and myxovirescin; and (b) RCAM/sequential transformations for the synthesis of citreofuran by RCAM/cycloisomerisation and of amphidinolide V by RCAM/ene-yne metathesis (Scheme VI). The RCAM approach can accommodate a broad range of functionalities, comparable to RCM. However, further developments in catalyst design are needed in order to improve understanding and broaden the applicability of the RCAM strategy for natural product synthesis.

An excellent account of temporary silicon-tethered RCM (TST-RCM) reactions, mainly promoted by ruthenium-based catalysts, is to be found in Chapter 8, written by P. Andrew Evans (University of Liverpool, UK). This approach avoids the problems frequently associated with entropically unfavourable reactions and offers a practical way to achieve target-directed synthesis. Examples of O-SiR<sub>2</sub>-O tethered substrates (symmetrical and unsymmetrical silaketals), O-SiR<sub>2</sub>-C tethered substrates (allyl- and vinylsiloxanes), and enyne and dienyne TST-RCM, are given to illustrate the versatility of this strategy for the synthesis of challenging structures encountered in total synthesis protocols.

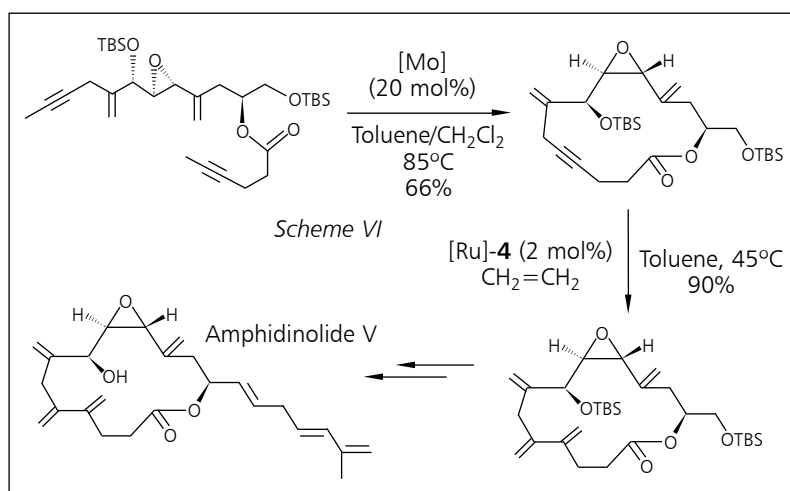
Applications of RCM involving a relay process (RRCM), initiated at a remote site within the substrate, are surveyed in Chapter 9 by Thomas R. Hoye and Junha Jeon (University of Minnesota, USA). After a basic presentation of the relay concept, the authors deal with the first successful use of RRCM in natural product synthesis (oximidine III), then expand the

discussion of the efficiency of RRCM to the synthesis of new valuable products such as longithorones, trienomycin, mucocin, phoslactomycin B, tricholomenyn A, asperpentyn and harveynone. For a better understanding of this innovative technique, particular cases in which the desired relay process is prevented by interference from a truncation event or premature macrocyclisation are highlighted.

