Synthesis of Natural Products Containing Medium-size Carbocycles by Ring-closing Alkene Metathesis

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1.1 Introduction

This chapter deals with the synthesis of naturally occurring molecules (or related models) and focuses on the construction of medium-size carbocycles by ring-closing metathesis (RCM). We have arbitrarily chosen to organize this chapter by increasing ring size. Strategic aspects and potential problems are discussed.

1.2 Formation of Five-membered Carbocycles by RCM

Strategic positioning of the double bonds of a 1,6-diene prior to RCM can be efficiently accomplished via [3,3]-sigmatropic rearrangements. Only selected examples are discussed below, based on originality and efficiency criteria. Catalytic asymmetric Claisen rearrangement was reported by Hiersemann et al. in the enantioselective synthesis of the C10–C18 segment of ecklonialactone B (1), a C18-oxylipin isolated from the brown algae Ecklonia stolonifera and Egregia menziessi [1]. The [3,3]-sigmatropic rearrangement of 2 using catalyst 3 led to the acyclic α-keto ester 4 that can be reduced and cyclized to the corresponding disubstituted cyclopentene 5 using [Ru]II. Further functional group transformations led to the desired C10–C18 fragment 6 of the natural product (Scheme 1.1).

A [3,3]-sigmatropic rearrangement/RCM sequence [2] was also used as a key step in the total synthesis of a bioactive spirobenzofuran 7 isolated from the mycelium cultures of Acremonium sp. HKI 0230 [3]. The two consecutive quaternary centers embedded in the 1,6-diene 9 are worthy of note in the context of cyclopentene formation by RCM, and the five-membered ring compound 10 was obtained in high yield (97%) using catalyst [Ru]I. The same type of strategy was applied for the efficient construction of the two vicinal quaternary carbon atoms present in the herbertanes sesquiterpenes (Scheme 1.2) [4].

Besides the Ireland–Claisen [3,3]-sigmatropic rearrangement/RCM sequence, some examples of Johnson–Claisen/RCM were reported by Ghosh and Maity [5].
Scheme 1.1

Scheme 1.2

Scheme 1.3

In the first total synthesis of sequosempervirin A (11), a norlignan isolated from *Sequoia sempervirens*, the γ,δ-unsaturated carbonyl derivative 13 was prepared from 12 by Johnson–Claisen rearrangement. Further steps led to 14, the precursor of the key RCM reaction catalyzed by [Ru]–I, which established the desired spiro structure of compound 15 (Scheme 1.3).

An analogous Johnson–Claisen rearrangement/RCM sequence was used by Ghosh et al. in the synthesis of the carbocyclic core of the nucleoside (−)-BCA (16), a potential inhibitor of HIV reverse transcriptase (Scheme 1.4) [6]. The chiral cyclopentene 20 was obtained in excellent yield through a [Ru]–I-mediated RCM of 1,6-diene 19. Further epoxidation and functional group transformations led to (−)-BCA core structure 23.
1.2 Formation of Five-membered Carbocycles by RCM

Bis(hydroxymethyl)cyclopentenyl adenine, (-)-BCA (16)

\[\begin{align*}
\text{HO} & \quad \text{HO} \\
\text{N} & \quad \text{N} \\
\text{NH}_2 & \quad \text{N} \\
\text{HO} & \quad \text{HO}
\end{align*}\]

Steps

\[\begin{align*}
\text{EtO}_2\text{C} & \quad \text{H} \\
\text{BnO} & \quad \text{H} \\
\text{BnO} & \quad \text{H} \\
\text{BnO} & \quad \text{O}
\end{align*}\]

\[\text{m-CPBA} \quad 85\%\]

Steps

\[\begin{align*}
\text{HO} & \quad \text{NH}_2
\end{align*}\]

Scheme 1.4

Another [3,3]-sigmatropic rearrangement/RCM sequence was developed by Srikrishna and coworkers in the first total synthesis of the aromatic sesquiterpene (±)-laurokamurene B (24) (Scheme 1.5) [7]. RCM of 27 led to cyclopentenol 28 bearing a labile hydroxyl moiety, both benzylic and allylic. The latter compound was found to be unstable and when treated with silica gel delivered the rearranged alcohol 29 in a one-pot operation.

Derivatives of nitiol (30), a novel complex sesterterpenoid that acts as a modulator of IL-2 gene expression, were prepared using RCM of vinyl ketone 33 as a key step (Scheme 1.6) [8]. Worthy of note is the use of catalyst [Ru]-XIII [9] as [Ru]-II was found to increase intermolecular cross-metathesis at the expense of the desired
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Scheme 1.6

RCM. Conjugate reduction of enone 34 using L-selecride followed by trapping of the resulting enolate with PhNTf₂ delivered enol triflate 35. The latter was then submitted to a Stille cross-coupling reaction with vinyl stannane 36 leading to the advanced intermediate 37 in the synthesis of 1,22-dihydroxynitianes.

In the total synthesis of (−)-allosamizoline (38), the carbocyclic fragment of the chitinase inhibitor allosamidin, Donohoe and Rosa reported the efficient elaboration of the cyclopentenyl moiety via the RCM of a 1,6-diene (Scheme 1.7) [10]. Wittig olefination of aldehyde 39, readily obtained from D-glucosamine, proved troublesome when basic phosphorus ylide 40 was used and the 1,6-diene 42 was isolated in 18% yield. Since the terminal substituents of the alkenes are not transferred into the cyclized products during RCM reactions, the reactivity of acrylate 43 was evaluated as the latter was obtained in high yield (91%) using the less basic ylide 41. RCM proceeds equally well, delivering cyclopentene 44 in 88% yield.

Formation of cyclopentenes through the RCM of 1,6-dienes can prove itself difficult in very crowded environment. During synthetic efforts toward the tetracyclic skeleton of the sesquiterpenoid tashironin (47), Mehta and Maity reported the efficient RCM of 50 using [Ru]-I that led to 51 in 86% yield [11]. However, the RCM of 52 having a methyl substituent in allylic position led to 53 in considerably lower yield (25%) even in the presence of the more active [Ru]-II catalyst (Scheme 1.8).

