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Diene, Enyne, and Diyne Metathesis in Natural Product Synthesis

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Abstract With the commercial availability of well-defined ruthenium metathesis catalysts which combine high stability and broad functional group compatibility, metathesis has firmly established itself in the toolbox of target-oriented chemists. RCM is now routinely integrated in the retrosynthetic planning of natural product syntheses. The availability of metathesis catalysts with different activity, and hence chemoselectivity, allows one increasingly to influence the regio- and stereoselectivity of metathesis events. With the advent of the highly active NHC-bearing catalysts, CM also began to emerge from the shadow of RCM as a novel and economical alternative for the formation of electron-deficient and highly substituted double bonds. This progress in olefin CM translates into an increasing number of natural product-directed fragment syntheses and has also been useful for convergent assembly of main fragments. An increasing number of uniquely short and atom-economical natural product syntheses feature sequences of several metathesis events, by combining ring-opening metathesis with RCM and/or CM with concomitant chirality transfer to transform one ring into a thermodynamically more stable one. Enyne metathesis, which can be performed by the same catalysts, produces synthetically useful 1,3-dienes that lend themselves to further structural elaboration through subsequent cycloadditions or metathesis cascades. However, although many general studies have demonstrated the preparative use of inter- and intramolecular enyne metathesis, natural product-directed applications are, if compared with diene metathesis, still relatively scarce. The remaining drawback of macrocyclic RCM is the lack of control over the stereochemistry of the newly formed double bond. A solution to this problem is provided by a sequence of ring-closing diyne metathesis and stereoselective partial hydrogenation. As diyne metathesis demands different catalyst systems, sequences of chemoselective olefin, alkene, and alkyne metathesis events have been used in the synthesis of increasingly complex natural products.

Keywords Alkenes · Alkynes · Carbene complexes · Ruthenium · Tandem reactions

Abbreviations

ACM	Alkyne cross metathesis
ADMET	Acyclic diene metathesis
ARCM	Asymmetric ring-closing metathesis
AROM	Asymmetric ring-opening metathesis
CM	Cross metathesis
CsA	Cyclosporin A
Cy	Cyclohexyl
DET	Diethyl tartrate
epoA (*B*, *C*...)	Epothilone A (B, C...)
Mes	2,4,6-Trimethylphenyl (mesityl)
NHC	*N*-Heterocyclic carbene
PMB	*p*-Methoxybenzyl
PMP	*p*-Methoxyphenyl
Pyr	Pyridine
RCAM	Ring-closing alkyne metathesis
RCM	Ring-closing metathesis
ROCM	Ring-opening cross metathesis
ROM	Ring-opening metathesis
ROMP	Ring-opening metathesis polymerization
RRM	Ring-rearrangement metathesis
TADA	Transannular Diels–Alder
TBS	*Tert*-butyldimethylsilyl
TES	Triethylsilyl

1 Introduction

Over the past few years, metathesis reactions catalyzed by well-defined alkylidene complexes that combine excellent activity with broad functional group tolerance have emerged as a powerful tool for carbon–carbon bond formation in natural product-directed organic chemistry. Many general reviews on metathesis reactions in organic synthesis [1] and catalyst development [2] have appeared during the past 5 years, including the most recent contributions concerning enyne metathesis [3], olefin cross metathesis [4], and alkyne metathesis in natural product synthesis [5]. A number of reviews have focused on special applications in organic synthesis, such as olefin metathesis in carbohydrate chemistry [6], RCM leading to medium-sized rings [7] or to heterocycles, alkaloids, and peptidomimetics [8], macrocyclizations leading to (*E*) double bonds [9], RCM in the synthesis of epothilones and polyether natural products [10], and in the total synthesis of laulimalide [11].

Depending on the types of unsaturated functional units involved in the metathesis process, the reactions can be classified into three major categories: diene, enyne, and diyne metathesis (Figs. 1–3). Another mode of classification

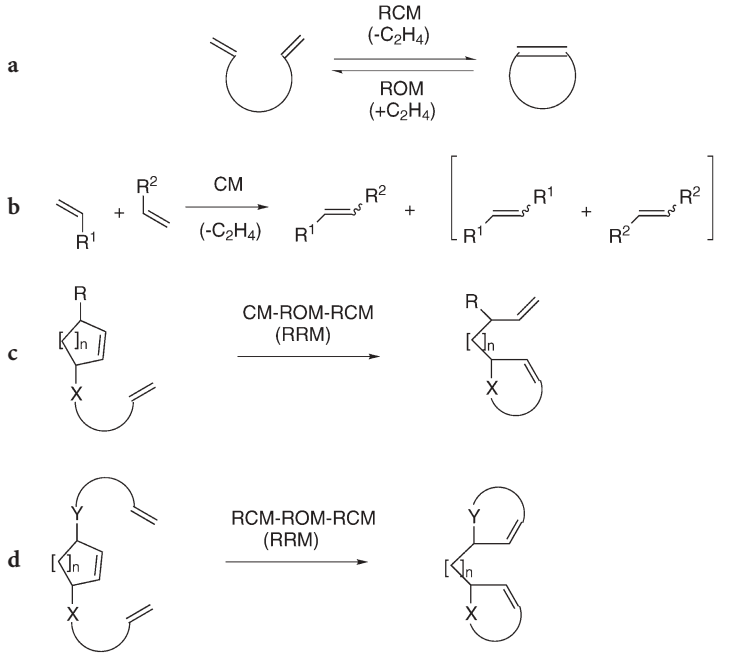


Fig. 1a–d Typical alkene metathesis reactions: ring-closing (RCM) and ring-opening (ROM) metathesis (**a**), diene cross metathesis (CM, **b**), ROM–RCM (**c**), and ROM–double RCM (**d**) sequences (ring-rearrangement reactions, RRM)

results from the structural changes during the metathesis reaction: ring closing (RCM), ring opening (ROM), cross metathesis (CM), and tandem reactions that combine two or more of these reaction types. Among these subclasses, ring-closing diene metathesis (Fig. 1a) has drawn by far the most attention in natural product synthesis, despite the fact that in the macrocyclic series the reaction often proceeds with low stereoselectivity. Olefin cross metathesis (Fig. 1b), which for decades has found numerous industrial uses is, due to problems with chemo- and stereoselectivity, not yet common in the area of natural products. However, with the advent of a second generation of highly potent and commercially available ruthenium catalysts (see below), CM reactions with an electron-deficient olefin as one of the reaction partners can be considered as a useful alternative for the formation of C=C double bonds. A growing number of interesting natural products have been prepared by combining sequential ROM–RCM (Fig. 1c) and ROM–double RCM (Fig. 1d) processes, also known as ring-rearrangement metathesis (RRM) reactions, which lead from a (strained) cycloalkene to one or two thermodynamically favored heterocycles.

While diene metathesis or diyne metathesis are driven by the loss of a (volatile) alkene or alkyne by-product, *enyne metathesis* (Fig. 2) cannot benefit from this contributing feature to the ΔS term of the reaction, since the event is entirely atom economic. Instead, the reaction is driven by the formation of conjugated dienes, which ensures that once these dienes have been formed, the process is no longer a reversible one. Enyne metathesis can also be considered as an alkylidene migration reaction, because the alkylidene unit migrates from the alkene part to one of the alkyne carbons. The mechanism of enyne metathesis is not well described, as two possible complexation sites (alkene or alkyne) exist for the ruthenium carbene, leading to different reaction pathways, and the situation is further complicated when the reaction is conducted under an atmosphere of ethylene. Despite its enormous potential to form mul-

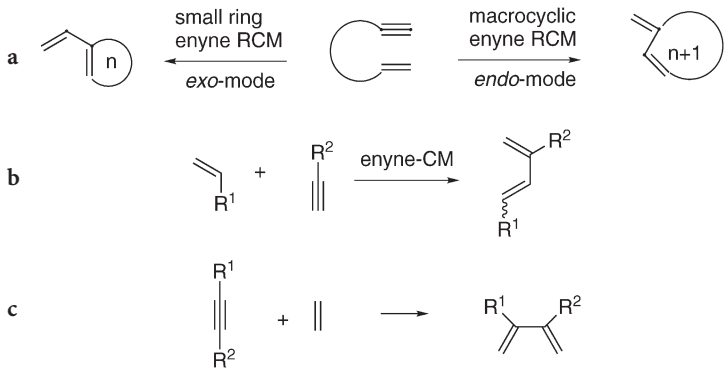


Fig. 2a–c Typical enyne metathesis reactions: ring-closing enyne metathesis (**a**); enyne cross metathesis (**b** and **c**)

tiple C–C bonds and polycyclic systems, enyne metathesis, which is catalyzed by the same catalysts, has rarely been exploited in the area of natural products. In particular, enyne CM between a terminal olefin and a terminal alkyne is hampered by the formation of isomers (Fig. 2b), albeit recent progress was made in this field when the reactions were performed in the presence of ethylene (Fig. 2c).

The regiochemical course of *enyne RCM* (ring closure by the *exo* or *endo* mode shown in Fig. 2a) is not only determined by the substitution pattern of the substrate, but also by the size of the ring to be formed and the choice of catalyst. Therefore, the reaction can lead either to vinylcycloalkenes (*exo* path) or to the enlarged ring system, where both alkyne carbons are integrated in the ring (*endo* path). Both types of the resulting 1,3-diene systems possess high potency for further manipulation. Since the first enyne RCM-based natural product synthesis in 1996 by Mori, the synthetic potential of ring-closing enyne and dienyne metathesis following the *exo* path has been highlighted by several natural product syntheses. Macrocyclic enyne RCM, which apparently follows the *endo* mode by integrating both alkyne carbons in the cycloalkene, seems to be an area of interest and deeper investigation [12] but is to date only represented by a single total synthesis.

Ring-closing alkyne metathesis (RCAM, Fig. 3a) and *alkyne cross metathesis* (ACM, Fig. 3b), which are mediated by tungsten and molybdenum catalysts (see below), seem to offer a simple solution to stereochemistry problems frequently encountered in the macrocyclic olefin series, as the resulting (cyclo)alkynes can be transformed to *E*- or *Z*-(cyclo)alkenes by appropriate semihydrogenation methods. Although the power of the method has been demonstrated in various natural product syntheses by Fürstner and coworkers, alkyne metathesis has remained in the shadow of alkene-based metathesis reactions and was – until now – not widely used by other target-orientated groups, certainly due to the lack of commercially available and stable catalyst systems.

The acceptance of a (new) catalytically mediated methodology by the target-directed synthetic community strongly depends on the availability, stability, and functional group tolerance of the respective catalysts. With the commercial availability of Grubbs' benzylidene ruthenium catalyst **A** [13] and Schrock's even more active, yet highly air- and moisture-sensitive molybdenum catalyst **B** [14]

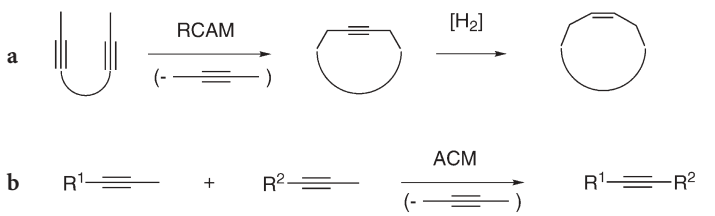


Fig. 3a,b Typical diyne metathesis reactions: ring-closing alkyne metathesis (RCAM, **a**); diyne cross metathesis (ACM, **b**)

(Fig. 4), RCM started rapidly to establish itself in the "toolbox" of target-orientated organic chemists as a method to generate the heterocyclic and macrocyclic motifs present in many natural products. The exchange of one PCy_3 ligand of the "classical" Grubbs' catalyst **A** by an *N*-heterocyclic carbene (NHC) ligand, reported in 1999 independently and almost simultaneously by three groups [15–17], led to a "second generation" of metathesis catalysts (**C** and **E**) with even superior reactivity and increased stability. The NHCs are particularly strong σ-donors but poor π-acceptor ligands with little tendency to dissociate from the metal center. The sterically demanding mesityl substituents on their N atoms are able to stabilize the catalytically relevant intermediates by electronic and steric means against decomposition. These properties translate into highly improved reactivity as well as higher stability which surpass those of the parent complex **A** and also, in many cases, those of molybdenum complex **B**. In 2000, the number of innovative ruthenium catalysts was expanded by catalyst **D** [18], now commonly designed as Hoveyda's catalyst. The phosphine-free catalyst **D** bears, in addition to the NHC ligand, a styrenyl ether that allows for the easy recovery of the catalyst by chromatography. Catalysts **C** and **D** are now also commercially available, and have set new standards in the rapidly expanding field of diene and enyne metathesis reactions, as they also allow the formation of tri- and in some cases tetra-substituted cycloalkenes and the cyclization of conformationally handicapped substrates, as well as stereoselective CM reactions with electron-deficient conjugated olefins. The less common indenylidene ruthenium complex **F** is a catalyst of the first generation. It is not commercially available, but is readily prepared from commercial products, and exhibited favorable selectivity in several natural product syntheses by Fürstner.

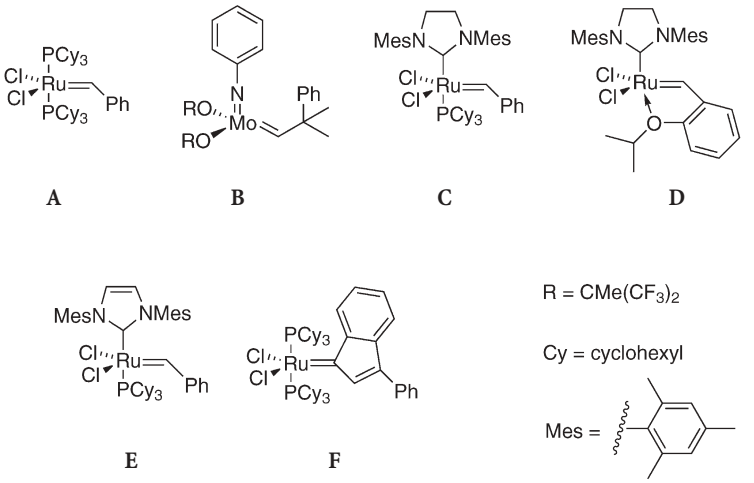


Fig. 4 Commonly used (**A**–**D**) and less commonly used (**E**, **F**) initiators for diene and enyne metathesis

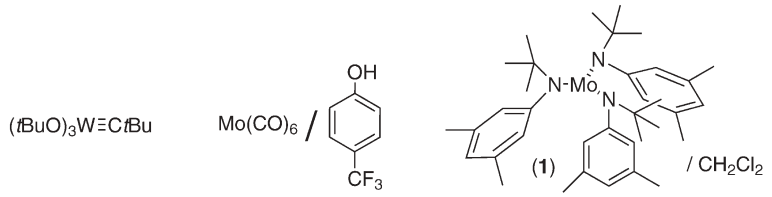


Fig. 5 Diyne metathesis initiators used in Fürstner's natural product syntheses

The alkyne metathesis catalysts used to date in natural product-directed syntheses (Fig. 5), fall into two categories [19]. Tungsten complex **G** belongs to the structurally well-defined Schrock-type alkylidyne transition metal complexes, that are thoroughly studied from the mechanistic point of view. Catalyst systems **H** and **I** belong to the other class of initiator systems, in which a structurally unknown catalyst is formed in situ from two reagents. The "user-friendly" combination of $Mo(CO)_6$ and a phenol additive (**H**) is restricted in its scope by the harsh reaction conditions required. Catalyst system **I**, formed in situ from the trisamido-molybdenum complex **1** and dichloromethane, features broad functional group tolerance and high reactivity under mild conditions. However, due to the extreme reactivity of the basic complex toward small molecules (including nitrogen) [20], its broad acceptance by the synthetic community will be limited.

Following the guidelines of typical metathesis reactions outlined in Figs. 1–3, the present review will concentrate – with only a few exceptions – on the most recent applications of metathesis reactions in the total synthesis of natural products.

2
Diene Metathesis

2.1
Ring-Closing Diene Metathesis (RCM)

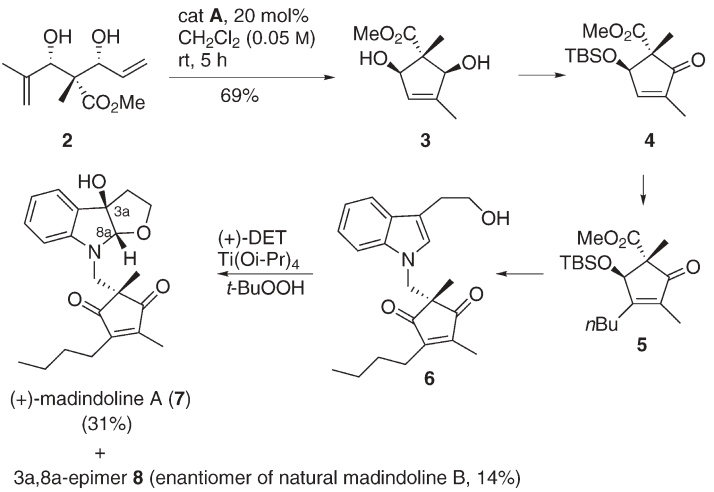
Without question, the area of olefin metathesis that has expanded most dramatically in recent years is ring-closing diene metathesis. RCM is proving useful in total syntheses where it has been applied to targets ranging from relatively small molecules or cyclic fragments of natural products, to highly complex ones that contain multiple unsaturations. One of the major applications of RCM has been the synthesis of natural products with medium-sized (8–11-membered) carbo- and heterocyclic rings, as well as chemo- and stereoselective macrocyclizations of increasingly complex substrates such as diene-enes and even precursors with two terminal 1,3-diene units.

2.1.1 Formation of 5-, 6-, and 7-Membered Rings

In recent years, a wealth of information has accumulated on RCM reactions leading to 5-, 6-, and 7-membered carbocycles and heterocycles, so that it is impossible to refer to all the new, natural product-directed work. Therefore, we will concentrate here on a few selected examples that can illustrate (1) the progress made by the advent of the second-generation ruthenium catalysts **C**–**E**, (2) the use of RCM in concert with other innovative methodology, and (3) the use of RCM in total syntheses of newly discovered natural products which, due to an outstanding biological profile, have attracted specific interest by the synthetic community.

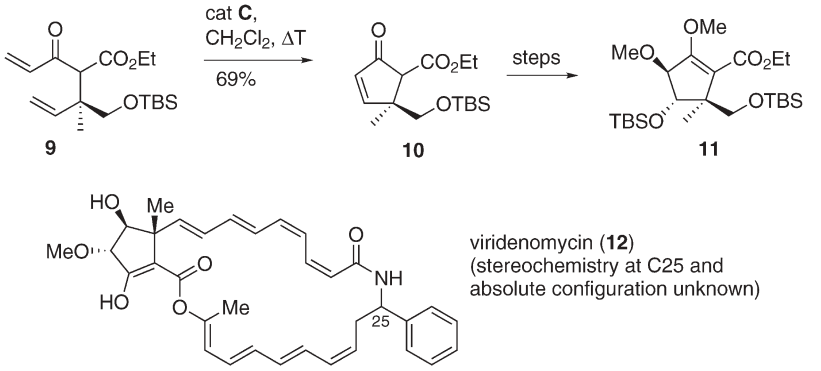
2.1.1.1 Carbocycles

Madindoline A (**7**) and B (*ent*-**8**) are potent inhibitors of interleukin 6. In a total synthesis [21] that also intended to determine the relative and absolute configurations of these novel antibiotics, the densely functionalized cyclopentene-1,3-dione ring of **7** and **8** was elaborated via RCM of diene-diol **2** (Scheme 1).



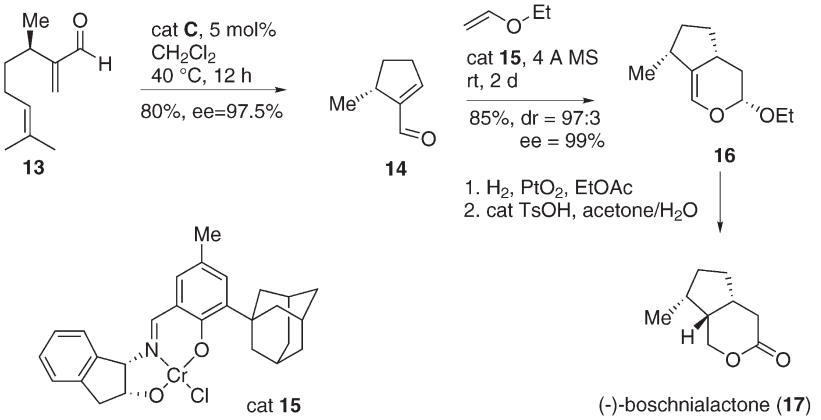
Scheme 1 RCM-based formation of a densely substituted cyclopentene in the first total synthesis of madindoline A (**7**) and *ent*-madindoline B (**8**) [21]

The densely functionalized cyclopentenyl core **11** of the potent antitumor antibiotic viridenomycin (**12**) was most recently prepared by treatment of enone **9** with second-generation Ru catalyst **C** (Scheme 2) [22]. This reaction proved to be very slow, requiring 3.5 days to give only incomplete formation of cyclization product **10** in 69% yield (86%, based on recovered **9**).



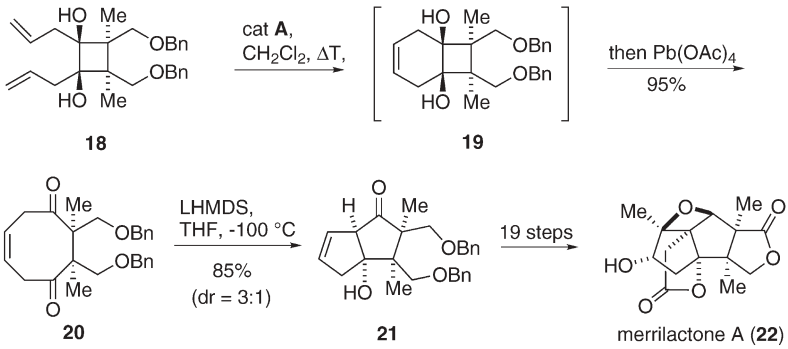
Scheme 2 RCM-based formation of a highly substituted cyclopentenone in Trost's synthesis of the cyclopentenyl core of viridenomycin (**12**) [22]

A striking example of the power of NHC-bearing catalysts with sterically demanding substrates was disclosed by Chavez and Jacobsen [23], who presented a novel route to several iridoid natural products, exemplified by the enantio- and diastereoselective synthesis of boschnialactone (**17**) outlined in Scheme 3. Chiral aldehyde **13**, available from citronellal by Eschenmoser methylenation in a single step, reacted despite the presence of an isoprenyl moiety and a *gem*-disubstituted double bond, in the presence of second-generation catalyst **C** smoothly to form cyclopentene carboxaldehyde **14**. Aldehyde **14** in turn underwent, in the presence of tridentate (Schiff base) Cr(III) complex **15**, an efficient and highly selective inverse-electron-demand hetero-Diels–Alder reaction with ethyl vinyl ether to produce cycloadduct **16** in 85% yield. Compound **16** was then converted into boschnialactone (**17**) by hydrogenation and subsequent introduction of the carbonyl group.



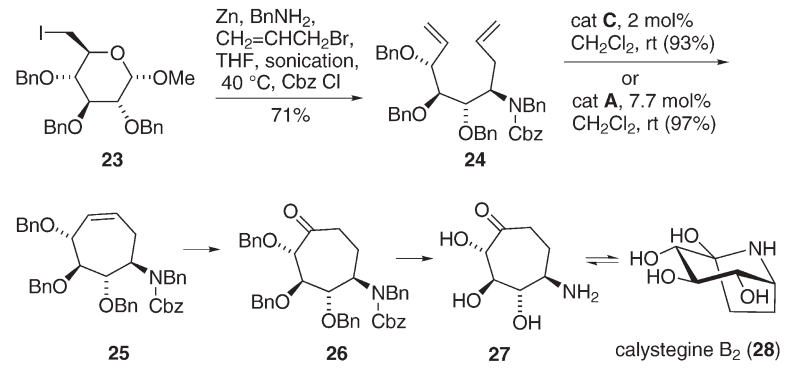
Scheme 3 RCM of a diene with trisubstituted and *gem*-disubstituted double bond en route to iridoid natural products [23]

In a recent total synthesis of the novel neurotrophic agent merrilactone A (**22**, Scheme 4) by Inoue and Hirama [24], key intermediate **21** with the *cis*-bicyclo[3.3.0]octane framework embedded within the caged pentacycle **22** was elaborated from cyclobutane **18** by a sequence of RCM and immediate cleavage of the resulting bicyclic vicinal diol **19** to *meso*-diketone **20**. Cyclooctenedione **20** then underwent regioselective transannular aldol reaction at low temperature (LHMDS, THF, –100 °C) to produce a 3:1 mixture of isomers in 85% combined yield. The major isomer **21** with the required stereochemistry was then converted into the racemic natural compound (±)-**22** in 19 steps.



Scheme 4 A sequence of RCM–glycol cleavage–transannular aldol reaction in Inoue's total synthesis of merrilactone A (**22**) [24]

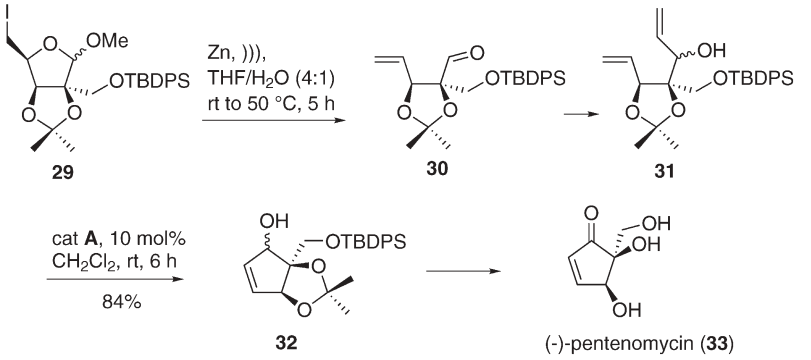
The widespread occurrence and biological significance of polyoxygenated carbocycles provided the impetus to apply RCM to sugar-derived dienes. Carbohydrate carbocyclization based on a sequence of Vasella reductive opening of iodo-substituted methyl glycosides [25], and RCM of the dienes available from the resulting unsaturated aldehydes, were used to prepare a series of natural compounds (Schemes 5–7).



Scheme 5 Carbohydrate carbocyclization in the total synthesis of calystegine B_2 (**28**) [27, 28]

Two groups reported independently the synthesis of the potent glucosidase inhibitor calystegine B_2 (**28**), a polyhydroxylated alkaloid with a nortropane ring system (Scheme 5). The RCM precursor **24** was prepared from the iodo-substituted methyl pyranoside **23** by using a zinc-mediated triple domino reaction (ultrasound-accelerated reductive fragmentation of **23** to generate the 5,6-unsaturated aldehyde, trapping of the aldehyde as the benzylimine, and zinc-mediated allylation of the latter) [26]. After Cbz protection, diene **24** was exposed to first-generation catalyst **A** [27] or to the second-generation catalyst **C** [28], to provide in both cases the desired cycloheptene **25** in good yield. The synthesis was then completed by regioselective introduction of the carbonyl group. The 5-amino-cycloheptanone **27** formed in the deprotection step finally cyclized to the bicyclic aminoketal structure of **28**.

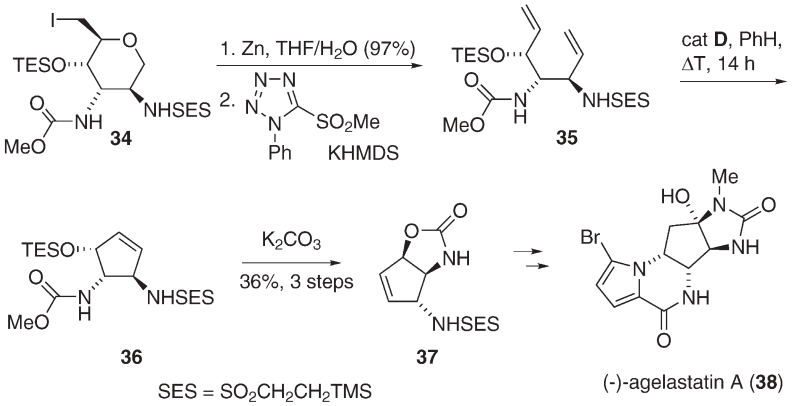
(–)-Pentenomycin (**33**), a highly oxygenated cyclopentenoid with a quaternary chiral center (Scheme 6), was prepared by a similar reaction sequence [29]. The RCM precursor **31** was prepared in eight steps from D-mannose via iodo compound **29** and aldehyde **30** (1:1 diastereomeric mixture). RCM of **31** led to the epimeric cyclopentenols **32**.



Scheme 6 Synthesis of pentenomycin (**33**) via RCM-based carbocyclization [29]

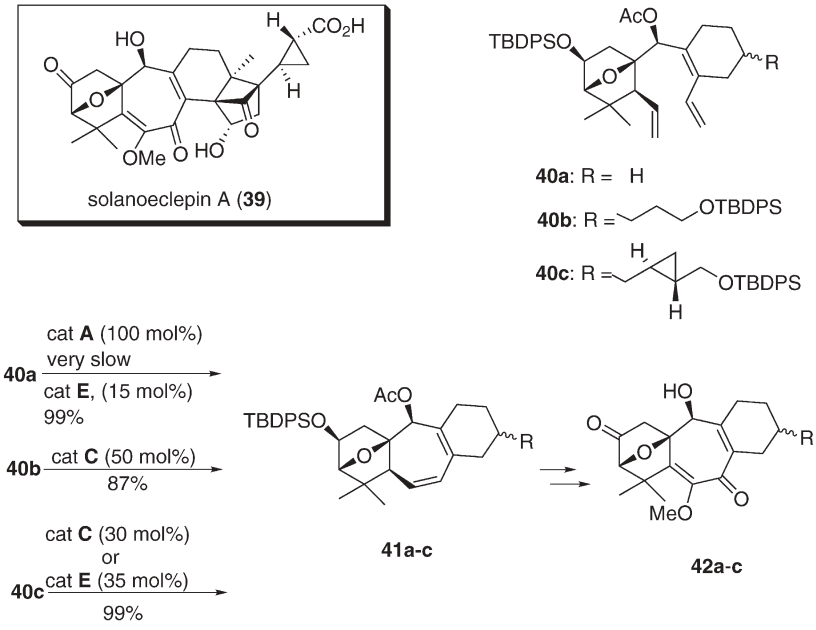
Recently, a formal total synthesis of the antitumor agent and glycogen synthase kinase-3β-inhibiting alkaloid (–)-agelastatin A (**38**) was disclosed by a British team (Scheme 7) [30]. The highly functionalized diene **35** was prepared from iodo compound **34** via Vasella-type reductive ring opening [25], followed by Julia–Kocienski methylenation of the resulting aldehyde. The ring closure to cyclopentene **36** in the presence of Hoveyda's highly active ruthenium catalyst **D** proceeded smoothly (benzene, ΔT, 14 h), notwithstanding the presence of the urethane and sulfonamido groups in **35**. (Due to difficulties in removing a tetrazole by-product formed in the Julia olefination, only the overall yield for the transformation to bicycle **37** was given).

Solanoeclepin A (**39**), a natural hatching agent of potato cyst nematodes, possesses a seven-membered ring in a complex pentacyclic framework. Hiemstra and coworkers achieved the synthesis of several analogs **42** containing the



Scheme 7 Cyclopentene ring closure in the presence of urethane and sulfonamido groups in total synthesis of agelastatin (**38**) [30]

enantiopure tetracyclic left-hand substructure of **39** (Scheme 8) [31]. When the cyclization experiments on triene **40a** were performed with Grubbs' catalyst **A**, the cycloheptadiene-forming process to **41a** was very slow requiring a stoichiometric amount of the catalyst for completion. The use of the more reactive second-generation catalyst **E**, however, provided the tetracyclic diene **41a**



Scheme 8 Efficient formation of the conjugated cycloheptadiene core in tetracyclic compounds **42** during studies toward solanoeclepin A (**39**) [31]

with only 15 mol% of **E** after 16 h in refluxing toluene. The more elaborate precursors **40b** and **40c** reacted sluggishly, but the use of 0.35–0.50 equivalents of catalysts **C** or **E** led to cyclization products **41b** and **41c** in high yield.

2.1.1.2 Cyclic Ethers

5,6-Dihydro-2*H*-pyran-2-ones (α-pyrones **II**) and dihydropyrans (**VIII**) are present in a large number of biologically active natural products. Both types of compounds are now routinely prepared by RCM, either via path A or via path B in Fig. 6. Additionally, chiral lactones **II** can be used to induce stereospecificity to the neighboring carbons via substrate-controlled reactions, as illustrated by the transformation **II**→**IV** or **II**→**V** in the scheme. While the formation of pentenolides by RCM of acrylates (path A) mediated by Grubbs' first-generation catalyst **A** often proceeded sluggishly, needing $Ti(OiPr)_4$ as an additive in many cases, the ring closure occurs generally without problems in the presence of second-generation catalysts **C**, **D**, and **E**. Disubstituted dihydropyrans of the type **VIII** are prepared preferably via path B, by RCM of mixed acrolein acetals **VI**, rather than via the corresponding lactones **II**, as the former cyclize uneventfully with catalyst **A**.

