1
Synthesis of Natural Products Containing Medium-size Carbocycles by Ring-closing Alkene Metathesis

Nicolas Blanchard and Jacques Eustache

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].

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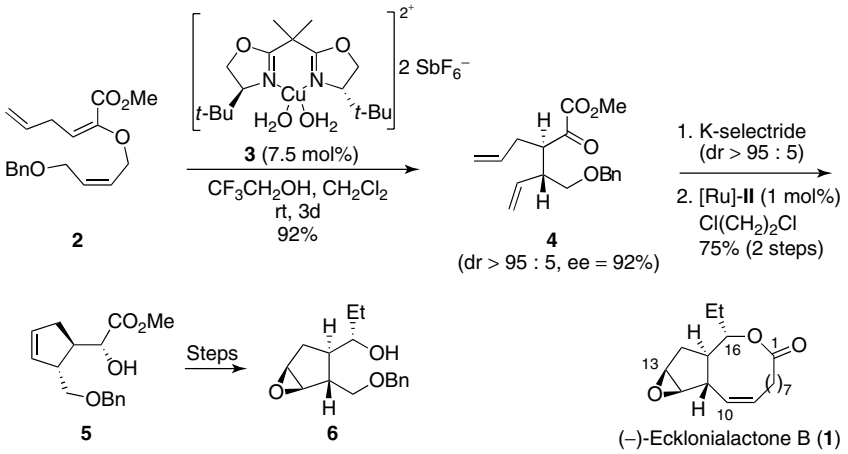
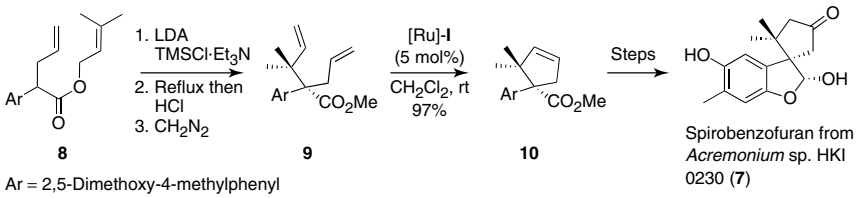
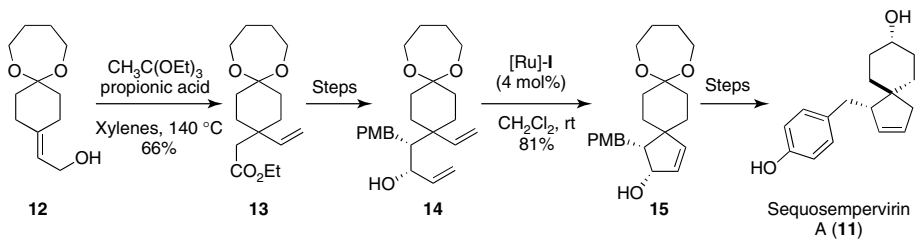


Scheme 1.1



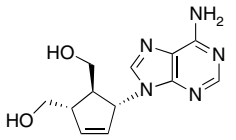
Scheme 1.2



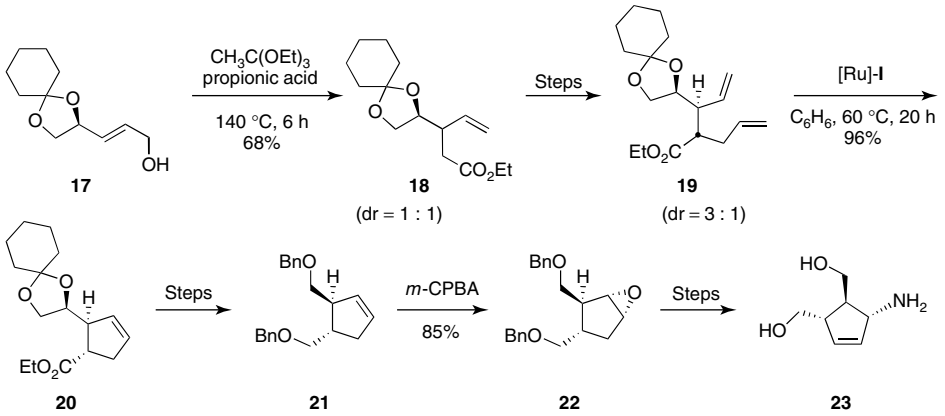
Scheme 1.3

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).

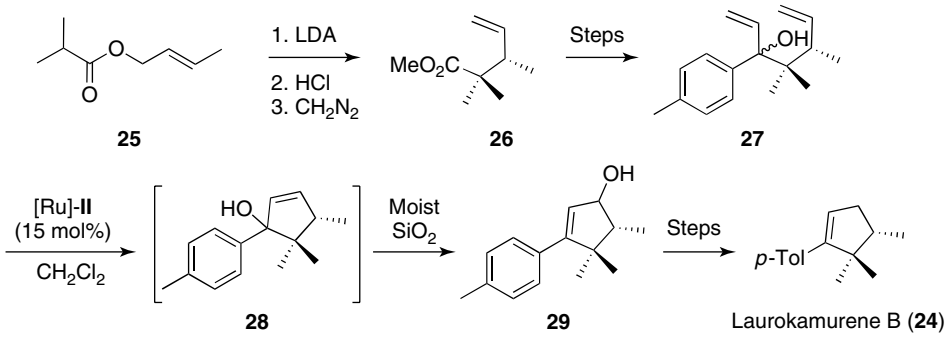
An analogous Johnson–Claisen rearrangement/RCM sequence was used by Ghosh *et al.* in the synthesis of the carbocyclic core of the nucleoside (−)-BCA (**16**), a potential inhibitor of HIV reverse transcriptase (Scheme 1.4) [6]. The chiral cyclopentene **20** was obtained in excellent yield through a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



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



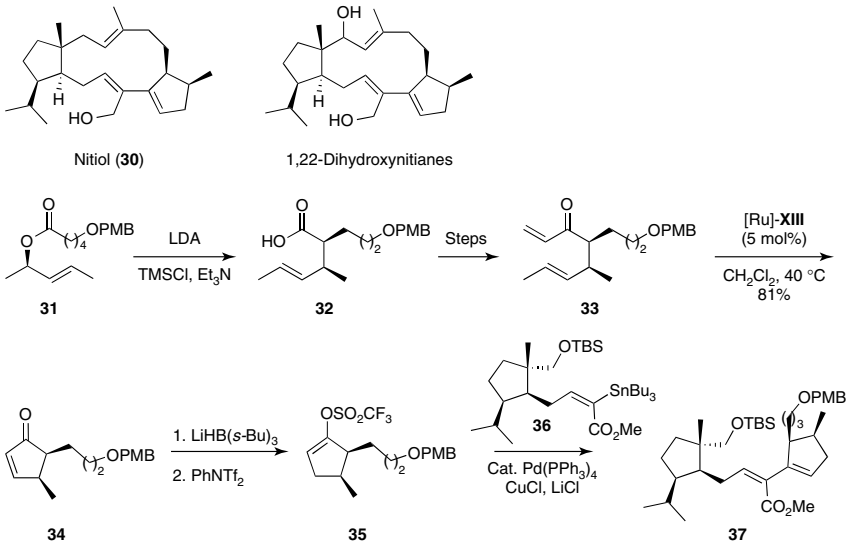
Scheme 1.4



Scheme 1.5

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



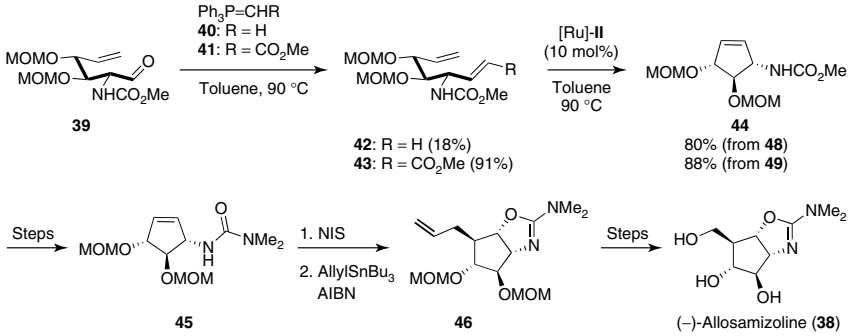
Scheme 1.6

RCM. Conjugate reduction of enone **34** using L-selectride followed by trapping of the resulting enolate with $PhNTf_2$ 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.

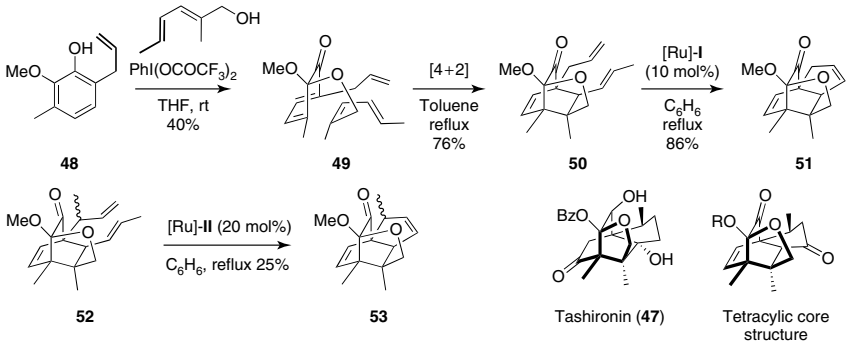
In the total synthesis of (−)-allosamizoline (**38**), the carbocyclic fragment of the chitinase inhibitor allosamidin, Donohoe and Rosa reported the efficient elaboration of the cyclopentenyl moiety via the RCM of a 1,6-diene (Scheme 1.7) [10]. Wittig olefination of aldehyde **39**, readily obtained 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).

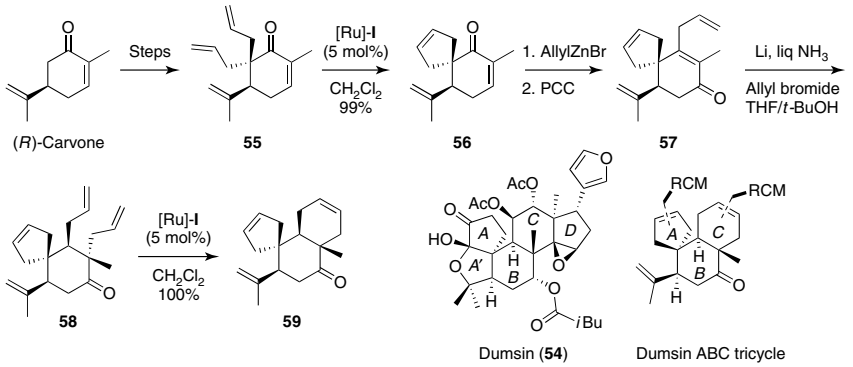
A rapid elaboration of the ABC core structure of the tetranortriterpene dumsin (**54**) was reported by Srikrishna *et al*. starting from the readily available (*R*)-carvone [12]. Two independent efficient RCM reactions, catalyzed by [Ru]-**I**, were used as