A rapid elaboration of the ABC core structure of the tetraneurterpenone dunsin (54) was reported by Srikrishna et al. starting from the readily available (R)-carvone [12]. Two independent efficient RCM reactions, catalyzed by [Ru]-I, were used as
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Steps

Scheme 1.7

Scheme 1.8

Scheme 1.9

key steps to create the spiro cyclopentene in compound 56 and the trans-fused BC rings in compound 59 (Scheme 1.9).

In challenging cases, simple transformations of the allylic substituents may promote a productive RCM of 1,6-dienes to the corresponding cyclopentenes as shown by Eustache et al. in the stereoselective synthesis of spiroepoxide 61, a
potential methionine aminopeptidase-2 inhibitor related to the natural product fumagillin (60) (Scheme 1.10) [13]. Actually, the RCM of vinyl ketone 62 was found to be sluggish using catalyst [Ru]II (toluene, 70 °C) yielding only 30% of the cyclopentenone 63. The enhanced reactivity of the corresponding allylic alcohol 64 allowed a significant yield increase (55%, over three steps from 62). However, the presence of a potential coordination site for the catalyst could also be detrimental to the efficiency of the RCM. Thus, RCM of the Methoxymethyl (MOM) ether 66 gave cyclopentene 67 in moderate yield (42%), whereas the corresponding free alcohol 68 cyclized to 69 in 80% yield with a threefold decrease in catalyst loading (Scheme 1.10).

Cyclopentenes bearing a trisubstituted double bond could be efficiently prepared via the RCM of the corresponding 1,6-diene. Catalyst [Ru]II is well suited for this transformation since [Ru]I usually leads to inferior yields. The prochiral trisubstituted olefin could then be further reduced or oxidized, thus creating a new tertiary or quaternary stereogenic center.

Trauner et al. used RCM as a key step to elaborate the cyclopentyl core of (−)-guanacastepene E (70) and (−)-heptemerone B (71) (Scheme 1.11) [14]. The cyclization precursor was prepared via an asymmetric ene reaction of glyoxylate 72. Further transformations led to 1,6-diene 74 that could be cyclized to cyclopentenone 75 in 86% yield using [Ru]II (5 mol%). Conjugate addition of the organocuprate 76 then established the C11 quaternary stereocenter. The central seven-membered ring was then closed with an electrochemical oxidation.

Fomannosin (79) is a sesquiterpene metabolite isolated from the wood-destroying Basidiomycetes fungus Fomes annosus (Fr.) Karst. Its inherent instability and very congested structure have elicited a great deal of interest from the synthetic
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Scheme 1.11

Scheme 1.12

community. Paquette et al. reported a straightforward strategy for the elaboration of both antipodes of fomannosin. Compound 80 (prepared from \(\alpha\)-d-glucose) underwent a zirconium-promoted ring contraction providing the four-membered ring 81. The challenging RCM of 82 catalyzed by [Ru]-II was used as a key step, and led to cyclopentene derivative 83 featuring a trisubstituted double bond adjacent to
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1. Synthesis of (+)-Puraquinonic Acid

**Scheme 1.13**

a quaternary stereocenter (Scheme 1.12) [15]. The lactone ring was then elaborated by an intramolecular Knoevenagel reaction.

RCM was used as a key step in the total synthesis of (+)-puraquinonic acid (86), a fungal metabolite that induces differentiation in HL-60 cells [16]. Starting from aromatic aldehyde 87, the RCM precursor 88 was prepared in a few steps. Following RCM leading to 89 (88%), the newly formed trisubstituted alkene was involved in a radical cyclization. Bromo acetal 90 was treated with Bu3SnH and AIBN thus triggering a stereoselective 5-exo trig cyclization reaction. Further steps led to the natural product 86 (Scheme 1.13).

Carbahexofuranoses and carbapentofuranoses syntheses have been intensively investigated and RCM reaction emerged as one of the most practical and efficient methods to this effect. Among the numerous syntheses of such derivatives,
the synthesis of 4α-carba-β-d-galactofuranose 93 is worthy of note [17]. A dramatic protecting group effect was observed during the RCM of 94 and 96. Whereas free allylic alcohols are known to enhance reactivity, RCM of 94 leads to the five-membered ring 95 in poor yield (24%). Under the same conditions, the diacetate 96 undergoes an efficient RCM providing 97 in 89% yield (Scheme 1.14).

Two simultaneous RCM have been used in efforts toward the core structure of the elisabethin diterpenoids [18]. Trisallylcarveol (99), accessible from (R)-carvone, can be transformed in a single step under mild conditions albeit with a moderate yield into the tricyclic compound 100 possessing the core structure of the desired target molecule (Scheme 1.15).

Tetrasubstituted double bonds embedded in a five-membered ring can also be efficiently prepared via RCM. In the total synthesis of (±)-spirotenuipesines A (101)

**Scheme 1.15**

(R)-Carvone

**Scheme 1.16**

1. KOH
2. HCl
3. I₂, KI
NaHCO₃

109

Spirotenuipesine B (102)

Spirotenuipesine A (101)
and B (102), Danishefsky et al. simplified the preparation of a key intermediate, compound 104, from nine steps [19] to three steps when an RCM strategy was adopted (Scheme 1.16) [20]. The resulting tetrasubstituted double bond in 104 was then submitted to an intramolecular diazoester cyclopropanation reaction. Radical opening of the resulting strained cyclopropyl group in 107 delivered bicyclic lactone 108, which was converted to 109 by iodolactonization. The latter compound could be further transformed to (±)-spirotenuipesines A (101) and B (102).

Another example of elaboration of tetrasubstituted double bonds by RCM was disclosed by Kotora et al. in a formal total synthesis of estrone (Scheme 1.17). Starting from 110, two zirconium-mediated cyclizations enabled the preparation of compound 112 whose RCM catalyzed by [Ru]-II (20 mol%) (toluene, 90 °C) provided estrone precursor 113 in 82% yield [21].

![Scheme 1.17](image)

Another example is the elaboration of steps 115, 116, and 117, where 115 undergoes a three-step reaction to yield 116, followed by the preparation of 118 which is then transformed into Fumagillol (114).