### Cross-Metathesis

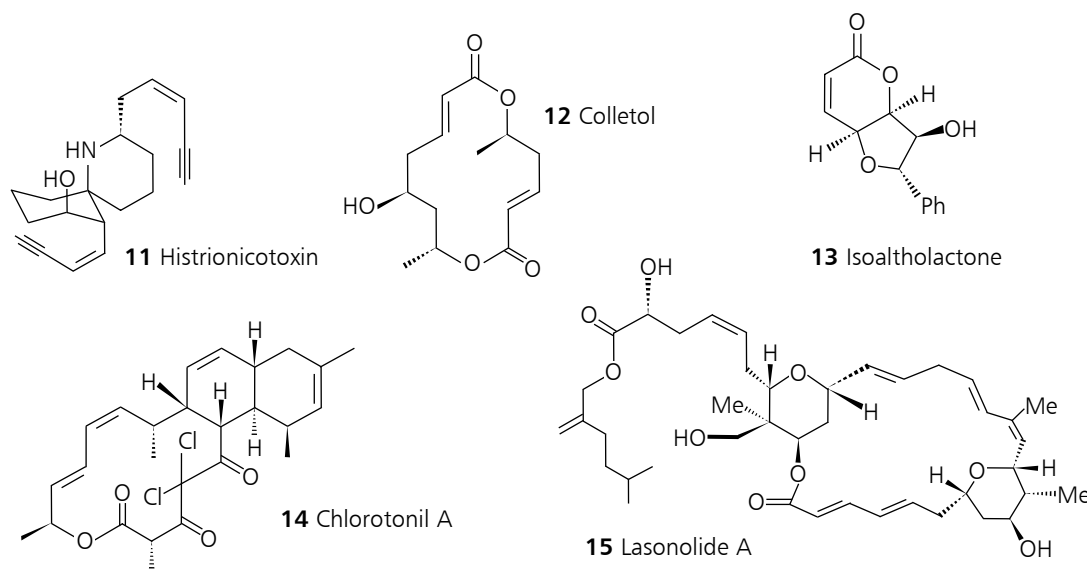
The importance of CM for functionalising terminal alkenes, appending a side chain to the core of a complex compound, or coupling two fragments in order to build the entire framework of the target molecule, is shown in Chapter 10 by Joëlle Prunet (Ecole Polytechnique, Palaiseau, France) and Laurence Grimaud (Ecole Nationale Supérieure des Techniques Avancées, Paris, France). Many natural compounds (including histrionicotoxin, **11**, colletol, **12**, cylindramide A, isoalcoholactone, **13**, amphidinol, chlorotonil A, **14**, lasonolide A, **15**, and asimicin) have been prepared by combining this unique method with more conventional synthetic procedures. Moreover, employing CM in tandem or cascade ruthenium-based metathesis processes (ROM/CM, ROM/CM/RCM, ROM/RCM/CM, CM/RCM, and ring-closing enyne metathesis (RCEYM)/CM) and on enyne and alkyne substrates has proved to be a very fruitful concept leading to other products such as cylindrocyclophanes, squamostolide, routiennocin and anthramycin.

With these useful principles of CM reactions in mind, the reader is well prepared to navigate easily



Scheme VI. Synthesis of amphidinolide V using complementary metathesis methods with molybdenum- and ruthenium-based catalysts

Some examples of natural compounds accessed by the ring-closing metathesis method:



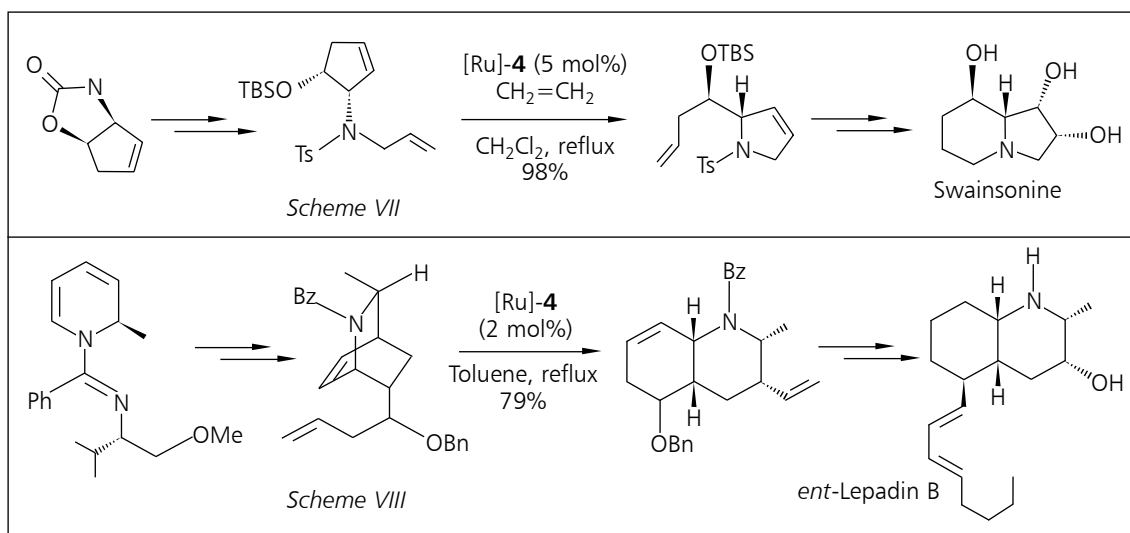
through the next chapter on cascade metathesis reactions in natural product synthesis, authoritatively written by Marta Porta and Siegfried Blechert (Technische Universität Berlin, Germany). The enormous potential of these transformations is given a fresh look in a collection of elegant syntheses of selected natural products, for example: panaxytriol, securinine, swainsonine (**Scheme VII**) castanospermine, *ent*-lepadin B (**Scheme VIII**), etc., obtained *via* ingeniously designed cascade reactions. Insights into the ROM/CM, RCM/CM, ene-yne RCM/RCM and RCM/RCM cascades, and how to steer selectivity in ene-yne-ene metathesis cascade, prove the efficiency and versatility of these methods for building the carbocyclic, heterocyclic and polycyclic units found in natural products. The authors conclude that, given the advantages of metathesis cascades in terms of atom economy and catalytic productivity, further significant applications of these processes are to be expected, contributing to the wider usefulness of olefin metathesis in natural product chemistry.