Scheme 1.7



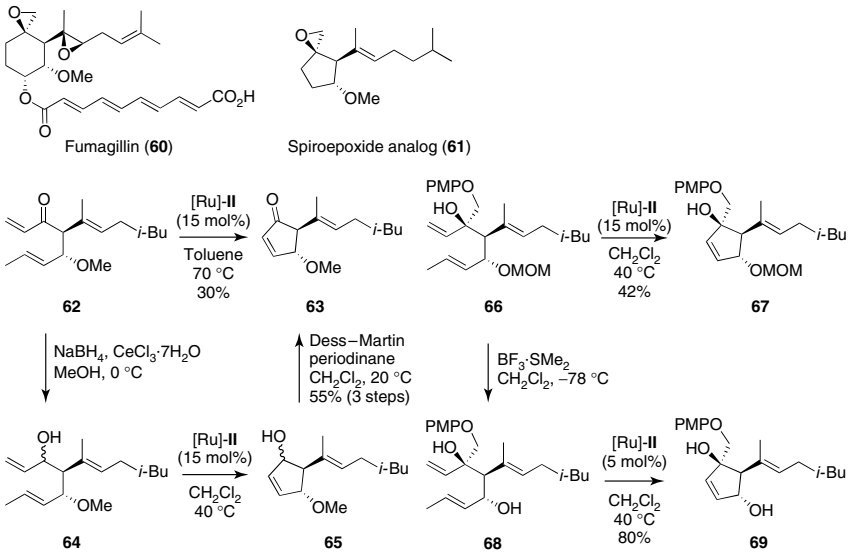
Scheme 1.8



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



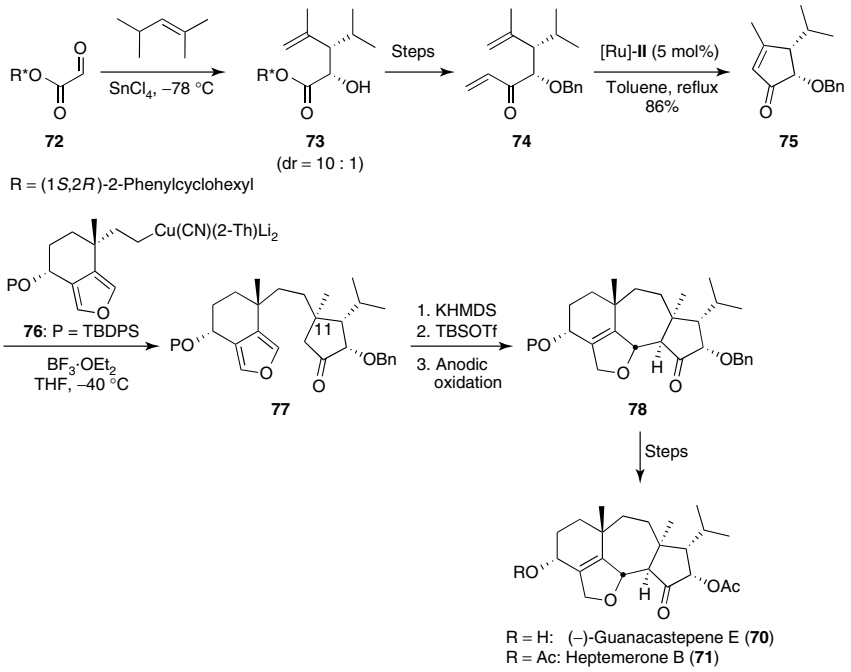
Scheme 1.10

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).

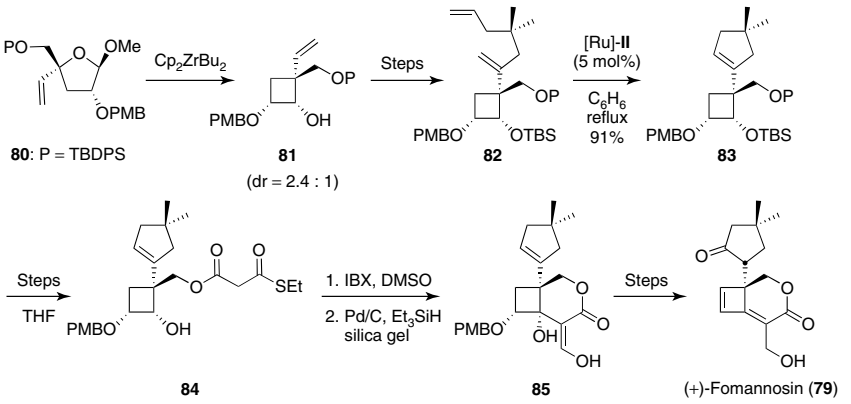
Cyclopentenes bearing a trisubstituted double bond could be efficiently prepared via the RCM of the corresponding 1,6-diene. Catalyst [Ru]-**II** is well suited for this transformation since [Ru]-**I** usually leads to inferior yields. The prochiral trisubstituted olefin could then be further reduced 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 annonsus* (Fr.) Karst. Its inherent instability and very congested structure have elicited a great deal of interest from the synthetic

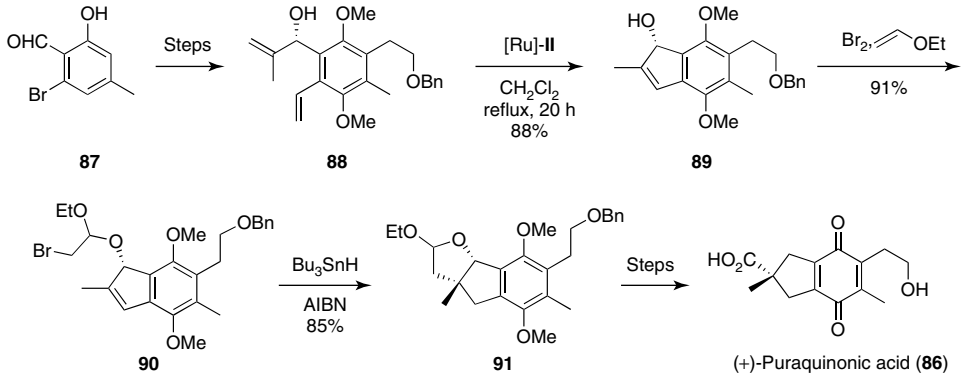


Scheme 1.11

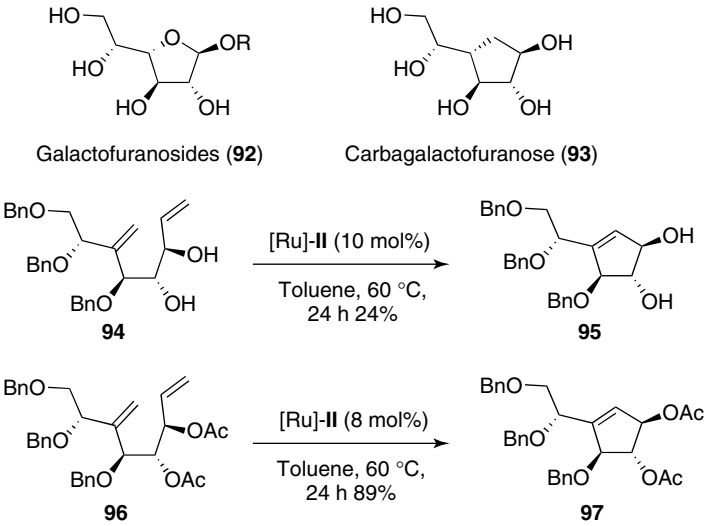


Scheme 1.12

community. Paquette *et al.* reported a straightforward strategy for the elaboration of both antipodes of fomannosin. Compound **80** (prepared from α-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



Scheme 1.13



Scheme 1.14

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

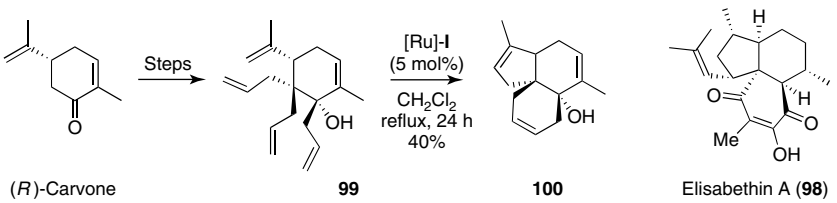
RCM was used as a key step in the total synthesis of (+)-puraquinonic acid (**86**), a fungal metabolite that induces differentiation in HL-60 cells [16]. Starting from aromatic aldehyde **87**, the RCM precursor **88** was prepared in a few steps. Following RCM leading to **89** (88%), the newly formed trisubstituted alkene was involved in a radical cyclization. Bromo acetal **90** was treated with Bu_3SnH 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,

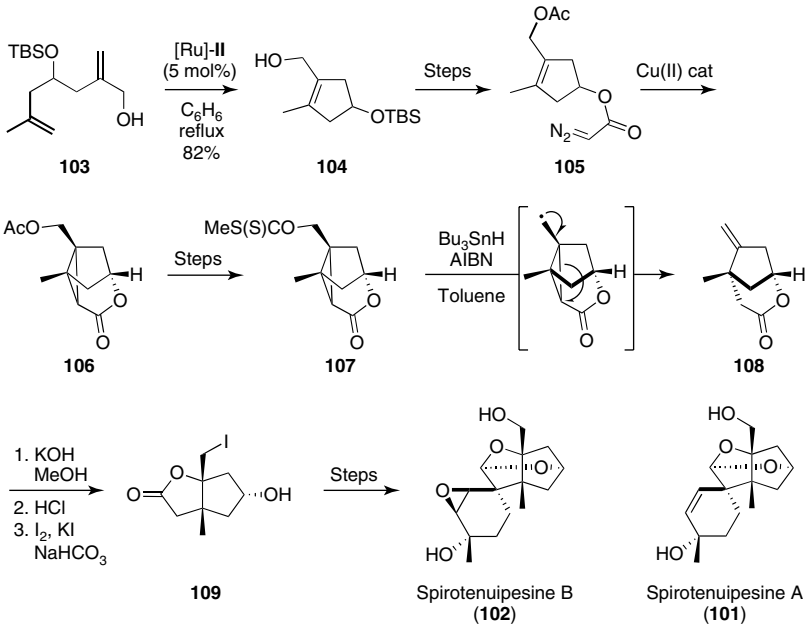
the synthesis of 4α-carba-β-D-galactofuranose **93** is worthy of note [17]. A dramatic protecting group effect was observed during the RCM of **94** and **96**. Whereas free allylic alcohols are known to enhance reactivity, RCM of **94** leads to the five-membered ring **95** in poor yield (24%). Under 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**)



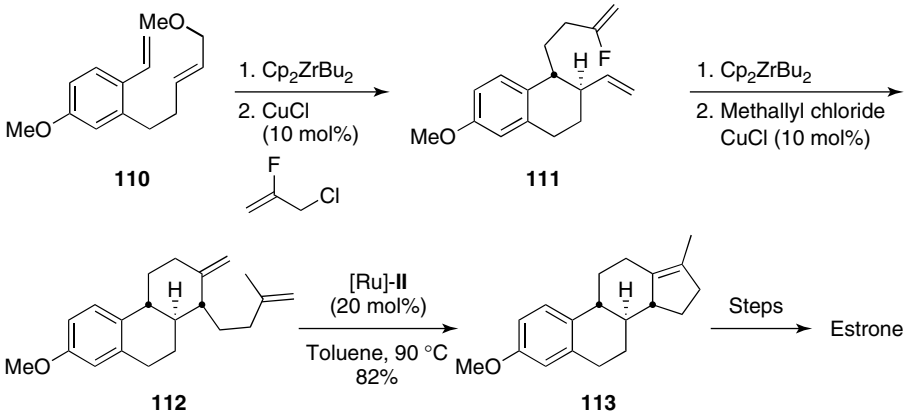
Scheme 1.15



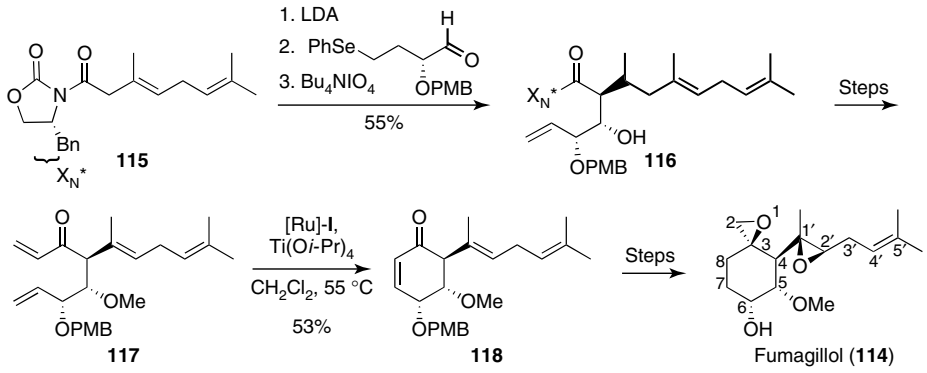
Scheme 1.16

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

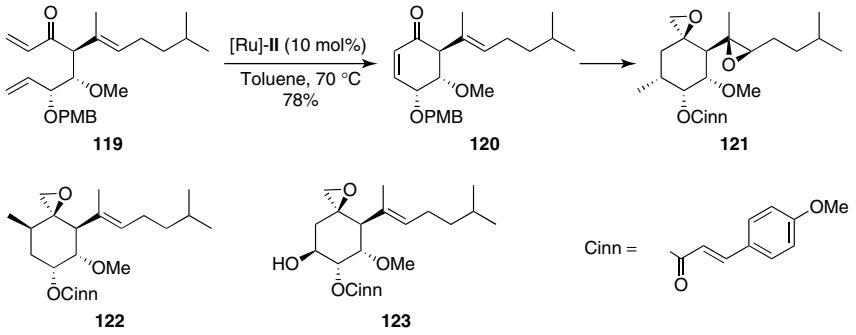


Scheme 1.18

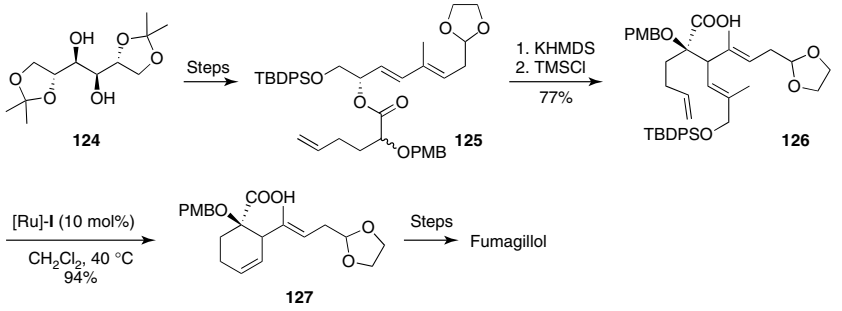
1.3
Formation of Six-membered Carbocycles by RCM