The difference in reactivity is perfectly revealed in Metz's total synthesis of the molluscicidal furanosesquiterpene lactones ricciocarpin A (**50**) and B (**51**) (Scheme 9) [32]. Attempts to convert acrylate **43** to lactone **44** using Grubbs' catalyst **A** or Schrock's molybdenum catalyst **B** resulted in very low yields of the

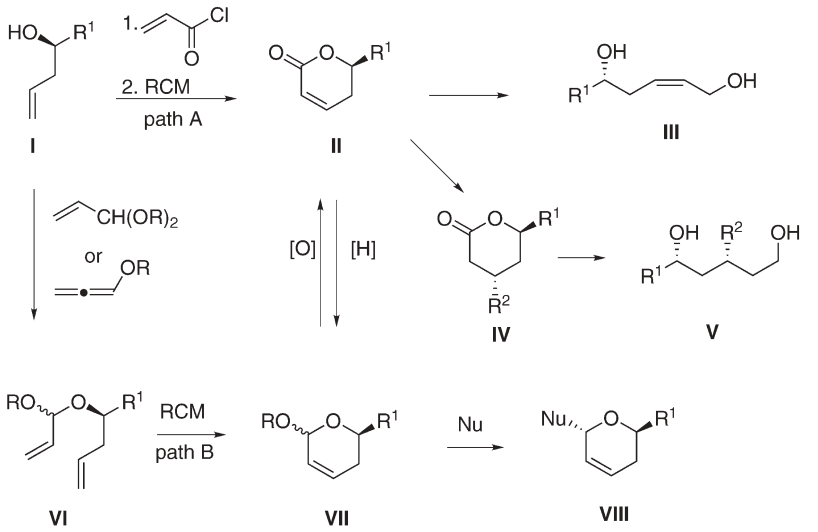
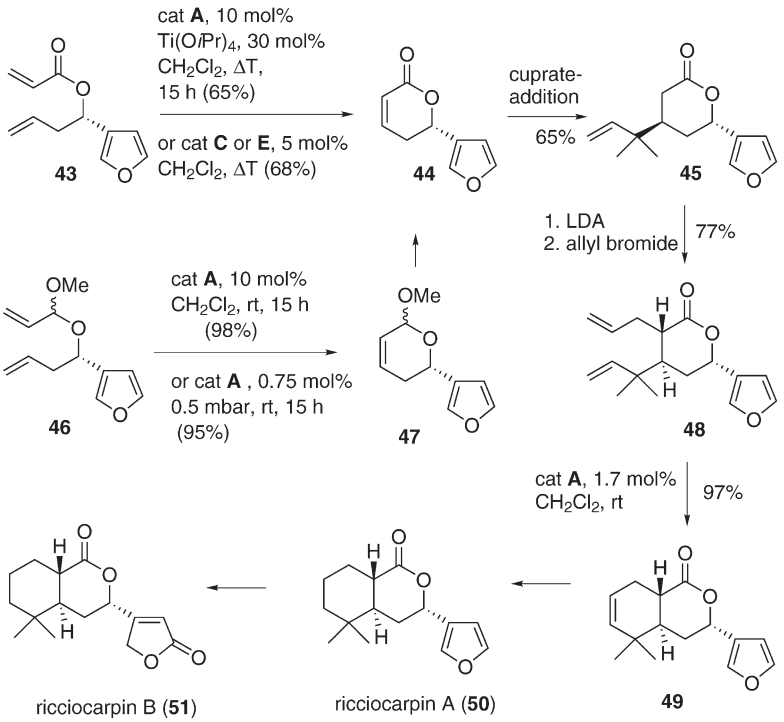


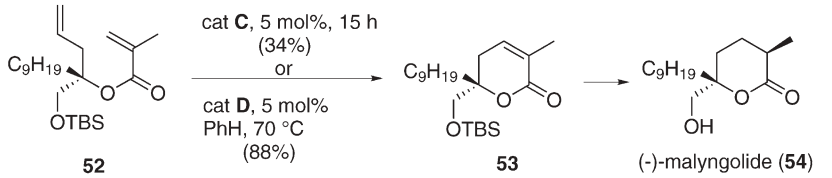
Fig. 6 RCM-based formation and synthetic potential of dihydropyrans **VIII** and α-pyrones **II**



Scheme 9 Comparison of substrate reactivity and catalyst activity in total synthesis of ricciocarpin A (**50**) and B (**51**) [32]

desired product. With $Ti(OiPr)_4$ as an additive, which is suggested to reduce deactivation of catalytic intermediates by the Lewis basic carbonyl oxygen [33], the yield was improved to 65%. With second-generation catalysts **C** and **E** the catalyst loading could be reduced, and the reaction led – without additive – to comparable yields of **44**. RCM of mixed acetal **46** [34] proceeded smoothly with catalyst **A** at room temperature leading to dihydropyran **47** in almost quantitative yield. The best results, however, were obtained when the reaction was performed without any solvent using only 0.75 mol% of catalyst **A** at reduced pressure, which guaranteed the efficient removal of ethylene produced during metathesis. The conversion of lactone **44** to the natural compounds was continued by sequential *trans*-selective conjugate addition of a cuprate and α-allylation of intermediate **45**. The resulting diene **48** was subjected to another high-yielding RCM reaction to **49**, which finally was transformed into **50** and **51**.

The unique power of Hoveyda's recyclable ruthenium catalyst **D** in RCM with electron-deficient and sterically demanding substrates is illustrated in Honda's total synthesis of the simple marine lactone (–)-malyngolide (**54**), which contains a chiral quaternary carbon center (Scheme 10) [35]. Attempted RCM of diene **52** with 5 mol% of NHC catalyst **C** for 15 h produced the desired



Scheme 10 The power of Hoveyda's catalyst **D** in total synthesis of malyngolide (**54**) [35]

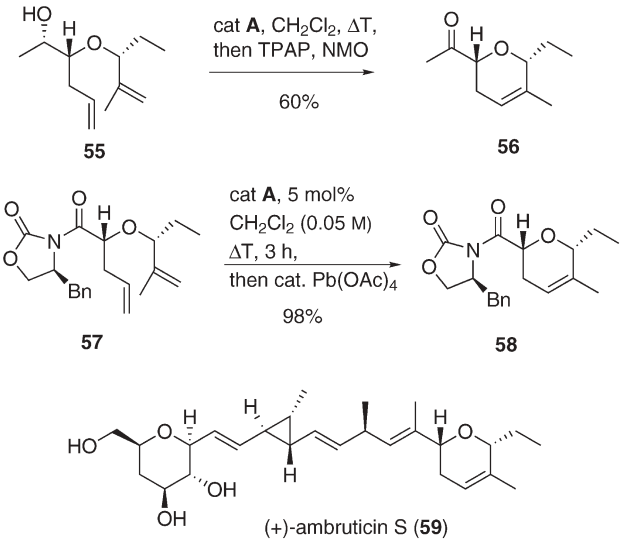
product **53** only in 34% yield. When 5 mol% of catalyst **D** was used, the yield was improved to 88%.

RCM was also one of the key steps in many other total or partial syntheses of natural products with a δ-lactone moiety. The α-pyrone moiety of the potent antitumor agent (+)-fostriecin has been closed in Hatakeyama's total synthesis [36] and in Cossy's synthesis of an advanced intermediate [37]. Also the cytotoxic styryllactone (+)-goniodiol [38] and the plant metabolite (+)-boronolide [39] were prepared via ruthenium-catalyzed RCM. RCM-based synthesis of some lactones with the proposed structures of passifloricin A [40], and a recent total synthesis [41] have led to a correction of the structure of the natural compound. Syntheses of an advanced fragment of the microbial metabolite and dimeric polyketide SCH 351448 [42], of the saturated lactone moiety of the potent HMG-Co A reductase inhibitors compactin and mevinolin [43], and Ghosh's recent synthesis of the highly functionalized C1–C9 segment of the novel microtubule-stabilizing agent peloruside A [44] are examples of the additional introduction of stereocenters to the lactone after the RCM step.

The utility of RCM methodology for the synthesis of open-chain building blocks from α,β-unsaturated δ-lactones is exemplified by the partial syntheses of Cossy aimed for (+)-methynolide (the aglycon of the methymicin family of macrolide antibiotics) [45], and the anticancer agent discodermolide [46], as well as during a recent total synthesis of the highly cytotoxic marine natural depsipeptide apratoxin A by Forsyth and Chen [47].

The orally active antifungal agent ambruticin S (**59**), that exhibits activity against a variety of pathogenic fungi, has attracted intense synthetic interest. In two of the more recent total syntheses the 2,6-*cis*-disubstituted tetrahydropyran unit in **59** was prepared by RCM (Scheme 11). In Martin's synthesis [48], secondary alcohol **55** was used as the metathesis substrate, and the reaction led to ketone **56** in 60% yield after TPAP oxidation (substrate concentration, catalyst loading, and reaction time were not given). In Lee's work [49], the ring closure of diene **57** was effected under high dilution with catalyst **A**, leading to cyclization product **58** in 98% yield, when $Pb(OAc)_4$ was added to the reaction mixture before workup to remove traces of ruthenium and phosphine by-products derived from the catalyst [50].

The novel marine natural product laulimalide (**65**), a metabolite of various sponges, has received attention as a potential antitumor agent due to its "taxol-like" ability to stabilize microtubules. There has been considerable synthetic effort toward **65**, culminating within not more than 2 years in as many as ten



Scheme 11 RCM-based synthesis of dihydropyran fragments **56** [48] and **58** [49] in total synthesis of the antifungal agent ambruticin S (**59**)

total syntheses by seven groups and numerous fragment syntheses [51]. Both, the exocyclic and the inner 2,6-*trans*-disubstituted dihydropyran unit in **65** have been prepared by RCM [52], and it was shown that the ring closure can also be performed chemoselectively in the presence of additional double bonds leading to the advanced intermediates **60**–**64** depicted in Fig. 7. Intermediate **64**

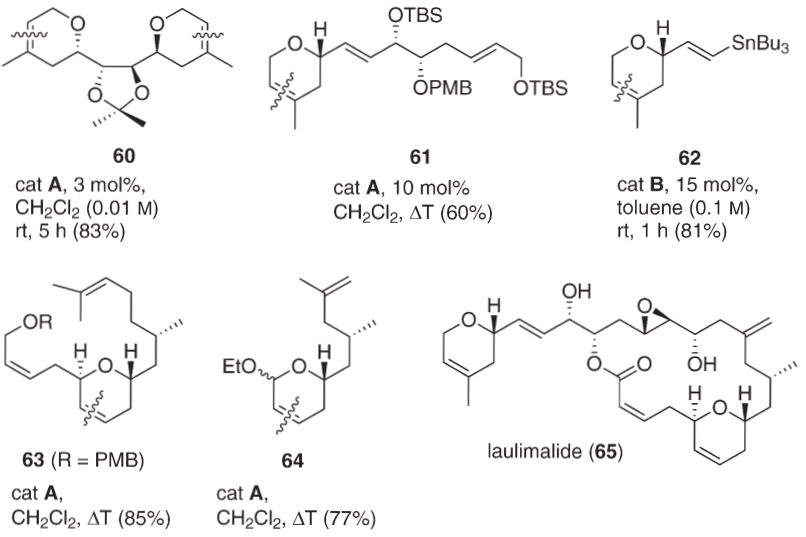
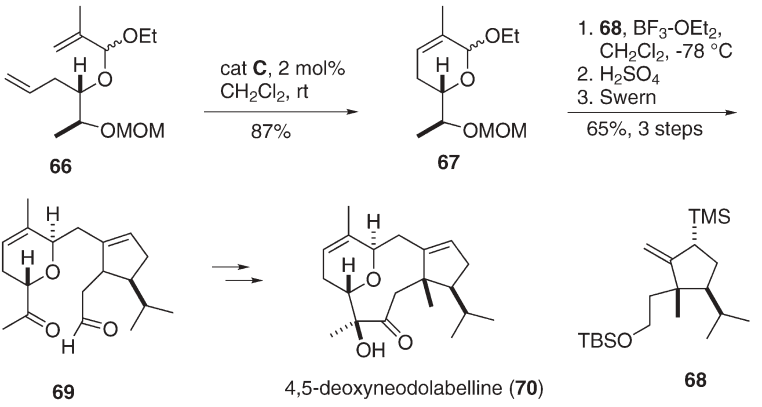


Fig. 7 Advanced dihydropyran fragments used in total syntheses of laulimalide (**65**)

was prepared by twodirectional RCM under high dilution from the corresponding D-mannose-derived tetraene, and served as an efficient precursor for the volatile dihydropyran carboxaldehyde [53]. The RCM reactions leading to dihydropyrans **60**, **61** [54], **63** [55], and **64** [56] were all performed with first-generation Grubbs' catalyst **A**, while the tributylstannyl-substituted dihydropyran **62** [57] was prepared with Schrock's molybdenum catalyst **B**.

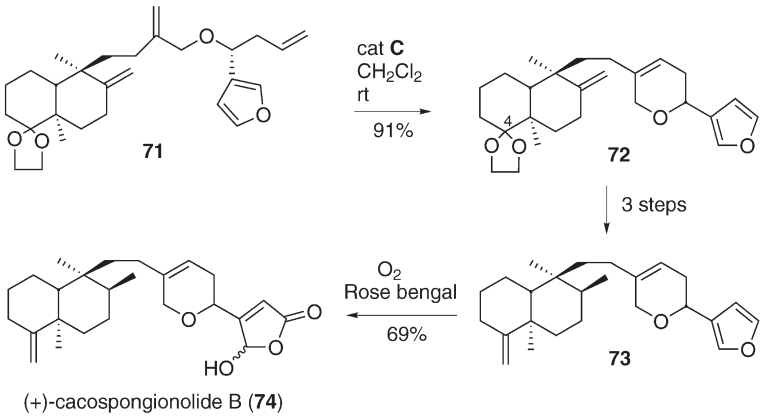
The first total synthesis of the marine dolabellane diterpene (+)-4,5-deoxyneodolabelline (**70**) was accomplished by D. R. Williams et al. [58]. The *trans*-disubstituted dihydropyran moiety in key intermediate **69** was efficiently prepared from mixed acetal **66** by RCM with second-generation catalyst **C** and subsequent Lewis acid-catalyzed allylation of ethyl glycosides **67** with allylsilane **68** (Scheme 12) [59].



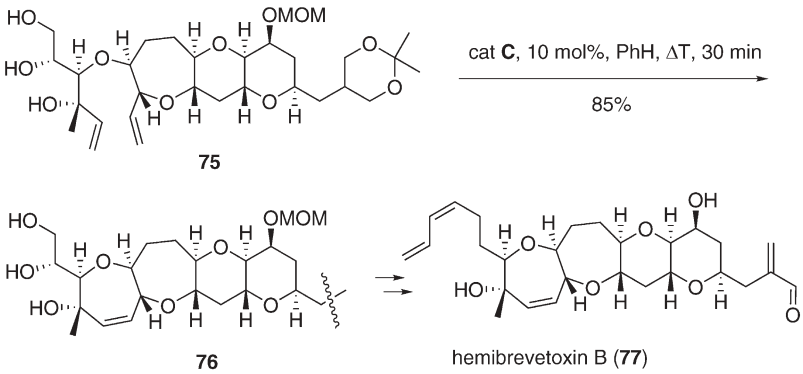
Scheme 12 Stereoselective synthesis of main fragment **69** by sequential RCM and allylation in total synthesis of 4,5-deoxyneodolabelline (**70**) [58]

The formation of a highly complex 2,5-disubstituted dihydropyran by RCM was one of the key steps in Snapper's total synthesis of the cytotoxic marine natural product (+)-cacospongionolide B (**74**) (Scheme 13) [60]. Despite the use of second-generation catalyst **C**, RCM of triene **71** proceeded regioselectively to produce only the dihydropyran ring, leading to compound **72** in 91% yield. The first total synthesis of **74** was then completed in four steps, by selective reduction of the *exo* methylene group, followed by introduction of the methylene group at C4 and photooxygenation of the furan ring in intermediate **73**.

In the first convergent total synthesis of the marine neurotoxin hemibrevetoxin B (**77**) [61], dienetriol **75** was used as an RCM substrate for elaboration of the seven-membered A ring in **77** (Scheme 14). While first-generation catalyst **A** was ineffective in this case, the ring closure occurred smoothly with second-generation catalyst **C**, providing the tetracyclic intermediate **76** in high yield.



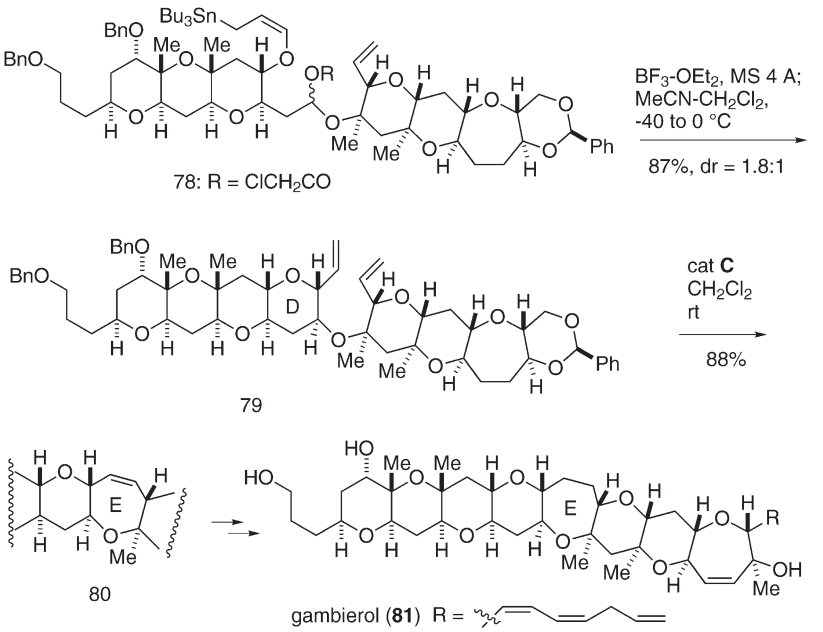
Scheme 13 RCM-based formation of the advanced dihydropyran fragment **72** in the first total synthesis of cacospongionolide B (**74**) [60]



Scheme 14 Efficient formation of the seven-membered A ring from unprotected triol **75** in Holton's total synthesis of hemibrevetoxin B (**77**) [61]

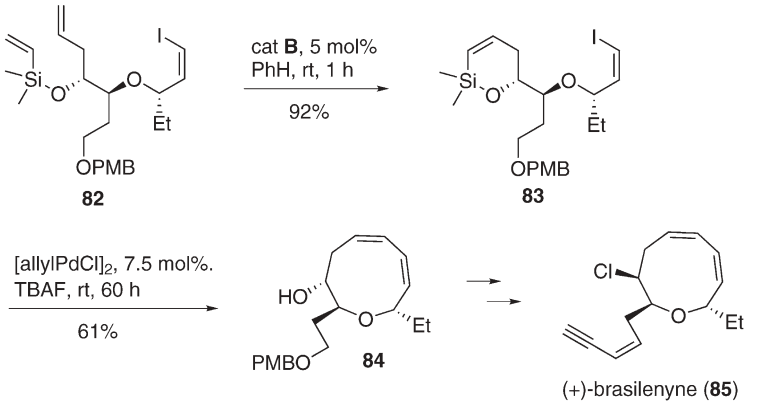
RCM was also used in Yamamoto's total synthesis of the marine neurotoxin gambierol (**81**) [62], to close the central seven-membered E ring, thereby completing the octacyclic polyether core **80** (Scheme 15). Following previously developed methodology [63], metathesis precursor **79** was produced as the major epimer, by boron trifluoride etherate-mediated intramolecular allylation of α-chloroacetoxy ether **78**. Subsequent treatment of **79** with catalyst **C** produced the octacyclic ether **80** in 88% yield.

Following a previously developed strategy in the group for the synthesis of medium-sized rings containing a 1,3-*cis*,*cis*-diene unit [64], Denmark disclosed the first total synthesis of the nine-membered cyclic ether (+)-brasilenyne (**85**), through a sequence of RCM with formation of a six-membered cyclic silyl ether followed by silicon-assisted intramolecular cross coupling (Scheme 16) [65]. When RCM precursor **82** was subjected to Schrock's catalyst **B**, compound **83**



Scheme 15 Formation of the central rings D and E by sequential intramolecular allylation and RCM in Yamamoto's total synthesis of the marine neurotoxin gambierol (**81**) [62]

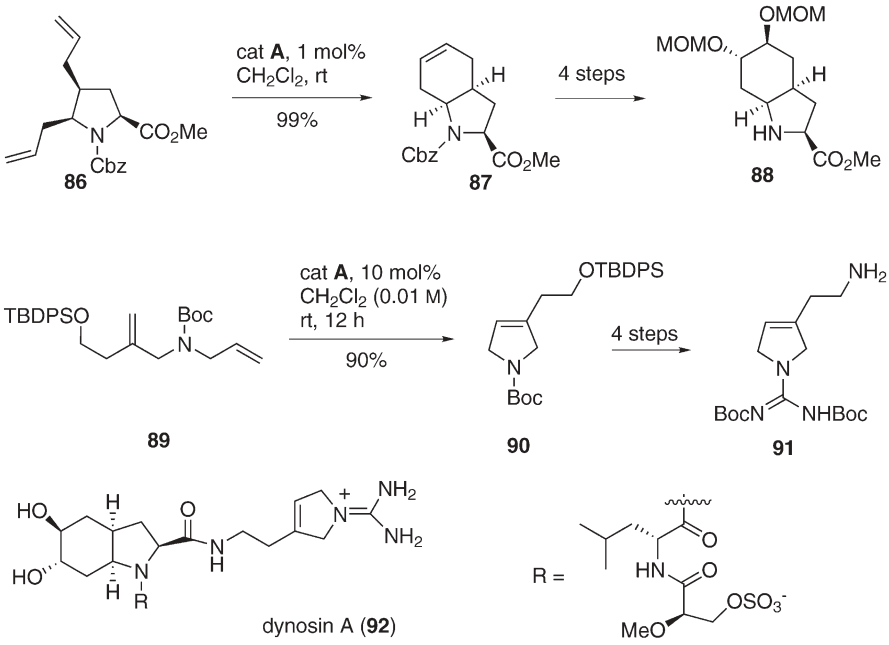
with the silicon-based temporary linker was formed in 92% yield. The intramolecular cross coupling leading to the nine-membered ring was then carried out with $[allylPdCl]_2$ as the catalyst and TBAF as the activator, which led to intermediate **84** in 61% yield. (For the total synthesis of various other medium-sized ring ethers of marine origin by direct RCM methods, see Schemes 31–35).



Scheme 16 Construction of a nine-membered cyclic ether with a (*Z*,*Z*)-1,3-diene unit by sequential RCM and silicon-assisted intramolecular cross coupling in Denmark's synthesis of brasilenyne (**85**) [65]

2.1.1.3 Alkaloids

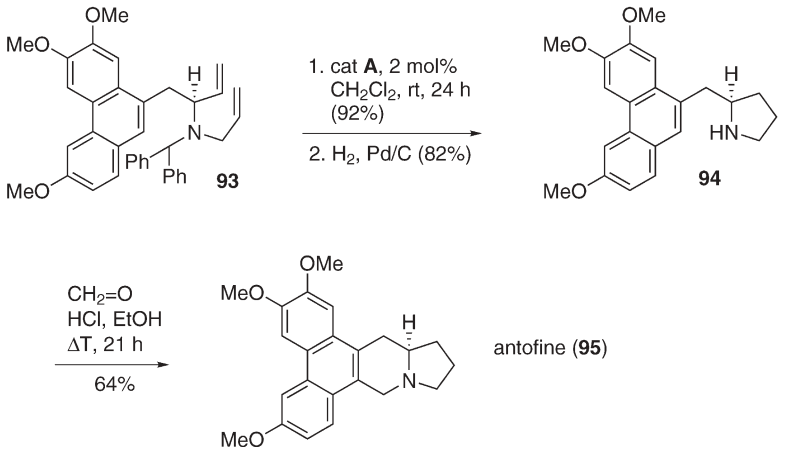
The marine natural product dynosin A (**92**) is a new member of the aeruginosin family and a novel inhibitor of thrombin and Factor VIIa. In Hanessian's total synthesis of **92** [66], both the dihydroxyoctahydroindole **88** and the Δ3 pyrroline moiety **91** were prepared by RCM-based routes (Scheme 17).



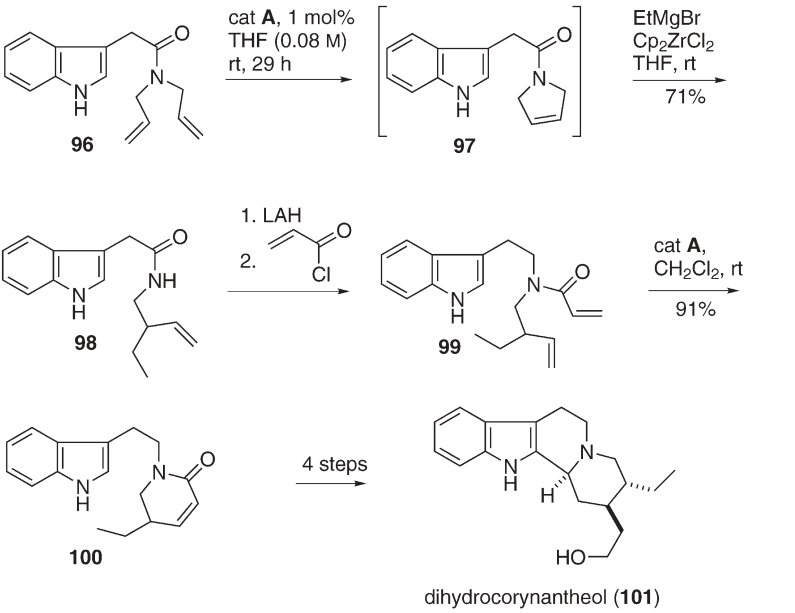
Scheme 17 RCM-based synthesis of octahydroindole **87** and pyrroline **90** in the first total synthesis of dynosin A (**92**) [66]

The phenanthroindolizidine alkaloid (–)-antofine (**95**) exhibits high cytotoxicity to drug-sensitive and multidrug-resistant cancer cells by arresting the G2/M phase of the cell cycle. In the first asymmetric total synthesis of (–)-**95**, the late-stage construction of pyrrolidine **94** for the final Pictet–Spengler cyclomethylenation to **95** was performed by RCM and subsequent hydrogenation (Scheme 18) [67].

A concise total synthesis of the indole alkaloid dihydrocorynantheol (**101**) (Scheme 19), that features two RCM steps and a zirconocene-catalyzed carbomagnesation [68], is a further example of Martin's interest in applying RCM as a key reaction for the construction of alkaloid frameworks [69]. The first RCM step was applied to bis-allyl amide **96.** The resulting intermediate **97** was directly subjected to carbomagnesation and subsequent elimination to deliver **98** in 71% yield from **96.** Amide **98** was then transformed into acrylamide **99** in



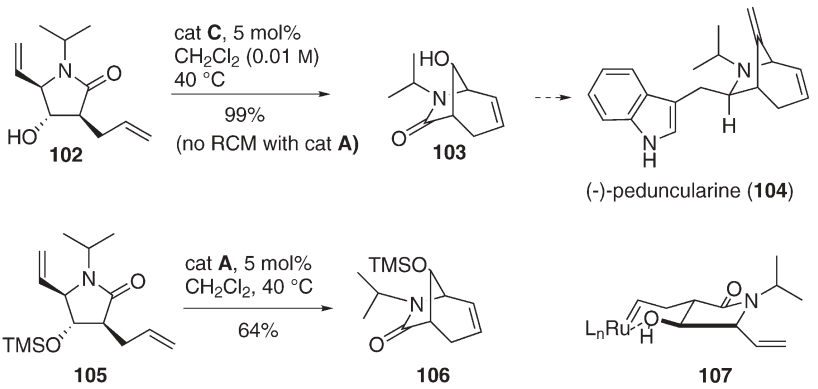
Scheme 18 Synthesis of the phenanthroindolizine alkaloid antofine (**95**) by a sequence of RCM, hydrogenation, and Pictet–Spengler cyclomethylenation [67]



Scheme 19 Construction of key lactam **100** via two RCM steps and a zirconocene-mediated carbomagnesation in Martin's total synthesis of dihydrocorynantheol (**101**) [68]

two steps. RCM of **99** furnished lactam **100** in 91% yield, which was converted into racemic **101** in four additional steps.

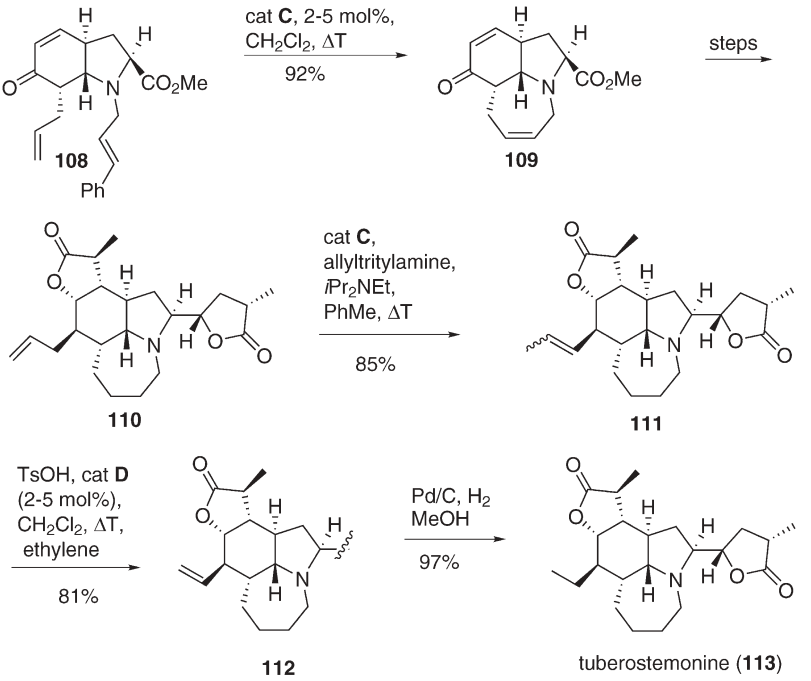
Also, a novel RCM-based approach to the 6-aza[3.2.1]bicyclooct-3-ene **103**, and hence a formal total synthesis of the antitumor antibiotic (–)-pedunculare (**104**) (Scheme 20), was recently disclosed by Martin's group [70]. Initial ex-



Scheme 20 RCM-based construction of key intermediate **103** in a formal total synthesis of the antitumor antibiotic peduncularine (**104**) [70]

periments to effect the RCM of alcohol **102** with first-generation catalyst **A** were not successful (possibly by formation of unreactive intermediate **107**), while TMS ether **105** led to cyclization product **106** in 64% yield. When alcohol **106** was treated with second-generation catalyst **C**, the ring closure proceeded smoothly leading to **103** in nearly quantitative yield.

A further example of the rapid progress in Ru-catalyzed metathesis reactions is Wipf's total synthesis of (–)-tuberostemonine (**113**) [71]. This complex polycycle belongs to the family of *Stemona* alkaloids, which cover a broad range of biological activities including applications in Eastern folk medicine against pulmonary tuberculosis and bronchitis. The first total synthesis of **113** (Scheme 21) highlights the threefold use of Ru catalysts, first by an azepine ring-closing step and, in the endgame of the synthesis, by a Ru-catalyzed allyl to 1-propenyl isomerization/Ru-catalyzed cross metathesis (CM) sequence leading to a propenyl–vinyl interchange. When key intermediate **108** was exposed to 2–5% of NHC catalyst **C**, tricyclic azepine **109** was smoothly formed in high yield. After stereoselective elaboration of the complete pentacyclic skeleton, the allyl substituent in the advanced intermediate **110** was isomerized using a modification of a method developed by Roy et al. for allyl ethers [72]. Thus, heating a solution of **110** in toluene in the presence of catalyst **C**, allyl tritylamine, and diisopropylethylamine led to the 1-propenyl-substituted isomer **111** in high yield. Subsequent CM of **111** with ethylene in the presence of Hoveyda's catalyst **D** and TsOH gave access to the desired vinyl group in **112**, which was hydrogenated to provide (–)-**113**.



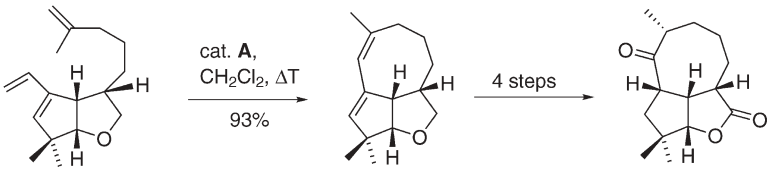
Scheme 21 Threefold use of ruthenium catalysts in the first total synthesis of *Stemona* alkaloid tuberostemonine (**113**) [71]

2.1.2 Formation of Medium-Sized Rings

Because of enthalpic (increasing strain in the transition state) and entropic influence (probability of the chain ends meeting), medium-sized rings are the most difficult to prepare. Additionally, the formation of medium-sized rings by RCM may pose considerable challenges as, due to the inherent ring strain, 8–11-membered cycloalkenes are prone to the reverse process, that is, to ROM or ring-opening metathesis polymerization (ROMP) sequences. One approach to circumvent this problem is to incorporate control elements (cyclic conformational constraints by preexisting rings or acyclic constraints by the substitution pattern of the cyclization precursor) that force the cyclization substrate to adopt a conformation suitable for ring closure. These constraints will facilitate RCM and stabilize the product against the competing ROMP pathway. While up to early 2000 only a limited number of successful RCM reactions for the synthesis of natural products with medium-sized rings were reported [73], the number has rapidly increased during the last 3 years [74]. Most importantly, we will see that in some cases the stereochemical outcome of the reactions could also be mediated by the choice of the catalyst, which is deemed to reflect kinetic versus thermodynamic control of the cyclization reaction.

2.1.2.1 Carbocycles

The importance of conformational restriction for the ring-closing reaction is nicely demonstrated during Paquette's concise total synthesis of natural (+)-asteriscanolide (**116**) [75], whose framework consists of a rather uncommon bicyclo[6.3.0]octane ring system bridged by a butyrolactone fragment (Scheme 22). Despite the presence of a conjugated diene unit and a *gem*-disubstituted double bond in precursor triene **114**, the cyclooctene ring in **115** was formed in high yield (93%, based on recovered starting material) when a total of 30 mol% of Ru catalyst **A** was sequentially added within 48 h to a boiling solution of **114** in dichloromethane.

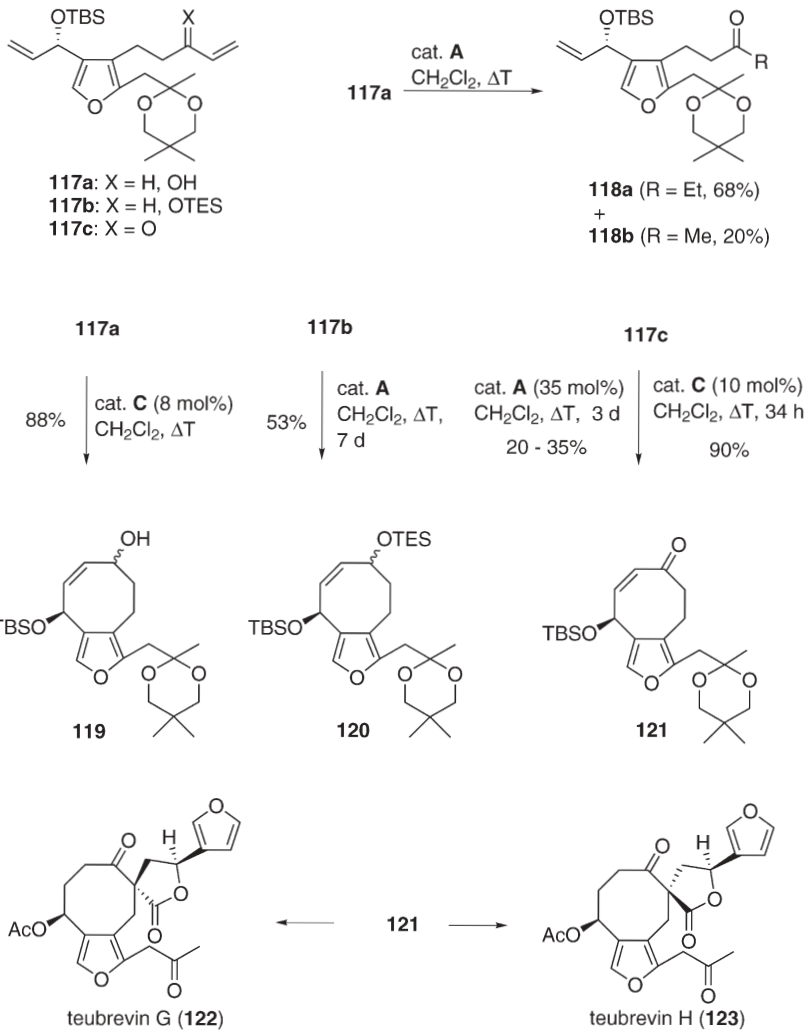


Scheme 22 Efficient cyclooctene-forming diene-ene RCM, facilitated by cyclic constraint in Paquette's total synthesis of asteriscanolide (**116**) [75]

An illustrative example of the potency of the second-generation Ru catalyst **C** is found in Paquette's highly efficient total synthesis of the natural products teubrevin G (**122**) and teubrevin H (**123**), which feature a cyclooctane core fused and spiroannulated to smaller oxygen-containing rings [76]. In the retrosynthetic analysis, the viability of an RCM step for annulation of a cyclooctenone ring to the furan played a central role.