### Novel Pathways

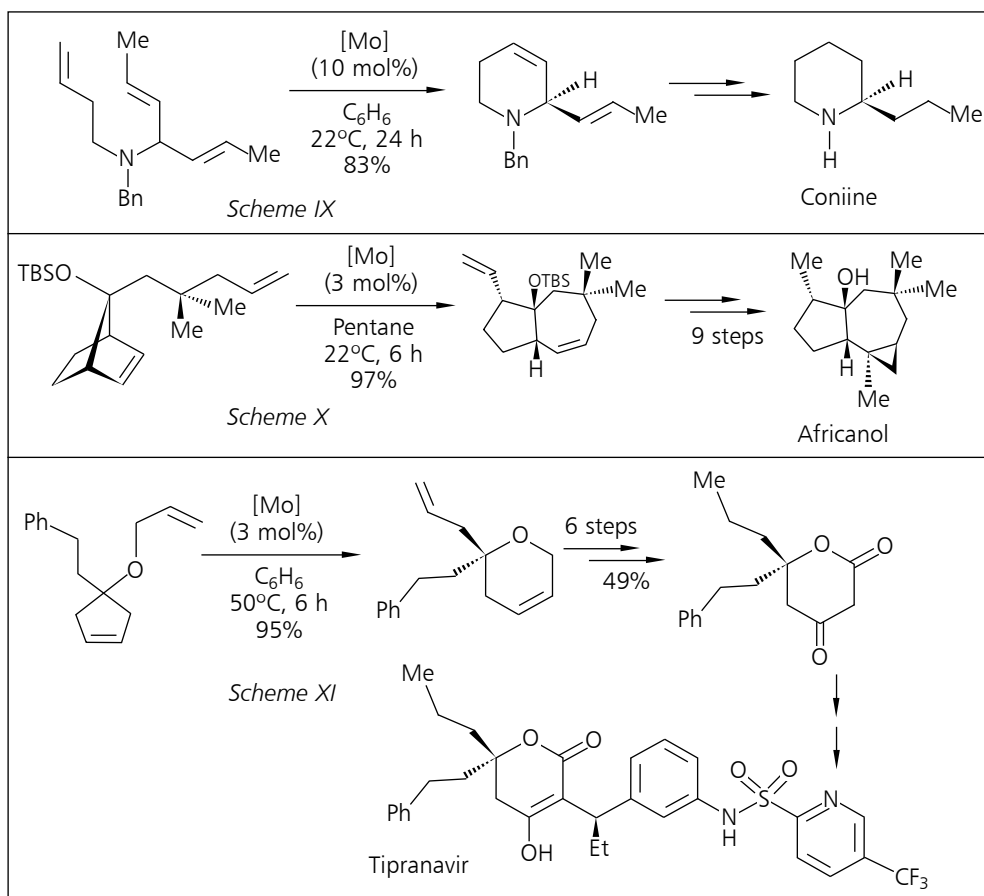
In a brief yet essential account (Chapter 12), Amir H. Hoveyda, Steven J. Malcolmson, Simon J. Meek and