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 C7–C8 bond was established through an RCM/hydrogenation sequence. In agreement with Fürstner's observations, adding Ti(O*i*-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(O*i*-Pr)$_4$ in the RCM of **119** to **120**.

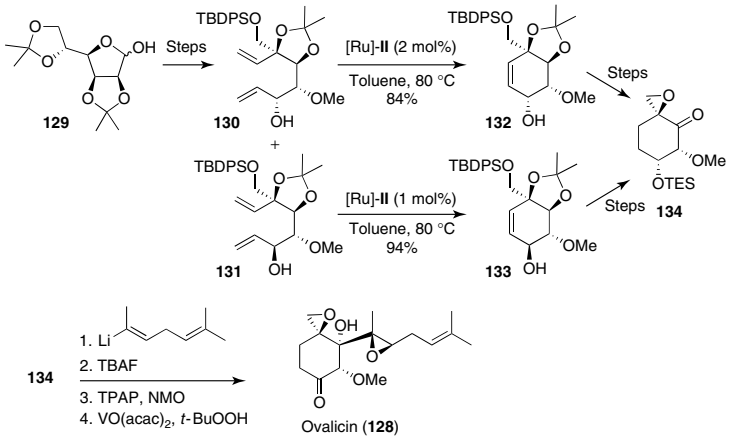
The second approach to fumagillol (**114**) relies on a Claisen/RCM sequence (Scheme 1.20) [23c]. Starting from 1,2;5,6-di-*O*-isopropylidene D-mannitol (**124**), the ester **125** was prepared and subjected to a glycolate-Claisen rearrangement leading to **126** (77%). RCM of **126** afforded cyclohexene **127** in high yield (94%), which was converted to an advanced intermediate previously used by Sorensen *et al*. in their synthesis of fumagillol [26].



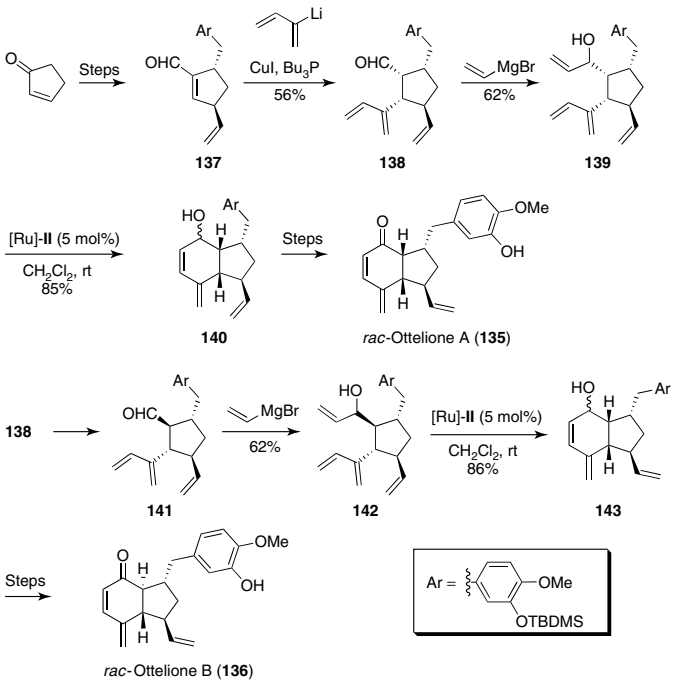
Scheme 1.19



Scheme 1.20



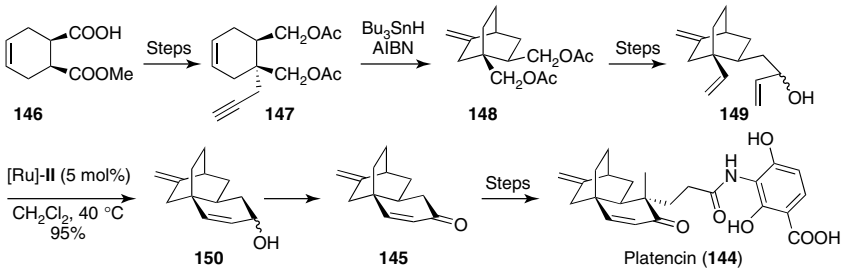
Scheme 1.21



Scheme 1.22

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-D-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



Scheme 1.23

(Scheme 1.22) [27]. Starting from cyclopentenone, the cyclopentene carboxaldehyde **137** was prepared. Conjugate addition of the organocopper derived from 2-butadienyllithium 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).

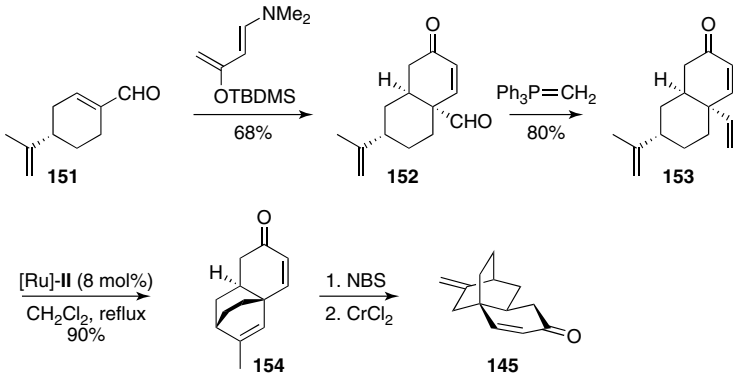
Mulzer's *et al.* approach implies a nonobvious construction of the strained bicyclo[2.2.2]octane skeleton by RCM (Scheme 1.24) [29]. Starting from (−)-perillaldehyde (**151**), the decaline **152** was prepared. Wittig reaction afforded triene **153**, which was submitted to RCM conditions ([Ru]-**II**, CH_2Cl_2, 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].

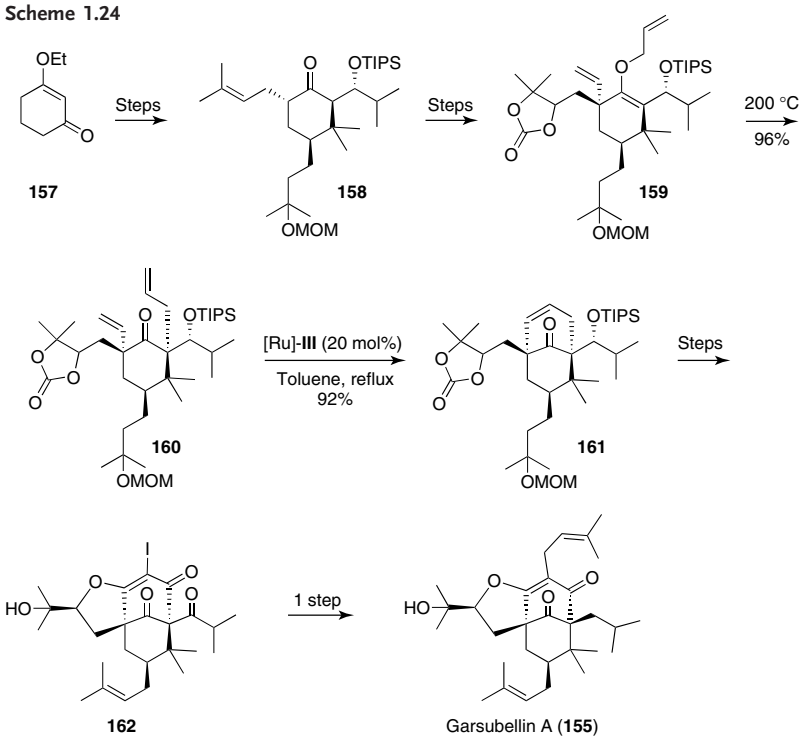
The α,β-unsaturated ketone **157** was converted to cyclohexanone **158** and a Claisen rearrangement/RCM sequence was used to construct the characteristic bicyclo[3.3.1]nonane skeleton.[1)] Thus, enol ether **159** cleanly rearranged at high temperature to diene **160**.[2)] Treatment of **160** by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



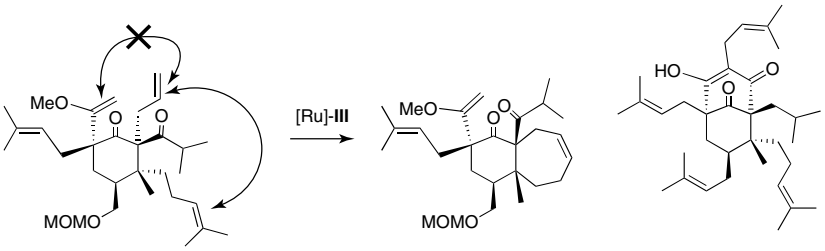
Scheme 1.24



Scheme 1.25

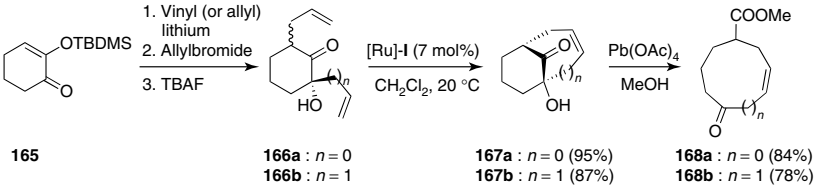
48 hours] led to intermediate **161** in excellent yield [34]. Finally, **161** was converted to **162** and then to (±)-garsubellin A (**155**). As shown in Scheme 1.26, the method could not be extended to hyperforin (**156**) as RCM of **163** led to **164** possessing a seven-membered ring (Scheme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



163 **164** Hyperforin A (**156**)

Scheme 1.26



165 **166a** : $n = 0$; **166b** : $n = 1$ **167a** : $n = 0$ (95%); **167b** : $n = 1$ (87%) **168a** : $n = 0$ (84%); **168b** : $n = 1$ (78%)

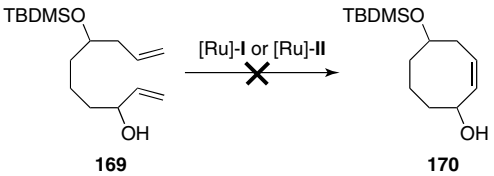
Scheme 1.27

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-*, 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