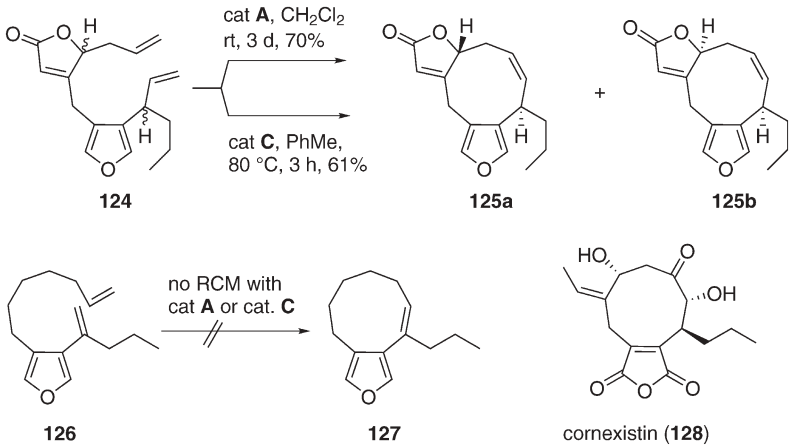
Despite the presence of a conformational constraint by the furan ring in the cyclization substrate, only poor results were obtained when Grubbs' first-generation Ru catalyst **A** was examined to effect the ring closure of TES ether **117b** and ketone **117c** (Scheme 23). Using very high catalyst loading and reaction times up to 1 week in boiling dichloromethane produced the desired RCM products **120** and **121** only in low yield (53 and 35%, respectively). In the case of allylic alcohol **117a**, catalyst **A** provided no cyclization product (**119**) at all, leading instead to ethyl ketone **118a** (68%) and methyl ketone **118b** (20%) as the sole reaction products. When the cyclization was performed in the presence of 10 mol% of Ru catalyst **C**, the RCM reaction of allylic alcohol **117a** and vinyl ketone **117c** proceeded smoothly within several hours to furnish alcohol **119** and ketone **121** in high yield. Cyclooctenone **121** was then successfully converted to **122** and **123**.

En route to a planned total synthesis of the phytotoxic natural compound cornexistin (**128**), Stephen Clark recently reported the first example of the



Scheme 23 Improved formation of cyclooctene ring with second-generation catalyst **C** in Paquette's total synthesis of teubrevins G (**122**) and H (**123**) [76]

direct construction of a nine-membered carbocycle, using a novel sequence of Pd-catalyzed fragment coupling followed by RCM (Scheme 24) [77]. With Grubbs' second-generation catalyst **C** in toluene at 80 °C, the RCM of precursor **124** (1:1 mixture of diastereomers) was complete within 3 h leading to isomers **125** in 61% yield. When the cyclization was performed with catalyst **A**, the reaction was only complete after 3 days. However, when the RCM reaction was attempted with model compound **126** containing a *gem*-disubstituted double bond in conjugation to the furan ring, both catalysts failed to provide the ring closure to **127**.

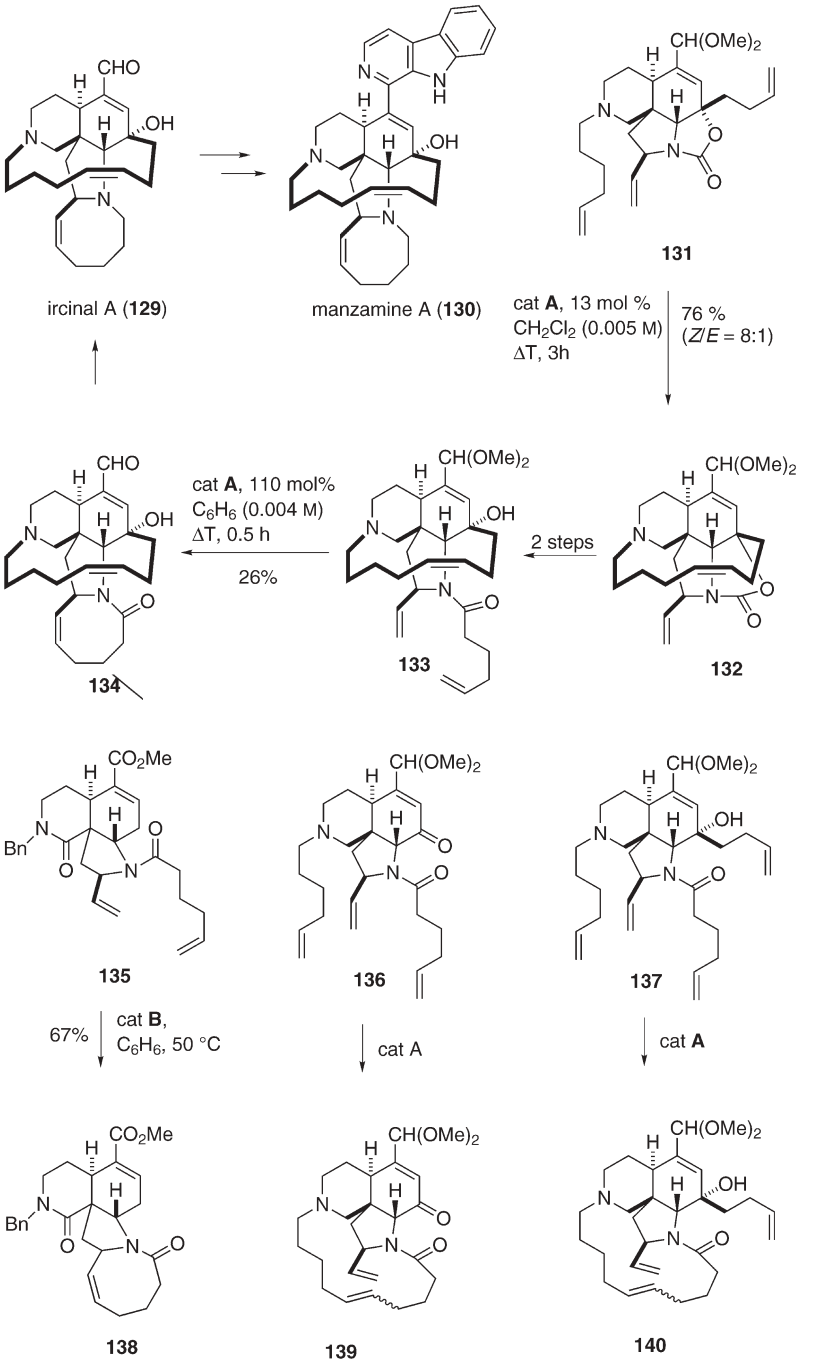


Scheme 24 First example of RCM-based construction of a nine-membered carbocycle by altering the key disconnection in cornexistin (**128**)-directed work [77]

2.1.2.2 Alkaloids

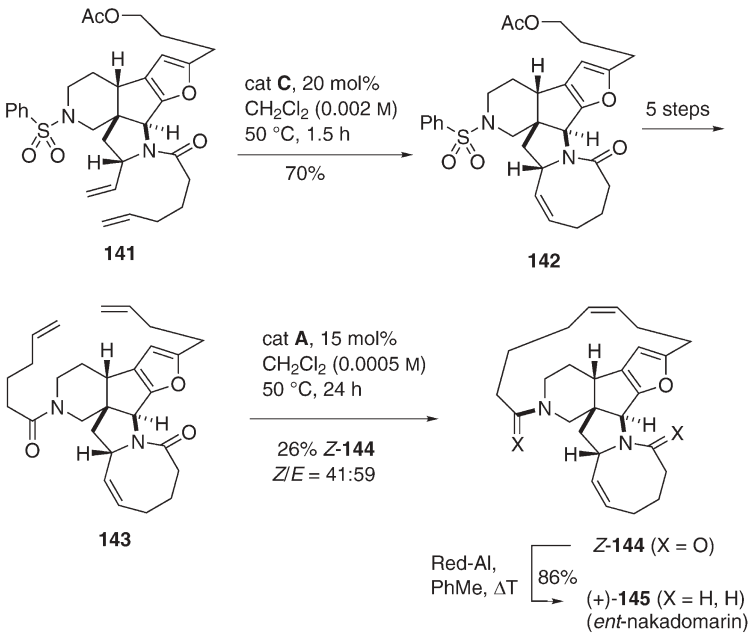
In 1999, a total synthesis of ircinal A (**129**) and hence a formal synthesis of the potent antitumor agent manzamine A (**130**) was disclosed by the team of Stephen Martin (Scheme 25) [78]. Two RCM reactions were exploited to elaborate sequentially the requisite 13- and 8-membered rings. When triene **131** (0.005 M in dichloromethane) was exposed to Ru catalyst **A** (13 mol%), a facile and regioselective RCM reaction occurred to furnish a mixture (*Z*/*E*=ca. 8:1) of geometric isomers from which the major isomer **132** was isolated in 67% yield. In contrast to a previous observation [79], protonation of the tertiary amine prior to the metathesis reaction was not necessary in this case. Hydrolytic removal of the cyclic carbamate in **132** followed by acylation led to the precursor **133** for the second RCM reaction. However, the formation of the eight-membered lactam was problematic, leading to the desired reaction product **134** in only 26% yield despite the use of as much as 1.1 equivalents of catalyst **A**. In the subsequent full account from 2002, additional details concerning the RCM steps were revealed. In initial experiments, it had been shown that model compound **135** underwent smooth ring closure with Schrock's molybdenum catalyst **B** to provide the tetracyclic product **138**. It was also attempted to effect double RCM to construct the pentacyclic skeleton in a single operation. However, compound **137** reacted only to form tetracycle **140** with a 15-membered ring. Also, compound **136** underwent rapid ring closure in the presence of catalyst **A**, leading to **139** as a mixture (ca. 1:1) of *E*/*Z* isomers. The inability to effect double RCM made it necessary to elaborate the 8- and 13-membered rings in a serial fashion.

Nakadomarin A ((–)-**145**) is a marine natural product with a unique hexacyclic structure (Scheme 26). Recently, the first total synthesis of its enantiomer



Scheme 25 Sequential formation of 13- and 8-membered azacycles in Martin's total synthesis of ircinal A (**129**) and related manzamine alkaloids [78]

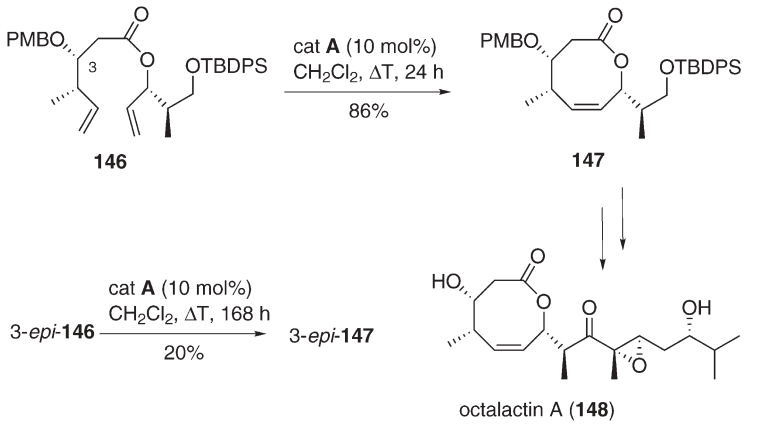
(+)-**145** was achieved, which also features two sequential RCM reactions to form the 8- and 15-membered azacycles [80]. However, compared with the above synthesis of ircinal A, the order of ring-closing steps was reversed. When diene **141** (0.002 M in dichloromethane) was exposed to Grubbs' catalyst **C**, a facile RCM reaction ensued leading within 1.5 h to azocine lactam **142** in 70% yield. Note that when **141** was exposed to catalyst **A**, **142** was obtained in only 15% yield after 48 h with recovery of **141** (36%), underlining again the high potential of the second-generation Ru catalysts. Pentacyclic compound **142** was then elaborated to diene **143** in five steps. The second RCM reaction to close the 15-membered lactam was performed with Ru catalyst **A** and delivered a mixture (*Z*/*E*≈2:3) of isomers, from which the desired minor isomer (*Z*)-**144** was separated in only 26% yield. Reductive removal of both carbonyl groups in bislactam (*Z*)-**144** finally led to (+)-**145**.



Scheme 26 Sequential formation of 8- and 15-membered azacycles in total synthesis of *ent*-nakadomarin A (**145**) [80]

2.1.2.3 Lactones

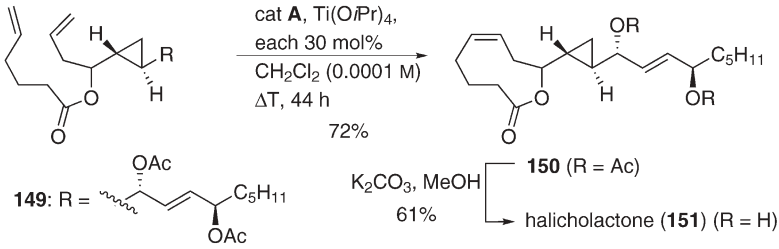
An example of a surprisingly facile and stereoselective formation of an eight-membered lactone from an acyclic precursor diene ester was observed during the total synthesis of the antitumor agent octalactin A (**148**) (Scheme 27) [81]. The dense substitution pattern in cyclization substrate **146** presumably imposes



Scheme 27 Influence of remote substrate substituents on RCM efficiency, observed during total synthesis of octalactin A (**148**) [81]

conformational constraints in a way that leads to a conformation favorably disposed for the ring closure. Thus, exposure of **146** to 10–20 mol% of catalyst **A** afforded cyclization product **147** within 24 h in 86% yield. In contrast, the diene ester with epimeric PMB ether group (3-*epi*-**146**) underwent ring closure under analogous conditions only with difficulty, leading to lactone 3-*epi*-**147** in 20% yield after 7 days in boiling dichloromethane.

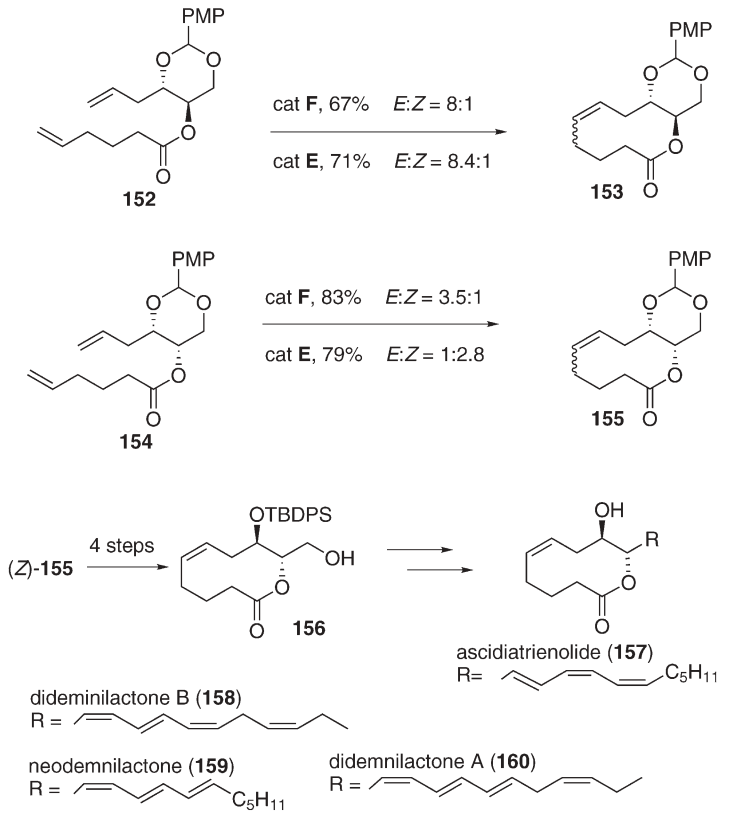
Halicholactone (**151**), a marine metabolite with lipoxygenase inhibitory activity, belongs to the family of oxylipins which all contain a lactone moiety substituted by a *trans*-disubstituted cyclopropane subunit. Stereoselective RCM for the formation of the nine-membered lactone core in **151** was the penultimate step (**149**→**150**) in an asymmetric total synthesis of **151** by a Japanese group (Scheme 28) [82]. After extensive experimentation, it was found that reaction of **149** with catalyst **A** under high dilution (0.1 mM in boiling dichloromethane) in the presence of a catalytic amount of $Ti(OiPr)_4$ gave rise to the desired (*Z*)-isomer **150** in 72% yield along with the corresponding dimer (11%). When the reaction was performed under more than 1.0 mM concentration, monomer **150** and the dimer were formed in almost equal amounts (each



Scheme 28 (*Z*)-selective RCM-based macrocyclization in the penultimate step in the total synthesis of halicholactone (**151**) [82]

20–30%). Note that the (*E*)-isomer of **150** was not detected under any reaction conditions. The total synthesis of **151** was then completed by methanolysis of the two acetyl groups.

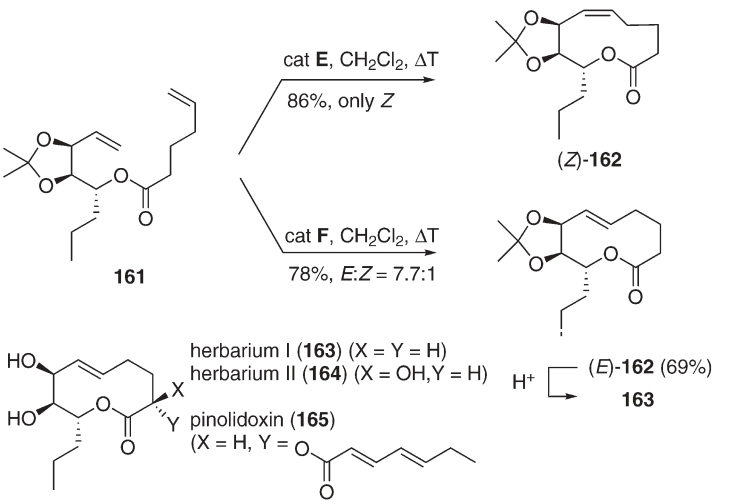
The marine natural product ascidiatrienolide (**157**) is a strong inhibitor of phospholipase A2. Compound **157** and the closely related didemnilactones **158–160** feature a common hydroxy-substituted (*anti* to the ring oxygen) (*Z*)-nonenolide core. Lactone **156**, that constituted the key intermediate in a previous total synthesis of **157** and can also be elaborated to lactones **158–160**, has been the subject of an interesting study by Fürstner's group [83] that revealed once more the very subtle and cooperative influence of different parameters on the stereochemical course of metathesis reactions. Thus, it was shown that the *E*/*Z* ratio obtained in an RCM step is not only dependent on the relative configuration of the cyclization substrate, but also on the chosen catalyst (Scheme 29). When applied to the *anti*-configured diene ester **152**, both ruthenium indenylidene complex **F** and second-generation catalyst **E** induced the preferential (*E*/*Z*≈8:1) formation of the undesired lactone (*E*)-**153** in compara-



Scheme 29 Effect of substrate substituents and catalyst activity on RCM stereochemistry, observed during the total synthesis of ascidiatrienolide (**157**) [83]

ble yield, but opposite results were obtained with the *syn* analog **154**. Specifically, indenylidene catalyst **F** still favored (3.5:1) the (*E*)-isomer of **155**, while NHC catalyst **E** favored the formation of the required nonenolide (*Z*)-**155** (*Z*:*E*=2.8:1), which was converted to target **156** in four steps.

In related contributions, Fürstner disclosed a concise RCM-based approach to a family of potent herbicidal ten-membered lactones with an (*E*) double bond, which led to the first total syntheses of herbarium I (**163**) [84a] and II (**164**) [84b], and also allowed the stereostructure of pinolidoxin (**165**) to be established (Scheme 30) [84b]. Again, the stereochemical outcome of the ring-closing step could be controlled by the choice of the catalyst, which is deemed to reflect kinetic versus thermodynamic control. En route to herbarium I (**163**), cyclization precursor **161** containing an isopropylidene protecting group, which should align the olefinic side chain in a "cyclization-friendly" conformation, was prepared in six steps from protected D-ribonolactone. Semiempirical calculations carried out for both possible cyclization products derived from **161** indicated that isomer (*Z*)-**162** is about 3.5 kcal mol^{-1} more stable than (*E*)-**162**. That means that only under kinetic control would it be possible to obtain the desired (*E*)-isomer, and that highly active catalysts known to favor the retro reaction, and hence leading to equilibration, would be counterproductive. The results obtained with indenylidene catalyst **F** and with the second-generation NHC catalyst **E** were fully consistent with the above predictions: catalyst **F** exhibited activity similar to Grubbs' benzylidene catalyst **A** and produced mainly (7.7:1) the less stable and desired (*E*)-**162** (the *E*/*Z* ratio did not evolve with time), while catalyst **E** led exclusively to the thermodynamically more stable (*Z*)-isomer. It seems that complex **E** and congeners, due to their higher overall activity, are able to isomerize the cycloalkenes formed during the course of the reaction and



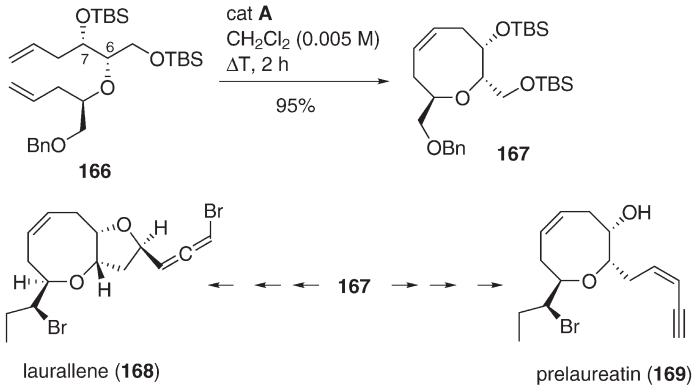
Scheme 30 Kinetically and thermodynamically controlled RCM in Fürstner's total synthesis of herbarium I (**163**) [84]

hence enrich the mixture in the thermodynamically favored product. Further support for this interpretation was provided by a control experiment showing that pure (*E*)-**162** was slowly isomerized to (*Z*)-**162** in the presence of catalyst **E** when the reaction was performed under an atmosphere of ethylene.

2.1.2.4 Cyclic Ethers

A range of topographically unique structures with seven- to nine-membered ether rings are produced by marine organisms. Several total syntheses of natural monocyclic eight-membered ring ethers (oxocenes) and the less common homologous oxonenes, produced by *laurencia* red algae, were reported by Crimmins' team by merging asymmetric aldol addition (or alkylation) of glycolates with an RCM reaction. Thereby it was demonstrated that medium-sized cyclic ethers are readily available without cyclic conformational constraint by exploiting the acyclic bias of the gauche effect of substituents on the carbons flanking the ether linkage.

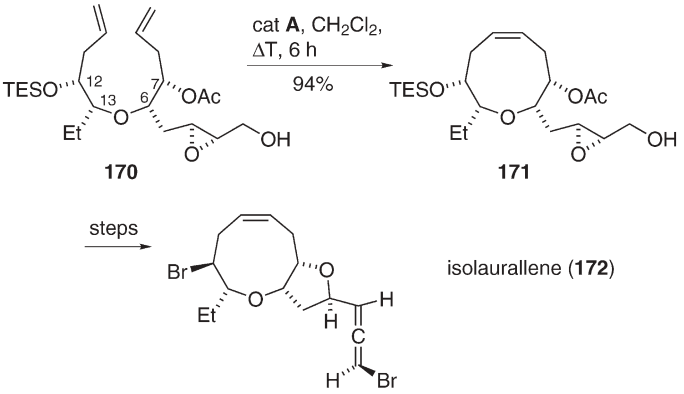
A year after the total synthesis of (+)-laurencin [85], Crimmins disclosed the total syntheses of (+)-prelaureatin (**169**) and (+)-laurallene (**168**) by applying a similar strategy (Scheme 31) [86]. The critical RCM reaction was undertaken



Scheme 31 Efficient RCM to Δ4-oxocene **167** in Crimmins' total syntheses of the marine natural products laurallene (**168**) and prelaureatin (**169**) [86]

with precursor **166**, anticipating that the gauche effect of the C6 and C7 oxygens would accelerate the ring closure. Exposure of **166** (0.005 M in dichloromethane) to Grubbs' catalyst **A** proceeded smoothly to provide the key Δ^4-oxocene **167** in 95% yield with no detectable dimerization.

In subsequent reports [87], the principle of asymmetric glycolate alkylation/RCM sequence was applied to the first total synthesis of isolaurallene (**172**), that contains a densely functionalized Δ^5-oxonene core (Scheme 32). Anticipating that the gearing effect created by two synergistic gauche effects at C6–C7 and



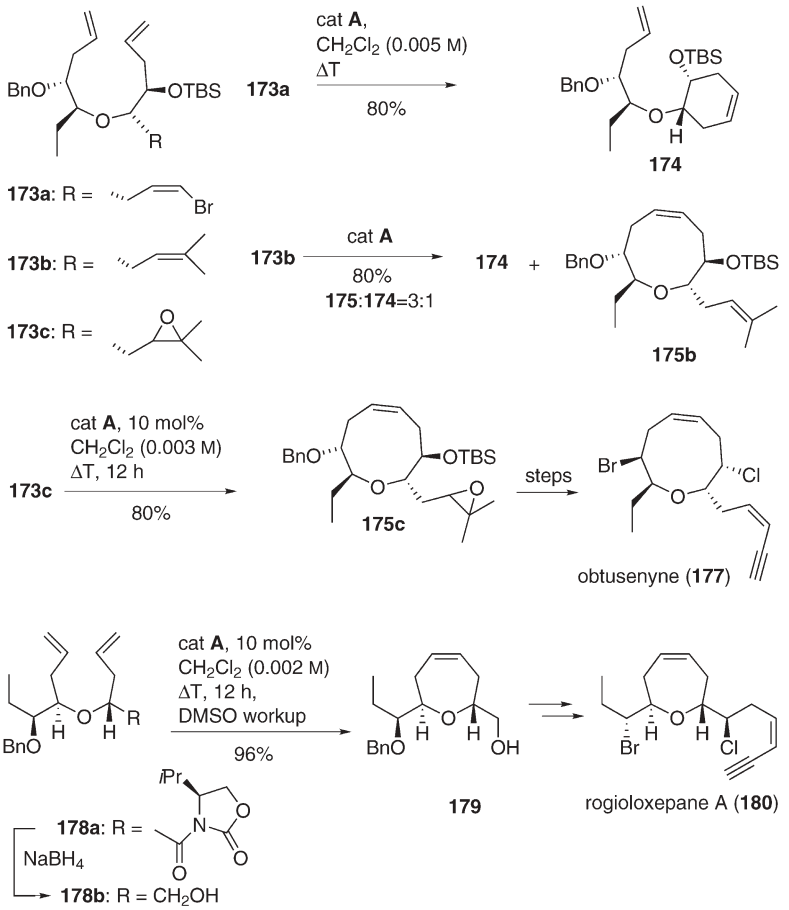
Scheme 32 RCM-based synthesis of the Δ5-oxonene **171** in Crimmins' total synthesis of isolaurallene (**172**) [87]

C12–C13 would facilitate the ring closure, monocyclic diene **170** was chosen as the metathesis substrate. Indeed, exposure of **170** to catalyst **A** provided cyclization product **171** in 94% yield within 6 h, without the aid of a cyclic conformational constraint.

To date, the most recent of Crimmins' contributions in this series are the total syntheses of the nine-membered cyclic ether obtusenyne (**177**) [88] and the oxepene rogioloxepane A (**180**) [89], which both feature a *trans*-orientation of the substituents flanking the ether linkage (Scheme 33). Three different RCM precursors (**173a–c**) were investigated during the synthesis of **177**. Attempts to form the nine-membered ring from the bromo-substituted triene **173a** resulted in loss of the vinyl halide by regioselective formation of cyclohexene derivative **174** in 80% yield. Triene **173b** with a trisubstituted double bond provided a 3:1 mixture of oxonene **175b** and cyclohexene **174**. Finally, conversion of **173b** to epoxy-diene **173c** followed by treatment with catalyst **A** effected rapid closure to **175c** that was converted to **177** in 13 steps.

In the total synthesis of rogioloxepane A (**180**), oxazolidinone **178a** was primarily examined as the metathesis substrate. However, the subsequent removal of the auxiliary with sodium borohydride proceeded with low yield due to concomitant hydrogenation of the oxepene by remaining traces of the ruthenium catalyst. Therefore the order of steps was reversed and the RCM step performed with primary alcohol **178b**, which additionally could bias the diene conformation by a hydrogen bond with the ether oxygen. Treatment of **178b** with catalyst **A**, followed by DMSO workup to remove traces of catalyst-derived materials [50b], then led to key intermediate **179** in excellent yield.

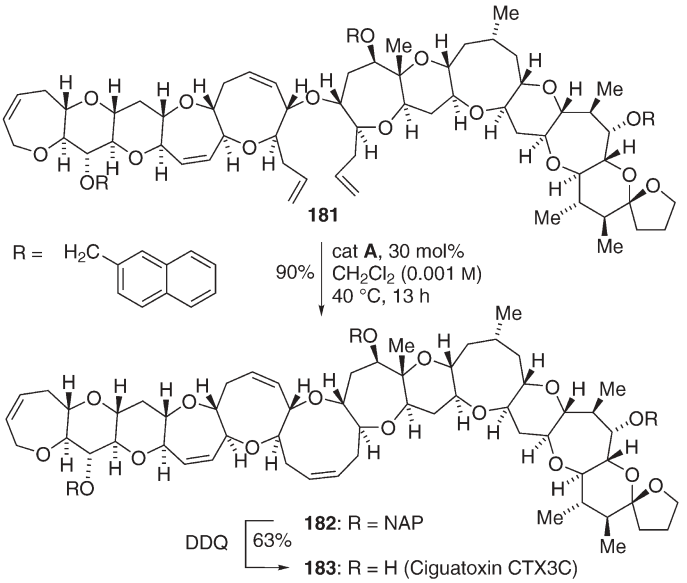
A highlight in the application of RCM methodology in natural product synthesis is Hirama's total synthesis of ciguatoxin CTX3C (**183**) [90], including the more recent improved protective group strategy, as depicted in Scheme 34 [90b]. The structure of **183** spans more than 3 nm and is characterized by 12 six- to nine-membered *trans*-fused cyclic ethers and a spiroannulated terminal tetra-



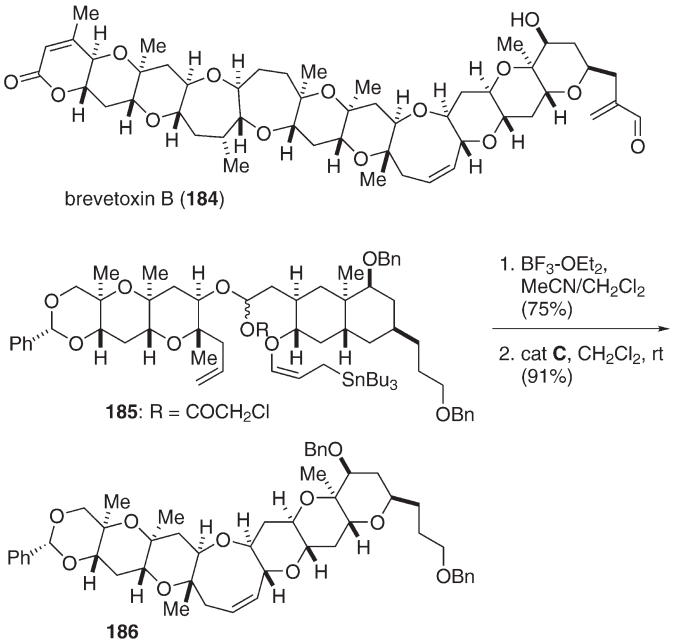
Scheme 33 RCM-based total synthesis of the marine cyclic ethers obtusenyne (**177**) [88] and rogioloxepane (**180**) [89] by Crimmins and coworkers

hydrofuran ring. Causative toxins such as **183** are produced by the marine dinoflagellate *Gambierdiscus toxicus* and accumulate in fish of many species through the food chain. In the penultimate step of the improved total synthesis, pentaene **181**, that is only missing the central nine-membered ring, was exposed to catalyst **A** in boiling dichloromethane to provide 2-naphthylmethyl (NAP)-protected CTX3C (**182**) chemoselectively in 90% yield and to set all rings in place. The three NAP groups in **182** (the deprotection of the corresponding tris-benzyl ether in the original synthesis proceeded with low yield) were then removed with DDQ to furnish the natural compound **183** in 63% yield.

Intramolecular allylation of α-chloroacetoxy ether **185** followed by RCM (Scheme 35) was used by Yamamoto and coworkers to construct the eight-membered cyclic ether in the F–K ring segment **186** of the marine neurotoxin brevetoxin B (**184**) [91].