![Scheme 1.18](image)
1.3 Formation of Six-membered Carbocycles by RCM

Among the recently reported synthetic approaches to angiogenesis inhibitors such as ovalicin, fumagillin, and synthetic analogs, several use RCM to construct the six-membered ring characteristic of this family of molecules [22–24]. In the first metathesis-based synthesis of fumagillol (114) (Scheme 1.18) [22a], the nonfunctionalized $\text{C}_7$–C8 bond was established through an RCM/hydrogenation sequence. In agreement with Fürstner’s observations, adding Ti(Oi-Pr)$_4$ was required for the RCM of 117 to proceed with catalyst [Ru]-I [25]. The resulting advanced intermediate 118 was easily converted to fumagillol. The approach was used for the preparation of fumagillin analogs 121–123. (Scheme 1.19) [22b] Using the more active [Ru]-II eliminated the need for Ti(Oi-Pr)$_4$ in the RCM of 119 to 120.

The second approach to fumagillol (114) relies on a Claisen/RCM sequence (Scheme 1.20) [23c]. Starting from 1,2,5,6-di-O-isopropylidene $\alpha$-mannitol (124), the ester 125 was prepared and subjected to a glycolate-Claisen rearrangement leading to 126 (77%). RCM of 126 afforded cyclohexene 127 in high yield (94%), which was converted to an advanced intermediate previously used by Sorensen et al. in their synthesis of fumagillol [26].
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In contrast to the two previous syntheses, the six-membered ring was constructed first in Takahashi’s et al. synthesis of ovalicin (128) (Scheme 1.21) [24]. Thus, 2,3,5,6-di-O-isopropylidene-α-mannose (129) was converted to the diastereomeric RCM substrates 130 and 131, which smoothly cyclized to compounds 132 and 133 in the presence of [Ru]−II catalyst.

Clive et al. designed a synthesis of both otteliones A (135) and B (136), featuring an efficient cuprate conjugate addition/Grignard reaction/RCM sequence...
1.3 Formation of Six-membered Carbocycles by RCM

(Scheme 1.22) [27]. Starting from cyclopentenone, the cyclopentene carboxaldehyde 137 was prepared. Conjugate addition of the organocopper derived from 2-butenyllithium generated 138 and subsequent treatment with vinylmagnesium bromide afforded the RCM substrate 139. This compound was cyclized using catalyst [Ru-II] to furnish intermediate 140, which was converted to rac-ottelione A in two steps. Using the same sequence, the epimeric trans-aldehyde 141 (obtained by equilibration of 138) afforded rac-ottelione B via 142 and 143. An asymmetric version of these syntheses was also developed.

Very recently, two RCM-based but conceptually different formal syntheses of platencin 144 were disclosed [28, 29]. In both cases, the target was intermediate 145 that has been previously converted to platencin by Nicolaou et al. [30a] and Rawal et al. [30c].

In Lee’s et al. synthesis [28], the bicyclo[2.2.2]octane moiety was assembled through a radical cyclization/skeletal rearrangement [31]. Standard chemical manipulation then led to triene 149 whose RCM ([Ru-II] afforded cyclohexenol 150 in 95% yield (Scheme 1.23).

Mulzer’s et al. approach implies a nonobvious construction of the strained bicyclo[2.2.2]octane skeleton by RCM (Scheme 1.24) [29]. Starting from (−)-perillaldehyde (151), the decaline 152 was prepared. Wittig reaction afforded triene 153, which was submitted to RCM conditions ([Ru-II], CH₂Cl₂, reflux). RCM completion required more than 24 hours and 8 mol% of catalyst but the yield of 154 was excellent (90%) and no side-products were reported. Compound 154b was then converted to intermediate 145 in two steps (Scheme 1.24).

Polyprenylated acylphloroglucinols, such as garsubellin A (155) and hyperforin A (156), are bioactive molecules characterized by a polycyclic bridged system [32]. In 2005, Shibasaki et al. described a RCM-based total synthesis of (±)-garsubellin A (Scheme 1.25) [33].

The α,β-unsaturated ketone 157 was converted to cyclohexanone 158 and a Claisen rearrangement/RCM sequence was used to construct the characteristic bicyclo[3.3.1]nonane skeleton. [1] Thus, enol ether 159 cleanly rearranged at high temperature to diene 160. [2] Treatment of 160 by [Ru-III] ([20 mol%]), toluene, reflux,

1) The Claisen/RCM sequence has been used repeatedly for constructing various ring systems.
2) Ethylene carbonate was added to the reaction mixture to compensate for carbonate hydrolysis in 183.
1 Synthesis of Natural Products Containing Medium-size Carbocycles

48 hours led to intermediate 161 in excellent yield [34]. Finally, 161 was converted to 162 and then to (±)-garsubellin A (155). As shown in Scheme 1.26, the method could not be extended to hyperforin (156) as RCM of 163 led to 164 possessing a seven-membered ring (Scheme 1.26).

Eight to ten-membered rings, which are common in natural products [35], can be prepared by heterolytic fragmentation of bicyclic systems [36]. The latter can be formed by several methods among which RCM is one of the most efficient.
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Mascareñas et al. reported an RCM/ring fragmentation strategy to eight- and nine-membered carbocycles (Scheme 1.27) [37]. Starting from 1,2-cyclohexanedione, the dienes 166a and 166b were obtained. When submitted to RCM conditions ([Ru]-I, 20°C), only the diastereomers having the two unsaturated side chains in a syn relationship reacted. The resulting bridged compounds 167a and 167b were cleaved by lead tetraacetate to afford ketoesters 168a and 168b. By contrast, direct construction of the eight-membered ring 170 by RCM of 169 was unsuccessful (Scheme 1.28) [37a].

A related RCM/fragmentation protocol was used for preparing germacranolides that may exist as E,E-, E,Z-, E,E-, or Z,Z-10-membered rings (Figure 1.1) [38]. Starting from (R)-carvone, the trienes 171 and 172 were prepared and RCM provided decalines 173 and 174, respectively (Scheme 1.29). Selective conversion of the secondary alcohols in 173 and 174 to the corresponding mesylates and Wharton fragmentation [39] led to (Z,Z)- and (E,Z)-germacratrienes 177 and 178. The more substituted germacrenes 179–182 were also prepared using this strategy [38].