169 **170**

Scheme 1.28

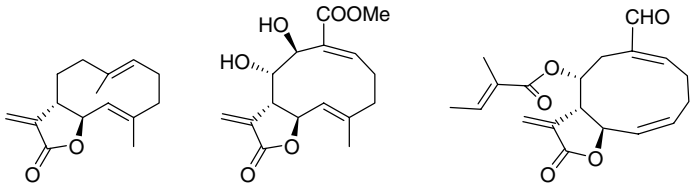
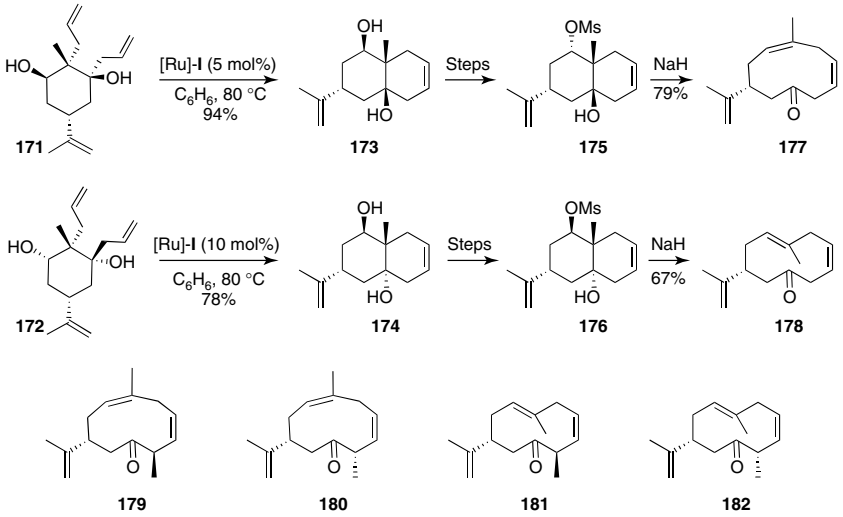
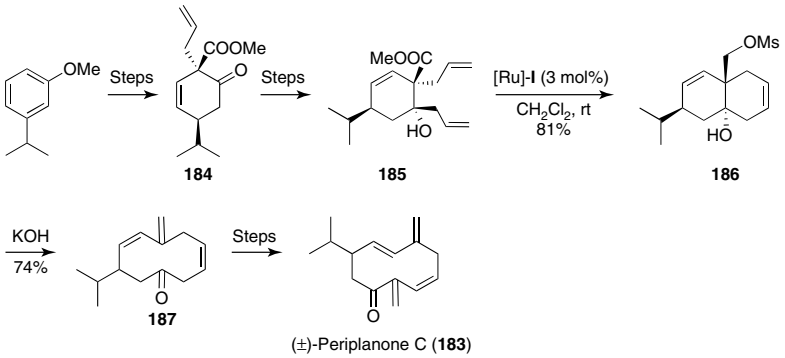


Figure 1.1 Various types of germacranolides.

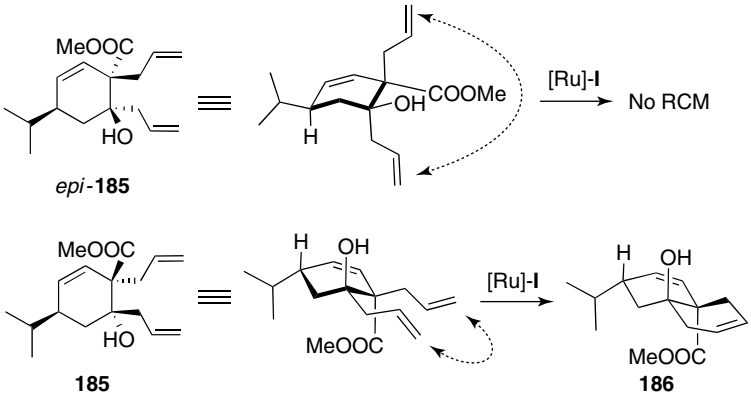


Scheme 1.29

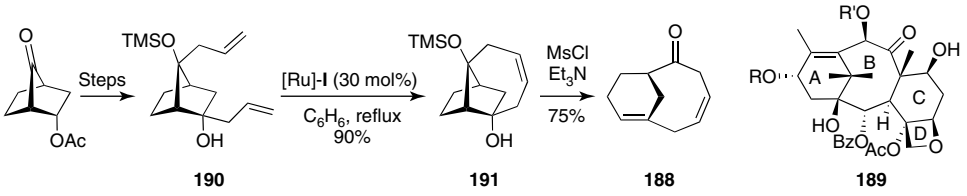


Scheme 1.30

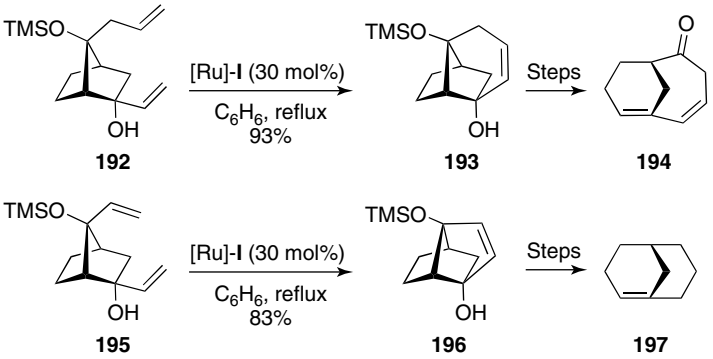
186 (81%). Mono-*O*-mesylation and treatment with KOH afforded cyclodecanone **187**, which was converted to (±)-periplanone C (**183**) in a few steps. Interestingly, using the same conditions, *epi*-**185** did not cyclize. This was attributed to the favorable preorganization of **185**, favoring RCM,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



Scheme 1.31



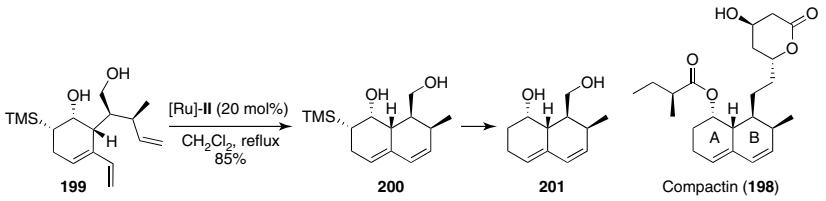
Scheme 1.32



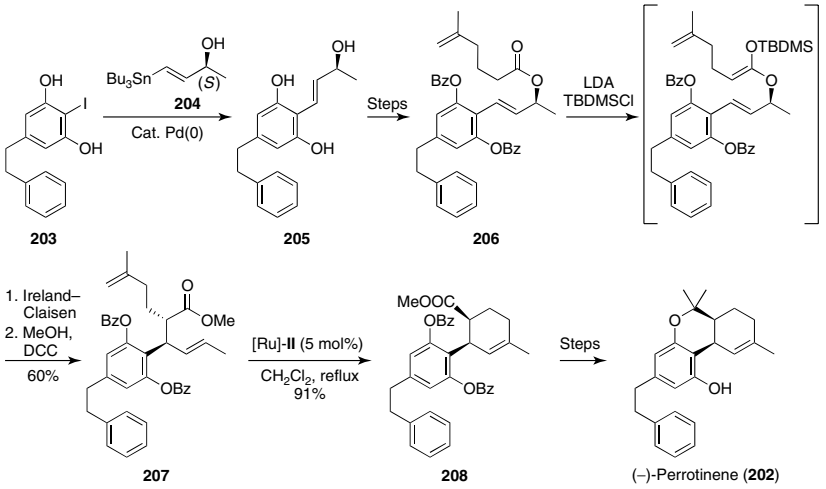
Scheme 1.33

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



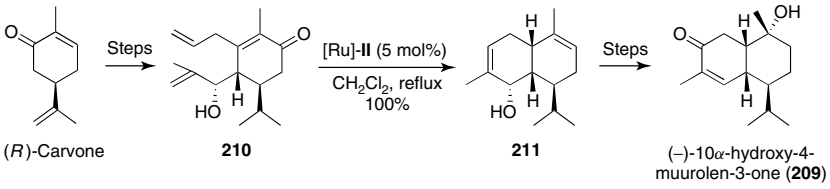
Scheme 1.35

ring, thus completing the elaboration of the fully functionalized decaline 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).

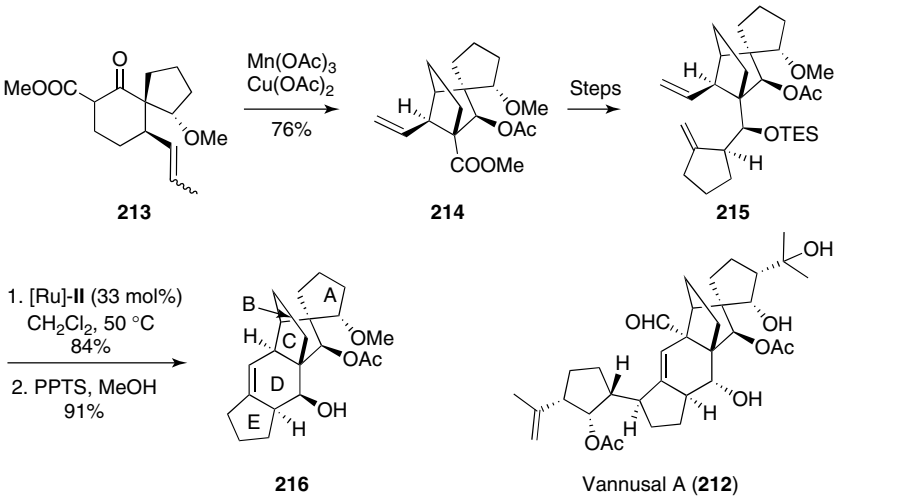
The first synthesis of (−)-perrotinene **202** was reported in 2008 [44]. The strategy is again characterized by an Ireland–Claisen rearrangement/RCM key sequence (Scheme 1.35). Alcohol **205** was prepared by Stille coupling between the aryl iodide **203** and the enantiomerically pure vinyl stannane **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).

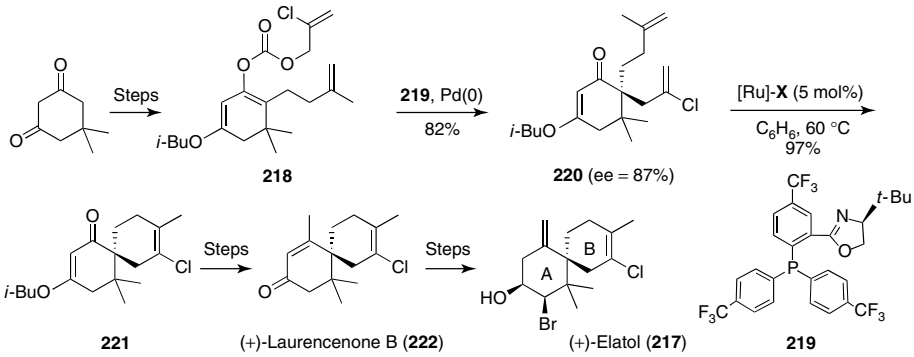
Vannusal A (**212**) is a complex triterpene characterized by a pentacyclic bridged core. Nicolaou *et al.* have devised a synthetic approach to compound **216** possessing the core structure of vannusal A (Scheme 1.37) [46]. A Mn(III)-induced radical



Scheme 1.36



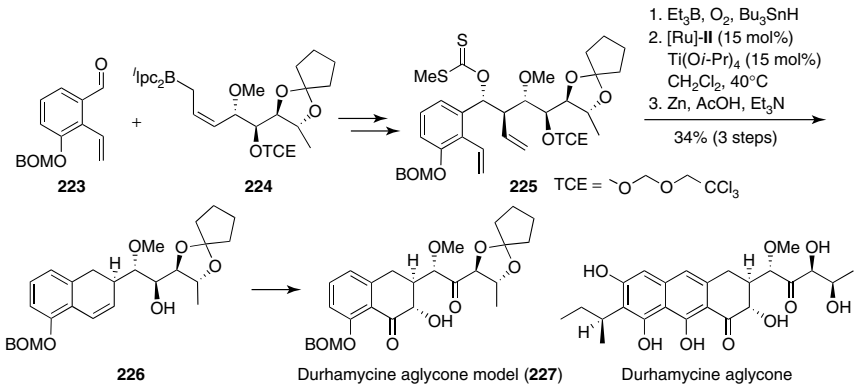
Scheme 1.37



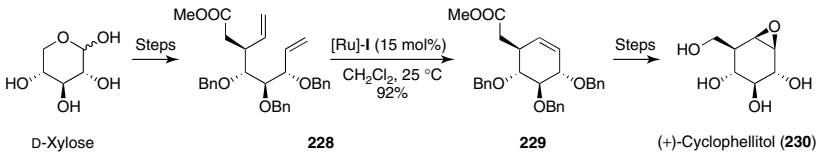
Scheme 1.38

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 dimedone, 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



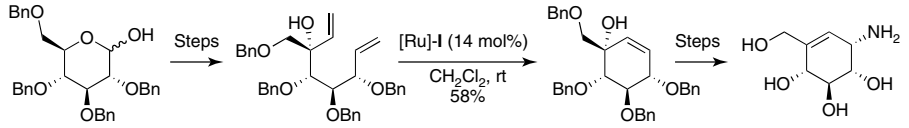
Scheme 1.40

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(O*i*-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).