Scheme 34 Formation of the central nine-membered ring and completion of the carbon skeleton in Hirama's improved total synthesis of the marine neurotoxin ciguatoxin CTX3C (**183**) [90b]



Scheme 35 Sequential formation of rings I and H by intramolecular allylation/RCM in Yamamoto's synthesis of the F–K ring segment **186** of brevetoxin B (**184**) [91]

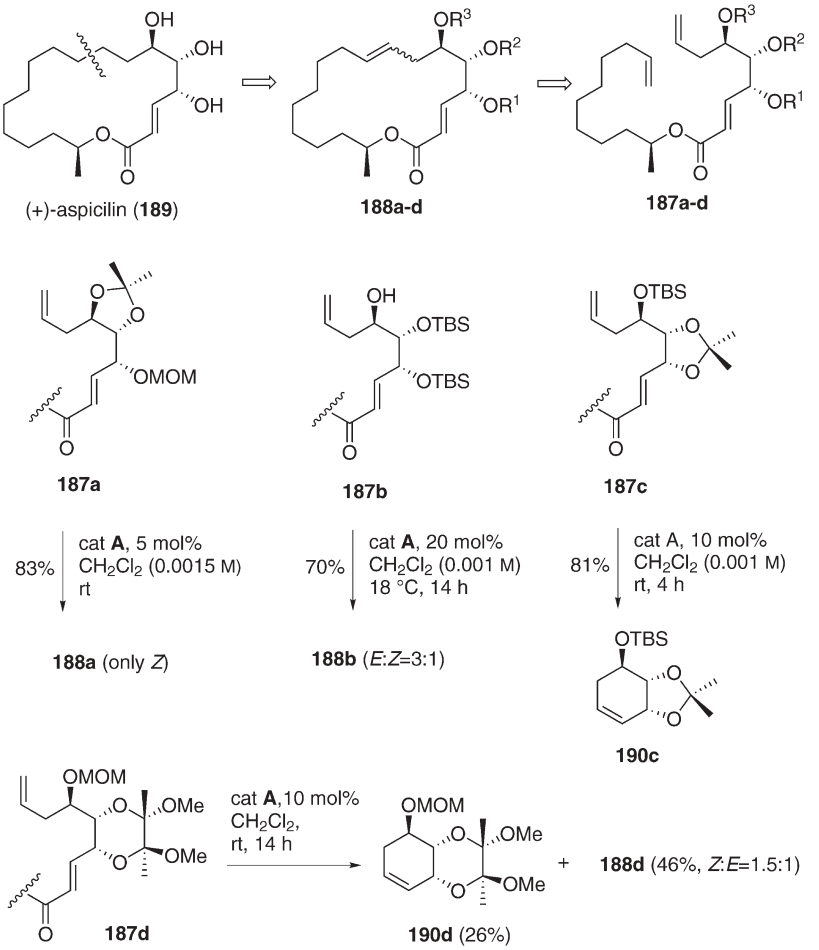
2.1.3 Formation of Macrocycles

RCM-based formation of – unstrained – macrocycles is, due to the concomitant loss of a volatile alkene, mainly entropically driven and therefore a high yielding process. However, there exists still a lack of prediction for the configuration of the newly formed double bond of cycloalkenes with more than ten ring atoms. The products formed are frequently obtained as *E*/*Z* mixtures with the (*E*)-isomer dominating in most of the recorded cases. This obvious drawback in target-oriented synthesis was already evident from the early and most prominent RCM-based epothilone syntheses [92], which suffered from very low stereoselectivity in the formation of the required (*Z*)-12,13 double bond. The following examples of RCM-based syntheses of macrocyclic natural products will reveal that the success and/or the stereochemical outcome of macrocyclic RCM is highly sensitive to steric or electronic substituent effects in the precursor diene, and can also depend on the choice of the catalyst, as well as on the solvent and the reaction temperature applied in the metathesis process. Additionally we will see that, for the formation of strained products, large enthalpic barriers can be overcome by altering the shape of the metathesis substrate through the introduction of additional conformational constraints.

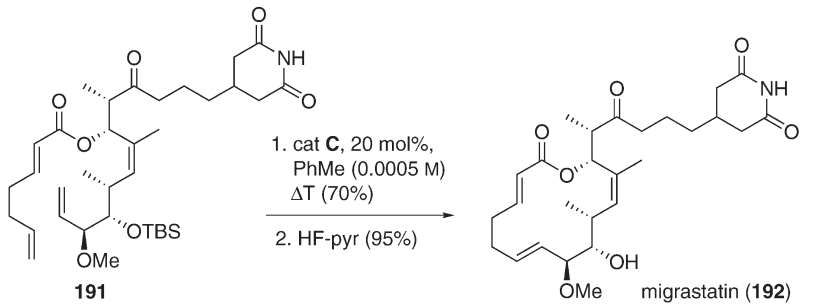
2.1.3.1 Macrolides

Three RCM-based syntheses of the 18-membered α,β-unsaturated macrolide aspicilin (**189**), all performed with Grubbs' first-generation catalyst **A** and differently protected precursor trienes **187a–d** (Scheme 36) [93], illustrate the importance of substituent effects on the regio- and stereochemistry of the metathesis reaction, albeit in this case the stereochemical outcome of the ring-closing step is inconsequential. Hatakeyama's isopropylidene-protected precursor **187a** led exclusively to macrolactone **188a** with (*Z*) configuration at the newly formed double bond. In contrast, Banwell's first precursor **187c** reacted regioselectively with formation of the undesired cyclohexene **190c**, while the open-chain precursor **187b** furnished a 3:1 mixture of macrolides in favor of the (*E*)-isomer. Partial cyclohexene formation was also observed by Ley, who isolated from the cyclic metathesis substrate **187d** a mixture of macrolide **188d** (1.5:1 *Z*/*E*-mixture) and cyclohexene **190d**.

Migrastatin (**192**) (Scheme 37) is a novel macrolide natural product that displays an inhibitory effect on the migration of human tumor cells. After an RCM-based synthesis of the 14-membered macrolide core of **192** [94], Danishefsky also achieved the first total synthesis of the natural compound [95], using the fully functionalized tetraene **191** as the metathesis precursor. Under the conditions shown in Scheme 37, the ring-closing step proceeded (*E*)-selectively with exclusive participation of the two terminal double bonds in **191**, delivering only the (*E*,*E*,*Z*)-trienyl arrangement present in **192**.

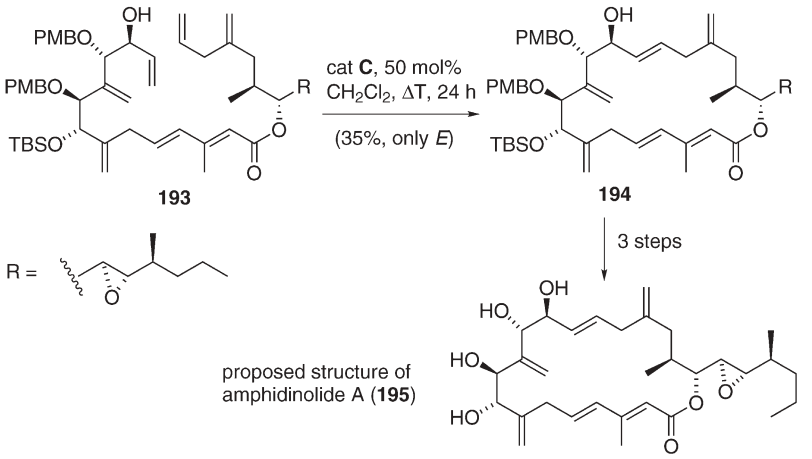


Scheme 36 RCM-based synthesis of aspicilin (**189**): effect of substrate substitution on regio- and stereochemistry [93]



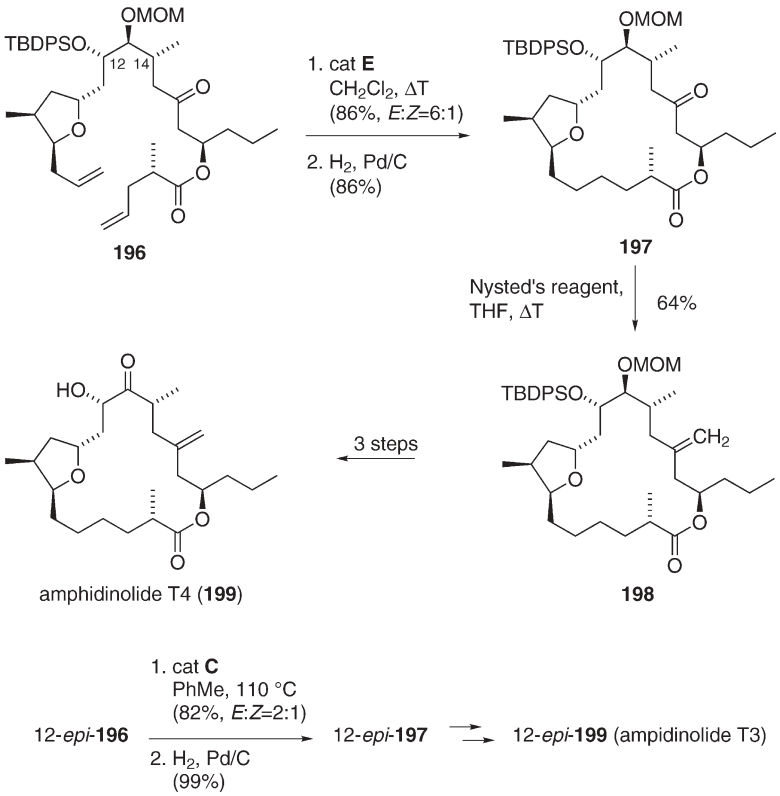
Scheme 37 Regioselective RCM of tetraene **191** in Danishefsky's total synthesis of migrastatin (**192**) [95]

Three total syntheses of the highly unsaturated macrolactone **195**, featuring the structure proposed for the cytotoxic marine natural product amphidinolide A (Scheme 38) were disclosed in 2002 [96], which all confirmed that the structure of **195** proposed for the natural product needs to be revised. In Maleczka's synthesis [96a], the highly unsaturated 20-membered ring of **195** was formed by a late-stage RCM reaction. Given the array of olefinic functionality in metathesis substrate **193**, the authors used the less active first-generation catalyst **A** in their first attempt, which should guarantee regioselectivity, but this catalyst only truncated the allylic alcohol in **193** leading to the corresponding methyl ketone [97]. With second-generation catalyst **C**, the ring closure occurred, but 0.5 equivalents of the catalyst were necessary to provide regio- and (*E*)-stereoselectively macrolide **194** in low yield.



Scheme 38 Regioselective RCM of heptaene **193** in Maleczka's synthesis of the structure **195** proposed for amphidinolide A [96a]

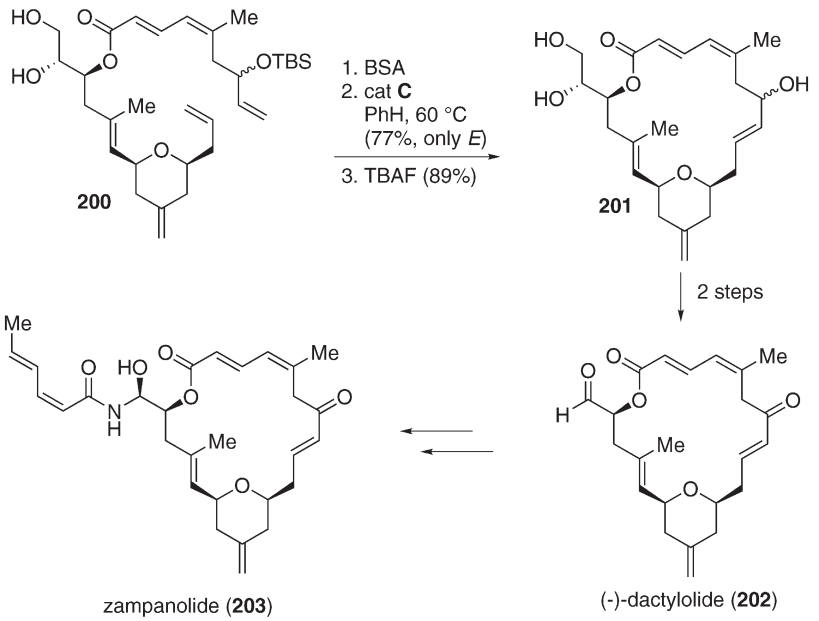
Several members of the structurally quite diverse amphidinolide T family containing a saturated 19-membered lactone core were recently synthesized by Fürstner and coworkers [98]. Amphidinolide T4 (**199**, Scheme 39) [98a] and also T1 and T5 (not shown in the scheme) [98b] were prepared from compound **196** as a common intermediate. The macrocyclic ring was efficiently formed by a high-yielding RCM of diene **196** in the presence of second-generation catalyst **E** bearing an imidazol-2-ylidene ligand. The efficiency of the RCM transformation was mainly attributed to the conformational bias introduced by the *syn–syn* configured stereotriad at C12–C14 in **196**. The resulting cycloalkenes obtained in 86% yield as an inconsequential isomeric mixture (*E*:*Z*=6:1) were hydrogenated to **197**. After methylenation to **198**, the synthesis of **199** was completed by three additional steps. En route to amphidinolide T3 (12-*epi*-**199**) [98b] via RCM of 12-*epi*-**196**, it turned out that the efficiency and stereochemical outcome of the ring closure was distinctly affected by the configurational



Scheme 39 Influence of a remote substituent on efficiency and stereochemistry of the RCM step in Fürstner's total synthesis of amphidinolide T4 (**199**) [98a] and amphidinolide T3 (12-*epi*-**199**) [98b]

change (*anti–syn* stereotriad at C12–C14) at the seemingly remote stereocenter C12. Good conversion could only be attained in the presence of catalyst **C** (bearing a saturated NHC ligand), and by exchanging the solvent from dichloromethane to toluene with concomitant increase of the reaction temperature to 110 °C.

Recently, Hoye described an RCM-based total synthesis of the 20-membered marine macrolide dactylolide (**202**) and its subsequent conversion to the natural carbinolamide zampanolide (**203**) (Scheme 40), which feature a common highly unsaturated macrolide core, bridging a *cis*-2,6-disubstituted 4-methylene tetrahydropyran unit [99]. When the polyunsaturated acyclic lactone **200** (1:1 epimeric mixture around the TBS-protected carbinol center) was in situ protected with bis-trimethylsilylacetamide (BSA) and then treated with catalyst **C** in benzene at 60 °C, each diastereomer smoothly cyclized to the corresponding cycloalkene with exclusive (*E*) geometry at the newly formed double bond, demonstrating that configurational change at this position had (in this special case) no influence on the results.

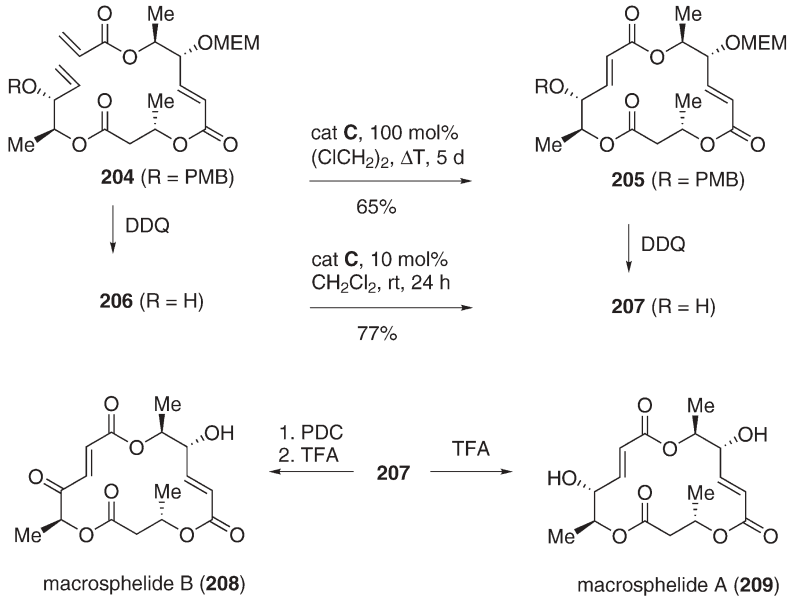


Scheme 40 (*E*)-Selective macrocyclization in the total synthesis of the marine macrolides dactylolide (**202**) and zampanolide (**203**) [99]

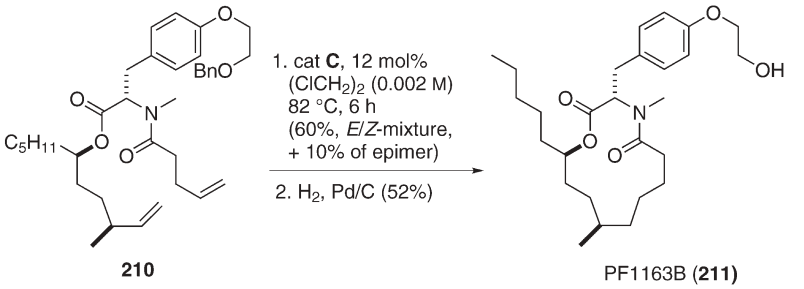
An example of the efficient formation of an electron-deficient double bond by RCM was disclosed by a Japanese group in a novel total synthesis of the macrosphelides A (**209**) and B (**208**) (Scheme 41) [100]. When the PMB-protected compound **204** was examined as a metathesis substrate, the ring closure did not proceed at all in dichloromethane using catalysts **A** or **C**. When the reaction was carried out using equimolar amounts of catalyst **C** in refluxing 1,2-dichloroethane, the cyclized product **205** was obtained in 65% yield after 5 days. On the other hand, the free allylic alcohol **206** reacted smoothly at room temperature leading to the desired macrocycle **207** in improved yield.

Also the novel antifungal antibiotic (–)-PF1163B (**211**), isolated from *Streptomyces* sp., which features a 13-membered macrocycle incorporating both a lactone and a lactam unit, was synthesized by an RCM route (Scheme 42) [101]. While only poor results were obtained by treatment of diene **210** (containing 8% of an unidentified epimer) with catalyst **A**, the use of NHC catalyst **C** led, under the conditions outlined in the scheme, to the corresponding cyclization product in 60% yield along with 10% of a diastereomer resulting from epimerization in a previous step.

The salicylihalamides A (**215a**) [102] and B (**215b**) are the first members of a growing class of secondary marine metabolites with a 12-membered benzolactone core incorporating salicylic acid in conjunction with a dienylenamide side chain (Scheme 43). Salicylihalamide A (**215a**) was reported to be a unique and highly differential cytotoxin and a potent inhibitor of the mammalian vac-



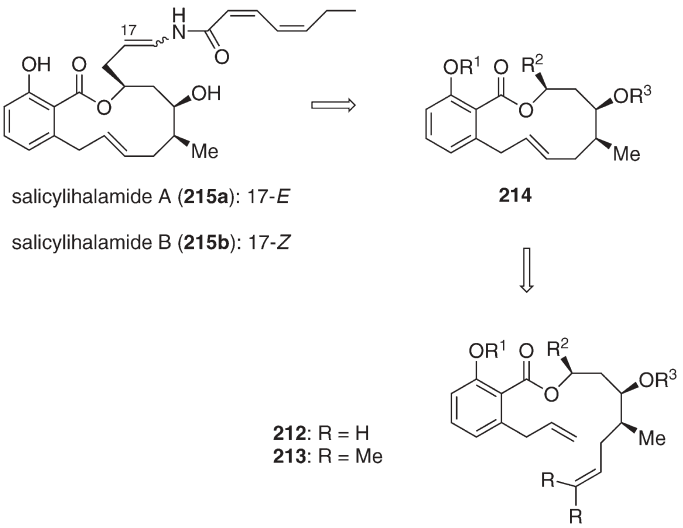
Scheme 41 (*E*)-Selective RCM of acrylate **204** in the total syntheses of the macrosphelides A (**209**) and B (**208**) [100]



Scheme 42 Macrocyclization by RCM in the total synthesis of the antifungal antibiotic PF1163B (**211**) [101]

uolar (H^+)-ATPase. To date, there exist several total syntheses of **215a** that rely on an (*E*)-selective RCM of dienes **212** or **213** to construct the benzolactone core **214** [103].

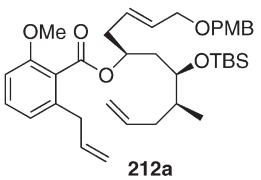
The results obtained with the various metathesis substrates depicted in Scheme 44 demonstrate the lack of a stereopredictive model for the RCM-based formation of macrocycles, not only by the strong influence that may be exhibited by *remote* substituents, but also by the fact that the use of more reactive second-generation catalysts may be unfavorable for the stereochemical outcome of the reaction. Dienes **212a–f** illustrate the influence of the substitution pattern. All reactions were performed with Grubbs' first-generation catalyst **A**



Scheme 43 Structure and retrosynthetic analysis of the salicylate macrolides salicylihalamide A (**215a**) and B (**215b**) by various groups [103]

in dichloromethane, but the isomeric ratio varied from the favorable *E*/*Z*=10:1 obtained by Smith [103d] with **212a**, to the "mainly *Z*" observed by Snider [103a] with **212e** featuring a remote free phenolic hydroxy group, while no ring closure occurred with Snider's bicyclic model **212f**. The RCM precursors **213a–d** used by Fürstner's group [103c] differ from compounds of the type **212** mainly by the *gem*-disubstitution at one of the olefinic moieties, so that the ring-closing step had – in this case – to be conducted with a more reactive ruthenium catalyst of the second generation. The macrocyclizations with compounds **213a–d** were all performed with catalyst **E** in toluene at 80 °C, and again it turned out that the stereochemical outcome was strongly dependent on the phenolic protective group, ranging from "only *Z*" for the unprotected phenol **213a**, 1.5:1 in favor of the (*Z*)-isomer for the corresponding silyl ether **213b**, to a 2:1 ratio in favor of the required (*E*)-isomer for both the methyl and the MOM ether derivatives **213c,d**. Finally, a detailed study of the metathesis step conducted with dienes **212g** and **212h** in De Brabander's full account [103e] brought partial light to this confusing situation, identifying the high (*E*) stereoselection obtained with catalyst **A** at room temperature as a result of a kinetically favored process. On the other hand, with second-generation catalyst **C** (or **E**), an equilibrium is quickly reached, so that the identical isomeric ratios (*E*:*Z*≈2:1) obtained with Fürstner's precursors **103c,d** and Brabander's substrates **101g,h** reflect a thermodynamic distribution, where secondary metathesis isomerization can compete at the timescale of the experiment. (It should be pointed out, however, that the pronounced influence of a remote phenolic OH group, which favors the undesired (*Z*) stereochemistry with catalysts **A** and **E**, still remains unclear).

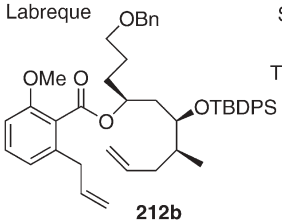
Smith



212a

cat **A**, 10 mol%
CH_2Cl_2, 0.008 M,
rt, 40 min,
(85%, *E*:*Z*=10:1)

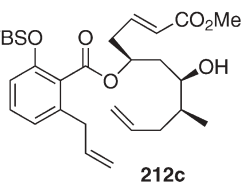
Labreque



212b

cat **A**
CH_2Cl_2, ΔT, 3 h
(75%, *E*:*Z*=9:1)

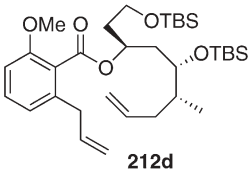
Snider



212c

cat **A**
CH_2Cl_2, ΔT, 5 h
(71%, *E*:*Z*=4:1)

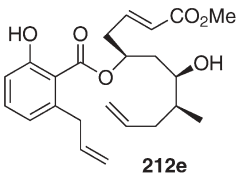
De Brabander



212d

cat **A**, 10 mol%
CH_2Cl_2, 0.008 M,
rt, 3 h,
(100%, *E*:*Z*=1:4)

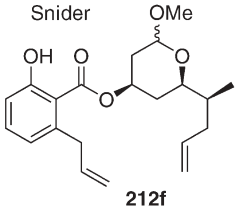
Snider



212e

cat **A**
CH_2Cl_2, ΔT, 3-4 d
("mainly *Z*")

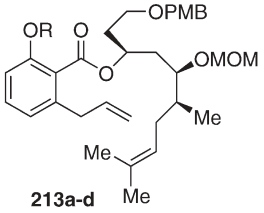
Snider



212f

"no RCM with cat **A**"

Fürstner (all reactions performed with cat **E**)



213a-d

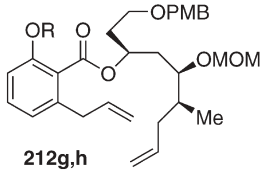
213a (R=H) cat **E**, 10 mol% PhMe, 80 °C, 20 h (69%, only *Z*)

213b (R=TBS) cat **E**, 5 mol% PhMe, 80 °C, 1 h (91%, *E*:*Z*=1:1.5)

213c (R=Me) cat **E**, 5 mol% PhMe, 80 °C, 1.5 h (93%, *E*:*Z*=1.9:1)

213d (R=MOM) cat **E**,10 mol% PhMe, 80 °C, 3 h (91%, *E*:*Z*=2.1:1)

De Brabander (reactions performed with cat **A** or cat **C**, 10 mol%, CH_2Cl_2, rt, all combined yields > 93%)

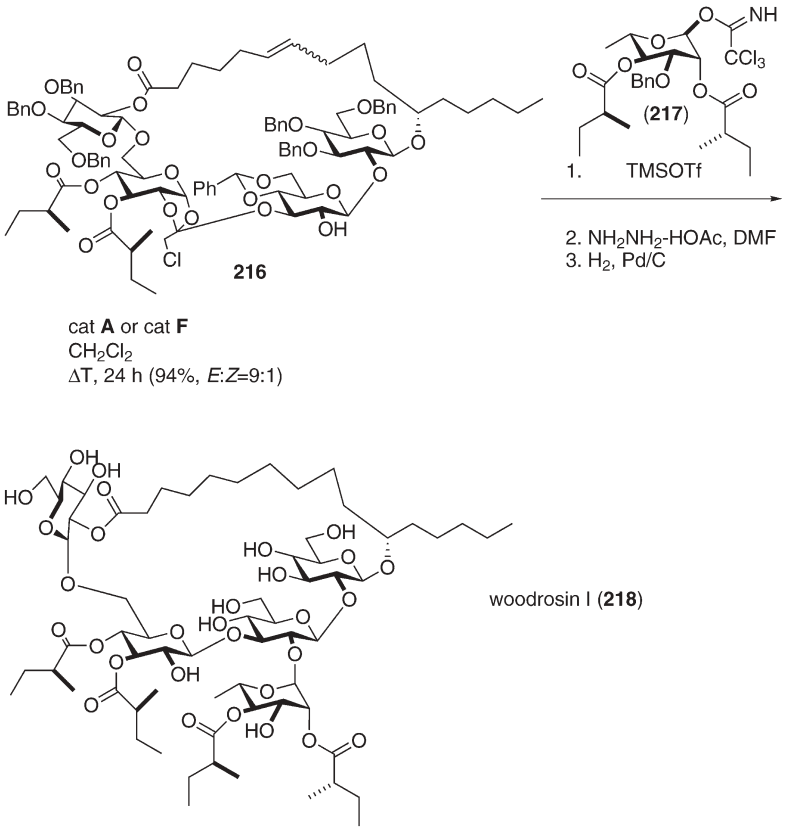


212g,h

	cat **A**	cat **C**
212g (R=Me)	1.3 h (*E*:Z=9:1) 18.3 h (*E*:*Z*=4:1)	1.3 h (*E*:Z=1.9:1) 18.3 h (*E*:*Z*=2:1)
212h (R=MOM)	1.3 h (*E*:*Z*=9:1) 18.3 h (*E*:*Z*=5:1)	1.3 h (*E*:*Z*=1.8:1) 18.3 h (*E*:*Z*=2.1:1)

Scheme 44 Influence of remote substituents in RCM precursors **212** and **213** and of catalyst activity on stereochemistry in salicylihalamide synthesis [103]

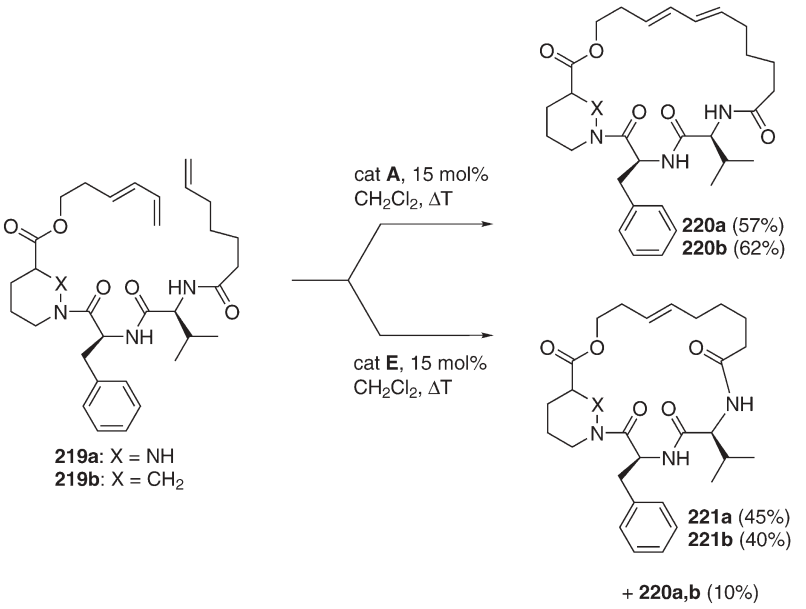
A recent example of RCM-based macrocyclization with a highly complex metathesis substrate is the formation of macrolide **216** from the corresponding diene precursor in Fürstner's total synthesis of the resin glycoside woodrosin I (**218**) (Scheme 45) [104]. The site of ring closure was chosen far away from potential donor sites in the oligosaccharide scaffold, so that the formation of unreactive metal chelate complexes was avoided. Accordingly, a virtually quantitative formation of **216** (*E*:*Z*=9:1) was observed on treatment with catalysts **A** or **F**. Subsequent exposure of **216** to glycosyl donor **217** led not only to the introduction of the missing rhamnose unit, but also to concomitant rearrangement of the *ortho* ester into the desired *β*-glycoside. The synthesis of **218** was then completed in two steps.



Scheme 45 Macrocyclization by RCM in Fürstner's total synthesis of the resin glycoside woodrosin I (**218**) [104]

2.1.3.2 RCM of Diene-Ene Systems

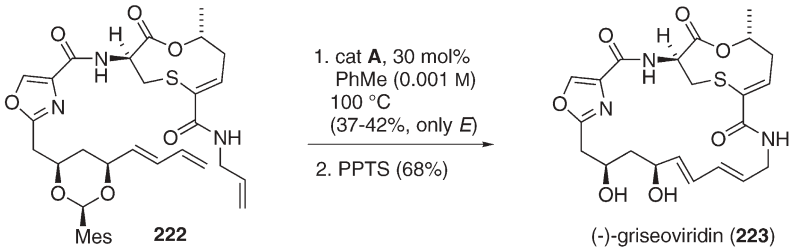
An increasing number of natural product syntheses feature the RCM of diene-ene systems to produce macrocyclic dienes. However in some cases, divergences in regioselectivity of catalyst attack were observed depending on the structural features of the metathesis substrate and also on the catalyst used to promote the metathesis event [105]. The first example of regioselective diene-ene metathesis was contributed by a Novartis group in 1999, during synthesis of simplified macrolide analogs of the immunosuppressant sanglifehrin (Scheme 46) [106].



Scheme 46 Diene-ene RCM: influence of catalyst activity on the regiochemistry during the synthesis of simplified analogs of sanglifehrin [106b]

Treatment of trienes **219a,b** with first-generation catalyst **A** led to the desired cyclic (*E*,*E*)-dienes **220** in satisfactory yield, along with the corresponding (*E*,*Z*)-analogs as minor components (<5%). In subsequent work [106b], it unexpectedly turned out that second-generation catalyst **E** involved predominantly the more substituted internal double bond in precursors **219**, leading to the ring-contracted cyclic monoenes **221** in moderate yield, while the desired cyclodienes **220** were detected only as minor components.

Another example of macrocyclic RCM with a diene-ene was disclosed in 2000 by Meyers and coworkers in the first total synthesis of griseoviridin (**223**) [107]. Griseoviridin is a highly complex member of the family of streptogramin antibiotics, featuring a 23-membered unsaturated bis-lactam core incorporat-



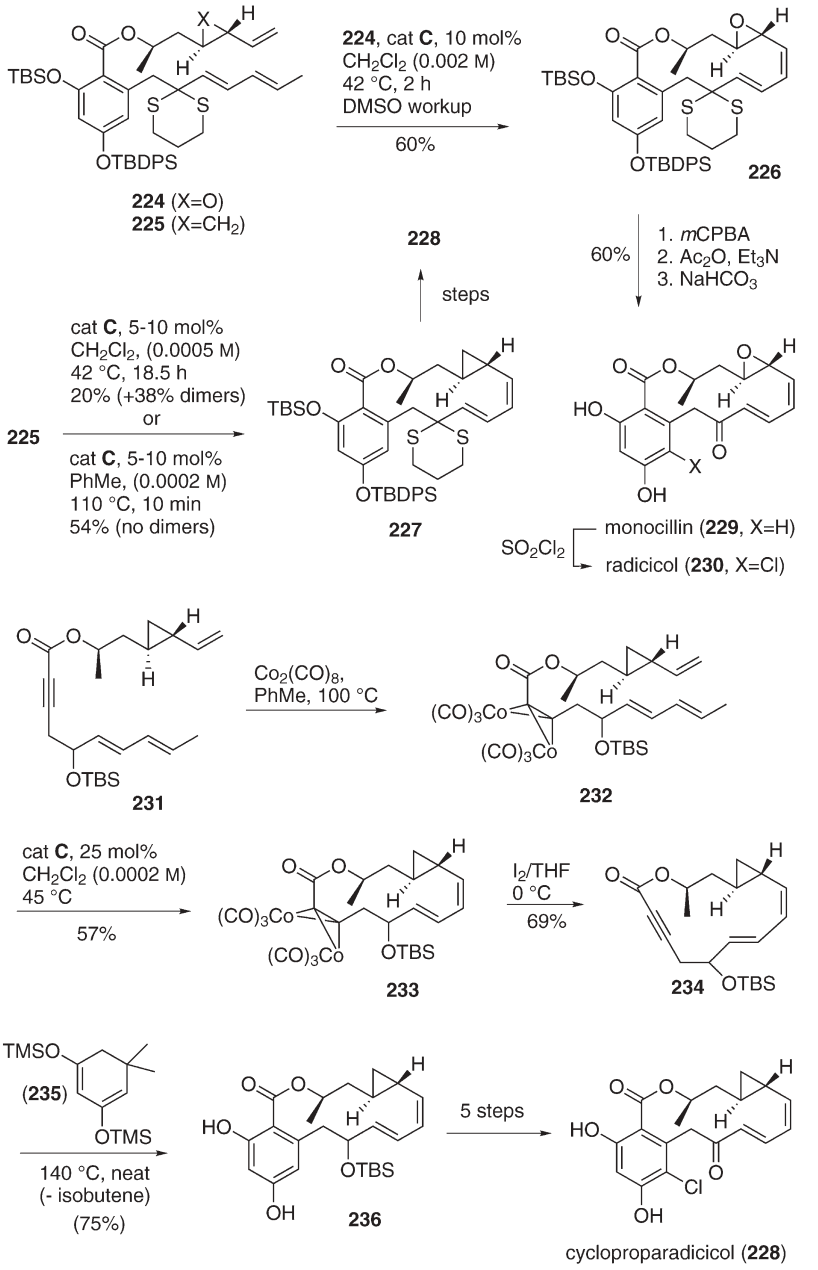
Scheme 47 Macrocyclization via diene-ene RCM in the first total synthesis of griseoviridin (**223**) [107]

ing an oxazole and a nine-membered lactone with an ene–thio linkage. The macrocyclic ring of **223** was (*E*)-selectively elaborated in the penultimate step, by exposing allylamine **222** to catalyst **A** (Scheme 47).