A similar strategy was reported for a synthesis of (±)-periplanone C (183) (Scheme 1.30) [40]. The triene 185 was prepared in a few steps from 3-isopropylanisole and smoothly cyclized using [Ru]-I (3 mol%) to the trans-decaline

Scheme 1.27

Scheme 1.28
Figure 1.1 Various types of germacranolides.

Scheme 1.29

Scheme 1.30

186 (81%). Mono-O-mesylation and treatment with KOH afforded cyclodecanone 187, which was converted to (+)-periplanone C (183) in a few steps. Interestingly, using the same conditions, epi-185 did not cyclize. This was attributed to the favorable preorganization of 185, favoring RCM, whereas the more stable conformation of epi-185 places the two olefins away from each other (Scheme 1.31) [41].
1.3 Formation of Six-membered Carbocycles by RCM

Access to anti-Bredt alkenes is possible using an RCM/fragmentation sequence [42]. The strategy has been used for preparing the bicyclic ketone 188 having a structure similar to the AB rings of taxanes 189. RCM of 190 catalyzed by [Ru]-I afforded 191 (90%) and subsequent fragmentation provided ketone 188 (Scheme 1.32). Application to the construction of other bridged ring systems has been examined. RCM of 192 delivered 193 in high yield (93%) and the cyclization of 195 to afford the strained cycloalkene 196 (83%) is noteworthy (Scheme 1.33).

In 2006, Robichaud and Tremblay reported the first RCM-based formal synthesis of (+)-compactin (198) [43]. The functionalized cyclohexene 199 (ring A) was prepared and submitted to RCM conditions to construct the six-membered B
Scheme 1.34

ring, thus completing the elaboration of the fully functionalized decalin system 200. Removal of the trimethylsilyl (TMS) group was difficult, and provided the target compound 201 in 31% yield, whose transformation to compactin had been previously described (Scheme 1.34).

The first synthesis of (−)-perrotinene 202 was reported in 2008 [44]. The strategy is again characterized by an Ireland–Claisen rearrangement/RCM key sequence (Scheme 1.35). Alcohol 205 was prepared by Stille coupling between the aryl iodide 203 and the enantiomerically pure vinyl stannane 204. The ensuing, highly stereoselective, Ireland–Claisen rearrangement of the silyl ketene acetal derived from 206 allows a complete chirality transfer and the control of the configuration of the two stereogenic centers in 207. RCM of the latter substrate proceeded smoothly and gave cyclohexene 208 in high yield (91%).

Recently, Li et al. described a synthesis of (−)-10α- and (−)-10β-hydroxy-4-muurolen-3-one (209) [45]. Starting from (R)-carvone, compound 210 was prepared in a few steps and its RCM proceeded smoothly using catalyst [Ru]−II to afford intermediate 211 in quantitative yield (Scheme 1.36).

Vannusal A (212) is a complex triterpene characterized by a pentacyclic bridged core. Nicolaou et al. have devised a synthetic approach to compound 216 possessing the core structure of vannusal A (Scheme 1.37) [46]. A Mn(III)-induced radical
1.3 Formation of Six-membered Carbocycles by RCM

Scheme 1.36

\[
\text{[Ru]-II (5 mol\%)} \quad \text{CH}_2\text{Cl}_2, \text{reflux} \quad 100\% \quad (-\text{-10\textmu-hydroxy-4-}}
\]

muurolen-3-one (209)

Scheme 1.37

\[
\text{[Ru]-II (33 mol\%)} \quad \text{CH}_2\text{Cl}_2, \text{50 °C} \quad 84\% \quad (-\text{Elatol (217)})
\]

Scheme 1.38

cyclization of the β-ketoester 213 was used to prepare the bridged tricyclic system ABC 214. This compound was converted in a few steps to the RCM substrate 215 whose cyclization proceeded cleanly and in good yield (84\%) using catalyst [Ru]-II (33 mol%).

In 2008, Stoltz et al. reported the first synthesis of elatol 217 (Scheme 1.38) [47]. Starting from dimerone, the mixed carbonate 218 was prepared. Decarboxylative oxygen-to-carbon migration was effected using a Pd(0) complex based on the chiral
Scheme 1.39

Scheme 1.40

phosphine 219 [48] to afford the optically enriched ketone 220 (ee = 87%) in good yield (82%). The challenging RCM of 220, leading to a tetrasubstituted double bond, proceeded exceedingly well using catalyst [Ru]-X [49]. The RCM product 221 was then converted to (+)-laurencenone (222) then (+)-elatol (217) in a few steps.

Roush et al. have reported the synthesis of a durhamycin aglycon model (Scheme 1.39) [50]. Allylation of aldehyde 223 with the allylic borane 224 provided 225 after the formation of a xanthate. Deoxygenation gave the requisite RCM precursor whose cyclization proceeded reasonably well provided that Ti(Oi-Pr)4 was used as an additive. As suggested by model studies, this additive may avoid the coordination of the ruthenium carbene by either the aryl ether (OBOM) or the neighboring ethers (OMe, OTCE).

The mild conditions of the olefin metathesis reaction make it an ideal method for the preparation of cyclitols and carbasugars [51, 52]. In general, the syntheses start from readily available carbohydrate derivatives that are converted to dienes and then submitted to RCM conditions. The resulting functionalized cyclohexenes are then converted to the target molecules in a few straightforward steps [53b]. According to this principle, the syntheses of (+)-cyclophellitol (230) (Scheme 1.40) [54], valienamine (233) (Scheme 1.41) [53, 55], valiolamine (236) (Scheme 1.42) [56], conduritol derivatives 238–240 (Scheme 1.43) [57], phosphatidyl inositol [58], and analogs (243) (Scheme 1.44) [59] have been reported.