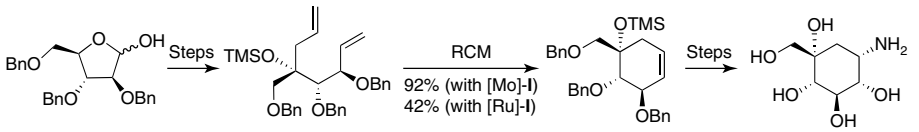
The mild conditions of the olefin metathesis reaction make it an ideal method for the preparation of cyclitols and carbasugars [51, 52]. In general, the syntheses start from readily available carbohydrate derivatives that are converted to dienes and then submitted to RCM conditions. The resulting functionalized 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



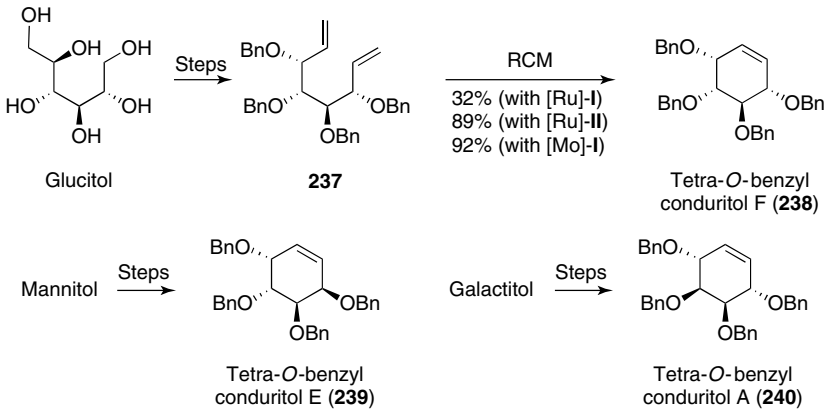
2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose — **231** — **232** — (+)-Valienamine (**233**)

Scheme 1.41



2,3,4-Tri-*O*-benzyl-D-arabinofuranose — **234** — **235** — (+)-Valiolamine (**236**)

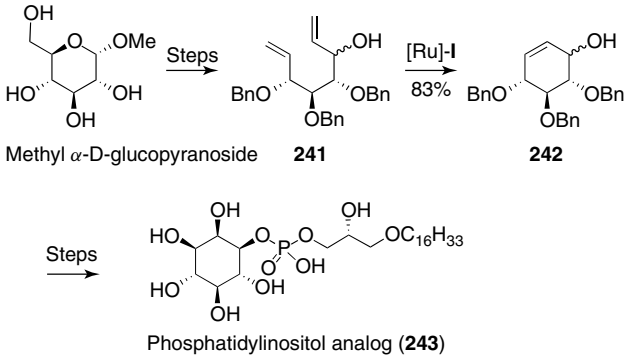
Scheme 1.42



Glucitol — **237** — Tetra-*O*-benzyl conduritol F (**238**)

Tetra-*O*-benzyl conduritol E (**239**) — Tetra-*O*-benzyl conduritol A (**240**)

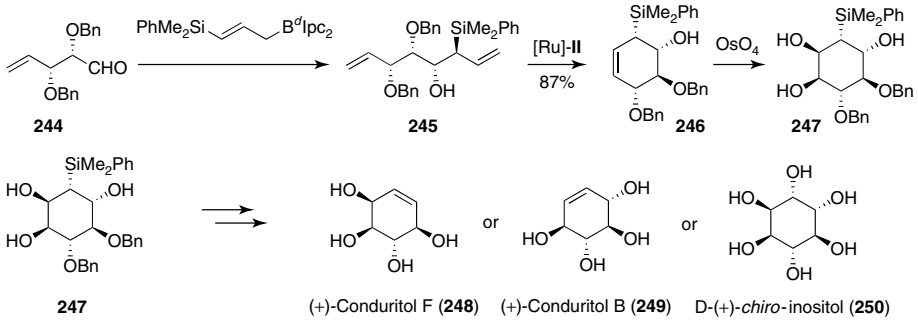
Scheme 1.43



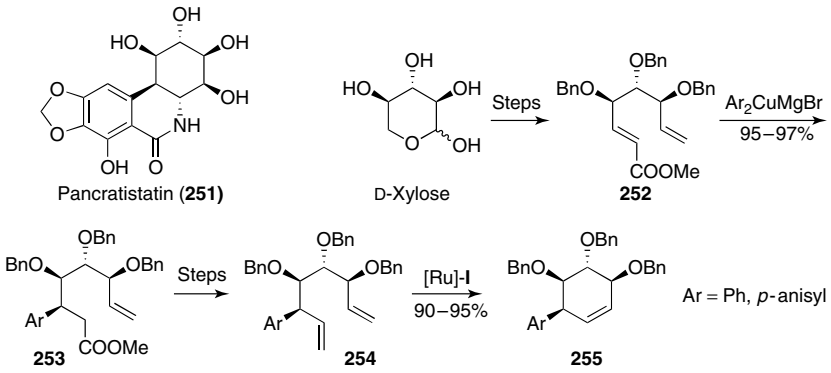
Methyl α-D-glucopyranoside — **241** — **242**

Phosphatidylinositol analog (**243**)

Scheme 1.44



Scheme 1.45



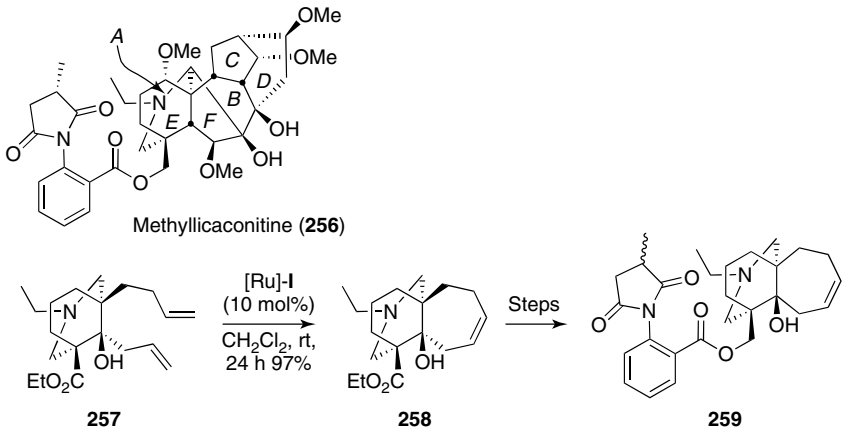
Scheme 1.46

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



Scheme 1.47

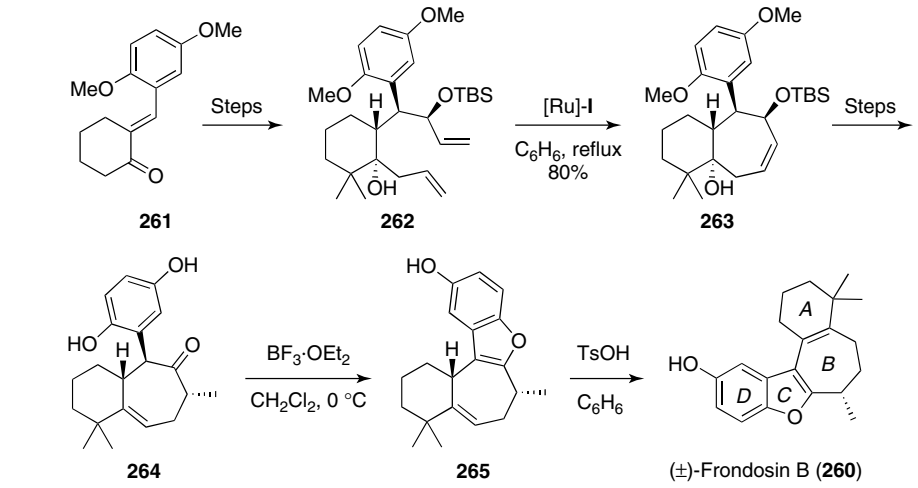
functional group tolerant catalysts as shown by Stoltz in the (−)-cyanthiwigin F synthesis. The following section, by no mean exhaustive, covers the more recent applications in RCM of 1,8-dienes applied to the synthesis of biologically relevant targets. When possible, comparison between various catalysts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

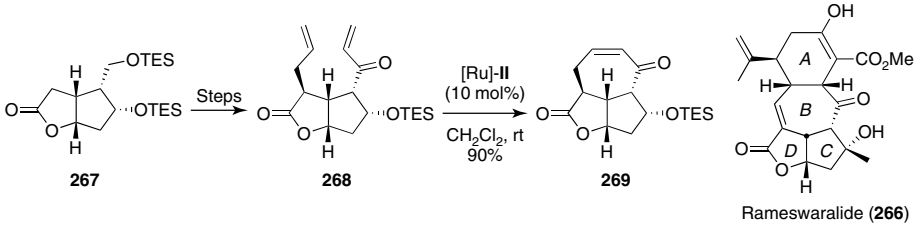
A key step in the total synthesis of (±)-frondosin B (**260**) reported by Mehta and Likhite is RCM of 1,8-diene **262** using [Ru]-**I** (C_6H_6, reflux) [64]. The corresponding bicyclic 6,7-fused ring system **263** was obtained in good yield (80%). Cyclization of **264** mediated by boron trifluoride 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%) (CH_2Cl_2, rt) in high yield (90%) (Scheme 1.49) [65].

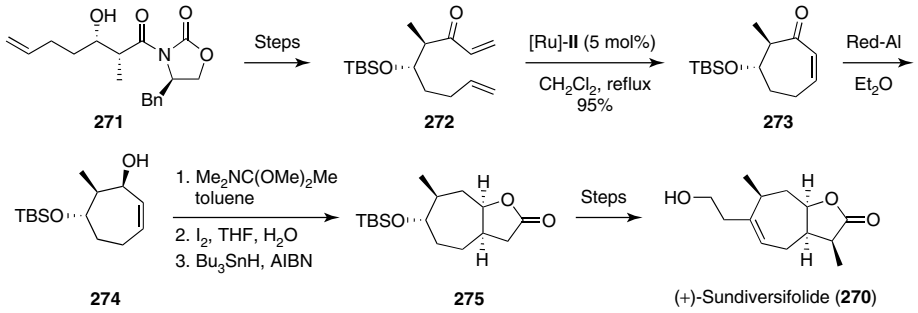
A related ω-alkenyl acrylate RCM was used in the first total synthesis of (+)-sundiversifolide (**270**) reported by Shishido *et al.* [66]. An excellent yield of chiral cycloheptenone **273** was obtained from **272** using catalyst [Ru]-**II**. Enone **273** was then chemoselectively reduced to the 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).



