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Application of ring-rearrangement metathesis in organic synthesis: A grand design

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ABSTRACT

In this report, we compiled various strategies involving a ring-rearrangement metathesis as a key step to assemble diverse molecules. Popular name reactions such as Grignard reaction, Overman rearrangement, Fischer indolization, Beckmann rearrangement and Diels–Alder reaction were used in combination with ring-rearrangement metathesis to construct complex targets. Additionally, C—H activation and RRM strategy has been used to assemble azacycles. In some instances, the ring-rearrangement metathesis was expected to occur; however, ring-opening metathesis products were realized. These methods were included in the miscellaneous section. We anticipate that the lessons learned here are useful in designing complex polycyclic and heterocyclic targets suitable for biological and material science applications. Beside our work, we have also included others work as a background information.

Introduction

Ruthenium-catalyzed metathetic processes [1] such as ring-closing metathesis (RCM), cross-metathesis (CM), enyne metathesis (EM), and ring-rearrangement metathesis (RRM) have received a great deal of attention and they are powerful tools for the construction of a variety of natural as well as unnatural products. These Ru-catalyzed metathesis processes are useful in organic synthesis for the construction of C—C multiple bonds. RRM involves the ring-opening metathesis (ROM) and RCM sequence, which occur simultaneously in one-pot operation to generate the rearranged products. There are limited number of reports where the RRM protocol has been successfully employed to assemble a narrow range of products [2,3]. Various factors such as release of ring-strain, which assist the RRM. For example, with bicyclo[2.2.1]heptene systems, RRM generate less strained final products. A general mechanism for RRM is shown in Fig. 1 [4].

For more details on previous examples of RRM strategy, the reader is requested to refer earlier reports [2e,5]. Here, we have included few selected approaches, as a background information in a chronological order. It is interesting to note that thousands of papers are available dealing with RCM, however, less than hundred papers are available involving RRM. It is difficult to conceive a RRM sequence to assemble meaningful targets due to the intricacies involved in the designing such strategies.

In 1986, Grubbs and co-workers [6] described the total synthesis of (±)-$\Delta^{(9,12)}$-capnellene (**11**) by employing RRM with the help of Tebbe's reagent **8**. To this end, the RRM precursor **7** was obtained from the lactone **6** in a five-step sequence. Interestingly, the rearrangement of the tricyclic olefin **7** with Tebbe's reagent **8** delivered the RRM product **9**, which was converted into the 1,3-dioxolane derivative **10**. Later, it was converted to capnellene (**11**) in a nine-step synthetic sequence (Scheme 1).

In another instance, Grubbs and co-workers [7] reported RRM sequence and in this regard, the cyclopentene precursor **15** was prepared from diketone **12** *via* selective reduction followed by *O*-allylation. The triolefin **15** was reacted with G-I catalyst to deliver rearranged product **16**. Similarly, the bicyclic compound **18** was also assembled from the cyclopentene derivative **17** (Scheme 2).

Hoveyda and co-workers [4] described the synthesis of chromenes *via* RRM with the aid of Grubbs catalyst **5**. To this end, the styrene derivative **19** was reacted with a catalytic amount of ruthenium carbene complex **5** to give the rearranged product **20**. This novel strategy converting carbocycle into heterocycles is unique and incorporate synthetic brevity. Such transformations are difficult to realize by conventional synthetic routes (Scheme 3).

Prunet and co-workers [8] described the synthesis of the fused tricyclic framework *via* domino metathesis reaction. In this regard, the enone **21** was treated with allylmagnesium bromide (**22**) in the presence of copper bromide to deliver the 1,4-addition product **23**. Later, allyl derivative **23** was reacted with catalytic amount of G-II catalyst to furnish the RRM products **24**. Similarly, the compound **26** was produced from **23** with allyltrimethylsilane (**25**) under RRM conditions (Scheme 4).

Spring and co-workers [9] reported an efficient and atom economical method for the construction of tricyclic compound **29** *via* a RRM sequence. For this purpose, the reaction of enyne derivative **27** with G-I catalyst and again treated with G-I and G-II catalysts after some interval of time followed by reaction with potassium salt **28** delivered the RRM product **29** in 87% yield (Scheme 5).