Noncarbohydrate starting materials may also be used for preparing carbasugars. For example, Roush’s et al. asymmetric allylation of chiral aldehyde 244 gave diene 245. Subsequent RCM catalyzed by [Ru]-II and dihydroxylation allowed access to
1.3 Formation of Six-membered Carbocycles by RCM

2,3,4,6-Tetra-O-benzyl-D-glucopyranose

Scheme 1.41

2,3,4-Tri-O-benzyl-D-arabinofuranose

Scheme 1.42

Glucitol

Mannitol

Galactitol

Scheme 1.43

Methyl α-D-glucopyranoside

Scheme 1.44
the pivotal intermediate 247. This compound was converted to conduritols F (248) and B (249) by stereospecific syn (basic conditions) or anti (acidic conditions) Peterson elimination, respectively, and debenzylation. Alternatively, Tamao–Fleming oxidation and debenzylation provided d-(+)-chiro-inositol (250) (Scheme 1.45) [60].

Pancratistatin (251), an important anticancer product, is structurally related to carbasugars. In 2004, Kornienko and Nadein reported a synthesis of 1-aryl-1-deoxyconduritols that were used as synthetic intermediates to prepare a series of simplified pancratistatin analogs. Compound 252, prepared from d-xylose, underwent conjugate addition of magnesium diarylcuprates to afford 253. Further steps led to 254 whose RCM catalyzed by [Ru]-I provided aryl deoxyconduritols 255 (Scheme 1.46) [61, 62].

1.4 Formation of Seven-membered Carbocycles by RCM

RCM of 1,8-dienes constitutes an efficient access to cycloheptenes since di-, tri-, and tetrasubstituted olefins could be elaborated in good yields with catalyst loading as low as 1 mol%. In this context, the highly demanding field of natural product synthesis constitutes an efficient test for the development of more active and
1.4 Formation of Seven-membered Carbocycles by RCM

...Functional group tolerant catalysts as shown by Stoltz in the (-)-cyanthiwigin F synthesis. The following section, by no mean exhaustive, covers the more recent applications in RCM of 1,8-dienes applied to the synthesis of biologically relevant targets. When possible, comparison between various catalysts and experimental conditions is also discussed.

Challenging RCM was reported during the synthesis of the ABE tricyclic analogs 259 of the alkaloid methyllicaconitine (256), a competitive antagonist of nicotine acetylcholine receptors [63]. The B ring system was synthesized via a [Ru]-I catalyzed RCM of the 1,8-diene 257 possessing two contiguous quaternary stereogenic centers. Compound 258 having the characteristic trans AB ring fusion of methyllicaconitine was obtained in excellent yield (97%) (Scheme 1.47).

A key step in the total synthesis of (+)-frondosin B (260) reported by Mehta and Likhite is RCM of 1,8-diene 262 using [Ru]-I (C₆H₆, reflux) [64]. The corresponding bicyclic 6,7-fused ring system 263 was obtained in good yield (80%). Cyclization of 264 mediated by boron trifluoride led to the corresponding benzofuran 265, and subsequent acid-catalyzed isomerization of the trisubstituted olefin then provided (+)-frondosin B (260) (Scheme 1.48).

In synthetic studies toward rameswaralide (266), a promising anti-inflammatory agent, the cycloheptenone tricyclic core 269 was efficiently prepared through RCM of the acyclic ω-alkenyl acrylate 268 under very mild conditions using [Ru]-II (10 mol%) (CH₂Cl₂, rt) in high yield (90%) (Scheme 1.49) [65].

A related ω-alkenyl acrylate RCM was used in the first total synthesis of (+)-sundiversifolide (270) reported by Shishido et al. [66]. An excellent yield of chiral cycloheptenone 273 was obtained from 272 using catalyst [Ru]-II. Enone 273 was then chemoselectively reduced to the corresponding allylic alcohol 274, thus setting the stage for an Eschenmoser–Claisen rearrangement. Further iodolactonization/radical reduction led to bicyclic lactone 275, a late intermediate in the synthesis of the natural product (Scheme 1.50).
Trisubstituted olefins embedded in seven-membered carbocycles are also synthesized in high yields from the corresponding 1,8-dienes. In their elegant total synthesis of (−)-cyanthiwigin F (276), Stoltz and Enquist used for the first time catalyst [Ru]-X [49] possessing an increased activity for the generation of trisubstituted olefins. A double Pd-catalyzed decarboxylative allylic alkylation of 277 in
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The guaianolide class of natural products is characterized by a tricyclic 5,7,5-ring system [68]. Among these promising sesquiterpene lactones were identified the thapsigargins (such as 282, Scheme 1.52), potent inhibitors of sarco/endoplasmic reticulum ATPases (SERCA). Recently, Ley reported a successful strategy to access these complex natural products based on the construction of the seven-membered ring by RCM. Compound 283, prepared from (S)-carvone, underwent Favorskii ring contraction and 284 was converted to enol ether 285. RCM of 285, using catalyst [Ru]-II (5 mol%) allows the formation of the bicyclic enol ether 286 in
excellent yield (88%) [69, 70]. The latter was then efficiently converted into the corresponding \( \alpha \)-hydroxyketone 287 via asymmetric dihydroxylation. The same key step was used in the total synthesis of closely related guaianolides, trilobolide, nortrilobolide and thapsivilllosin F [71].

Ingenol (288) is a diterpenoid possessing a fascinating bicyclo[4.4.1]undecane skeleton, with a highly strained intrabridgehead topology. RCM-based strategies for the construction of the B ring of ingenol were reported by Wood [72] and Kigoshi [73]. In Wood’s total synthesis, compound 289 (synthesized from 3-carene) underwent Diels–Alder cycloaddition with cyclopentadiene to afford 290 (Scheme 1.53). Ring-opening metathesis (ROM) with ethylene gave 291, which was further elaborated to the RCM precursors 292 and 293. Only 45% of

Scheme 1.53

In Scheme 1.54, the synthesis of ingenol (288) is further illustrated with additional steps involving the reaction of chlorocyclohexane with Et\(_3\)CONa and subsequent treatments with Et\(_3\)COH/xylene reflux, Et\(_3\)COH/xylene reflux, Toluene, reflux, and Dioxane. Winkler’s intermediate (300) is also highlighted.