Scheme 1.48

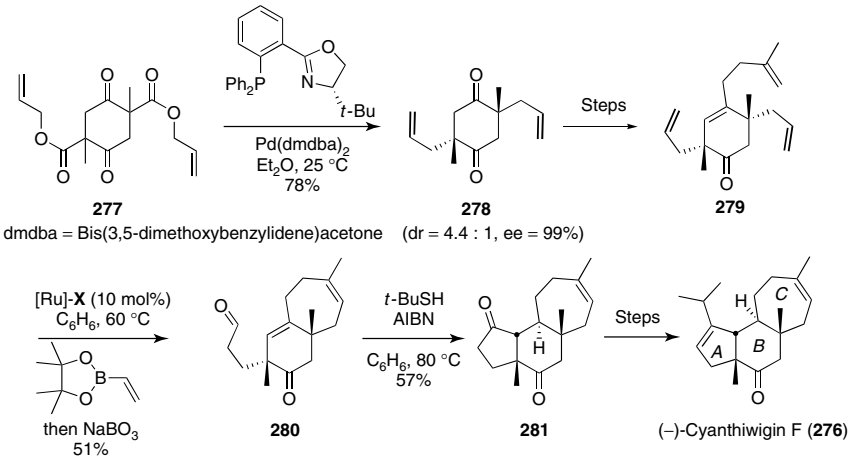


Scheme 1.49

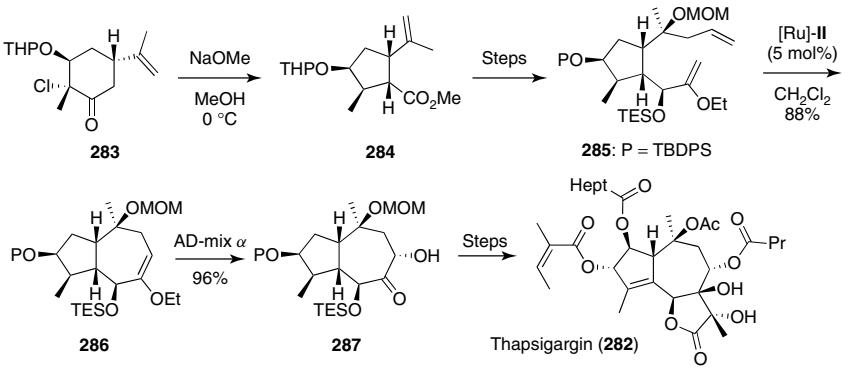


Scheme 1.50

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



Scheme 1.51



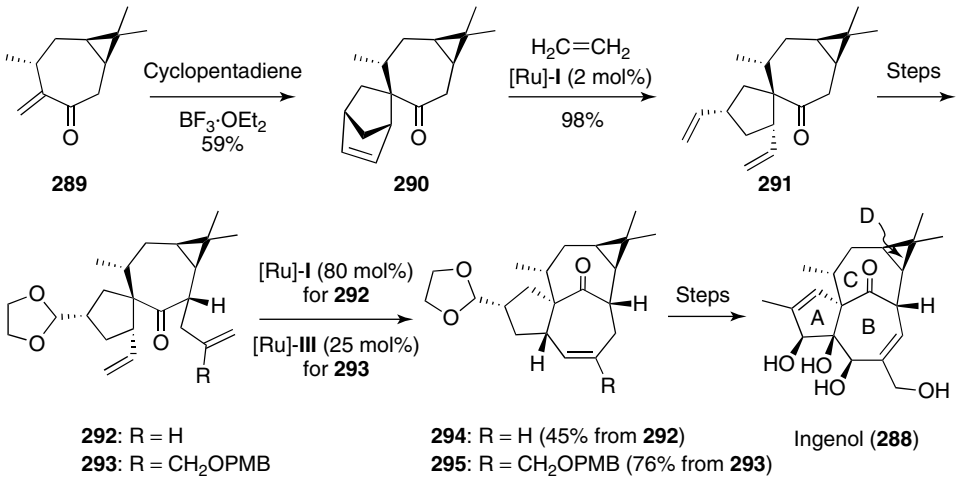
Scheme 1.52

the presence of a chiral ligand gave **278**, which was converted to tetraene **279** [67]. RCM of **279** followed by a one-pot cross-metathesis with vinylpinacolboronate led after oxidation to the bicyclic aldehyde **280** possessing the BC ring system of the natural product. Radical cyclization of the latter compound (*t*-BuSH, AIBN) established the desired ABC tricyclic motif **281** that could be further transformed to (−)-cyanthiwigin F (**276**) (Scheme 1.51).

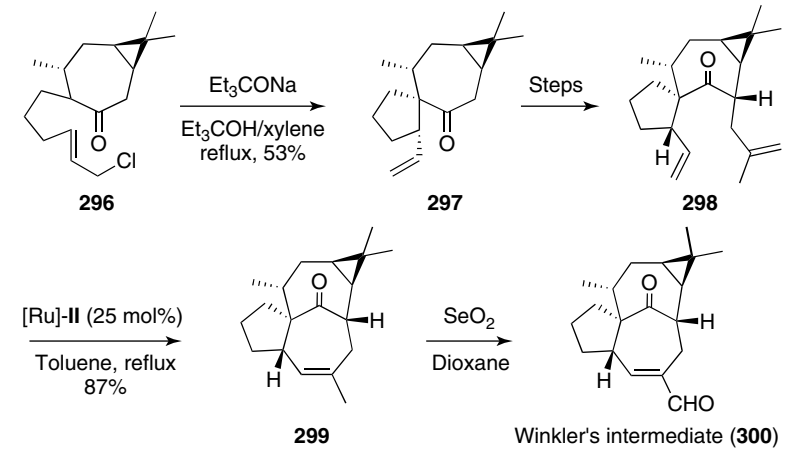
The guaianolide class of natural products is characterized by a tricyclic 5,7,5-ring system [68]. Among these promising sesquiterpene lactones were identified the thapsigargins (such as **282**, Scheme 1.52), potent inhibitors of sarco/endoplasmic reticulum ATPases (SERCAs). Recently, Ley reported a 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 α-hydroxyketone **287** via asymmetric dihydroxylation. The same key step was used in the total synthesis of closely related guaianolides, trilobolide, nortrilobolide and thapsivillosin 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



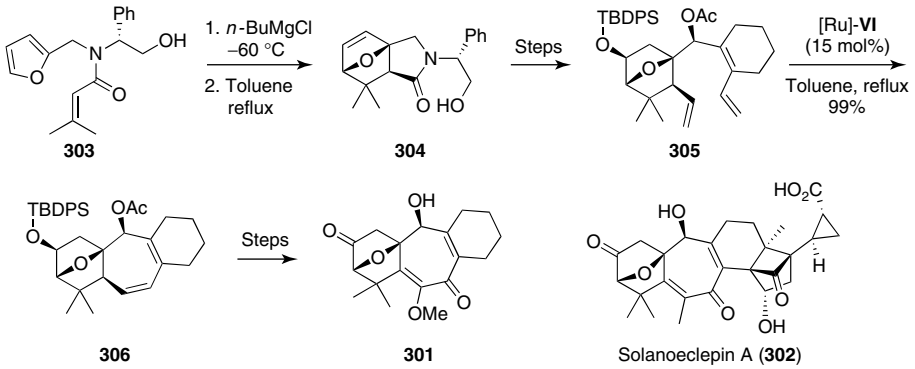
Scheme 1.54

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%).

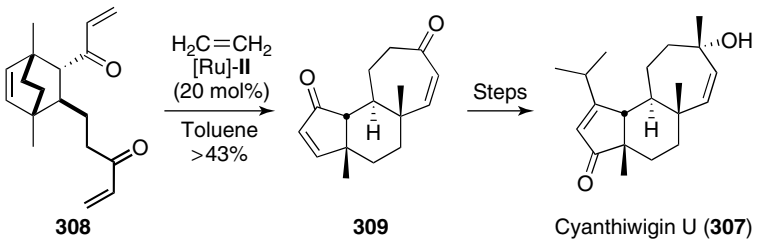
Kigoshi's formal synthesis (Scheme 1.54) relies on the efficient spirocyclization reaction of ketone **296** also prepared from 3-carene. The AC ring system was then further elaborated into 1,8-diene **298** that could be cyclized to **299** in 87% yield using [Ru]-**II** (25 mol%). A dramatic temperature 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 bicyclo[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



Scheme 1.55



Scheme 1.56

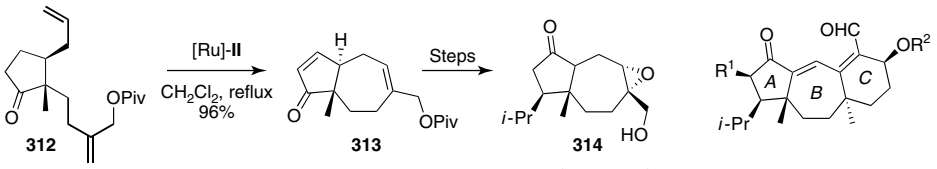
309 with great efficiency. This synthetic strategy was later extended to the synthesis of cyanthiwigin W and Z [77].

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.

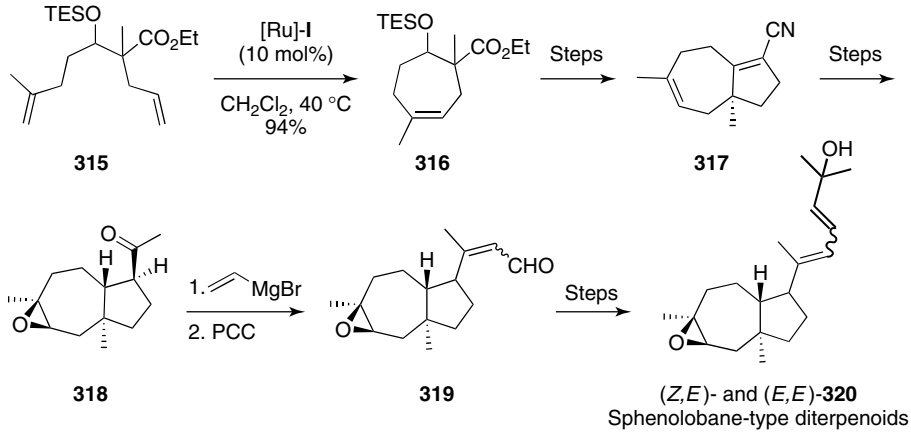
This very efficient RCM should not mask the fact that trisubstituted double bonds of terpenoids, imposed by the biosynthesis pathway from isoprene units, could be challenging to prepare through the RCM of 1,8-dienes as subtle differences in the metathesis precursor can have a dramatic impact on the reaction 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(O*i*-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



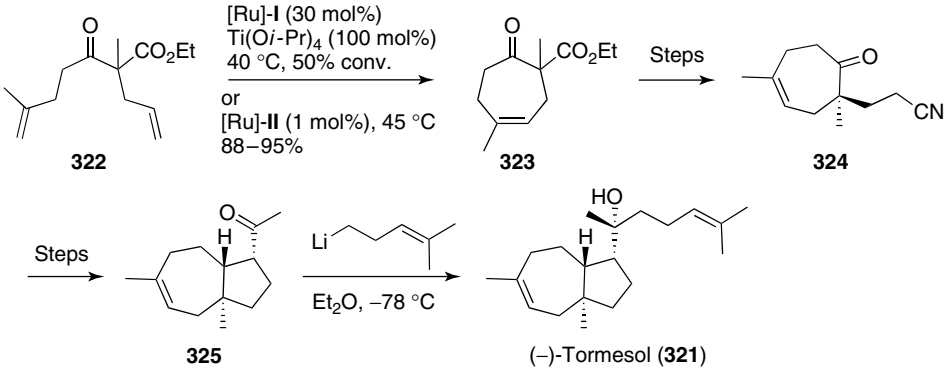
Scheme 1.57



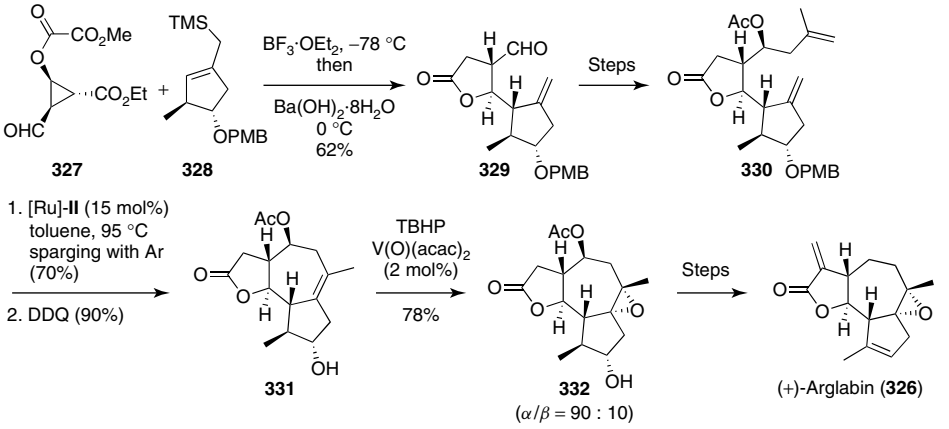
Scheme 1.58

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).