Adil R. Zhugralin (Boston College, USA) point out the crucial role of enantioselective olefin metathesis in the synthesis of natural products. Total syntheses of coniine (**Scheme IX**), africanol (**Scheme X**) and tipranivir (**Scheme XI**) by RCM using enantiomerically pure chiral molybdenum catalysts are presented. Also highlighted is the enantioselective synthesis of quebrachamine by RCM with a chiral molybdenum catalyst and that of baconipyron C through ROCM promoted by a chiral ruthenium catalyst. These few examples of catalytic enantioselective olefin metathesis, selected by the well-known Hoveyda group, clearly indicate that more active and robust stereoselective metathesis catalysts still need to be discovered in order to achieve the maximum potential of this method in natural product synthesis.

The final chapter, by Sofia Barluenga, Pierre-Yves Dakas, Rajamalleswaramma Jogireddy, Gaële Valot and Nicolas Winssinger (Université Louis-Pasteur Strasbourg I, France), is devoted to a topic which is currently gaining in importance due to growing demand for more cost-effective processes, namely solid-phase organic synthesis *via* metathesis reactions promoted by ruthenium catalysts. Relevant issues concern RCM with cleavage of the substrate



Schemes VII and VIII. Synthesis of swainsonine and ent-lepidin B by ring-rearrangement metathesis cascade



Schemes IX–XI. Enantioselective synthesis of coniine, africanol and tipranavir by ring-closing metathesis

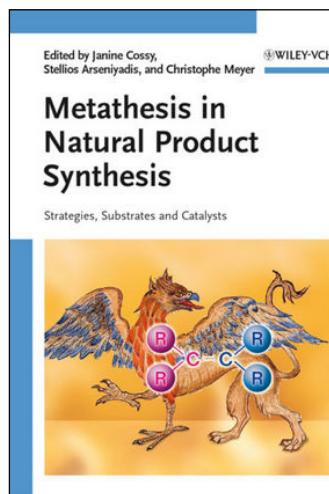
from the resin support, synthesis of small rings and macrocycles on the resin *via* RCM, dimerisation of polymer-bound small molecules by metathesis, RCM to construct peptide conformations, and solid-phase CM and ene-yne metathesis. Cyclorelease cleavage to obtain biologically active products can be used to prepare tetrapeptide macrocycles, epothilones, lactams and  $\beta$ -turn mimics. By using these solid-state techniques, with their inherent ease of separation, purification and manipulation, diversity-oriented synthesis based on metathesis aimed at chemical biology is expected to gain momentum.

### Concluding Remarks

The book highlights how the available library of functional group-tolerant and robust ruthenium metathesis catalysts, along with the highly active and air sensitive molybdenum-alkylidene complexes, has been successfully applied in total syntheses of numerous biologically active natural products, all having in common metathesis reactions as key steps. Nowadays, the application of ruthenium-based catalysts in natural product synthesis is one of the fastest growing metathesis domains, with great potential for drug development.

This valuable publication will be of great interest to academic and industrial specialists working in the areas of alkene or alkyne metathesis, transition metal catalysis, and the synthesis of natural products and biologically active compounds. Despite some minor errors in the text, overall the book is of high quality. The editors are well-recognised authorities in the field, and the contributions are written by highly-qualified authors. Throughout the text, the volume displays attractive, well-designed schemes and diagrams that substantially contribute to the high quality of this work. The book will be informative for professionals and will also be useful for

teaching staff, graduates and undergraduates in organic and medicinal chemistry and in materials science.



*"Metathesis in Natural Product Synthesis"*

### The Reviewers



Valerian Dragutan is a Senior Researcher at the Institute of Organic Chemistry of the Romanian Academy. His research interests are homogeneous catalysis by transition metals and Lewis acids, olefin metathesis and ring-opening metathesis polymerisation (ROMP) of cycloolefins, bioactive organometallic compounds, and mechanisms and stereochemistry of reactions in organic and polymer chemistry.



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