Hsp90 is a molecular chaperon required for the refolding of proteins in cells exposed to environmental stress. It contains an ATP-binding pocket in its amino terminus. Several natural products, for example radicicol (**230**) (Scheme 48), bind to this pocket and inhibit its chaperon function, which is mirrored in enhanced proteosomal degradation of Hsp90 client proteins, so that compounds like **230** are of interest as novel anticancer agents.

Danishefsky's total synthesis of **230** and its chlorine-free precursor monocillin I (**229**) [108] features a novel RCM reaction with a substrate (**224**) that, in addition to a dithiane protective group, contains a vinyl epoxide and a diene moiety at both the termini involved in the metathesis process (Scheme 48). Reaction of **224** with catalyst **A** furnished only traces of the desired product. Application of catalyst **C** gave the desired 14-membered benzolactone **226** with (*Z*) configuration at the newly formed double bond, which was deprotected to **229** and finally chlorinated to **230**. Later on, with the aim of improving the unfavorable pharmacokinetics of **230**, a similar RCM-based route was examined to obtain the cyclopropa- analog **228** [109]. Under the reaction conditions applied to **224**, cyclopropa-derivative **225** furnished the desired cyclization product **227** in only 20% yield together with substantial amounts of dimers. Carrying out RCM in refluxing toluene at higher dilution afforded an improved yield of the monomeric macrocycle when the reaction was quenched after a few minutes. Runs with prolonged reaction times resulted in the formation of more dimer, indicating that the monomer might eventually revert to the thermodynamically more favored dimers.

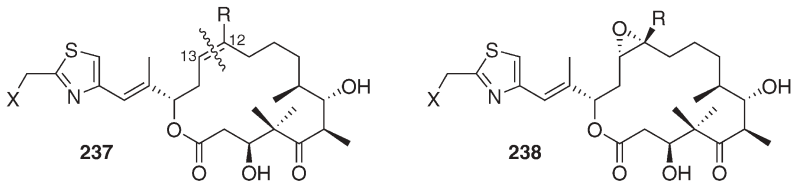
In a more recent and improved approach to cyclopropa-radicicol (**228**) [110], also outlined in Scheme 48, the synthesis was achieved via ynolide **231** which was transformed to the stable cobalt complex **232**. RCM of **232** mediated by catalyst **C** led to cyclization product **233** as a 2:1 mixture of isomers in 57% yield. Oxidative removal of cobalt from this mixture followed by cycloaddition of the resulting cycloalkyne **234** with the cyclic diene **235** led to the benzofused macrolactone **236**, which was converted to cyclopropa-radicicol (**228**).



Scheme 48 Diene-ene RCM in Danishefsky's total synthesis of radicicol (**230**) [108] and its cyclopropa-analog **228** [109, 110]

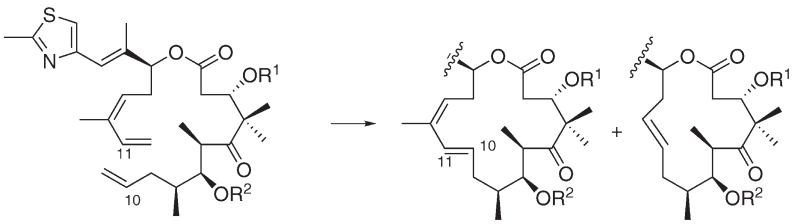
The epothilones **237** and **238** are 16-membered macrolides isolated from *myxobacteria* (Fig. 8). These compounds possess a taxol-like mode of action, epoB (**238b**) being the most active compound, and function through the stabilization of cellular microtubules, exhibiting cytotoxicity even in taxol-resistant cell lines. The emergence of epothilones as promising anticancer drug candidates has led to a worldwide effort to synthesize new analogs with a view to identifying and developing later-generation derivatives for clinical evaluation [111]. Previous attempts at applying RCM to epothilone syntheses have been repeatedly plagued by complete lack of stereocontrol in the generation of the desired (*Z*)-12,13-olefin geometry [112].

An alternative RCM-based *bond connection between C10 and C11* in the epothilone series was used in Danishefsky's total synthesis of epo490 (**240d**), a naturally occurring, recently discovered cometabolite, that differs from epoD (**237d**) by the presence of an additional (*E*)-10,11 double bond [113]. This alternative macrocyclization also proved to be a viable and novel route to **237d** (Scheme 49). Initially, the metathesis step was performed with differently protected precursor diene-enes **239a–c** using catalyst **C** in refluxing dichloromethane. It turned out that triene **239a** led to a mixture of two compounds in a 2.3:1 ratio with a total yield of 50% (no reaction at all was observed with ruthenium catalyst **A**, while molybdenum catalyst **B** led to decomposition of **239a**). The major component of the mixture was the desired RCM product **240a**, while the 14-membered by-product **241a** arose from extrusion of a propene unit from attack at the internal olefin [114]. When the cyclization of **239a** was performed in refluxing toluene for a few minutes, the yield of **240a** was distinctly improved, while the amount of the by-product decreased. (A similar beneficial effect by performing ene-diene RCM in toluene was also observed for analogous compounds with only slight structural variations). Performing the ring closure as the last synthetic step with unprotected diol **239d** led directly to epo490 (**240d**) in 64% yield; as both the C3 and C7 alcohols in **139d** are β to carbonyl groups, it is assumed that intramolecular H bonding contributes a higher degree of favorable rigidity to the cyclization precursor. Finally, selective diimide reduction of **240d** led to epoD (**237d**), a current clinical candidate in the epothilone series [115].

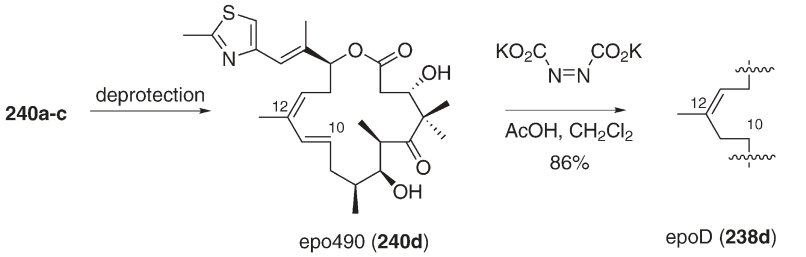


epoC (X=R=H, **237c**) epoA (X =R=H, **238a**) epoE (X=OH, R=H, **238e**)
epoD (X=H, R=Me, **237d**) epoB (X=H, R=Me, **238b**) epoF (X=OH, R=Me, **238f**)

Fig. 8 Structure of epothilones A–F

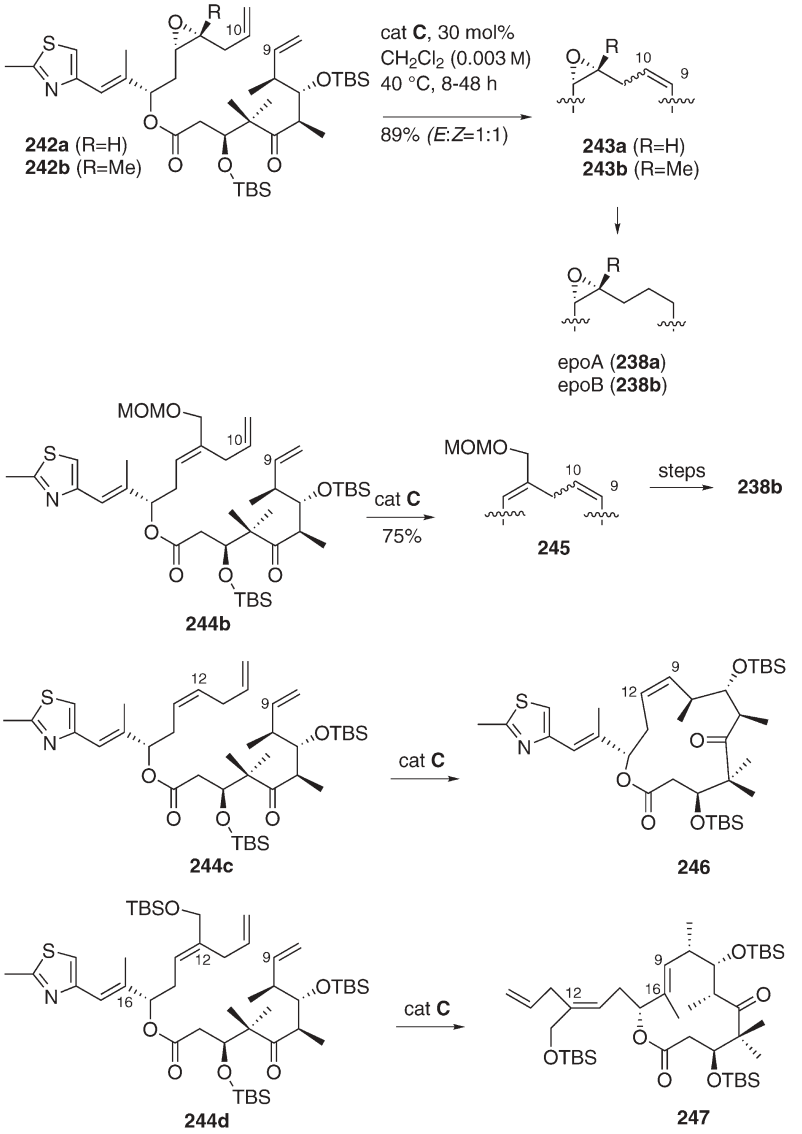


239		240	241
239a (R^1=TES, R^2=Troc)	cat **C**, 10 mol%, CH_2Cl_2 (0.002 M) 35 °C, 5.5 h	**240a** (35%)	**241a** (15%)
	cat **C**, 20 mol%, PhMe (0.0005 M) 110 °C, 25 min	**240a** (58%)	**241a** (5%)
239b (R^1=H, R^2=Troc)	cat **C**, 10 mol%, CH_2Cl_2 (0.002 M) 35 °C, 5.5 h	**240b** (41%)	**241b** (0%)
239c (R^1=TES, R^2=H)	cat **C**, 10 mol%, CH_2Cl_2 (0.002 M) 35 °C, 5.5 h	**240c** (57%)	**241c** (0%)
239d (R^1=R^2=H)	cat **C**, 10 mol%, CH_2Cl_2 (0.002 M) 35 °C, 5.5 h	**240d** (64%)	**241d** (0%)



Scheme 49 Total syntheses of epo490 (**240d**) and epoD (**237d**) by diene-ene RCM between C10 and C11: favorable influence of solvent toluene or unprotected hydroxy groups in metathesis substrates **239** [113]

The synthesis of an epothilone model system via an alternative *C9–C10 disconnection* was first examined by Danishefsky in 1997. However, extension of this C9–C10 strategy to a fully functionalized epothilone intermediate was not successful, demonstrating the limitations of RCM with the early catalysts **A** and **B** [116]. In 2002, Sinha and Sun disclosed the stereoselective total syntheses of epoA (**238a**) and epoB (**238b**) by the RCM of epoxy compounds **242** in the presence of catalyst **C** (Scheme 50) [117]. The reaction furnished an inconsequential mixture of isomers **243** (*E*/*Z*≈1:1) in high yield. Subsequent selective hydrogenation of the newly formed double bond followed by deprotection led to epothilones A and B.



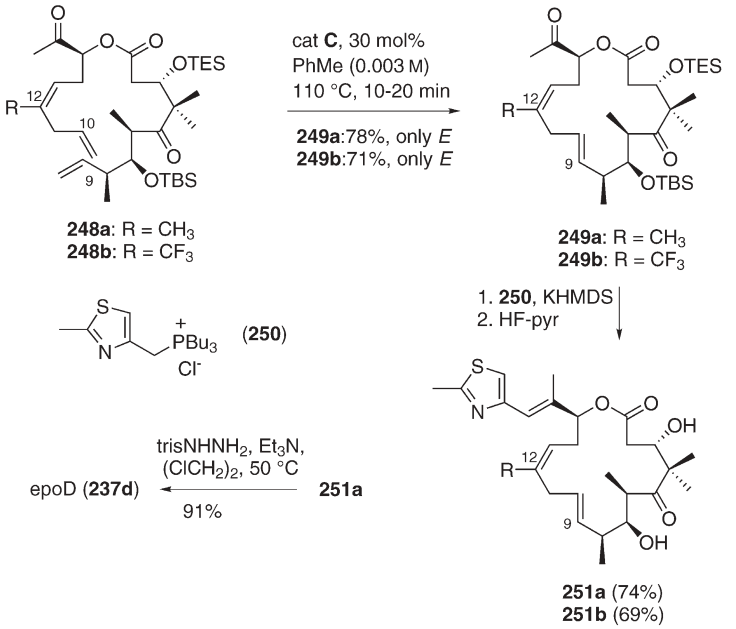
Scheme 50 Epothilone synthesis via RCM between C9 and C10: dependence of chemoselectivity on the size of the C12 substituent in metathesis substrates **244** [117]

Alternatively, diene-ene **244b** was also efficiently cyclized in the presence of catalyst **C** to produce macrolides **245b** (*E*/*Z* mixture at the newly formed double bond) in 75% yield. Global deprotection of **245b**, followed by a sequence of selective hydrogenation at C9–C10, Sharpless asymmetric epoxidation, and deoxygenation of the primary hydroxy group provided an alternative route to epoB (**238b**). In contrast analog **244c** with an unsubstituted 1,4-diene moiety

changed the course of the metathesis reaction, leading to the 13-membered macrocycle **246** instead, while tetraene **244d** with a bulky $TBSOCH_2$ group at C12 reacted with the thiazole-substituted double bond [118].

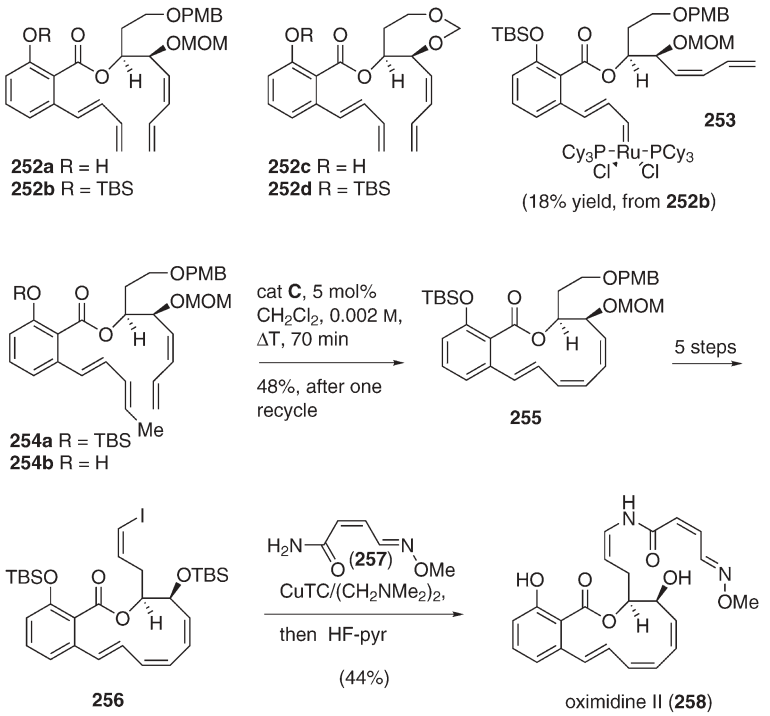
A similar approach, outlined in Scheme 51, was disclosed recently by Danishefsky using methyl ketones **248a** and **248b** as the RCM substrates [119]. Treatment of diene-enes **248** in refluxing toluene with catalyst **C** for a few minutes afforded exclusively (*E*)-isomers **249** in high yield. The thiazole moiety was then installed (*E*)-selectively by olefination with tributylphosphonium salt **250**. Subsequent deprotection of the olefination product obtained from **249a** led to (*E*)-9,10-dehydro-epoB (**251a**), which was *not identical* to a previously reported compound presumed to be the same entity [120]. Moreover, the novel compound **251a** proved to exhibit highly promising in vitro and in vivo potencies, as well as encouraging pharmacokinetic properties. Site-selective diimide reduction of **251a** led to epoD (**237d**). Note that the 12-CF_3 analog **251b** was recognized to feature even more favorable therapeutic activities, and alternative routes to the key fragments leading to metathesis substrate **248b** have been developed [119b]. (For an approach to epoA by ring-closing alkyne metathesis, see Scheme 90; for a sequence of ROM–CM to obtain epothilone analogs, see Scheme 81).

The first example of successful *diene–diene RCM* to construct a macrocyclic conjugated triene was disclosed by Wang and Porco in the first total synthesis of oximidine II (**258**) [121]. Oximidine II belongs to the family of salicylate en-



Scheme 51 Synthesis of novel (*E*)-9,10-dehydro analogs **251** of epoD, and a novel route to epoD (**237d**) via RCM between C9 and C10 [119]

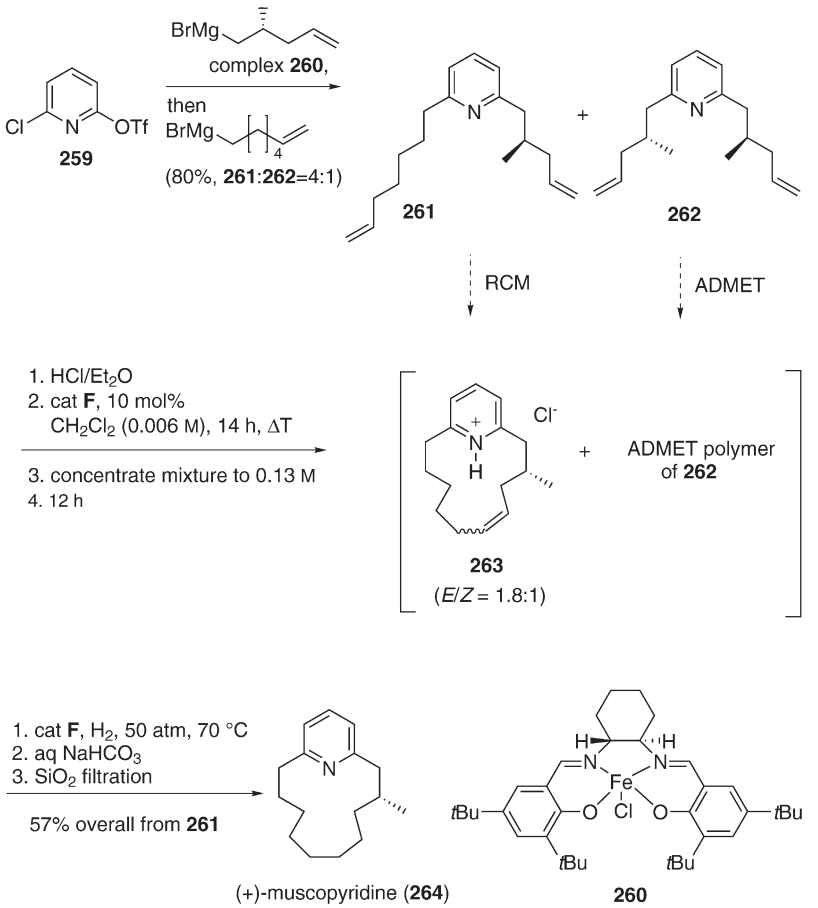
amide macrolides. It contains an (*E*,*Z*,*Z*)-conjugated triene unit in a 12-membered macrolactone core (Scheme 52). In the first attempts, tetraenes **252a–d** were chosen as metathesis substrates. Treatment with catalyst **A** afforded only products resulting from reaction of the *trans*-diene moiety, giving no further conversion, as exemplified by the formation of ruthenium complex **253** from **252b**. When treated with catalyst **C**, substrates **252a** and **252b** again reacted with the *trans*-diene, while the constrained substrates **252c** and **252d** afforded oligomeric products within 20 min, and only traces of undesired ten-membered product(s) were detected by HPLC–MS analysis. In an effort to initiate the ring closure at the *cis*-diene site, attempts were then undertaken with substrates **254** bearing an additional methyl substituent at the *trans*-diene moiety. Phenol **254b** afforded only oligomeric products, while the silyl ether **254a** eventually furnished the oximidine core **255** under the conditions outlined in the scheme. Cyclization product **255** with the required (*E*,*Z*,*Z*) geometry was selectively obtained in 39% yield, together with 49% of the precursor tetraene and oligomeric products. Extended reaction time resulted in decomposition of both starting material and product. The synthesis of **258** was then completed by conversion of **255** to (*Z*)-vinyl iodide **256** and copper-mediated amidation with **257** to construct the enamide side chain.



Scheme 52 Stereo- and regioselective diene–diene RCM of tetraene **254a** in the first total synthesis of oximidine II (**258**) [121]

2.1.3.3 Bridged Compounds

The possibility of distinguishing between medium-sized rings and macrocycles, as well as between terminal and internal (disubstituted) double bonds, and of performing "tandem catalysis" events (RCM/ADMET–hydrogenation) with a single ruthenium complex as the catalytically competent precursor, was nicely demonstrated in Fürstner's total synthesis of the natural *meta*-pyridinophane (+)-muscopyridine (**264**) (Scheme 53) [122]. Sequential coupling of pyridine derivative **259** with two different Grignard reagents mediated by iron complex **260** led to an inseparable 4:1 mixture of disubstituted pyridines **261** and **262**, with compound **262** formed in the first coupling step. As ruthenium-based metathesis catalysts are poisened by amines, pyridines **261** and **262** were pro-



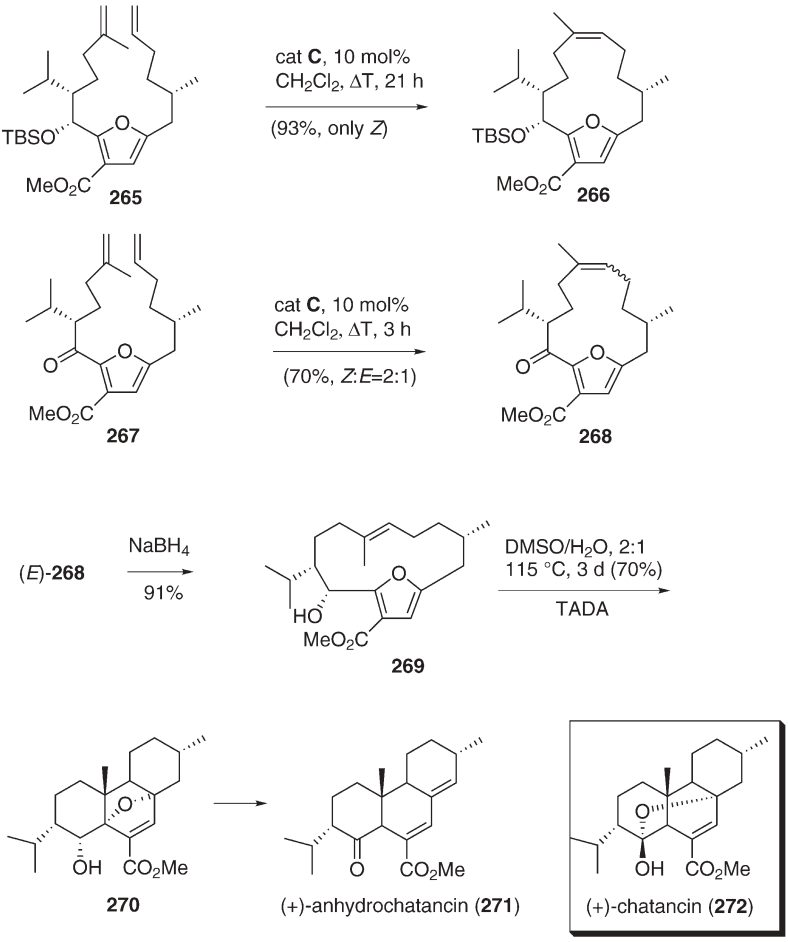
Scheme 53 Fürstner's RCM-based synthesis of muscopyridine (**264**) with integrated "self-clearance" by proper choice of catalyst activity [122]

tonated and the resulting hydrochlorides subjected to RCM under high dilution conditions (0.006 M) in the presence of Fürstner's catalyst **F** [123], which features a similar activity to Grubbs' first-generation catalyst **A**. Under these conditions, only the kinetically and thermodynamically favored 13-membered ring **263** derived from diene **261** was formed. On concentration of the reaction mixture (to 0.13 M), the residual hydrochloride of **262** was forced to polymerize by acyclic diene metathesis (ADMET), while hydrochloride **263**, now containing a less reactive (disubstituted) double bond, persisted. Notably, this would not be the case using a more reactive second-generation ruthenium catalyst. Further postponing workup, the crude mixture containing monomer **263**, the ADMET polymer, and the still-intact catalyst **F** was transferred into an autoclave and stirred under hydrogen for 14 h. Thereby, carbene complex **F** was converted into an active Ru hydride species, acting as an effective hydrogenation catalyst, so that after this procedure target **264** could be isolated in 57% overall yield from the starting mixture of dienes **261** and **262** by passing the mixture through silica.

The marine natural product (+)-chatancin (**272**), a platelet factor antagonist with several interesting biological activities, features a *cis-anti-cis*-dodecahydrophenanthrene framework possessing seven stereogenic centers (Scheme 54). In a recent attempt by Deslongchamps to prepare **272** by one of two proposed pathways involving transannular Diels–Alder (TADA) reaction [124], furanophane **269** was projected as a key intermediate to generate tetracycle **270** with stereofacial and diastereocontrol. Subsequent hydride-shift-mediated oxygen transposition should then generate **272**. The furanophane **269** in turn, featuring a trisubstituted double bond with (*E*) configuration (necessary for the success of the TADA reaction), was to be generated by RCM.

Diene **265**, substituted by a bulky silyl ether to prevent cycloaddition before the metathesis process, produced in the presence of catalyst **C** the undesired furanophane **266** with a (*Z*) double bond as the sole reaction product in high yield. The same compound was obtained with Schrock's molybdenum catalyst **B**, while first-generation catalyst **A** led even under very high dilution only to an isomeric mixture of dimerized products. The (*Z*)-configured furanophane **266** after desilylation did not, in accordance with earlier observations, produce any TADA product. On the other hand, dienone **267** furnished the desired macrocycle (*E*)-**268**, though as minor component in a 2:1 isomeric mixture with (*Z*)-**268**. Alcohol **269** derived from *E*-**268** then underwent the projected TADA reaction selectively to produce cycloadduct **270** (70% conversion) in a reversible process after 3 days. The final Lewis acid-mediated conversion to **272** however did not occur, delivering anhydrochatancin **271** instead.

Roseophilin (**273**), a deeply red-colored pentacyclic compound isolated from the culture broth of *Streptomyces griseoviridis*, is a novel antitumor antibiotic. Compound **273** possesses a topologically unique pentacyclic skeleton, consisting of a 13-membered macrocycle incorporated in an *ansa*-bridged azafulvene, which in turn is linked to a conjugated heterocyclic ring system. The absolute stereochemistry of roseophilin, as depicted in Fig. 9, was unknown until the first total synthesis published by Tius and Harrington in 2001 [125]. All syn-



Scheme 54 Sequential RCM and TADA reactions in Deslongchamps' biomimetic synthesis of anhydrochatancin **271** [124]

thetic approaches toward **273** known to date rely on tricyclic ketone **274** as one of two main fragments [126]. Various approaches to **274** (*ent*-**274** or *rac*-**274**) were performed via an RCM step to form the 13-membered macrocycle.

The respective metathesis substrates used by the different groups, as well as the reaction conditions used in the RCM step, are presented in Fig. 9. In the approach pursued by Fuchs [127], the racemic dienes **275a–e** were investigated. The unsubstituted compound **275a** and the diastereomeric alcohols **275b,c** did not cyclize in the presence of catalyst **A**. From the bulky silyl ethers derived from alcohols **275b,c**, only one (**275e**) underwent cyclization. Evidently, in this special case, the bulky TIPS ether helped to orient the olefinic side chains into a favorable conformation. In the approach of Hiemstra and coworkers leading to *ent*-**274** [128], the phenylsulfonyl-substituted diene **276** proved to be a very

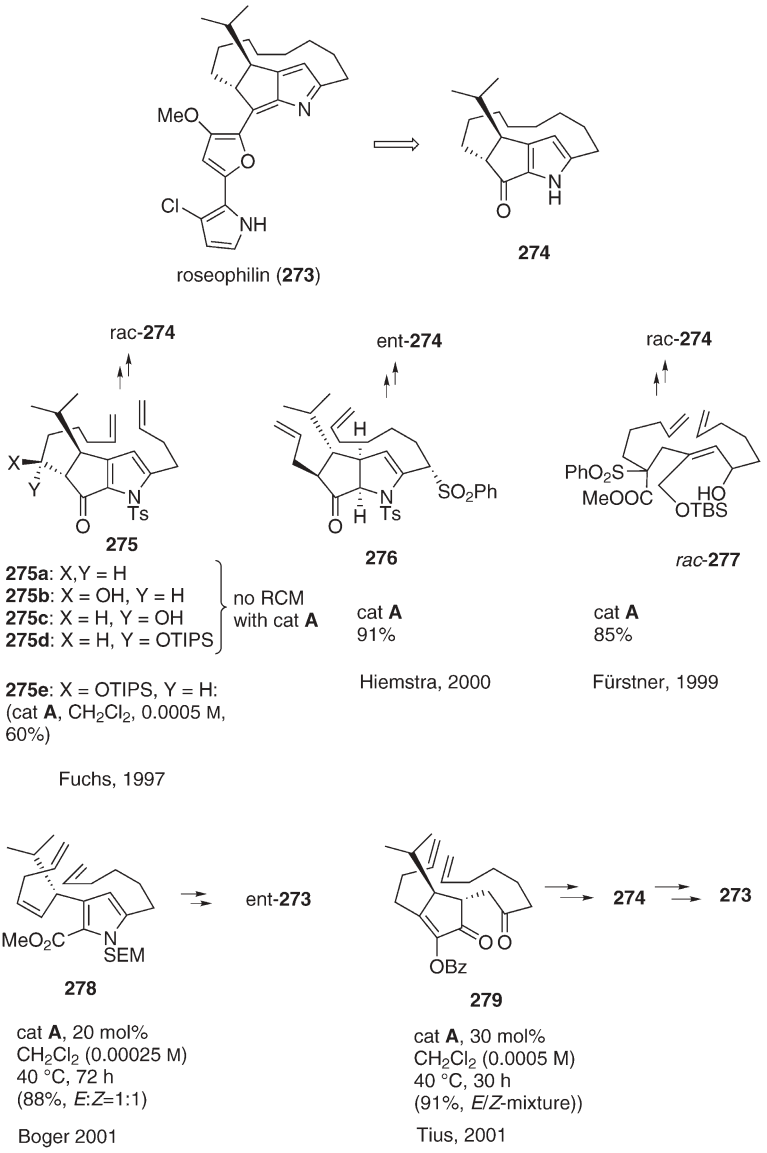


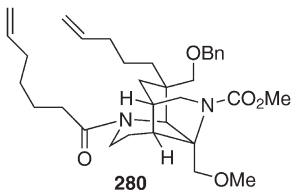
Fig. 9 Various RCM substrates used in total syntheses of roseophilin (**273**)

efficient metathesis substrate, providing the desired macrocycle (mixture of *E*/*Z*-isomers) in 91% yield. The efficiency of this reaction was ascribed to both the conformational restriction induced by the phenylsulfonyl group and the concave shape of the *cis*-fused bicyclic system present in **276**, which cooperatively bring the reacting double bonds in close proximity. In the case of Fürstner's acyclic metathesis substrate *rac*-**277** [129], no additional conformational

assistance was necessary, and treatment with catalyst **A** led to the corresponding macrocycles in high yield. In Boger's total synthesis of *ent*-**273** [130], the macrocycle was closed efficiently by treatment of the monocyclic triene **278** with catalyst **A**. The formation of the *ansa*-macrocycle prior to formation of the cyclopentanone avoids, to a large extent, the strain to be overcome in compounds **275**. The cyclopentanone ring was subsequently introduced by a 5-*exo-trig* radical-alkene cyclization of the acyl selenide derived from the ester group. Also in Tius' first total synthesis of enantiomerically pure **273** [125], a monocyclic diene (**279**) was used to produce the macrocycle efficiently. After selective hydrogenation of the newly formed double bond, the missing pyrrole ring was formed by involving the 1,4-dicarbonyl moiety in a Paal–Knorr reaction.

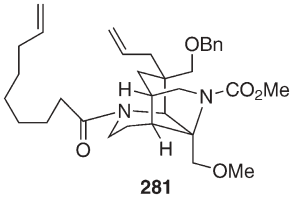
The marine alkaloid sarain A (**285**) features an exceptionally challenging pentacyclic architecture (Fig. 10). To date, **285** has not succumbed to a total synthesis. Two groups, however, have completed the tricyclic core of **285** and have annulated the western 13-membered ring using quite similar RCM approaches [131]. The results obtained with different metathesis substrates and catalysts are outlined in Fig. 10. RCM of Weinreb's dienes **280**, **281**, and **282** [131a], that differ by the site of ring closure, were mediated by first-generation catalyst **A**. Dienes **280** and **282** furnished comparable results leading to the corresponding cyclization products in moderate yield together with substantial amounts of *cyclic dimers*. RCM of diene **281**, however, proceeded very sluggishly leading to an inseparable mixture of the desired macrocycle along with a *linear dimer* in poor overall yield, suggesting that the allylic side chain was positioned too close to the tricyclic core to participate efficiently in the metathesis event. Four years later, when the strategy was adapted by Cha and coworkers [131b], RCM of dienes **283** and **284** was performed with catalyst **C**. In contrast to the uncomplicated ring closure of the *N*-PMB-protected derivative **283** (71% yield within 5 h), it was surprising that diene **284**, bearing a more elaborate alkyl chain instead, produced the macrocycle in distinctly lower yield (42%) along with a dimer. Silylation of **284** prior to RCM gave a reliable higher overall yield.