Scheme 1.59



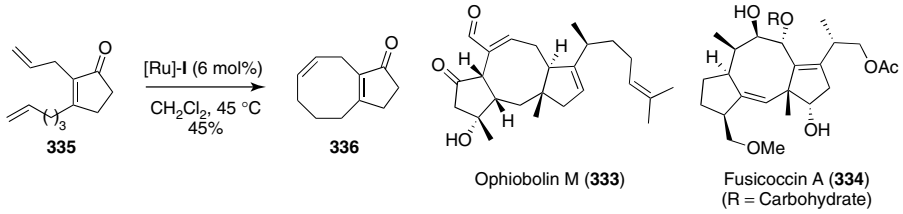
Scheme 1.60

1.5
Formation of Eight-membered Carbocycles by RCM

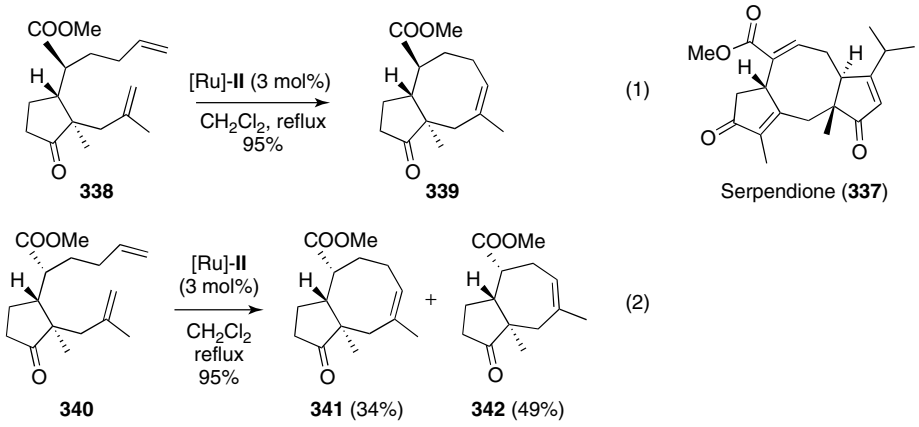
Cyclooctanoids are among the most difficult carbocycles to elaborate from acyclic precursors due to severe developing ring strain and restricted bond rotation in the precyclization conformer [84]. In the mid 1990s, RCM of 1,9-dienes emerged as a powerful strategy for the synthesis of carbocyclic eight-membered 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).

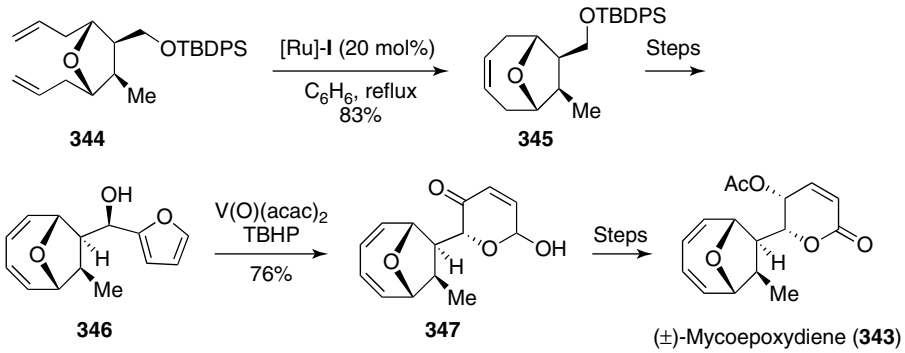
The second approach [90] reports the synthesis of the AB ring system of serpendione (**337**) via RCM reaction of **338** (Equation 1, Scheme 1.62) that contains



Scheme 1.61



Scheme 1.62



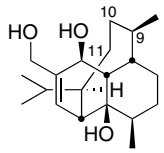
Scheme 1.63

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.

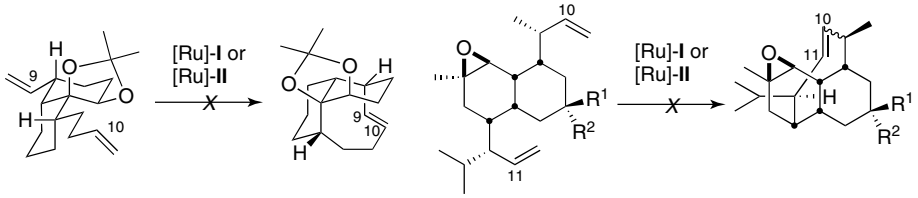
Imposing a conformational constraint that favors cyclization is a useful strategy for the RCM of 1,9-dienes. In the total synthesis of (±)-mycoepoxydiene (**343**), Tadano *et al.* reported the RCM of the diallylated tetrahydrofuran **344** using catalyst [Ru]-**I** under diluted conditions to prevent oligomerization [91]. A good yield of the desired oxygen-bridged cyclooctene **345** was obtained (83%). A dramatic solvent dependence was noted as CH_2Cl_2 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.$0^{4a,8a}$]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



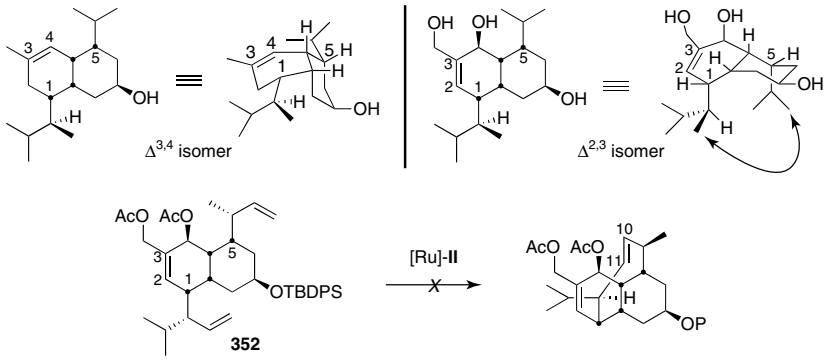
Vinigrol (**348**)



349

350: R^1, $R^2 = OCH_2CH_2O$
351: R^1 = OTBDPS, R^2 = H

Scheme 1.64

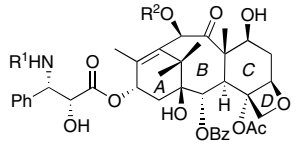


352

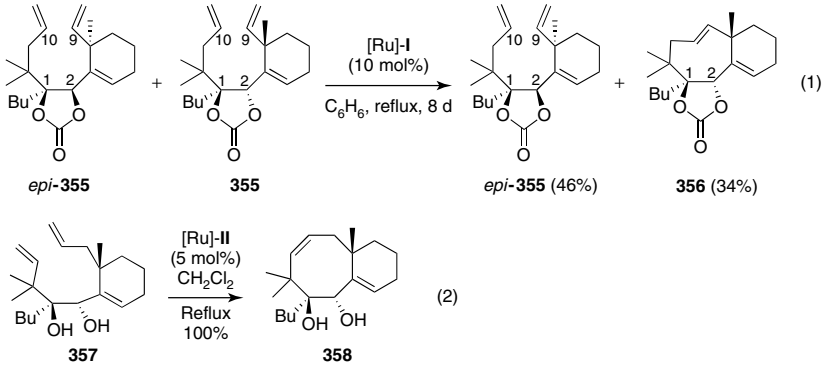
Scheme 1.65

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



R^1 = Bz, R^2 = Ac: Taxol (paclitaxel) (**353**)
R^1 = Boc, R^2 = H: Taxotere (docetaxel) (**354**)



Scheme 1.66

RCM strategy that was thwarted by conformational constraints imposing a cyclic carbonate protecting group of the C1–C2 diol motif.

1.6
Formation of Nine-membered Carbocycles by RCM

The failed metathesis-based synthesis of pestalotiopsin A **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 **360**–**362** was evaluated (Figure 1.2). For **360** and **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 **362** was isomerized to **363**.

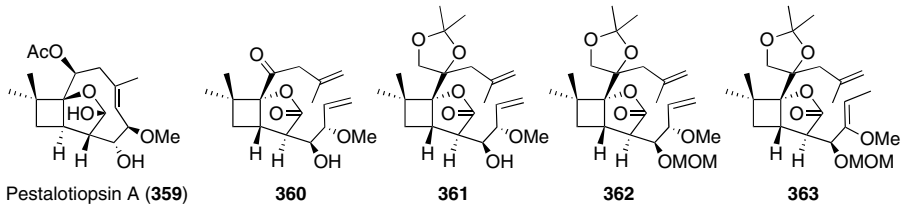
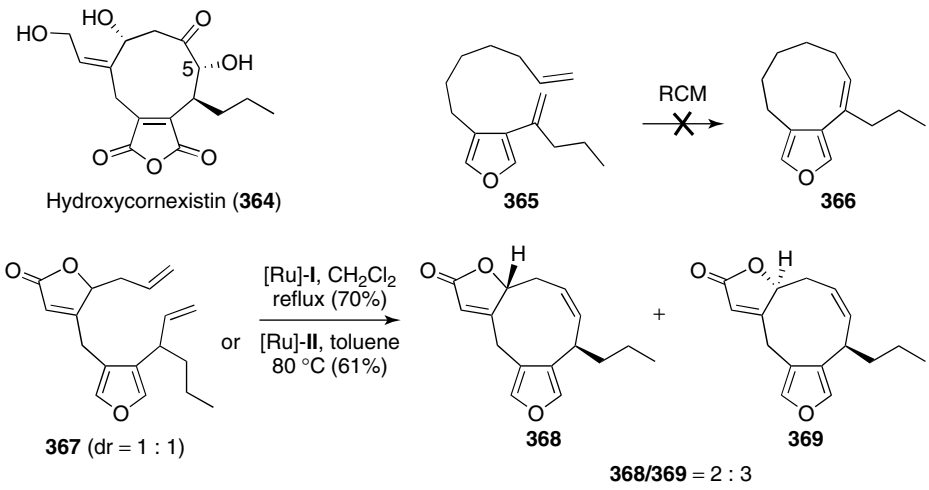


Figure 1.2 Pestalotiopsin a synthesis:unteactive RCM substrates.



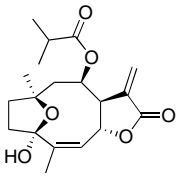
Scheme 1.67

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) [98].[3] Compound **368** was converted to (±)-5-*epi*-hydroxycornexistin in a few additional steps (Scheme 1.67).

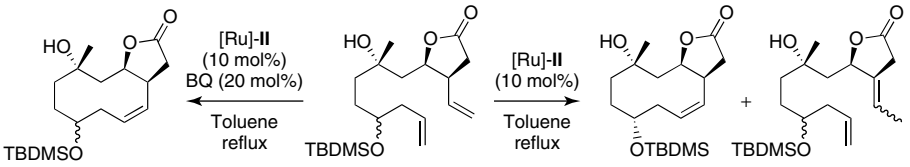
1.7 Formation of 10-membered Carbocycles by RCM

In 2001 and 2002, Koskinen *et al.* reported what appeared to be the first examples of 10-membered ring carbocycle syntheses via RCM [99]. 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** (*syn*/*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 Ti(O*i*-Pr)$_4$ was slightly beneficial. The roughly 2 : 1 *trans*/*cis* ratio of the major RCM products **371b** and **372b** compares well with the corresponding 2 : 1 *syn*/*anti* ratio of the substrate **370b** [99a]. When

3) [Ru]-I catalyst was used for this transformation (18 hours, CH_2Cl_2, reflux, 77%). [Ru]-II did not bring any significant improvement (personal communication from Dr Clark).