Scheme 1.54
the desired cycloheptenone 294 was obtained from 287 using [Ru]-I (80 mol%), whereas an excellent 87% yield of 295 was obtained from 293 with [Ru]-III (25 mol%).

Kigoshi’s formal synthesis (Scheme 1.54) relies on the efficient spirocyclization reaction of ketone 296 also prepared from 3-carene. The AC ring system was then further elaborated into 1,8-diene 298 that could be cyclized to 299 in 87% yield using [Ru]-II (25 mol%). A dramatic temperature and solvent effect was observed as no reaction took place in dichloromethane. Allylic oxidation then delivered aldehyde 300, an intermediate in Winkler’s total synthesis of ingenol [74].

A rare example of formation of cycloheptadiene from 1,3,8-triene was reported by Hiemstra et al. in the enantioselective synthesis of the tetracyclic left-hand substructure 301 of solanoeclepin A (302) (Scheme 1.55) [75]. Starting from compound 303, a [4+2]-cycloaddition was used to elaborate the oxabicyclic motif. Nolan’s catalyst [Ru]-VI (15 mol%) was used to cyclize the 1,3,8-triene 305 to the desired cycloheptadiene 306 in quantitative yield. It is worth mentioning that [Ru]-I was quite inefficient in this case even if a stoichiometric quantity was used.

A concise asymmetric total synthesis of (+)-cyanthiwigin U (307) was reported by Phillips and Pfeiffer relying on the clever use of tandem metathesis of bi-cyclo[2.2.2]octenes (Scheme 1.56) [76]. The two-directional tandem ROM–RCM of compound 308, using catalyst [Ru]-II under an atmosphere of ethylene, simultaneously generated the cyclopentenone and the cycloheptenone rings of...
Synthesis of Natural Products Containing Medium-size Carbocycles

An RCM was reported by Wicha et al. in a synthetic approach to the diterpenes guanacastepene A (310) and heptemerone G (311) (Scheme 1.57) [78]. The 1,8-diene 312 possessing a 1,1-disubstituted olefin was cyclized efficiently to 313 in high yield (96%) using catalyst [Ru]-II. Further functional group transformation including epoxidation and Dauben oxidation [79] led to the AB core structure 314 of the targeted diterpenes.

This very efficient RCM should not mask the fact that trisubstituted double bonds of terpenoids, imposed by the biosynthesis pathway from isoprene units, could be challenging to prepare through the RCM of 1,8-dienes as subtle differences in the metathesis precursor can have a dramatic impact on the reaction rate and yields [80]. For example, [Ru]-I could efficiently catalyze the RCM of the substituted 1,8-diene 315 to the corresponding trisubstituted cycloheptene 316 as demonstrated by Tori et al. in the total synthesis of two sphenolobane-type diterpenes (Z,E) and (E,E)-320 isolated from the liverwort Anastrophyllum aurium (Scheme 1.58) [81].

However, during a synthesis of (−)-tormesol (321), a diterpene isolated from Halimium viscosum, the cyclization of the related nonenolizable β-ketoester 322 proved sluggish as only 50% conversion was observed using catalyst [Ru]-I in combination with Ti(Oi-Pr)_4 (1 equiv). The more active [Ru]-II overcame this limitation and allowed the synthesis of cycloheptene 323 in excellent yield with a low

![Scheme 1.57](image1)

![Scheme 1.58](image2)
catalyst loading (1 mol%) [82]. Compound 323 was then converted to (−)-tormesol through intermediates 324 and 325 (Scheme 1.59) [81, 82].

A very challenging RCM was reported by Reiser et al. during the enantioselective synthesis of arglabin (326), a promising antitumor agent isolated from *Artemisia glabella* [83]. Condensation of cyclopropanecarbaldehyde 327 with allylic silane 328 led, after treatment under basic conditions, to adduct 329, which was further elaborated to 330. The tetrasubstituted double bond embedded into the seven-membered ring of 331 was efficiently prepared via the RCM of compound 330. Worthy of note is that an inert gas sparging of the reaction combined with catalyst [Ru]-II (15 mol%) had to be used to ensure complete conversion. Epoxidation from the α-face of the seven-membered ring proved troublesome since the more stable β-epoxide was obtained using dimethyldioxirane or peracids. A hydroxyl-directed vanadium-catalyzed epoxidation of the homoallylic alcohol 331 overcame the intrinsic bias of the system, leading to the desired epoxide 332 in good yield and selectivity (Scheme 1.60).
1.5 Formation of Eight-membered Carbocycles by RCM

Cyclooctanoids are among the most difficult carbocycles to elaborate from acyclic precursors due to severe developing ring strain and restricted bond rotation in the precyclization conformer [84]. In the mid 1990s, RCM of 1,9-diienes emerged as a powerful strategy for the synthesis of carbocyclic eight-membered ring [85]. Steric and conformational effects were found to have a dramatic impact on the rate and efficiency of cyclization reactions. High catalyst loading (up to 50 mol%), long reaction times, and elevated temperatures were usually reported. Up to 2006, an excellent review compiles the recent advances in the synthesis of challenging di[86] and trisubstituted [87] double bonds embedded in cyclooctenyl rings [88].

The dicyclo[a,b]cyclooctane ring systems found in ophiobolin M (333) and fusicoccin A (334) terpenes have stimulated a great deal of interest. The groups of Williams [89] and Wicha [90] reported two different RCM approaches aiming at the rapid elaboration of the eight-membered B ring system. The first approach relied on a [Ru]-I catalyzed RCM of triene 335 leading to cyclooctene 336 in moderate yield (Scheme 1.61) [89]. Worthy of note is the fact that [Ru]-II proved inferior as a catalyst leading to lower conversion and partial isomerization of the terminal olefin(s).