In the organization of RCM to strained products, it is essential to preorganize the substrate into a conformation that favors cyclization. In the above roseophilin case, the stereochemical outcome of the ring-closing step was inconsequential for the successful formation of a saturated macrocyclic ring. In Deslongchamps' synthesis of a strained furanophane, attempts to obtain the required (*E*) stereochemistry were only partially successful by alcohol to carbonyl interconversion in the RCM precursor. A highlight among RCM-based natural product syntheses, that pushes the limits of olefin metathesis as a means to construct highly strained and complex targets with total stereocontrol, is found in Nicolaou's first total synthesis of two members of the coleophomone family, namely coleophomone B (**287**) and C (**286**) [132]. These compounds differ only in the geometry of the double bond in the macrocyclic *ansa* bridge (Scheme 55). In addition to an interesting biological profile, the coleophomones feature a strained and rigid framework with a sensitive tricarbonyl system tethered to an 11-membered macrocycle, whose strain is derived from a fused aryl ring and



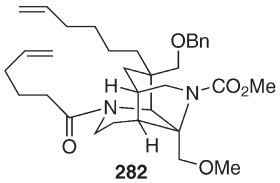
280

cat **A**, 20 mol%
CH_2Cl_2 (0.0005 M)
ΔT, 2 d
(49%, *E*/*Z*-mixture)
+
macrocyclic dimer (39%)



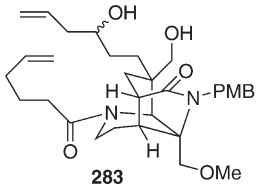
281

cat **A**, 20 mol%
CH_2Cl_2 (0.0005 M)
ΔT, "very slow"
(*E*/*Z*-mixture) +
linear dimer
(overall poor yield)



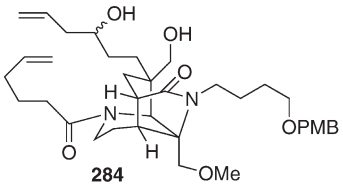
282

cat **A**, 20 mol%
CH_2Cl_2 (0.0005 M)
ΔT, 2 d
(39%, *E*/*Z*-mixture)
+
macrocyclic dimer (18%)



283

cat **C**, 10 mol%
CH_2Cl_2 (0.0004 M)
ΔT, 5 h
(71%, *E*/*Z*-mixture)

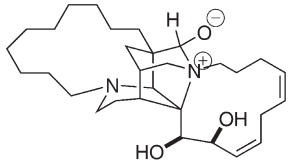


284

cat **C**, 10 mol%
CH_2Cl_2 (0.0004 M)
ΔT, 2 d
(42%, *E*/*Z*-mixture)

or

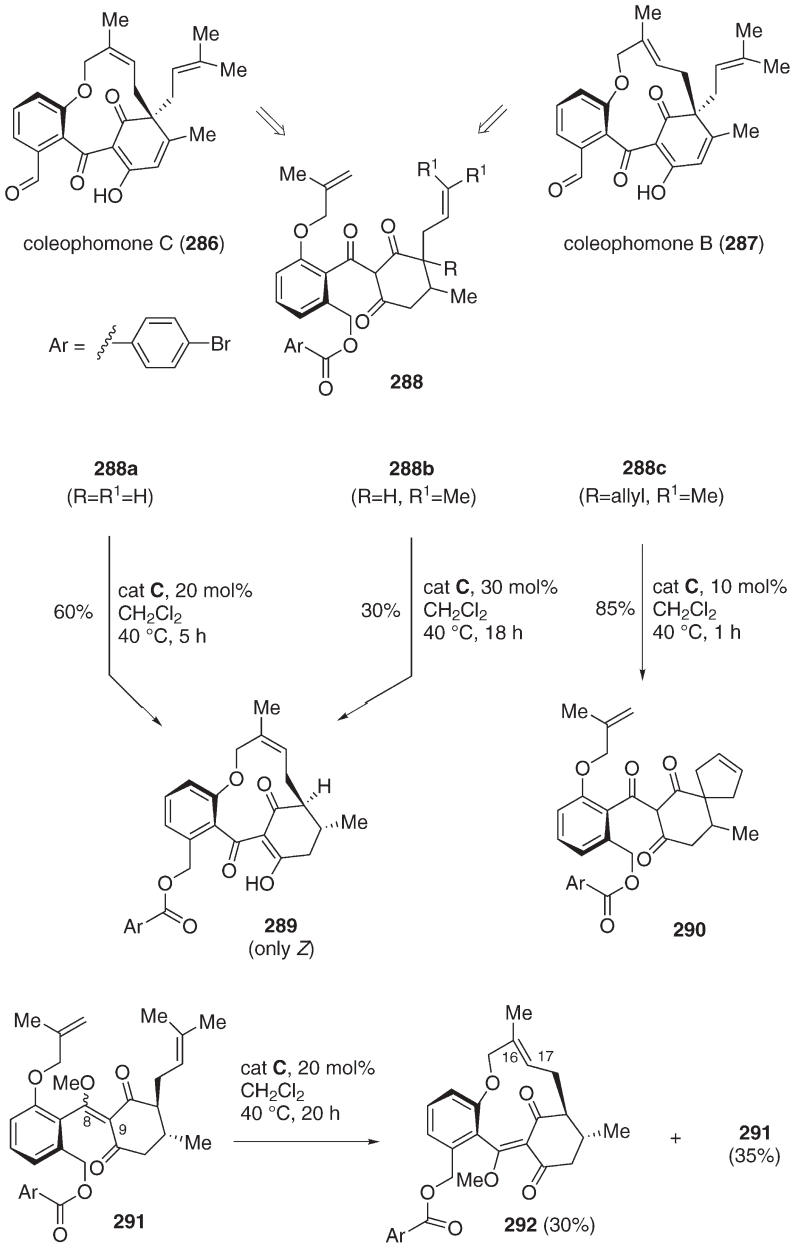
1. TBSOTf
2. cat **C**, 8.5 mol%
   CH_2Cl_2 (0.0004 M)
   ΔT, 2 h
3. TBAF
   (54%, *E*/*Z*-mixture)



sarain A (**285**)

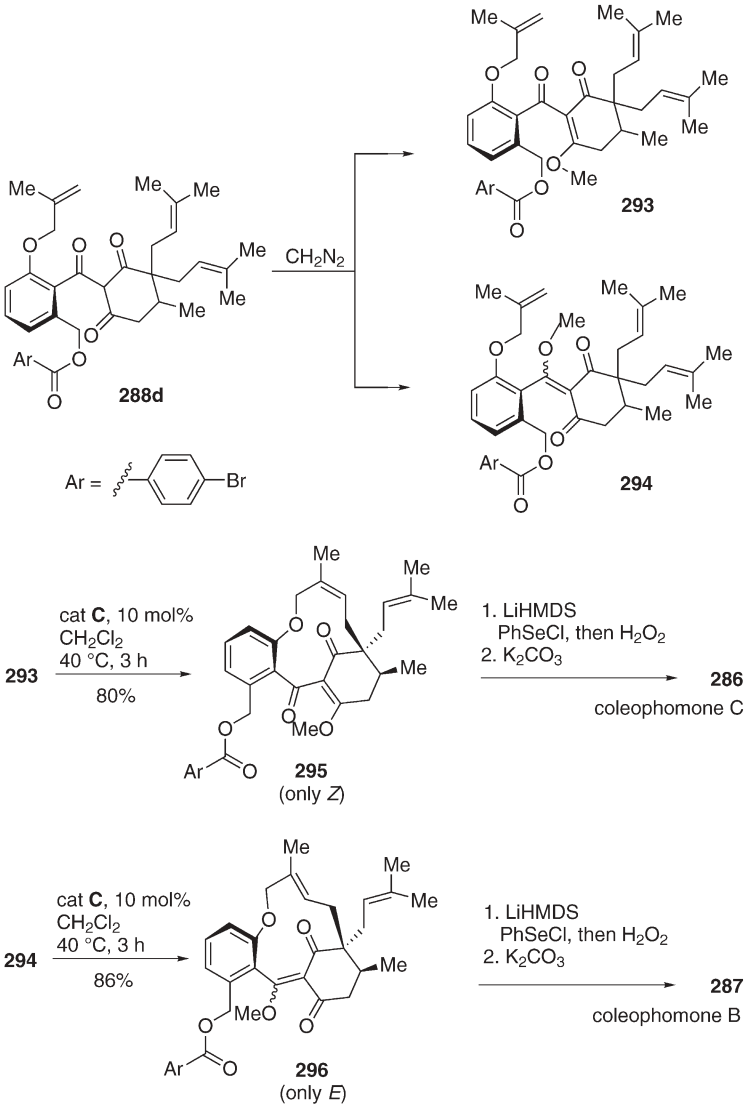
Fig. 10 Various RCM substrates used in synthetic work directed to the marine alkaloid sarain (**285**)

an internal cyclohexadienone. During the exploration of the crucial metathesis step, various dienes **288** and enol ether **291** synthesized from **288a** were investigated. In the case of the simplest substrate **288a** bearing a monoalkylated cyclohexadione moiety, first-generation catalyst **A** failed to induce ring closure. With second-generation catalyst **C**, the tricycle **289** with a (*Z*) double bond was formed in 60% yield. Also with diene **288b**, bearing a di- and a trisubstituted



Scheme 55 First retrosynthetic analysis and RCM substrates investigated during synthetic work directed to coleophomone B (**287**) and C (**286**) [132]

double bond, the exclusive formation of **289** was observed, albeit in reduced yield (30%). However, the simplest dialkylated cyclohexadione derivative, triene **288c** (bearing an allyl and a prenyl substituent), did produce rapidly within 1 h only spirocyclopentene **290** in 85% yield. Additional and unexpected information was gained by the RCM reaction of enol ether(s) **291** (1:1 mixture of $\Delta^{8,9}$-isomers, each of which consists of a 1:1 pair of atropisomers). When this mixture was subjected to the usual metathesis conditions, a single macrocycle



Scheme 56 Final solution of the coleophomone problem: stereoselective macrocyclization by RCM of enol ether derivatives **293** and **294** [132]

(**292**) with (*E*) configuration at both the $\Delta^{8,9}$ and the newly formed $\Delta^{16,17}$ double bond, was isolated in 30% yield, together with a considerable amount of the starting material which was found to be enriched in the (*Z*)-isomer around the enol ether ($\Delta^{8,9}$) double bond.

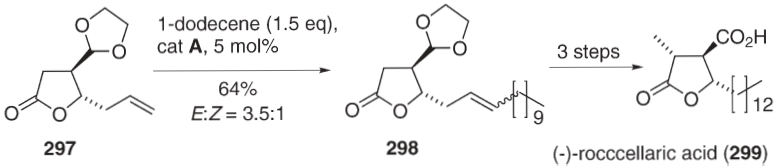
The final solution of the coleophomone problem is outlined in Scheme 56. The fully substituted diprenylated compound **288d**, itself a very poor RCM substrate, was treated with diazomethane, which led to a separable mixture of regioisomeric enol ethers **293** and **294**, the latter being a ca. 1.3:1 mixture of geometrical isomers ($\Delta^{8,9}$). Treatment of **293** with catalyst **C** led within 3 h exclusively to the (*Z*)-configured macrocycle **295** in 80% yield. Regioisomer **294** in turn furnished under the same conditions the (*E*)-configured macrocycles **296** (ca. 1:1 mixture of isomers at $\Delta^{8,9}$). Remarkably, in both cases only the prenyl group in the *cis* position to the vicinal C12 methyl group participated in the ring-closing step. Thus, two different coleophomone frameworks were obtained stereospecifically from a single precursor (**288d**). Conversion of compounds **295** and **296** to coleophomone C (**286**) and B (**287**), respectively, was accomplished in both series by introducing the missing $\Delta^{11,12}$ double bond and global deprotection.

2.2 Olefin Cross Metathesis (CM)

Olefin CM can be formally described as the mutual intermolecular exchange of alkylidene (or carbene) fragments between two olefins promoted by metal-carbene complexes [133]. For decades CM has found numerous industrial uses, but it is not yet in such widespread use in natural product synthesis as the more entropically favorable RCM reaction. This is largely due to inherent difficulties of controlling selectivities. Minimization of unproductive self-coupled alkenes and maximization of the crossed product is one of the crucial issues to be optimized in CM chemistry, as well as stereocontrol on the newly generated double bond. It is only in the last few years that, with the development of a second generation of highly active and stable ruthenium catalysts bearing *N*-heterocyclic carbene (NHC) ligands, the synthetic community has begun to accept CM reactions as a useful alternative in natural product synthesis. In the presence of NHC catalysts **C** and **D**, the range of substrates amenable to CM has been also expanded to trisubstituted and electron-deficient conjugated olefins. The latter are known to be poor substrates for homodimerization and allow the (*E*)-selective introduction of functionality to an α-olefin. CM with these substrates can therefore be considered as a formal vinylic C–H activation or a formal allylic oxidation [134]. The impressive developments in olefin CM, including a number of applications in the syntheses of biologically important molecules and natural products, have been the subject of an excellent review by Connon and Blechert [4]. In a recent and comprehensive article, Grubbs and coworkers have developed an important general model for the prediction of product selectivity and stereoselectivity in CM [135], by categorizing the olefins into four different types according to their relative abilities to undergo homodimerization and the

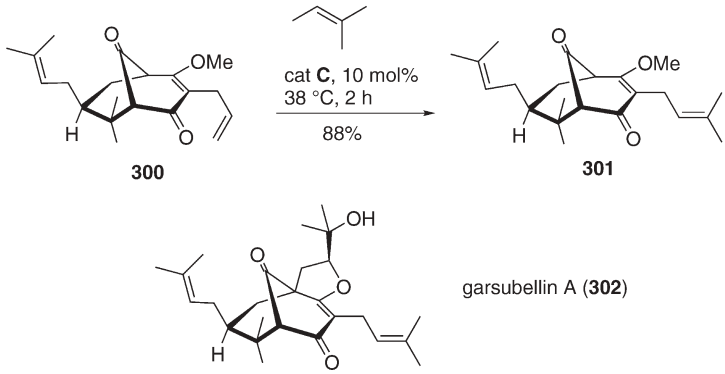
susceptibility of their homodimers toward secondary metathesis reactions. By means of many examples it was demonstrated that by employing a metathesis catalyst with the appropriate activity, selective CM reactions are possible with a variety of electron-rich, electron-deficient, and sterically demanding olefins. In the following, we will concentrate only on a few recent examples that highlight the growing use of CM in natural product syntheses.

An "early" example of nonstereoselective CM used in the synthesis of biologically interesting trisubstituted γ-lactones is the late-stage introduction of a large saturated alkyl chain by a CM–hydrogenation sequence in Reiser's synthesis of (+)-roccellaric acid (**299**, Scheme 57) [136]. The required tridecyl side chain was elaborated by exposing the allyl-substituted intermediate **297** and 1-dodecene (1.5 equiv) to Ru catalyst **A**. No self-condensation of **297** was observed, the homodimer of dodecene being the only by-product. CM product **298** was obtained in 64% yield as a 3.5:1 mixture of (*E*/*Z*)-isomers, which was hydrogenated and converted to **299**.



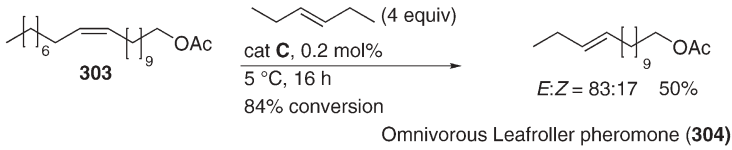
Scheme 57 CM in the total synthesis of roccellaric acid (**299**) [136]

The CM reaction between 2-methyl-2-butene (a *gem*-disubstituted olefin that served in this case also as solvent) and the allylated compound **300**, possessing the bicyclo[3.3.1]nonane core of the potential Alzheimer therapeutic garsubellin A (**302**) [137], underlines the increased activity of the second-generation ruthenium catalysts (Scheme 58). In the presence of 10 mol% of NHC catalyst **C**, the prenylated compound **301** was formed after only 2 h in 88% yield.



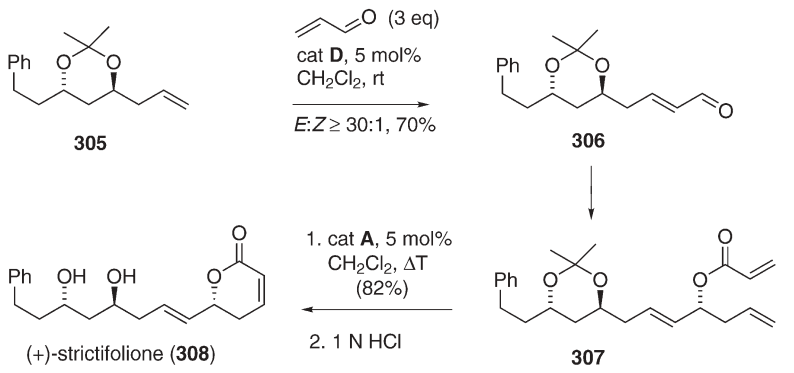
Scheme 58 Allyl to prenyl interconversion by the use of a trisubstituted olefin in CM, in garsubellin A (**302**)-directed work [137]

In an article dealing with applications of olefin CM to a series of commercial products [138], solvent-free CM between (*E*)-3-hexene (produced by homocoupling of 1-butene) and 11-eicosenyl acetate **303** (produced from jojoba oil) was used to produce acetate **304** (Scheme 59), which is – as a natural 82:18 (*E*/*Z*) mixture – the pheromone of omnivorous leafroller, and serves as an environment-friendly pest controlling agent. The CM reaction was performed without solvent at 5 °C with a 4:1 mixture of (*E*)-3-hexene and **303**, in the presence of only 0.2 mol% catalyst **C**, and furnished after 20 h coupling product **304** (*E*:*Z*=83:17) in 50% yield.



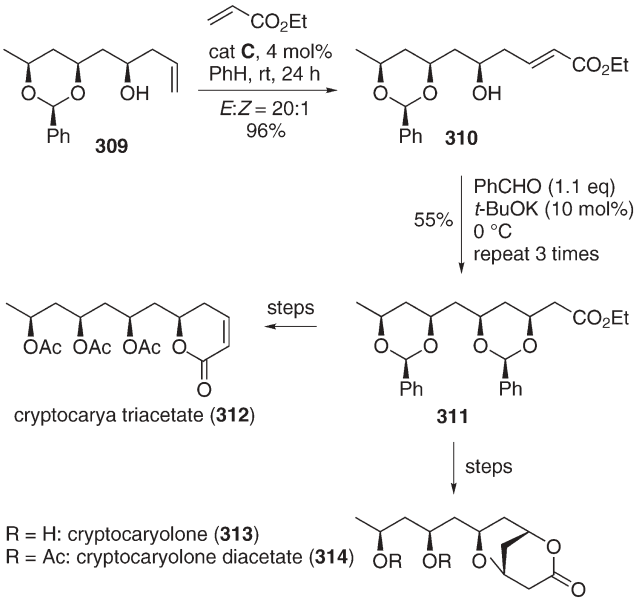
Scheme 59 Synthesis of omnivorous leafroller pheromone **304** via CM [138]

The high activity of the second-generation Ru catalysts also allows the use of conjugated electron-deficient olefins as efficient CM partners with low tendency to self-dimerization. Several syntheses of biologically interesting natural compounds [139], or advanced intermediates therefrom [140], have been disclosed by the group of Cossy using an iterative sequence of stereoselective allyl titanations and CM reactions of the resulting homoallylic alcohols [141]. En route to the natural compound (+)-strictifolione (**308**), metathesis precursor **305** (Scheme 60) was prepared from 3-phenylpropionaldehyde via two sequential allylations. CM with acrolein (3 equiv) in the presence of Hoveyda's recyclable catalyst **D** furnished enal **306** with complete (*E*) stereocontrol in 70% yield. Aldehyde **306** was then elaborated in four steps to the natural compound, the dihydropyrone ring being closed in the penultimate step by RCM of acrylate **307** with catalyst **A** [139b].



Scheme 60 (*E*)-Selective CM with electron-deficient alkene in Cossy's total synthesis of strictifolione (**308**) [139b]

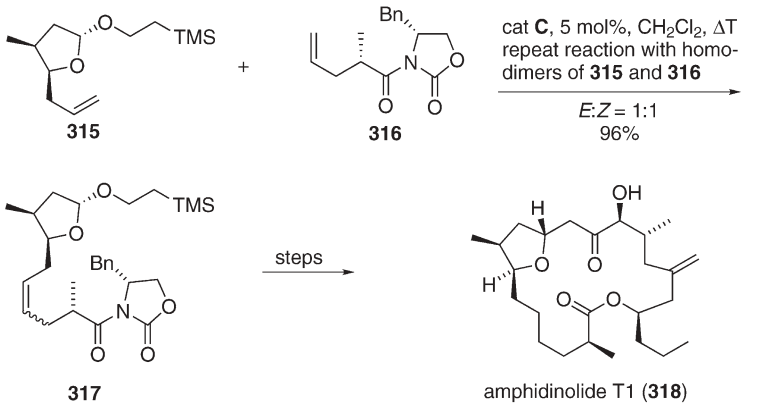
An (*E*)-selective CM reaction with an acrylate (Scheme 61) was applied by Smith and O'Doherty in the enantioselective synthesis of three natural products with cyclooxygenase inhibitory activity (cryptocarya triacetate (**312**), cryptocaryolone (**313**), and cryptocaryolone diacetate (**314**)) [142]. CM reaction of homoallylic alcohol **309** with ethyl acrylate mediated by catalyst **C** led (*E*)-selectively to *δ*-hydroxy enoate **310** in near quantitative yield. Subsequent Evans acetal-forming reaction of **310**, which required the *trans* double bond in **310** to prevent lactonization, led to key intermediate **311** that was converted to **312–314**.



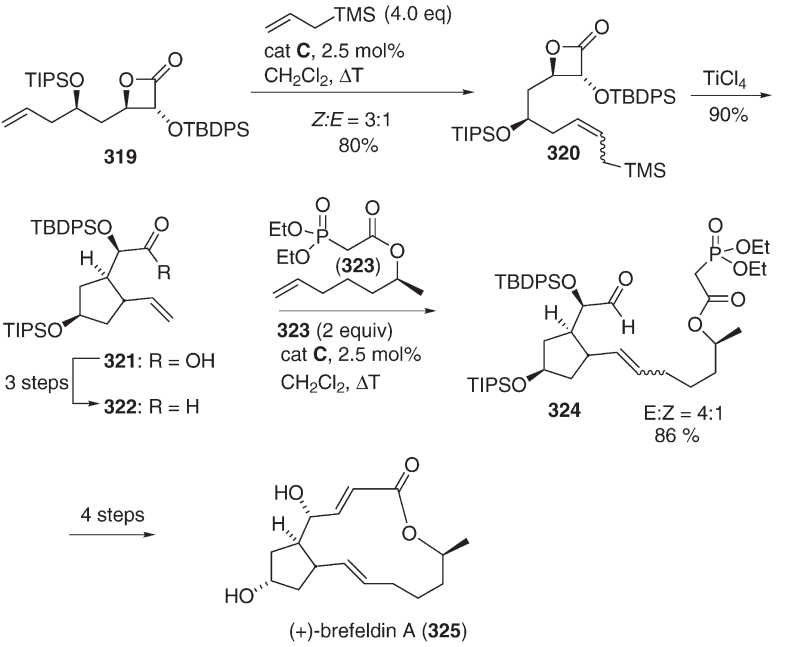
Scheme 61 (*E*)-Selective CM with ethyl acrylate in total syntheses of *Cryptocaria* natural products **312–314** [142]

In Ghosh's enantioselective total synthesis of the cytotoxic marine macrolide (+)-amphidinolide T1 (**318**) [143], the C1–C10 fragment **317** was constructed by CM of subunits **315** and **316** (Scheme 62). The reaction mediated by catalyst **C** (5 mol%) afforded in the first cycle an inconsequential 1:1 mixture of (*E*/*Z*)-isomeric CM products **317** in 60% yield, along with the homodimers of **315** and **316**. The self-coupling products were separated by chromatography and exposed to a second metathesis reaction to provide olefins **317** in additional 36% yield [144].

The fungal metabolite (+)-brefeldin A (**325**) displays potent antitumor, antifungal, antiviral, antimitotic, and immunosuppressive activities. Recently, Romo and Wang described a highly concise total synthesis of **325** by a combined *β*-lactone–CM approach (Scheme 63), that again underlines the high tolerance of sensitive functionality exhibited by the second-generation Ru catalysts [145].



Scheme 62 Efficient coupling of fragments **315** and **316** via CM in Ghosh's total synthesis of the cytotoxic marine macrolide amphidinolide T1 (**318**) [143]

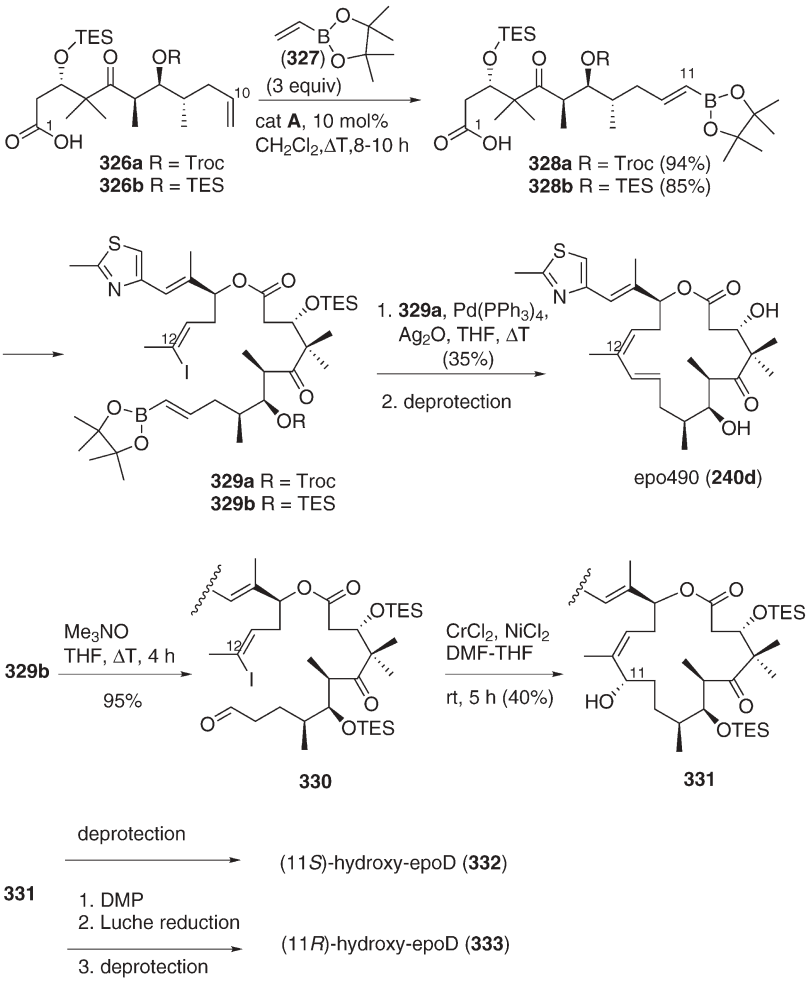


Scheme 63 Twofold use of CM in the total synthesis of brefeldin A (**325**) [145]

An allylsilane-generating CM using catalyst **C** between the sensitive β-lactone **319** and allyltrimethylsilane served to introduce the allylsilane moiety in intermediate **320** as an inconsequential mixture (ca. 3:1) of (*E*/*Z*)-isomers in 80% yield. Cyclization of β-lactone **320** with $TiCl_4$ smoothly delivered cyclopentane **321** with inversion at the β-carbon. Acid **321** was converted to key aldehyde **322** in three steps. The convergent fragment coupling was performed by a uniquely

complex CM reaction between epimerizable aldehyde **322** and phosphonoacetate **323**, again in the presence of catalyst **C**. Homodimerization of phosphonate **323** was found to be competitive with the CM process. However, it was shown that this dimer could also be used in a CM reaction with **322**. The metathesis product **324**, thus obtained in 86% yield as an isomeric mixture (*E*:*Z*=4:1), was then subjected to (*E*)-selective Horner–Wadsworth–Emmons cyclization. After deprotection, both hydroxy groups were inverted by the Mitsunobu protocol leading to **325**.

Application of vinyl boronate CM in epothilone chemistry, leading to epo490 (**240d**, a naturally occurring minor cometabolite, cf Scheme 49) and to novel 11-hydroxy and 11-fluoro analogs of epoD (Scheme 64), was reported by Dani-



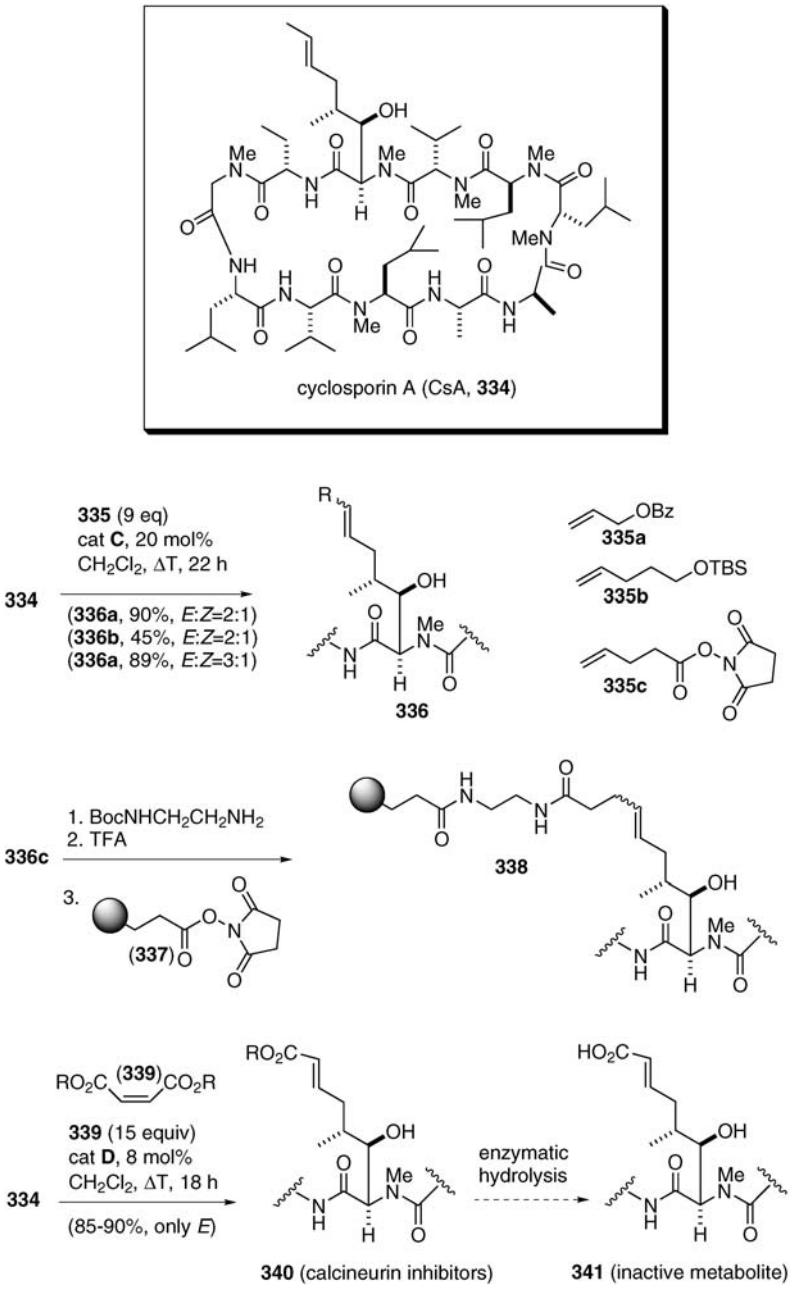
Scheme 64 CM with vinyl boronate **327** in novel syntheses of epo490 (**240d**) and 11-hydroxy analogs **332** and **333** of epoD [146]

shefsky and coworkers [146]. Treatment of acids **326** representing the C1–C11 moiety of epothilones, with an excess (3 equiv) of vinyl-pinacol boronate ester **327** in the presence of catalyst **A**, provided the corresponding CM products **328** almost exclusively as (*E*)-isomers in high yield. Esterification of compounds **328** provided seco compounds **329**. Suzuki macrocyclization of **329a** (R=Troc) under the conditions shown in the scheme led, after stepwise deprotection, to epo490 (**240d**) in low yield. (For alternative routes to **240d** by RCM macrocyclization, see Scheme 49). Through a novel alternative for the conventional hydroboration–oxidation method, analog **329b** (R=TES) was converted into aldehyde **330** by oxidation with trimethylamine *N*-oxide. Nozaki–Kishi macrocyclization of **330** led to protected (11*S*)-hydroxy-epoD (**331**) as the only diastereomer. Compound **331** was then converted to both possible 11-hydroxyepothilones and also to the pair of 11-fluoro analogs.

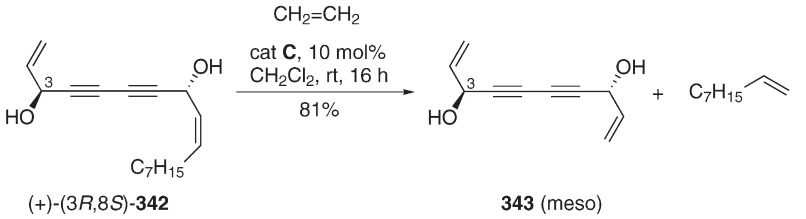
The important immunosuppressant cyclosporin A (CsA, **334**) (Scheme 65), known also by its trade name Sandimmune, is widely used to prevent organ rejection in transplant patients. CsA is also effective in the treatment of asthma patients, but in this case its chronic use is limited by the nephrotoxicity, caused by inhibition of calcineurin. CsA is a cyclic undecapeptide with an unusual unsaturated amino acid (MeBmt), which offers the possibility of structural modifications by CM. With the aim of investigating **334** as a metathesis substrate, and thus to gain new affinity reagents useful for detecting novel cyclophilins from cellular extracts, Diver and coworkers [147] treated **334** with several terminal olefins **335** in the presence of NHC catalyst **C** (benzylidene catalyst **A** was completely ineffective). CM products **336a–c** were obtained in good yields as a mixture of geometric isomers. The CM with olefin **335c** is notable because of the direct installation of an active ester onto an unprotected polypeptide. Metathesis product **336c** was then coupled with a sepharose resin **337** in three steps, as shown in Scheme 65, and the resulting resin-bound cyclosporin **338** could be used for the detection of novel cyclophilins from cell lysates.

A different task was pursued by the CM of CsA with various maleates **339** [148]. The CM demanded in this case the highly active Hoveyda catalyst **D**, that exhibits potency not reached by the phosphine-containing catalysts **C** and **E**. Under the conditions given in Scheme 65, metathesis with maleates **339** led (*E*)-selectively to the α,β-unsaturated ester derivatives **340** in high yield. Compounds **340** still demonstrated activity comparable to that of CsA and are thus potential "soft drugs" via esterase-mediated biotransformation to the corresponding inactive carboxylic acids **341**.

An interesting example of regioselective CM with ethylene as a tool in natural product *degradation* was recently disclosed by Hawaiian authors [149]. Thus, CM using catalyst **C** and ethylene gas was used to degrade the plant polyacetylene oxylipin (+)-falcarindiol (**342**) with uncertain stereochemistry at C3. As the reaction provided a *meso* product (**343**) in 81% yield by regioselective attack at the aliphatic side chain, the natural compound **342**, isolated from a Hawaiian endemic plant, had the 3*R*,8*S* configuration shown in Scheme 66.