Diversifolin (**374**)



(*R*)-**376** (31%)
(*S*)-**376** (40%)

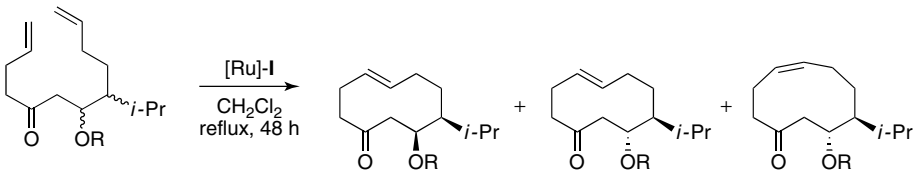
375
dr = 1 : 1

(*R*)-**376** (27%)
(*S*)-**376** (trace)

377 (35%)

Scheme 1.68

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



370a : R = H
370b : R = TBDMS
(*syn/anti* : 2 : 1)

371a
371b

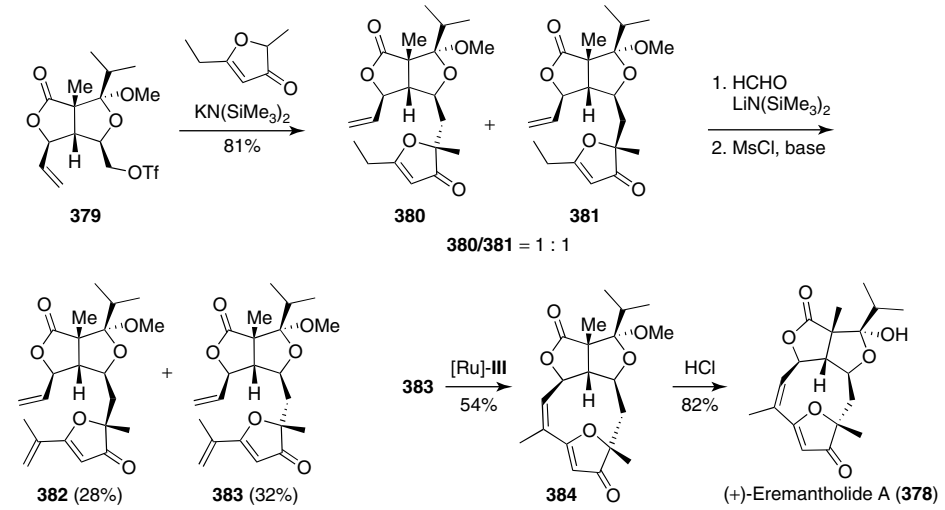
372a
372b

373a
373b

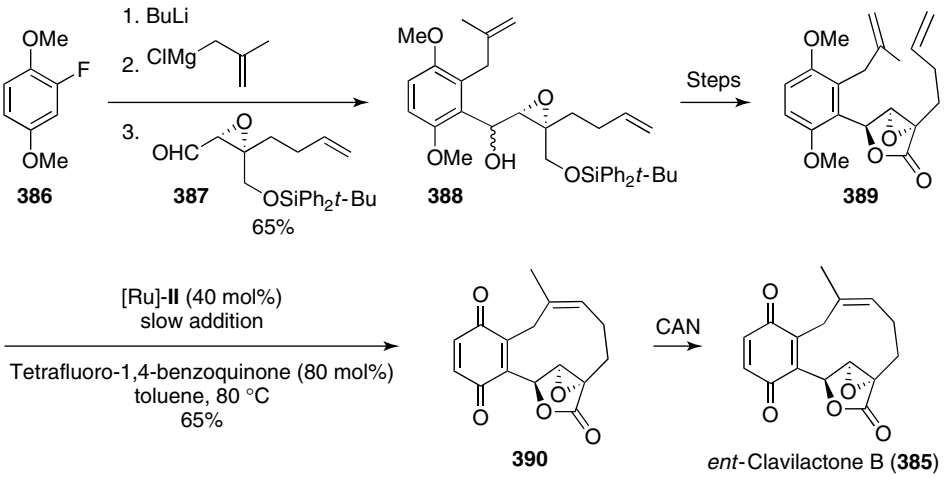
Substrate	Substrate recovery (%)	Products		
370a	25	**371a** (11%)	–	–
370b	6	**371b** (16%)	**372b** (35%)	**373b** (11%)
370b + $Ti(Oi\text{-}Pr)_4$ (20 mol%)	0	**371b** (21%)	**372b** (47%)	**373b** (8%)

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,



Scheme 1.69



Scheme 1.70

377 was obtained in 35% yield along with (3*R*)-**376** (27%), and some starting material was recovered. Only (3*R*)-**375** cyclizes rapidly and no (3*S*)-**376** was formed. RCM of (3*S*)-**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].

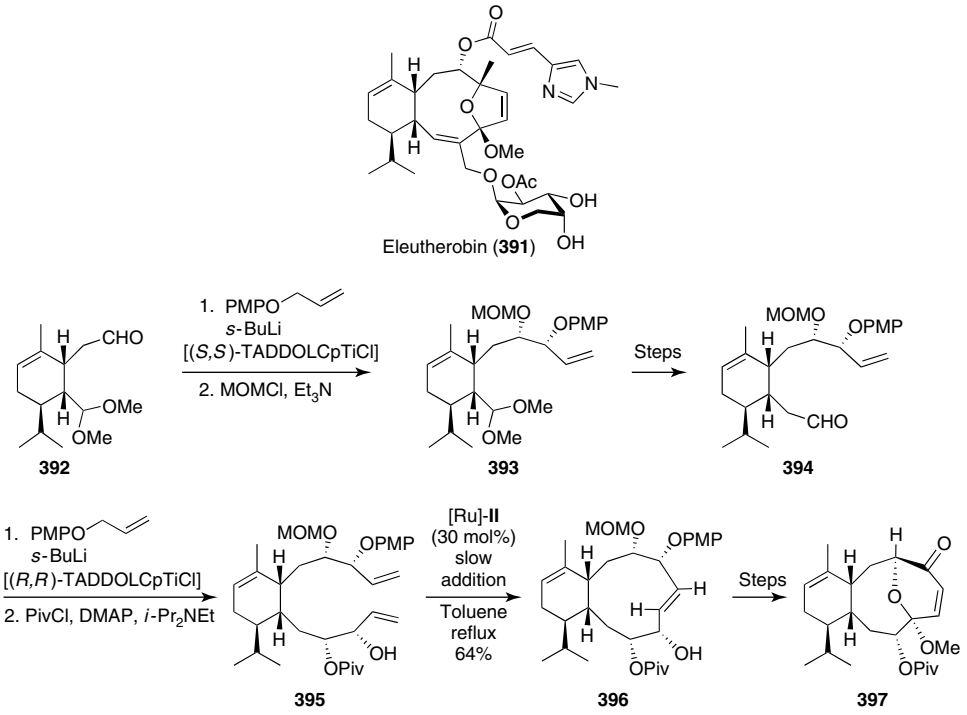
In Hale's and Li's synthesis of (+)-eremantholide A (**378**) (Scheme 1.69), the RCM step takes place almost at the end of the synthesis and involves a fairly

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].

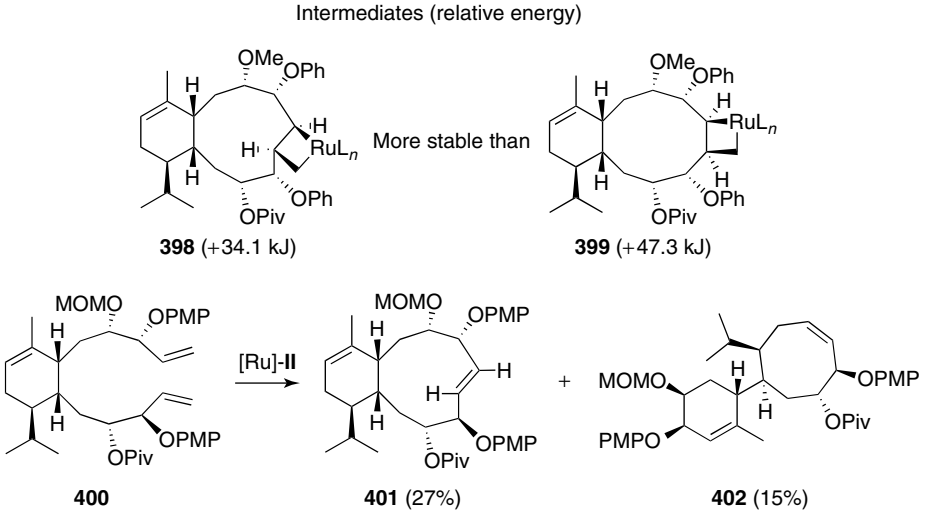
Starting from (*R*)-(−)-carvone, the half-protected dialdehyde **392** was prepared. Diastereoselective reagent-controlled oxyallyltitanations (with TADDOL as



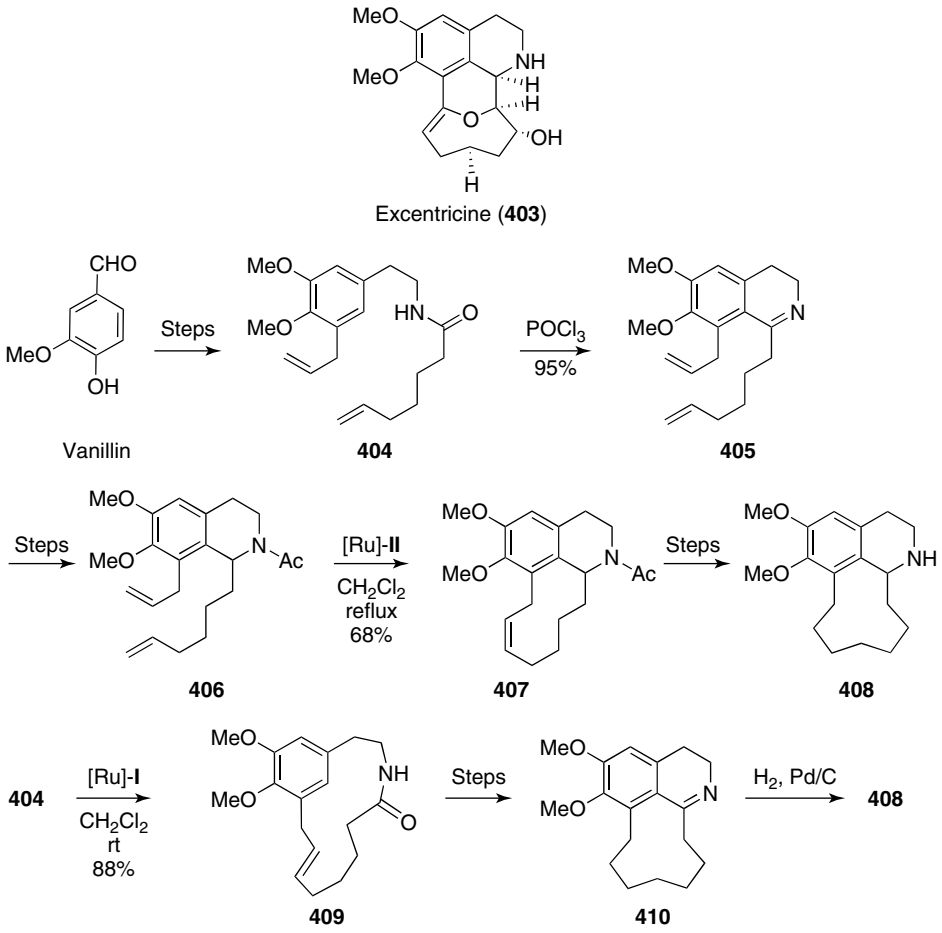
Scheme 1.71

the chiral ligand) of both aldehydic functions led to the RCM precursor **395**, which was cyclized using [Ru]-**II** 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 ([Ru]-**II** [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).

Excentricine **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 γ,δ- or δ,ε-unsaturated amides or esters). RCM of diene **406** proceeded smoothly using catalyst [Ru]-**II** 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 [Ru]-**I** 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



Scheme 1.73

1.8 Conclusion

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.

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