The second approach [90] reports the synthesis of the AB ring system of serpendione (337) via RCM reaction of 338 (Equation 1, Scheme 1.62) that contains...
1.5 Formation of Eight-membered Carbocycles by RCM

both a geminal disubstituted and a monosubstituted olefin. The [Ru]-II catalyzed transformation was extremely efficient and delivered compound 339 possessing the AB ring system in 95% yield. When exposed to [Ru]-II, the epimeric compound 340 could be transformed to the desired cyclooctene 341, albeit in low yield (34%). Isomerization of the allylic double bond prior to cyclization accounts for the major cycloheptene product 342 (49%) (Equation 2, Scheme 1.62), thus once again stressing the importance of subtle steric and conformational effects in the formation of medium rings by RCM. By contrast, the use of [Ru]-I led only to dimerization.

Imposing a conformational constraint that favors cyclization is a useful strategy for the RCM of 1,9-dienes. In the total synthesis of (±)-mycoepoxydiene (343), Tadano et al. reported the RCM of the diallylated tetrahydrofuran 344 using catalyst [Ru]-I under diluted conditions to prevent oligomerization [91]. A good yield of the desired oxygen-bridged cyclooctene 345 was obtained (83%). A dramatic solvent dependence was noted as CH2Cl2 induced only decomposition of the starting diene 344. Compound 345 was converted to (±)-mycoepoxydiene 343 in several steps including oxidation of furylcarbinol 346 to dihydropyranone 347 (Scheme 1.63).

Vinigrol (348) is a metabolite of the fungal strain Virgaria nigra that possesses a fascinating tricyclo[4.4.4.0\(^{4,8}\)]tetradecane skeleton [92]. Its biological activity, including antihypertensive, platelet aggregation-inhibiting, and tumor necrosis factor antagonist properties, has fueled a considerable synthetic interest. The groups of Barriault [93] and Paquette [94] investigated two different approaches involving disconnections of the carbocyclic eight-membered ring through RCM at the C9–C10 or C10–C11 positions, respectively. Unfortunately, these two strategies met with failure. As observed in previous studies, [Ru]-I was not active enough to promote the RCM of 1,9-dienes 349, 350, and 351, and [Ru]-II led to double bond migration (Scheme 1.64).

In order to increase conformational flexibility in the cyclization precursor, Paquette et al. considered the relocation of the double bond from the \(\Delta^{3,4}\) to the \(\Delta^{2,3}\) site to project axially the two C1 and C5 substituents. As shown by MM3 calculations on model systems, the closer proximity of these two substituents in the \(\Delta^{2,3}\) isomer could allow a more RCM. Diene 352 was then prepared and
subjected to catalyst [Ru]-II but unfortunately, only starting material was recovered (Scheme 1.65).

Prunet et al. have extensively investigated the possibility of synthesizing the B ring system of Taxol® (353) via the RCM of 1,9-diene 355 (Scheme 1.66) [95]. When a diastereomeric mixture of the latter compound and epi-355 was subjected to catalyst [Ru]-I, only compound 355 cyclized to cyclooctene 356 (possessing the C9–C10 unsaturation) albeit slowly, emphasizing once again that RCM is highly dependent upon the conformational and steric effects in the cyclization precursor (Equation 1, Scheme 1.66). Recently, the formation of the C10–C11 unsaturation by RCM was reported and proved more efficient in terms of protecting group compatibility and catalyst efficiency (Equation 2, Scheme 1.66). Unprotected diol 357 led to the desired cyclooctene ring 358 in an impressive quantitative yield, thus suggesting that the BC ring system of taxol may be synthesized according to this strategy. These recent results are in stark contrast to the previous C9–C10
1.6 Formation of Nine-membered Carbocycles by RCM

The failed metathesis-based synthesis of Pestalotiopsis A \ref{359}, compared to the successful synthesis of cornexistins, reported by Paquette et al. [96] and Clark et al. [97] illustrates well the uncertainty linked to RCM toward 8 to 10-membered rings. RCM of several substrates \ref{360}–\ref{362} was evaluated (Figure 1.2). For \ref{360} and \ref{361}, regardless of the catalyst used ([Ru]-I, II, III, VII, and XI), the starting diene was either recovered (when the reaction was performed below 80 °C) or decomposed (in refluxing toluene). The MOM ether \ref{362} was isomerized to \ref{363}.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{pestalotiopsis.png}
\caption{Pestalotiopsis A synthesis: unactive RCM substrates.}
\end{figure}
In 2003, Clark et al. reported a novel strategy for the preparation of cornexistins. In model studies, attempts to form intermediate 364, featuring a trisubstituted olefin, by the RCM of 365 were unsuccessful regardless of the catalyst used ([Ru]-I or [Ru]-II). In contrast, the cyclization of 367 (a racemic mixture of two diastereomers) led to the isomeric mixtures 368 and 369 in good yield. In subsequent studies, the RCM reaction was examined more closely and shown to be significantly stereoselective \(368/369 = 2 : 3\) \(^9\). Compound 368 was converted to \((\pm)-5\text{-epi-hydroxycornexistin}\) in a few additional steps (Scheme 1.67).

### 1.7 Formation of 10-membered Carbocycles by RCM

In 2001 and 2002, Koskinen et al. reported what appeared to be the first examples of 10-membered ring carbocycle syntheses via RCM \(^9\). As can be seen in Table 1.1, the reaction proved difficult to perform and yields remained moderate even under optimized conditions. Using alcohol 370a \((\text{syn}/\text{anti} = 2 : 1)\), a single cyclized product 371a was obtained in low yield and some starting material was recovered. With the silyl ether 370b as substrate, the reaction was cleaner, affording a mixture of three diastereomers in fair yield. Addition of \(\text{Ti(Oi-Pr)}_4\) was slightly beneficial. The roughly 2 : 1 \(\text{trans}/\text{cis}\) ratio of the major RCM products 371b and 372b compares well with the corresponding 2 : 1 \(\text{syn}/\text{anti}\) ratio of the substrate 370b \(^9\). When

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3) [Ru]-I catalyst was used for this transformation (18 hours, \(\text{CH}_2\text{Cl}_2\), reflux, 77%). [Ru]-II did not bring any significant improvement (personal communication from Dr Clark).
1.7 Formation of 10-membered Carbocycles by RCM

![Diversifolin (374)]

Scheme 1.68

Table 1.1 Cyclization of alcohol 370a and TBDMS ether 370b.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Substrate recovery (%)</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>370a : R = H</td>
<td>25</td>
<td>371a (11%)</td>
</tr>
<tr>
<td>370b : R = TBDMS</td>
<td>6</td>
<td>371b (16%)</td>
</tr>
<tr>
<td>370b + Ti(Oi-Pr)₄ (20 mol%)</td>
<td>0</td>
<td>371b (21%)</td>
</tr>
</tbody>
</table>

the more active [Ru]-II catalyst was used, only the syn-370b precursor cyclized to afford a mixture of 371b and 373b in a 1 : 6 ratio. The anti-370b isomer was not recovered and was probably converted to polymeric material [99b].