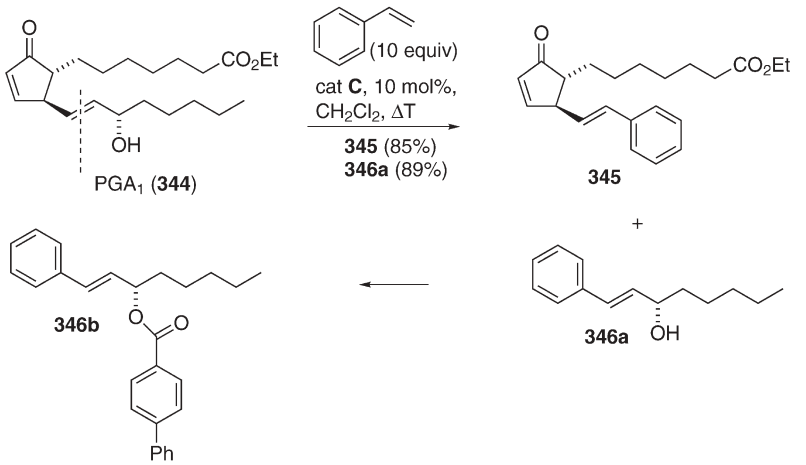


Scheme 65 Various modifications of cyclosporin A (**334**) via CM [147, 148]



Scheme 66 Olefin CM in natural product degradation: configurational assignment of falcarindiol (**342**) [149]

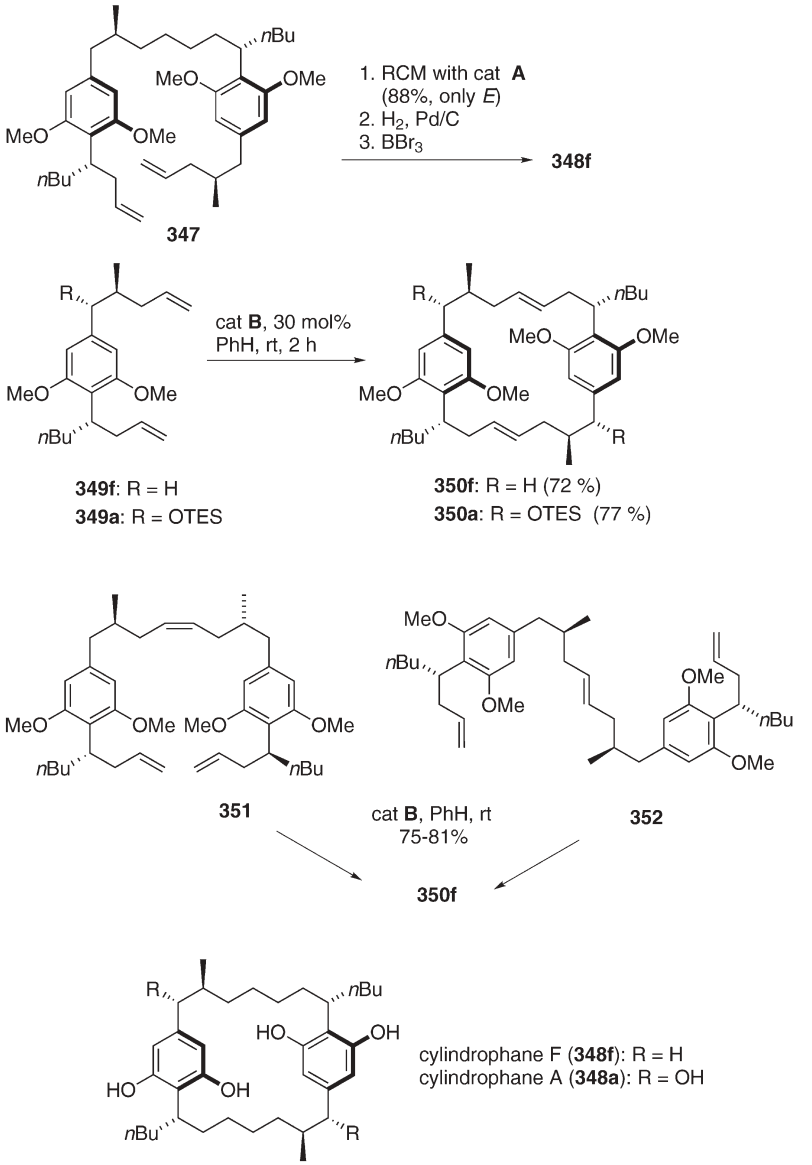
Recently, a microscale CM/exciton chirality protocol for the determination of absolute configurations of natural products with allylic alcohol or amine moieties was developed [150]. In Scheme 67, the method is exemplified on prostaglandin A_1 ethyl ester (PGA_1, **344**). Because **344** exhibits an intense Cotton effect due to the twisted enone chromophore and moreover is unstable under basic acylation conditions, the usual allylic benzoate method for determination of its absolute configuration is not applicable. When **344** was treated with excess styrene in the presence of 10 mol% of second-generation catalyst **C**, the resulting (*E*)-styrenoids **345** and **346a** (the latter in the form of its *p*-phenylbenzoate **346b**) were easily amenable to conventional configurational assignment.



Scheme 67 Olefin CM with styrene for configurational assignment of natural products [150]

The reversible nature of cross metathesis is of synthetic importance because, by the use of a sufficiently active metathesis catalyst, it generally ensures the preferential formation of the most thermodynamically stable product. This results in the transformation of terminal olefins into internal ones, and we have seen that undesired self-metathesis products can be recycled by exposing them to a second CM process.

Exploiting the reversible nature of CM, Smith and coworkers reported a highly impressive total synthesis of the naturally occurring cylindrophanes A (**348a**) and F (**348f**) [151]. Initially, the [7,7]-paracyclophane skeleton of (–)-**348f** was elaborated by "conventional" RCM macrocyclization, which led from diene **347** stereoselectively to the cyclization product with an (*E*) double bond in 88% yield (Scheme 68). In a second-generation strategy, however, a remark-



Scheme 68 Synthesis of cylindrophanes A (**348a**) and F (**348f**) via reversible olefin CM [151]

able CM dimerization cascade was described which served to assemble **348a** and **348f** from dienyl monomers **349a** and **f.** Ruthenium catalysts **A** and **C** and Schrock's Mo catalyst **B** were investigated under different conditions, and it turned out that catalyst **B** was the most effective, leading exclusively to cyclodimers **350.** In both cases, only the head-to-tail (*E*,*E*)-isomer was formed, and no "head-to-head" dimers or dimers with a (*Z*) double bond were detected, suggesting that compounds **350** are the most stable out of all other possible isomers. This was not only corroborated by MM2 force field calculations, but also by the outcome of metathesis reactions performed with trienes **351** and **352**, which both gave in a self-editing process only cyclodimer **350f** with the [7,7]-paracyclophane skeleton in good yield, despite their disposition to form [8,6]-cyclophanes.

2.3 Metathesis on Solid Support

Chemistry on solid support has gained tremendous importance during the last few years, mainly driven by the needs of the pharmaceutical sciences. Due to the robust and tolerable nature of the available catalysts, metathesis was soon recognized as a useful technique in this context. Three conceptually different, RCM-based strategies are outlined in Fig. 11. In the approach delineated in Fig. 11a, a polymer-bound diene **353** is subjected to RCM. The desired product **354** is formed with concomitant traceless release from the resin. This strategy is very favorable, since only compounds with the correct functionality will be liberated, while unwanted by-products remain attached to the polymer. However, as the catalyst is captured in this process by the matrix (**355**), a higher catalyst loading will be required, or "ancillary" alkenes have to be added to liberate the catalyst.

With polymer-bound diene **356**, two different strategies are possible. Following path A, RCM results in the formation of a (volatile) alkene **357a** and a

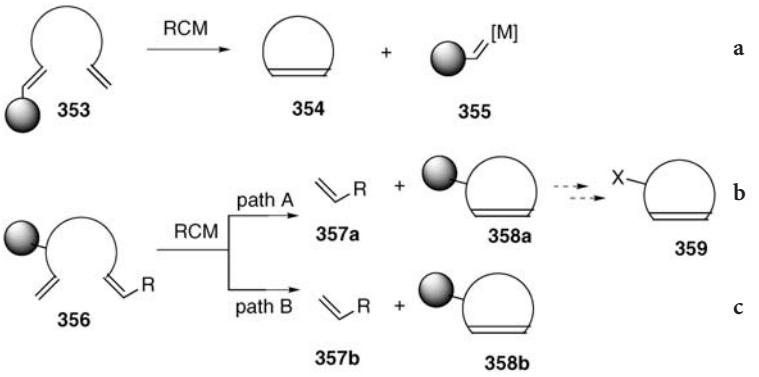
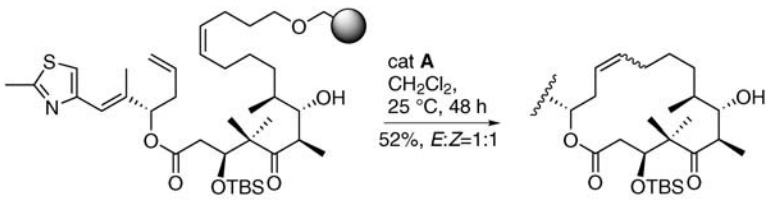


Fig. 11 Variations of RCM with polymer-bound substrates

cyclic product **358a**, which remains attached to the polymer support. This product can undergo further manipulation, with cleavage from the resin at a later stage (**358a**→**359**, Fig. 11b). Alternatively, RCM of diene **356** can also be used for the traceless release of a polymer-bound cycloalkene (**358b**), with concomitant formation of a terminal alkene (**357b**) as the desired reaction product (Fig. 11c).

The feasibility of multistep natural product total synthesis via solid-phase methodology, and its application to combinatorial chemistry, was first demonstrated by Nicolaou and coworkers in epothilone synthesis and in the generation of an epothilone library [152]. The traceless release of TBS-protected epoC **361** by RCM of resin-bound precursor **360** (Scheme 69) is an early and most prominent example for the strategy outlined in Fig. 11a.

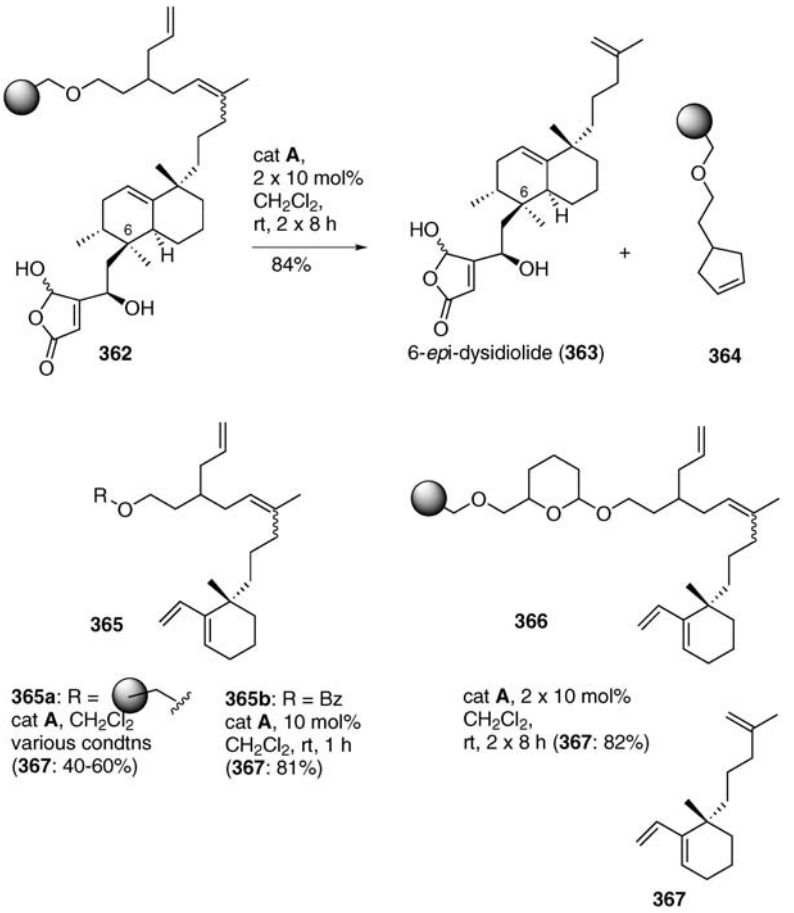


360 **361**

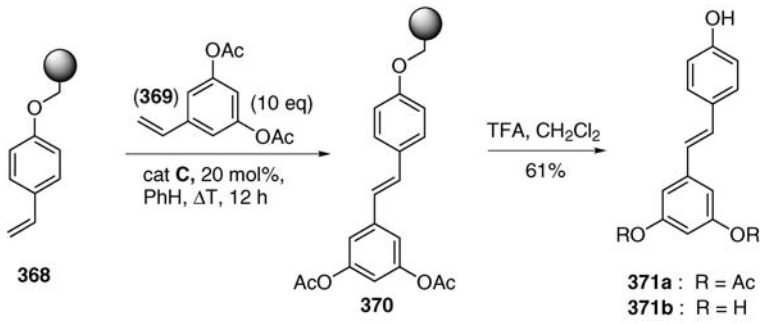
Scheme 69 Traceless release of epoC derivative **361** from solid support by RCM [152]

An illustrative example of an alternative strategy (cf Fig. 11c) involving the use of a novel traceless linker is found in the multistep synthesis of 6-*epi*-dysidiolide (**363**) and several dysidiolide-derived phosphatase inhibitors by Waldmann and coworkers [153], outlined in Scheme 70. During the synthesis, the growing skeleton of **363** remained attached to a robust dienic linker. After completion of intermediate **362**, the terminal olefin in **363** was liberated from the solid support by the final metathesis process with concomitant formation of a polymer-bound cyclopentene **364**. Notably, during the synthesis it turned out that polymer-bound intermediate **365a**, in contrast to soluble benzoate **365b**, produced diene **367** only in low yield. After introduction of an additional linker (cf intermediate **366**), diene **367** was released in distinctly improved yield by RCM.

A short and efficient synthetic approach to hydroxy-substituted (*E*)-stilbenoids, as exemplified by the natural compound resveratrol (**371b**) via solid-phase CM, was reported by a Korean group (Scheme 71) [154]. When two different stilbenes were allowed to couple by catalyst **C**, all three kinds of possible stilbenes were obtained as an inseparable mixture. Anchoring 4-vinylphenol to Merrifield resin, followed by exposing the supported styrenyl ether **368** and diacetoxy styrene **369** (10 equiv) to the catalyst, inhibited self-metathesis of the supported substrate. Sequential separation of the homodimer formed from **369** by washing and subsequent cleavage of the resin **370** with acid provided (*E*)-stilbene **371a** with complete stereocontrol in 61% yield.



Scheme 70 Traceless removal of polymer **364** by RCM in the synthesis of 6-*epi*-dysidiolide (**363**) [153]



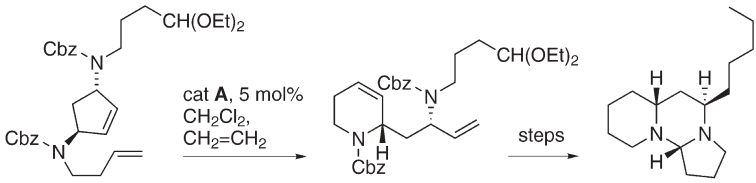
Scheme 71 Improved synthesis of (*E*)-stilbenoids by olefin CM on a solid phase [154]

2.4
Domino Metathesis Reactions

2.4.1
Ring-Rearrangement Reactions

An alternative access to complex heterocyclic structures is the Ru- or Mo-catalyzed ring-rearrangement metathesis (RRM), in which a strained carbocyclic alkene is transformed into a heterocyclic product by an intramolecular ring-opening/ring-closing or double ring-closing domino metathesis. Due to the reversibility of the processes involved, the amount of rearrangement product depends on thermodynamic effects, e.g., ring strain and substitution pattern of the starting cycloalkene. A particularly attractive aspect of these transformations is the catalytic transfer of stereochemical information from readily available carbocyclic olefins to one or two newly formed heterocyclic rings (cf Fig. 1c and d). This methodology, initially investigated by Grubbs [155], was extensively applied in natural product synthesis by Blechert et al.

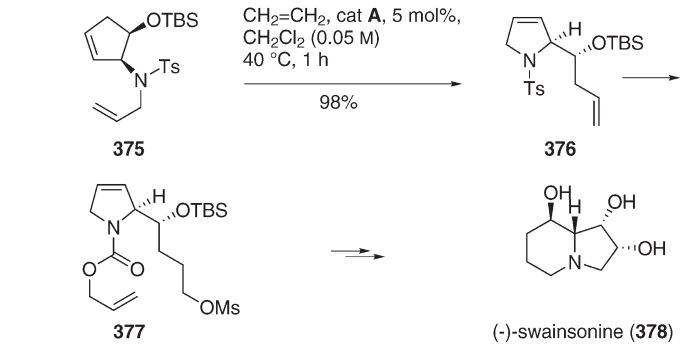
Four members of the tetraponerine family (the major constituents of the contact poison of the New Guinean ant *Tetraponera* sp.) were prepared by RRM methods [156]. The key step leading to tetraponerine T7 (**374**) from the readily available cyclopentene precursor **372** is shown in Scheme 72. When compound **372** was exposed to catalyst **A** in the presence of ethylene, the desired ROM–RCM sequence proceeded smoothly to furnish heterocycle **373** with complete conversion, whereas the corresponding di-nosyl (2-nitrophenylsulfonyl)-protected analog of **372** led only to a 1:2 equilibrium mixture of starting material and RRM product.



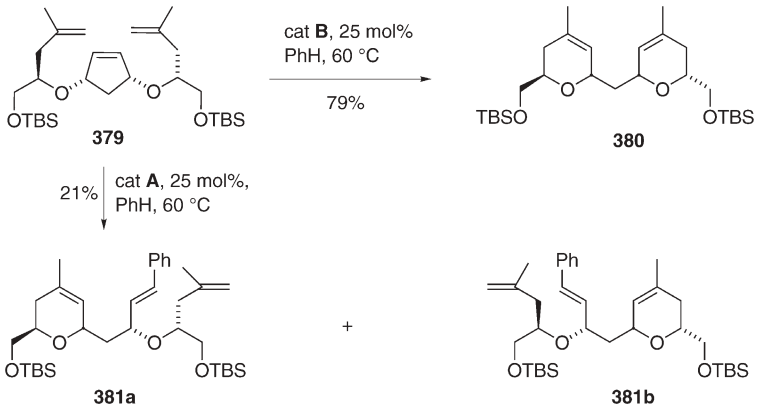
Scheme 72 Synthesis of tetraponerine T7 (**374**) via RRM of cyclopentene **372** [156]

The same principle of sequential cyclopentene-opening RCM resulting in the formation of a dihydropyrrole ring was the key step in Blechert's novel approach to the polyhydroxylated indolizine alkaloid (–)-swainsonine (**378**) via RRM of **375** (Scheme 73) [157].

An early example of cyclopentene-opening/double RCM leading to bis-dihydropyran **380** (the C22–C34 segment of the potent antitumor agent halichondrin A) was disclosed by Burke et al. (Scheme 74) [158]. In this case, the ROM–RCM sequence was performed with catalyst **B**, leading from cyclopentene **379** to **380** in 71% yield. When metathesis precursor **379** was exposed to catalyst **A**, only one



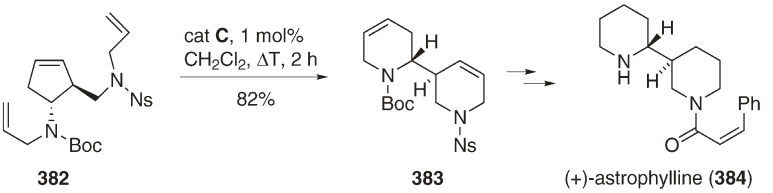
Scheme 73 Synthesis of swainsonine (**378**) via RRM of cyclopentene **375** [157]



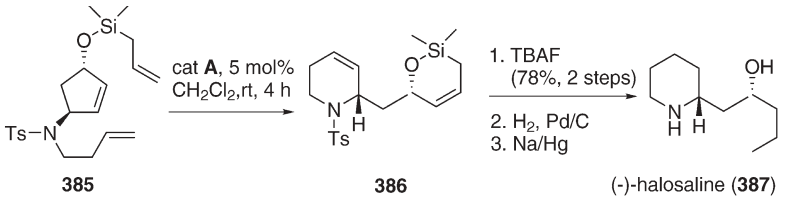
Scheme 74 Synthesis of bis-dihydropyran fragment **380** of halichondrin by tandem ROM–double RCM of cyclopentene **379** [158]

dihydropyran ring was formed and the reaction led to a mixture of the isomeric compounds **381a** and **381b** in low yield.

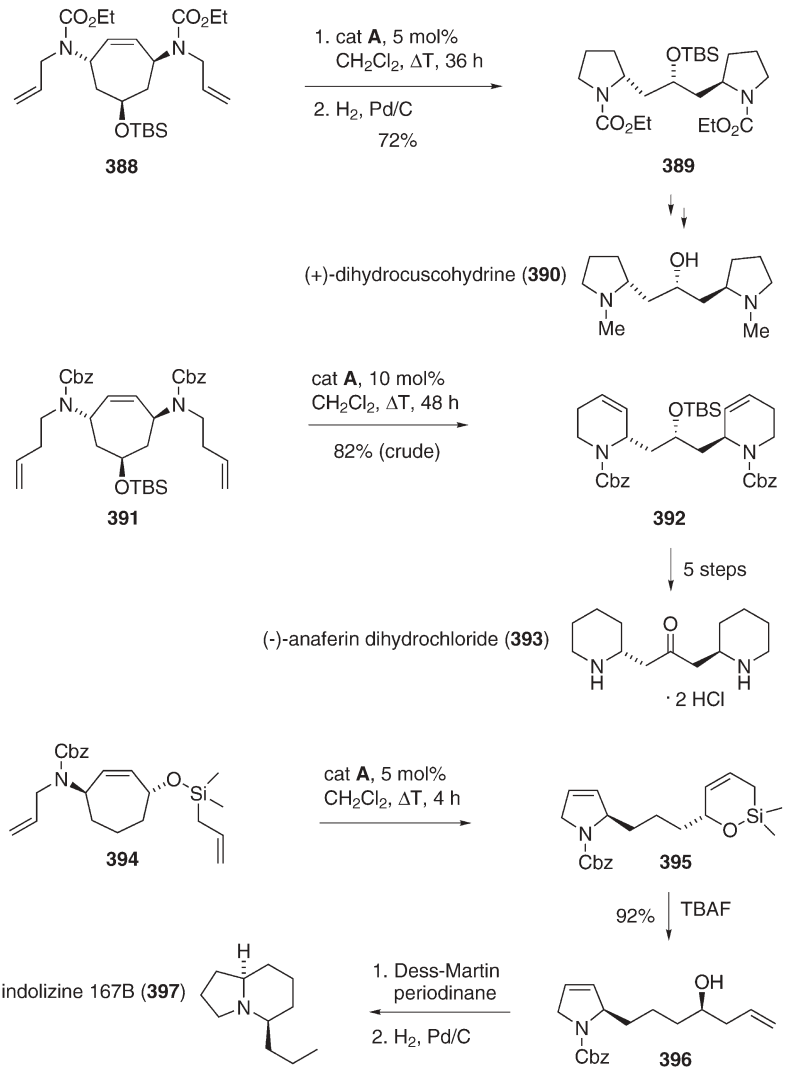
RRM of enantiopure cyclopentene **382,** induced by commercially available catalyst **C,** was the key step in Blechert's total synthesis of the bis-piperidine alkaloid (+)-astrophylline (**384**) [159]. Exposure of metathesis precursor **382** to only 1 mol% **C** provided within 2 h bicycle **383** in 82% yield (Scheme 75).



Scheme 75 Synthesis of astrophylline (**384**) via RRM of cyclopentene **382** [159]



Scheme 76 Total synthesis of halosaline (**387**) via RRM of cyclopentene **385** [160]

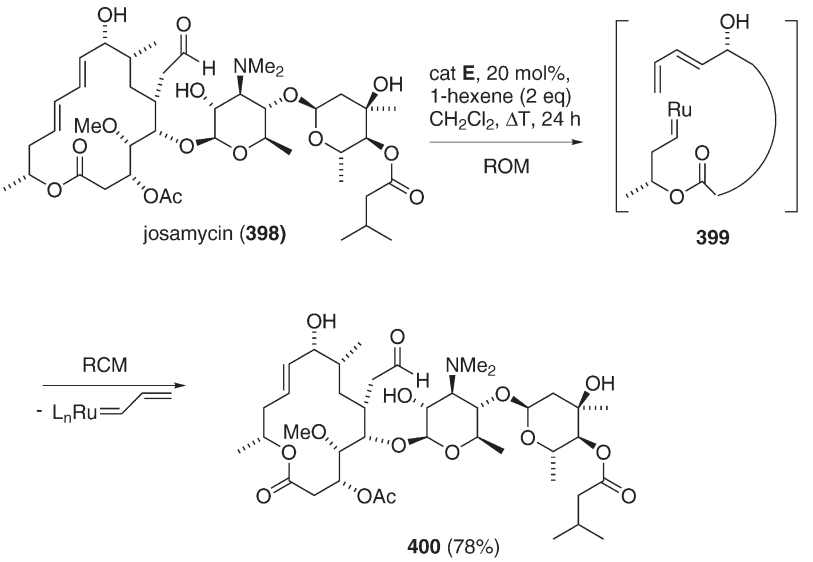


Scheme 77 RRM reactions of enantiopure cycloheptenes leading to dihydrocuscohydrine (**390**) [161], anaferin dihydrochloride (**393**) [162], and indolizine 167B (**397**) [163]

Blechert's synthesis of the piperidine alkaloid (–)-halosaline (**387**) by Ru-catalyzed RRM is outlined in Scheme 76 [160]. In the presence of 5 mol% of catalyst **A**, the ring rearrangement of metathesis precursor **385** proceeded cleanly with formation of both heterocyclic rings in **386**. In situ deprotection of the cyclic silyl ether in **386**, followed by selective reduction and removal of the tosyl group led to **387**.

The utility of strained disubstituted cycloheptenes in alkaloid syntheses is highlighted by Blechert's total syntheses of the bis-pyrrolidine alkaloid (+)-dihydrocuscohydrine (**390**) [161], the bis-piperidine alkaloid (–)-anaferin (in the form of its dihydrochloride **393**) [162], and indolizine 167B (**397**) [163] (Scheme 77).

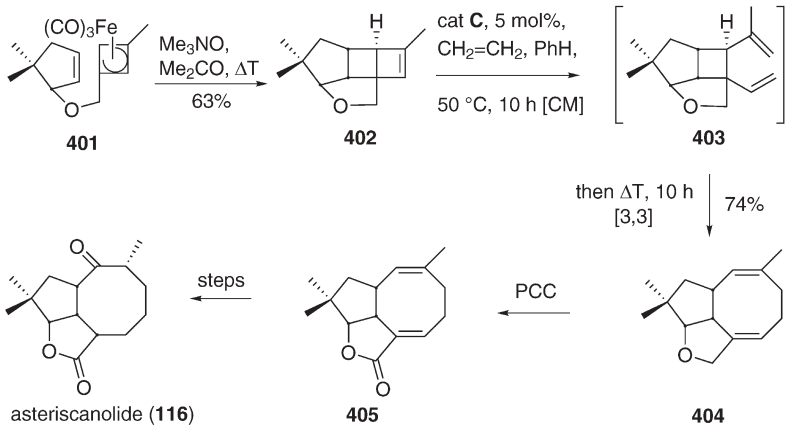
Recently, a novel type of ROM–RCM-based tandem reaction was discovered by Lazarova et al. [164]. When various natural 16-membered macrolide antibiotics with a 1,3-diene unit in the marocyclic core (e.g., josamycin (**398**)) were exposed to catalyst **E** (20 mol%) in the presence of 1-hexene (2 equiv), a ROM–RCM sequence occurred with excision of ethylene and ring contraction to 14-membered-ring lactones **400** (Scheme 78) [165]. The reaction did not occur with catalyst **A**, and demanded – without additives – a stoichiometric amount of catalyst **E**. 1-Hexene, which was added instead of ethylene to initiate and propagate the catalytic cycle by generating the highly active $L_nRu{=}CH_2$ species, could also be replaced by titanium isopropoxide, which is known to destabilize catalyst-deactivating chelates between the catalyst and hydrogen bond acceptors in the metathesis substrate [33].



Scheme 78 Novel ring-contraction metathesis of macrolide antibiotics with a 1,3-diene moiety [164]

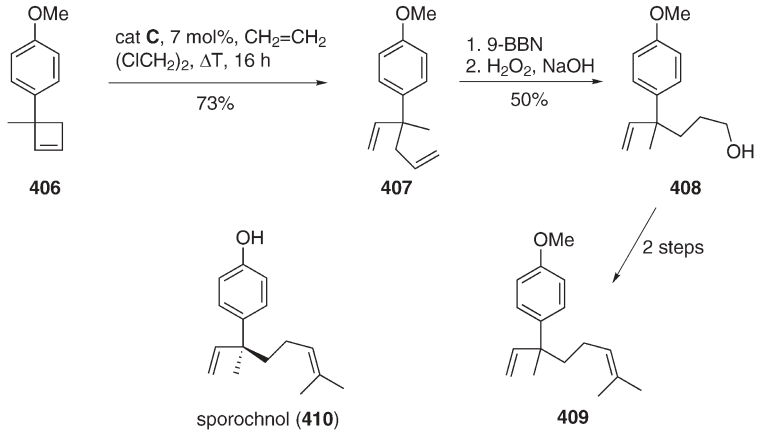
2.4.2
Ring-Opening Cross Metathesis (ROCM)

An important variation of CM methodology is ring-opening cross metathesis (ROCM) where one of the reacting substrates is a (strained) cycloalkene. ROCM reactions of highly strained cyclobutenes have been extensively studied by Snapper and coworkers and provided firm precedent for successful conversion to 1,5-dienes through the use of ethylene as the second component [166]. These investigations resulted in a novel approach to asteriscanolide (**116**, cf Scheme 22) by a novel sequence of intramolecular cyclobutadiene cycloaddition–cyclobutene ROCM–Cope rearrangement (Scheme 79) [167]. The highly functionalized cyclobutene **402** with a trisubstituted double bond was obtained by heating iron tricarbonyl-protected cyclobutadiene **401** with trimethylamine *N*-oxide in acetone. Cycloadduct **402** was the precursor for the ROCM reaction with ethylene. When a solution of **402** in benzene was exposed to catalyst **C** (5 mol%, 50 °C, 10 h) under an ethylene atmosphere, followed by refluxing (10 h), cyclooctadiene **404** was directly produced in 74% yield. Evidently, the initial ROCM product **403** underwent the Cope rearrangement to **404** under such mild reaction conditions. Completion of the formal synthesis of **116** was accomplished by allylic oxidation of **404** to lactone **405**, which was an intermediate in a previous synthesis of **116** [168, 169].

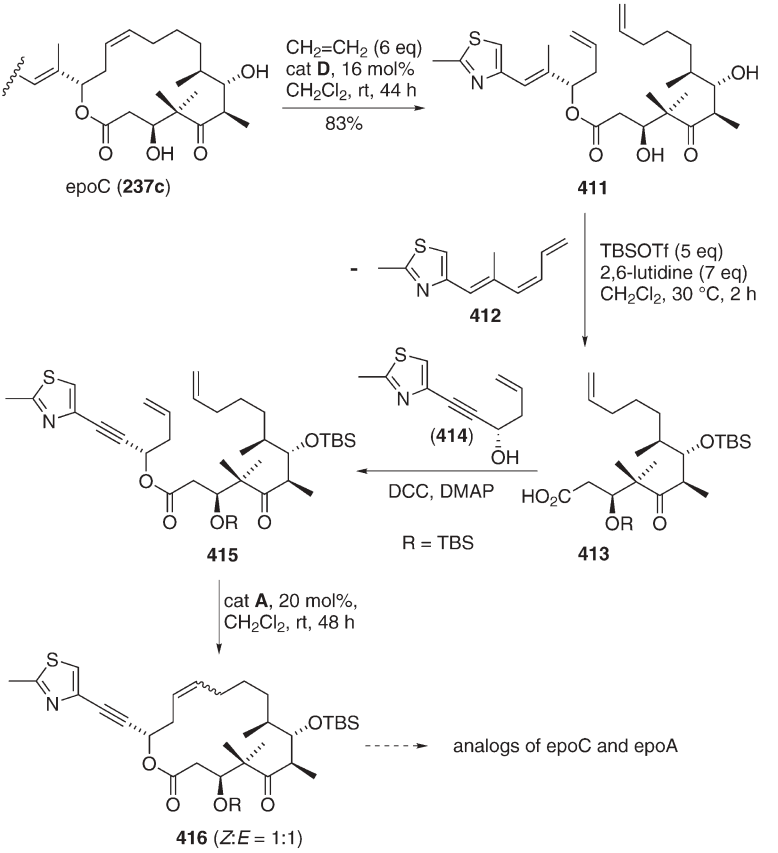


Scheme 79 Snapper's total synthesis of asteriscanolide (**116**) by sequential intramolecular cyclobutadiene cycloaddition, ring-opening CM (ROCM), and Cope rearrangement [167]

A cyclobutene ROCM sequence was also used in a synthesis of racemic sporochnol (**410**), a naturally occurring feeding deterrent toward herbivorous fish (Scheme 80) [170]. Exposing cyclobutene **406** (0.01 M in boiling 1,2-dichloroethane) in the presence of ethylene to second-generation catalyst **C** (8 mol%) led to 1,5-diene **407** in 73% yield, along with 9% of the homodimer derived from **407** by involving the less hindered double bond. Site-selective hy-



Scheme 80 Use of ROCM of cyclobutene **406** in synthetic work directed to sporochnol (**410**) [170]



Scheme 81 ROCM performed on epoC (**237c**), an unstrained natural macrocycle: synthesis of epoC analogs with modified side chain [171]

droboration of **407**, followed by alcohol to aldehyde interconversion and a Wittig reaction, led to the racemic methyl ether analog **409** of **410**.