A synthetic study toward diversifolin (374) was published in 2007 by Kobayashi et al. (Scheme 1.68) [100]. First, a long sequence (17 steps) led to the key RCM substrate 375, obtained as a mixture of epimers. RCM was difficult and required significant optimization. While using [Ru]-I no reaction was observed, whereas [Ru]-II in 1,2-dichloroethane (DCE) led to the formation of 377 in low yield (15%) in which one of the terminal olefin had shifted. When toluene was used as the solvent,
377 was obtained in 35% yield along with (3R)-376 (27%), and some starting material was recovered. Only (3R)-375 cyclizes rapidly and no (3S)-376 was formed. RCM of (3S)-375 is more difficult allowing the competing olefin isomerization to prevail. This may be avoided by adding 1,4-benzoquinone (BQ), whose role is probably to prevent the accumulation of ruthenium hydrides (decomposition products of [Ru-II]) that are thought to be responsible for olefin migration [101].

In Hale’s and Li’s synthesis of (+)-eremantholide A (378) (Scheme 1.69), the RCM step takes place almost at the end of the synthesis and involves a fairly
1.7 Formation of 10-membered Carbocycles by RCM

hindered substrate. Epimers 382 and 383 were prepared by alkylation of triflate 379 followed by hydroxymethylation and subsequent dehydration. Using [Ru]-III as catalyst, the reaction works well. Remarkably, only epimer 383 reacted, affording the desired bicyclic system 384 in 54% yield and (+)-eremantholide A, while the other diastereomer 382 cross-metathesized [102].

In Barrett’s synthesis of ent-clavilactone B 385 (Scheme 1.70), the benzyne intermediate generated from 386 was allowed to react with methallylmagnesium chloride and epoxy-aldehyde 387, leading to compound 388, which was converted to the RCM precursor 389. As expected, RCM proved to be difficult and had to be performed under special conditions: the catalyst [Ru]-II (40 mol%) was slowly added, along with tetrafluoro-1,4-BQ (to prevent olefin isomerization), and the formed ethylene was removed during the reaction. Under these conditions, the RCM product 390 was obtained in a satisfactory yield (65%) and converted to ent-clavilactone B [103].

During the period 2001–2006, Gennari et al. published a series of accounts describing the synthesis, via RCM, of simplified eleuthesides as potential anticancer agents [104–106]. In particular, these authors recently reported a novel formal synthesis of eleutherobin 391 (Scheme 1.71) [105, 106].

Starting from (R)-(−)-carvone, the half-protected dialdehyde 392 was prepared. Diastereoselective reagent-controlled oxallyltitanations (with TADDOL as
the chiral ligand) of both aldehydic functions led to the RCM precursor \(395\), which was cyclized using \([\text{Ru}]\) catalyst to afford the 10-membered carbocycle \(396\). The latter was converted to the advanced intermediate \(397\) that had previously been converted to eleutherobine. Forcing RCM conditions were necessary (\([\text{Ru}]\) [30 mol%], slow addition, toluene, reflux), and surprisingly, only the \((E)\)-cycloalkene \(396\) was obtained \([25, 106, 107]\).

Using simplified models of \(395\), Gennari et al. have shown by a variety of methods (molecular mechanics, DFT) that the \(trans\)-four-membered ruthenacycle intermediates \(398\) leading to \((E)\)-cyclodecenes are significantly more stable than the corresponding \(cis\)-ruthenacycles \(399\), leading to \((Z)\)-cyclodecenes (Scheme 1.72). RCM of diastereomer \(400\) was more difficult than that of \(395\), affording the ring-cyclized product \(401\) in low yield alongside with regioisomer \(402\) resulting from a metathetic ring rearrangement (RCM–ROM–RCM cascade).

Excisticine \(403\) belongs to a rare class of isoquinoline alkaloids featuring a bridged, bicyclic ether moiety. A possible approach to this class of compounds was illustrated by the synthesis of the simplified model compound \(408\) (Scheme 1.73) \([108]\). The strategy relies on a Bischler–Napieralski isoquinoline synthesis and an RCM as key reactions. The site of the RCM reaction was chosen so as to avoid the formation of inactive ruthenium complexes (likely to be observed for \(\gamma,\delta\)- or \(\delta,\epsilon\)-unsaturated amides or esters). RCM of diene \(406\) proceeded smoothly using catalyst \([\text{Ru}]\) to afford the desired 10-membered ring \(407\) in good yield (68%). However, the last deprotection step was unsatisfactory and proceeded only in low yield. The solution to this problem was provided by simply inverting the reaction sequence. Thus, a facile RCM in the presence of \([\text{Ru}]\) afforded the 14-membered macrocyclic lactam \(409\). After hydrogenation of the olefin, a Bischler–Napieralski reaction led to the 2,3-dihydroisoquinoline \(410\) that was reduced to \(408\).

**Scheme 1.72**

**Intermediates (relative energy)**
In the last decade, the alkene/alkyne metathesis reaction has become a major synthetic tool for the preparation of complex organic molecules and, not surprisingly, RCM has proved to be particularly useful for the synthesis of medium-size (5–10-membered) rings. For ring sizes of five to seven, the reaction works well but for larger (8–10-membered) rings, the metathesis is less predictable and its outcome depends on still imperfectly understood factors. Remarkable sequences, in particular [3,3]-sigmatropic rearrangement/RCM or RCM/fragmentation combinations, have been classically used as synthetic strategies.
References


References