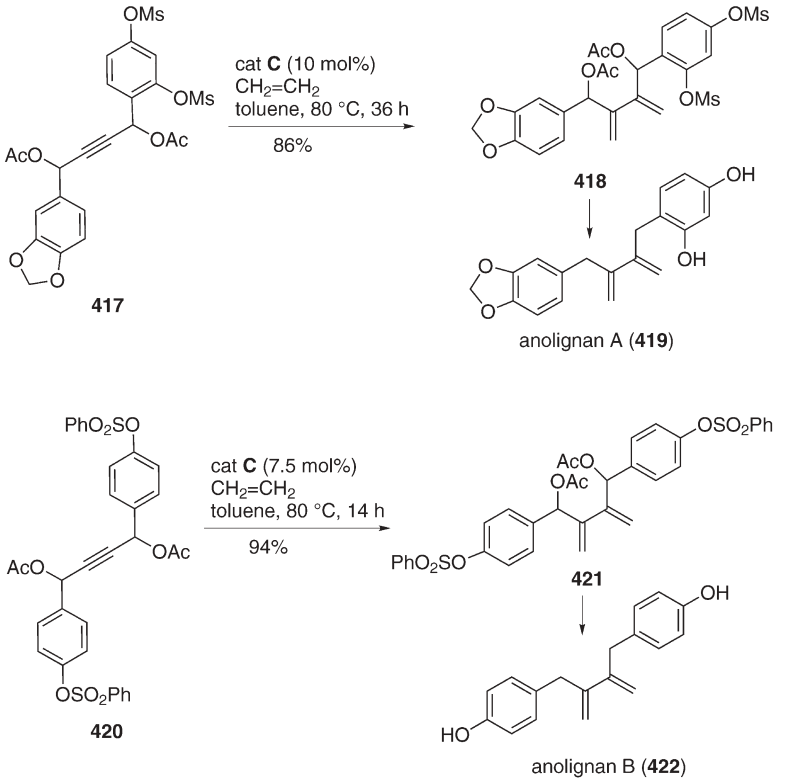
The first example of a ROM–CM sequence performed on an *unstrained macrocyclic* natural compound was recently presented by Höfle et al. [171]. ROCM of epoC (**237c**, cf Fig. 8), produced by fermentation with excess ethylene in the presence of catalyst **D** (16 mol%, added in two portions during 44 h), led to seco compound **411** in high yield (Scheme 81). Silylation of **411** with an excess of reagents not only protected the hydroxy groups but also cleaved the ester by elimination of triene **412** to furnish carboxylic acid **413** in 80% yield. Known building block **413** was then used for the synthesis of the novel 16,17-alkyne analogs **416** of epoC (**237c**) and epoA (**238a**), through esterification with **414** followed by (nonstereoselective) RCM with catalyst **A**.

3
Enyne Cross Metathesis and Ring-Closing Enyne Metathesis

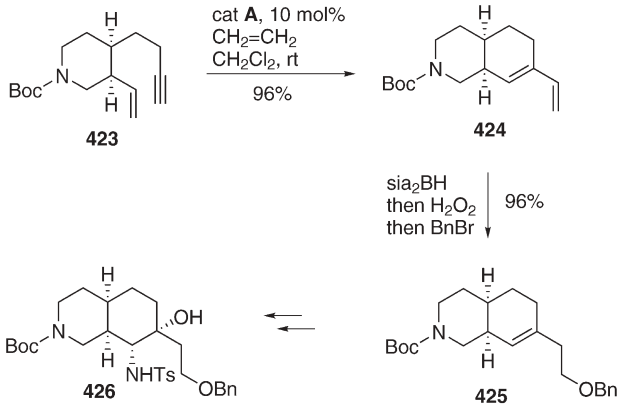
In contrast to diene metathesis, enyne metathesis (cf Fig. 2), which is catalyzed by the same catalysts, has not been developed as much, although the reaction produces synthetically useful 1,3-dienes [172]. Until recently, *intermolecular enyne metathesis* reactions were thought of as unselective with regard to both (*E*/*Z*) and chemoselectivity [173]. Competing CM homodimerization of the alkene, alkyne metathesis, and polymerization hampered the development of the intermolecular variant as a tool in natural product synthesis. Thus, it seems that to date, Mori's synthesis of the natural HIV-1 reverse transcriptase inhibitors anolignan A (**419**) and B (**422**), which both feature a 2,3-dibenzyl-substituted 1,3-butadiene skeleton [174], is a single example of the successful use of enyne CM in natural product synthesis (Scheme 82). In previous work in the group, it was shown that Ru-catalyzed CM between mono- or disubstituted alkynes and ethylene led to the introduction of a methylene group to both alkyne carbons providing substituted 1,3-butadienes (cf Fig. 2c) in good yield [175]. Applying this method, alkynes **417** and **420** (both compounds bear rate-accelerating acetoxy groups at each propargylic position) were exposed to catalyst **C** (10 mol%) under an atmosphere of ethylene, to furnish the desired 1,3-dienes **418** and **421** in high yield. The synthesis of **419** and **422** was completed by sequential hydrogenolytic removal of the propargylic acetoxy groups and deprotection.

More research efforts have focused on the *ring-closing enyne metathesis*, which usually [176] provides conjugated vinyl cycloalkenes (cf Fig. 2a, *exo* mode) useful for further manipulation, but also allows tandem metathesis processes for the formation of polycyclic compounds.

Clark and coworkers utilized enyne RCM for constructing the AB ring fragment of the manzamine alkaloids (Scheme 83) [177]. Exposing metathesis precursor **423** and ethylene gas to catalyst **A** provided bicycle **424** in near quantitative yield. Regioselective hydroboration of the vinyl group in **424**, followed



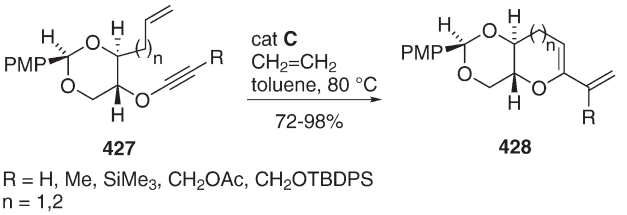
Scheme 82 Synthesis of anolignans A (**419**) and B (**422**) via enyne CM [174]



Scheme 83 Synthesis of the manzamine AB ring segment **426** via enyne RCM [177]

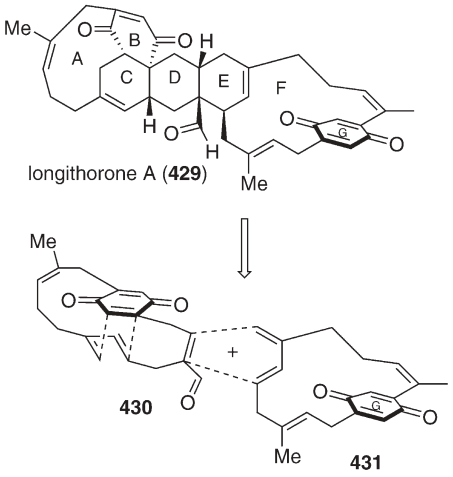
by O-benzylation to **425** and Sharpless aminohydroxylation led to fragment **426,** possessing most of the functionality required for further elaboration to the manzamine skeleton [178].

Clark's group also reported on ring-closing enyne metathesis for the preparation of six- and seven-membered cyclic enol ethers **428** (n=1, 2) as potential building blocks for the synthesis of marine polyether natural compounds such as brevetoxins and ciguatoxins. Metathesis products **428** were obtained from ene-ynes **427** in 72–98% yield when the NHC-bearing catalyst **C** was used (Scheme 84) [179].



Scheme 84 Synthesis of cyclic enol ethers **428** by enyne RCM [179]

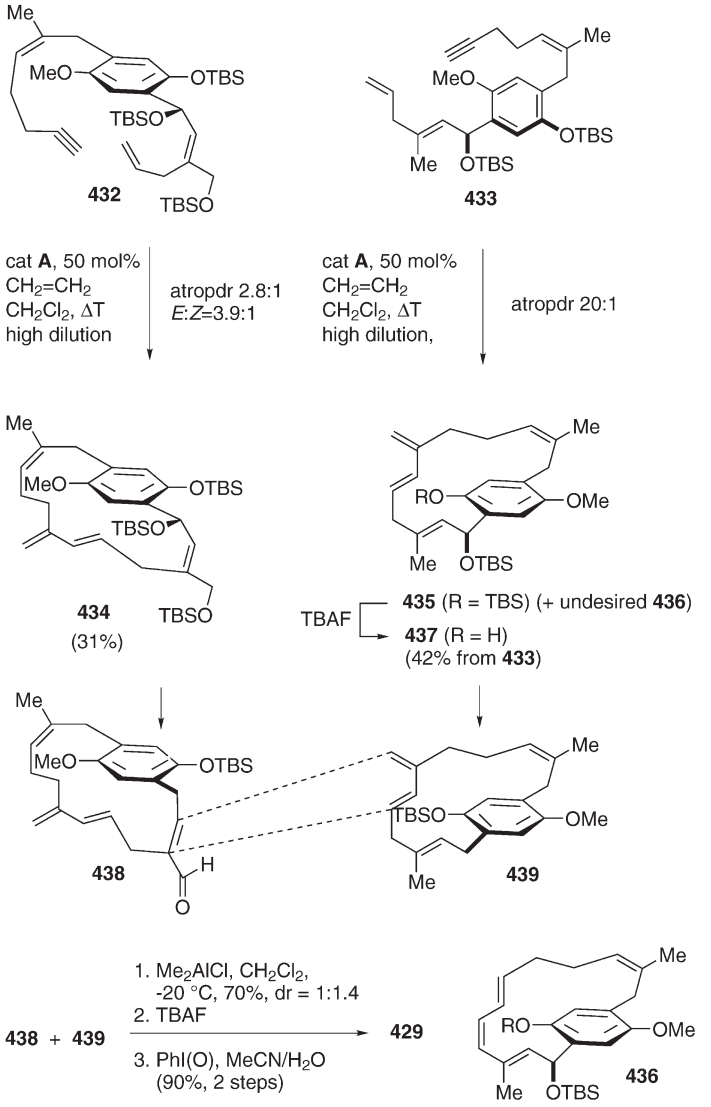
The first examples of *macrocyclization* by enyne RCM were used in Shair's impressive biomimetic total synthesis of the cytotoxic marine natural product longithorone A (**429**) [180]. This unique compound features an unusual heptacyclic structure which, in addition to the stereogenic centers in rings A–E, is also chiral by atropisomerism arising from hindered rotation of quinone ring G through macrocycle F (Scheme 85). It was assumed that biosynthesis of **429** could occur via an intermolecular Diels–Alder reaction between [12]paracy-



Scheme 85 Biomimetic retrosynthetic analysis of longithorone A (**429**)

clophanes **430** and **431** to form ring E, and a transannular Diels–Alder reaction across **430** to simultaneously assemble rings A, C, and D [181].

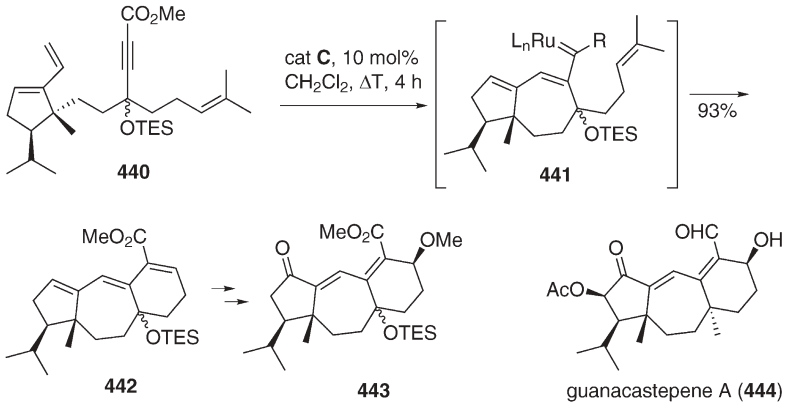
According to this hypothesis, Shair's synthesis began with the construction of the protected versions **438** and **439** of key fragments **430** and **431** as single atropisomers, by using for the first time enyne macrocyclization to generate the required 1,3-diene units present in both key fragments (Scheme 86). This plan



Scheme 86 Regioselective enyne RCM for the synthesis of 1,3-disubstituted macrocyclic 1,3-dienes **433** and **434**, main fragments in Shair's total synthesis of longithorone A [180]

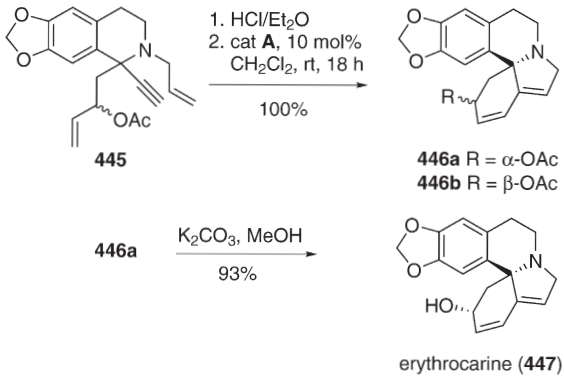
implicated that macrocyclization of metathesis substrates **432** and **433** would resemble *intermolecular* enyne metathesis and generate *1,3-disubstituted dienes* (via the *endo*-type cyclization, cf Fig. 2a), since the resulting [12]paracyclophanes would be less strained than the [11]paracyclophanes resulting from 1,2-disubstituted diene formation (cf *exo*-mode in Fig. 2a). The bulky benzylic silyl ethers in metathesis precursors **432** and **433** were used to gear the aromatic rings during the metathesis process in order to control the atropisomerism and enforce atropdiastereoselection during the ring closure. Exposure of **433** to catalyst **A** and ethylene at high dilution in dichloromethane at 40 °C did indeed afford the desired [12]paracyclophane **435** with ≥20:1 atropdiastereoselectivity. However, **435** was obtained as an inseparable 2.2:1 mixture with the undesired paracyclophane **436** that had lost a molecule of propene during cyclization and could only be separated after selective deprotection of **435** to **437**. An analogous *endo*-type enyne macrocyclization was performed by exposing the more complex substrate **432** to the same conditions. However, this reaction resulted in a 2.8:1 mixture of atropdiastereomers and in a 3.9:1 (*E*/*Z*) ratio of double bond isomers, favoring [12]paracyclophane **434**. Compounds **437** and **434** were then transformed in a few steps (including reductive removal of the benzylic silyl ethers that had served their purpose as control elements) into precursors **438** and **439** for the intermolecular Diels–Alder reaction. During oxidation of the cycloadduct generated from **438** and **439** to the corresponding bis-quinone, the transannular cycloaddition occurred, leading directly to longithorone A (**429**).

Guanacastepene A (**444**) is a novel tricyclic diterpene with fused five-, seven-, and six-membered rings. The possibility of constructing polycyclic compounds via *tandem RCM of dienynes* was used in Hanna's synthesis of a highly functionalized tricyclic system **443** related to **444**. Under the conditions outlined in Scheme 87, trienyne **440** provided the desired tricycle **442** in a single step, as a result of sequential enyne RCM followed by RCM of intermediate **441**. Compound **442** was then further functionalized to **443** [182].



Scheme 87 Synthesis of the tricyclic skeleton **443** of guanacastepene A (**444**) via diene-yne RCM [182]

RCM of a dienyne was also a key step in Mori's recent total synthesis of the alkaloid erythrocarine (**447**) [183]. The tetracyclic framework of **447** was elaborated in the penultimate step, by exposing the hydrochloride of metathesis precursor **445** (1:1 diastereomeric mixture at the carbinol center) to first-generation catalyst **A**. The tandem process occurred smoothly within 18 h at room temperature leading to tetracycles **446** (1:1 mixture) in quantitative yield. Deprotection of the α-acetoxy isomer **446a** led to **447** (Scheme 88).



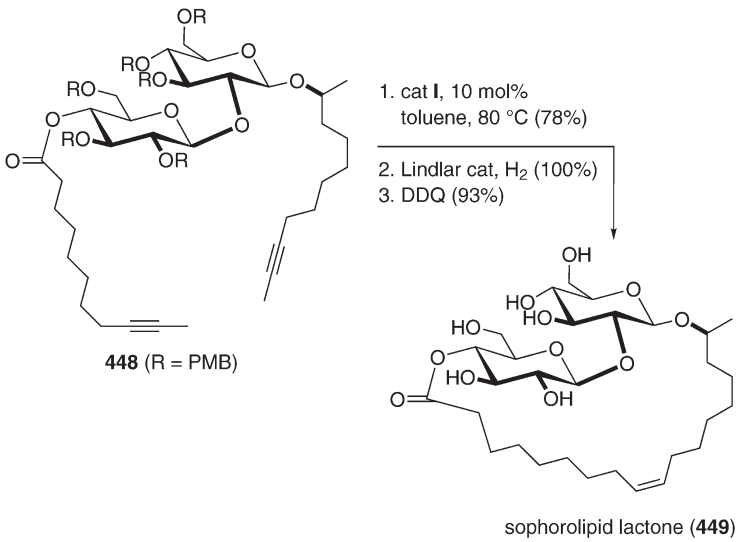
Scheme 88 Total synthesis of erythrocarine (**447**) via RCM of diene-yne **445** [183]

4
Ring-Closing Alkyne Metathesis (RCAM) and Alkyne Cross Metathesis (ACM)

An obvious drawback in RCM-based synthesis of unsaturated macrocyclic natural compounds is the lack of control over the newly formed double bond. The products formed are usually obtained as mixture of (*E*/*Z*)-isomers with the (*E*)-isomer dominating in most cases. The best solution for this problem might be a sequence of RCAM followed by (*E*)- or (*Z*)-selective partial reduction. Until now, alkyne metathesis has remained in the shadow of alkene-based metathesis reactions. One of the reasons may be the lack of commercially available catalysts for this type of reaction. When alkyne metathesis as a new synthetic tool was reviewed in early 1999 [184], there existed only a single report disclosed by Fürstner's laboratory [185] on the RCAM-based conversion of functionalized diynes to triple-bonded 12- to 28-membered macrocycles with the concomitant expulsion of 2-butyne (cf Fig. 3a). These reactions were catalyzed by Schrock's tungsten-carbyne complex **G**. Since then, Fürstner and coworkers have achieved a series of natural product syntheses, which seem to establish RCAM followed by partial reduction to (*Z*)- or (*E*)-cycloalkenes as a useful macrocyclization alternative to RCM. As work up to early 2000, including the development of alternative alkyne metathesis catalysts, is competently covered in Fürstner's excellent review [2a], we will concentrate here only on the most recent natural product syntheses, which were all achieved by Fürstner's team.

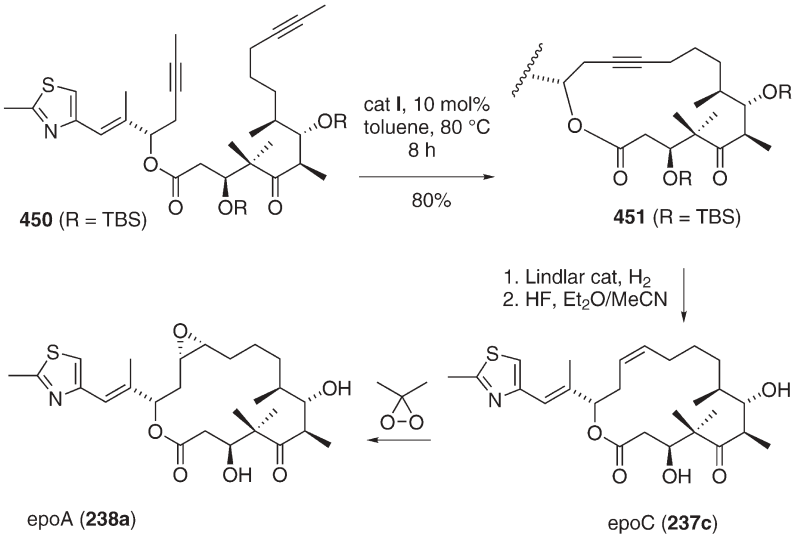
RCAM of diyne **448** catalyzed by the molybdenum-based system **I** followed by Lindlar reduction of the resulting cycloalkyne was the key step in the first total synthesis of the complex glycoconjugate and 26-membered macrolide sophorolipid lactone (**449**) [186] (Scheme 89), that together with the corresponding seco acid constitutes the major component of extracellular biosurfactants produced by the yeast *candida bombicola*. Applying the not rigorously defined catalyst system **I** (prepared in situ from Mo[N(*t*-Bu)(Ar)]$_3$ (**1**, R= 3,5-dimethylphenyl) and CH_2Cl_2 in toluene at 80 °C) to diyne **448** led smoothly to the desired macrocycle in 78% yield. Neither the PMB ethers nor the glycosidic linkages were damaged by the Lewis acidic metal center of the catalyst. Notably, RCM of a (differently protected) terminal diene mediated by various ruthenium catalysts of the first generation previously led to a mixture (*E*:*Z*≈3:1) of isomers.

In a subsequent report [187b], the high functional group tolerance of catalyst system **I** in RCAM reactions was demonstrated by the formation of an impressive number of nonnatural cycloalkynes with ring sizes varying from 12-membered to very large systems, and it was also shown that double bonds (isolated and conjugated) present in the cyclization substrate remained intact. Limits were encountered only with substrates containing acidic protons, including the protons of secondary amides. But it was also remembered that compounds of the basic type Mo[N(*t*-Bu)(Ar)]$_3$ are extremely reactive, being able to activate even molecular nitrogen at or below room temperature [20]. Therefore N_2 must not be used as a protecting atmosphere for any reactions involving these reagents. Application of the above catalyst system **I** culminated



Scheme 89 Total synthesis of sophorolipid lactone **449** by sequential RCAM and (*Z*)-selective partial hydrogenation [186]

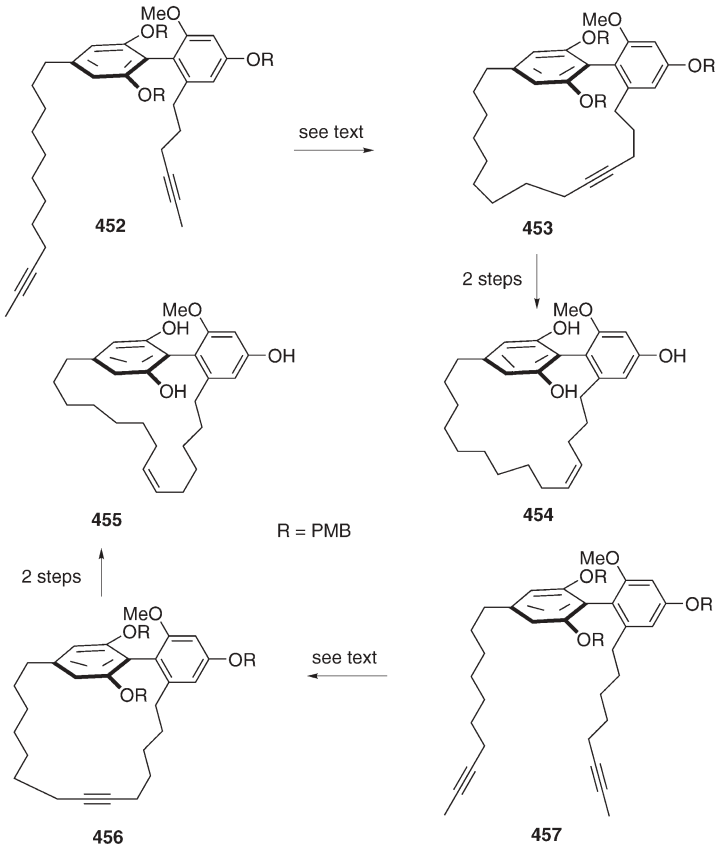
in a novel macrocyclization strategy for epoC (**237c**) by RCAM of the polyfunctional diyne **450** (Scheme 90) [187]. When **450** was exposed to catalyst system **I** (10 mol%, toluene, 80 °C, 8 h) the ring closure proceeded smoothly leading to cycloalkyne **451** in 80% yield. Neither the basic nitrogen nor the sulfur of the thiazole moiety interfered with the catalyst. No racemization at the chiral center α to the carbonyl group was encountered, and the protecting silyl ethers as well as the double bonds remained intact. The total synthesis of epoC (**237c**) was easily completed by Lindlar reduction of **451** followed by deprotection.



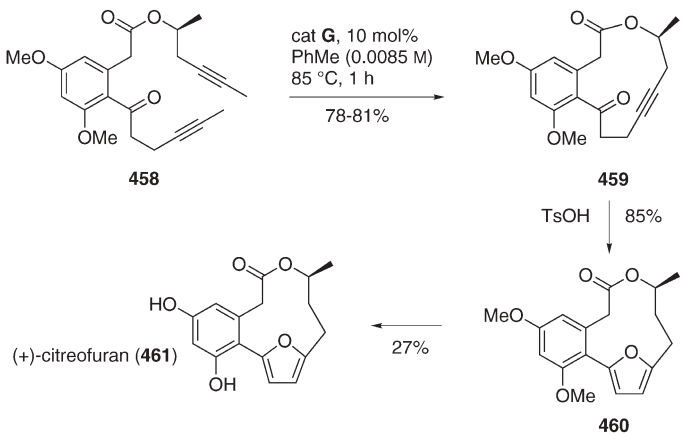
Scheme 90 Fürstner's total synthesis of epoC (**237c**) via sequential RCAM of diyne **450** and (*Z*)-selective partial hydrogenation [187]

The "user-friendly" catalyst **H**, prepared in situ from $Mo(CO)_6$ and *p*-trifluoromethylphenol, and also the well-defined tungsten complex **G** were used in the first total syntheses of the naturally occurring cyclophane derivatives **454** and **455** belonging to the turriane family [188] (Scheme 91). Exposing metathesis substrates **452** and **457** to tungsten complex **G** (10 mol%, toluene 80 °C, 16 h) led to cyclization products **453** and **456** in 64 and 61% yield, respectively. By the use of the less reactive, but more conveniently available, catalyst system **H** (10 mol%, chlorobenzene, 135 °C, 4 and 6 h, respectively), the yields were increased to 83 and 76%, and when the latter reactions were assisted by microwave heating, the RCAM proceeded within 5 min, leading to **453** and **456** in 69 and 71% yield, respectively.

A sequence of RCAM followed by transannular cycloaromatization in Fürstner's total synthesis of the natural 11-membered macrolide (+)-citreofuran (**461**) nicely demonstrates that RCAM has a broader scope than just the prepa-



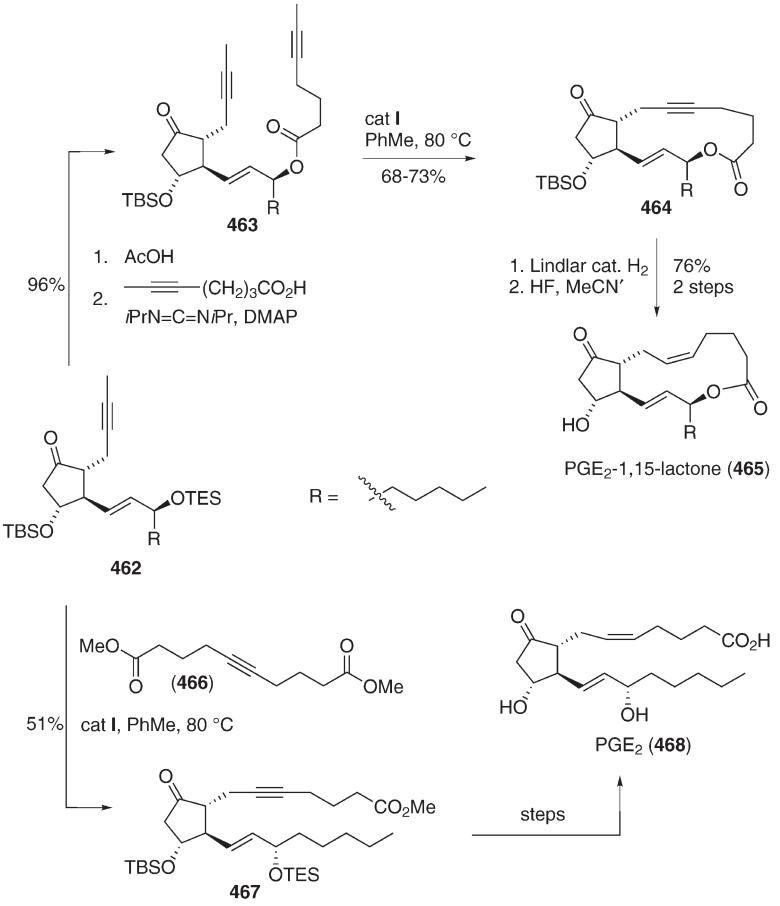
Scheme 91 RCAM-based synthesis of turrianes **454** and **455** by Fürstner and coworkers [188]



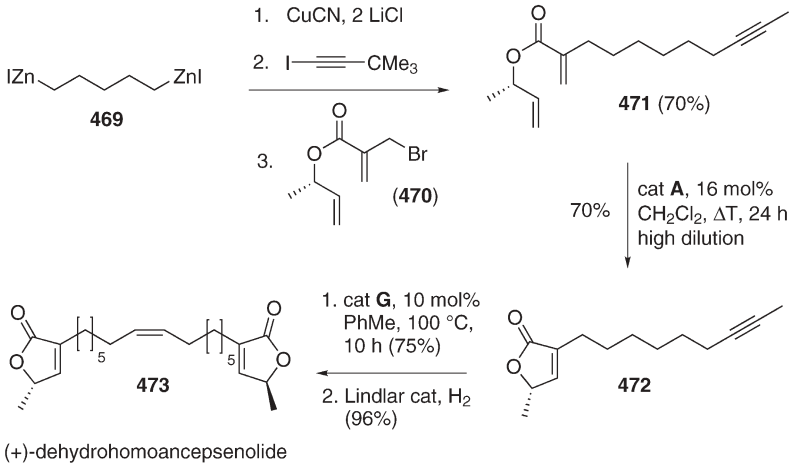
Scheme 92 Total synthesis of citreofuran (**461**) via RCAM of diyne **458** and subsequent transannular cycloaromatization [189]

ration of stereo-defined olefins [189] (Scheme 92). Exposure of metathesis precursor **458** to Schrock's tungsten complex **G** (10 mol%, toluene, 85 °C, 1 h) led to cyclization product **459** in 78% yield, provided the reaction mixture was devoid of any trace impurities, which underlines the high sensitivity of this catalyst. Subsequent treatment of **459** with TsOH smoothly generated the furan ring in **460** and completed the skeleton of the natural compound. The final removal of the methyl ethers from **460**, however, was very sluggish leading to **461** only in unsatisfactory yield.

A particularly flexible and novel entry into prostaglandins and analogs, either by RCAM (**463**→**464**) or by the intermolecular variant ACM (**462**+**466**→**467**) from a common intermediate (**462**), is outlined in Scheme 93 [190]. Prostaglandin E_2-1,15-lactone (**465**), an ichthyotoxic compound produced by a marine nudibranch for defense purposes, was produced in Fürstner's laboratory along the RCAM-based sequence **462**→**463**→**464**→**465**. Alternatively, the



Scheme 93 Prostaglandin synthesis based on RCAM or ACM [190]



Scheme 94 Total synthesis of the natural compound dehydrohomoancepsenolide (**473**) through sequential application of chemoselective ruthenium-catalyzed RCM and tungsten-catalyzed alkyne homodimerization [191]

parent prostaglandin **468** was prepared via the *inter*molecular ACM mode, by exposing alkynes **462** and **466** to the same catalyst system (**I**). The conversion **462**→**467**→**468**, which in the metathesis step proceeded without homodimerization of key fragment **462**, represents the first example of an ACM-based natural product synthesis.

An elegant combination of sequential ruthenium-catalyzed RCM and tungsten-catalyzed homodimerization of an alkyne (both types of metathesis reactions being totally selective with respect to the π-systems involved) is found in Fürstner's total synthesis of the marine metabolite dehydrohomoancepsenolide (**473**) [191] (Scheme 94). Copper-mediated "three-component coupling" of the bimetallic species **469** with 1-iodo-1-propine and the chiral methacrylate **470** led to the precursor **471** for the RCM reaction. The ring closure of dienyne **471** to butenolide **472** proceeded readily and chemoselectively in 70% yield when catalyst **A** was used and when the reaction was performed under high dilution. The more powerful NHC-bearing second-generation catalysts, however, turned out to be too reactive in this case as they did not distinguish between the alkyne and the alkene moieties in the metathesis substrate **471**. The dimerization of alkyne **472** with tungsten complex **G** (10 mol%, toluene, 100 °C, 10 h) provided with selective involvement of the triple bond the C2-symmetric alkyne that was partially hydrogenated to furnish **473**.

5
Conclusions and Outlook

The last few years have witnessed an exponential growth in the application of ruthenium-catalyzed metathesis reactions in target-oriented synthesis. The development of highly active metathesis catalysts, that are commercially available and combine high functional group tolerance with "user-friendly" low sensitivity to moisture and air, has rendered metathesis a mature tool for the rapid construction of small-, medium-, and large-ring carbo- and heterocycles. Consequently, the logic of modern retrosynthetic planning is strongly affected by metathesis, since this transformation can now be applied to increasingly complex targets, as exemplified by metathesis-based total syntheses of polyether marine toxins, as well as by regio- and stereoselective macrocyclizations of diene-enes in the epothilone series.

Olefin cross metathesis starts to compete with traditional C=C bond-forming reactions such as the Wittig reaction and its modifications, as illustrated by the increasing use of electron-deficient conjugated alkenes for the (*E*)-selective construction of enals and enoates.

The use of metathesis cascades applied in various ring-rearrangement reactions allowed for a uniquely short access to various heterocyclic natural compounds, while diene-yne metathesis led to the formation of complex polycyclic structures. Also, tandem sequences combining a metathesis event with other reactions in the current synthetic repertoire, such as [3.3]-sigmatropic rearrangement, Pd-catalyzed alkene coupling, or Diels–Alder reaction, have been used as key steps in total syntheses of highly complex natural products. Particularly attractive tandem processes occur when two or more sequential reactions are mediated by the same catalytic precursor. The ability of ruthenium alkylidenes to function directly, or by simple modifications also as precatalysts for nonmetathetic processes (radical additions, olefin and carbonyl hydrogenations, hydrogen transfer reactions, olefin isomerizations) [192], broadens their synthetic utility toward efficient catalytic tandem sequences that combine metathesis events with one or more nonmetathesis reactions. To date, this strategy has led to highly efficient syntheses of relatively simple natural products [122, 193] and will certainly be utilized for more complex targets in future work.

Thus far, chemists have been able to influence the stereoselectivity of macrocyclic RCM through steric and electronic substrate features or by the choice of a catalyst with appropriate activity, but there still exists a lack of prediction over the stereochemistry of macrocyclic RCM. One of the most important extensions of the original metathesis reaction for the synthesis of stereochemically defined (cyclo)alkenes is alkyne metathesis, followed by selective partial hydrogenation.

An area in which catalytic olefin metathesis could have a significant impact on future natural product-directed work would be the desymmetrization of achiral molecules through asymmetric RCM (ARCM) or asymmetric ROM

(AROM)-RCM- and -CM sequences initiated by chiral molybdenum-based catalysts [194] or, more recently, also by ruthenium-based [195] catalysts.

Ongoing research efforts will lead to the arrival of even more efficient and selective metathesis catalysts with specifically tailored properties [196]. Due to the synergistic relationship between catalyst design and subsequent application in advanced synthesis [197], this progress will further expand the scope of metathesis and its popularity amongst the synthetic community.

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