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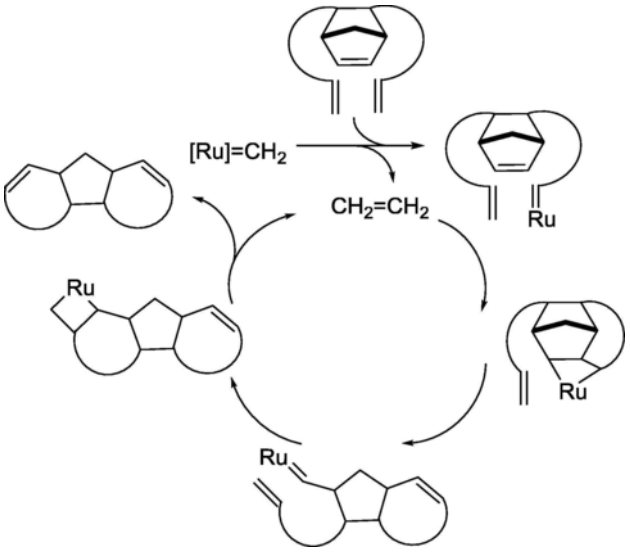


Fig. 1. A general mechanism for RRM process.

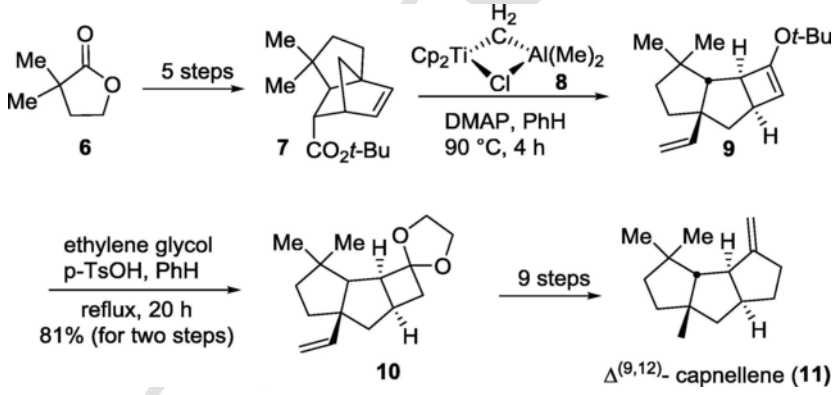
Groaz et al. [10] reported the synthesis of the tricyclic compound **33** *via* a RRM strategy. Treatment of the norbornene derivative **30** with propargyl bromide (**31**) in the presence of NaH gave the enyne building block **32** which on exposure to G-I catalyst under ethylene atmosphere produced the diene **33** in 43% yield (Scheme 6).

Fallis and co-workers [11] reported the synthesis of triquinane framework **38** *via* a one-pot tandem reaction. To this end, the cyclopentadiene (**35**) was alkylated with the tosyl derivative **34** under basic conditions to give the substituted cyclopentadiene **36**. Intramolecular DA reaction of compound **36** under thermal conditions gave the norbornene derivative **37** (80%). Finally, exposure of the DA adduct **37** to G-I catalyst delivered the triquinane-based compound **38** *via* RRM sequence (Scheme 7).

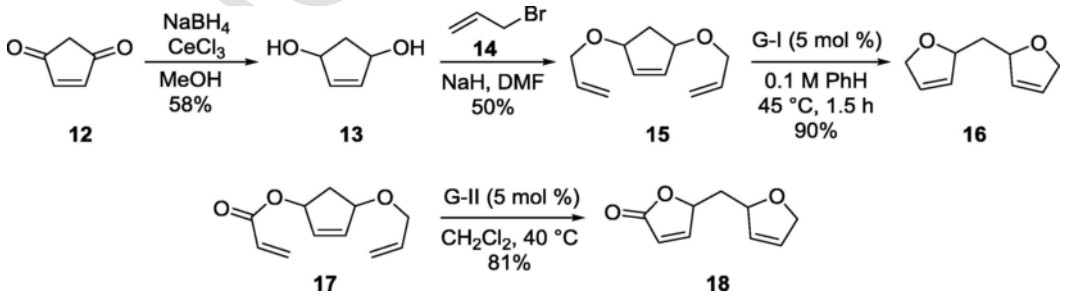
Takao et al. [12] described the total synthesis of clavilactones by employing a ROM/RCM sequence. To this end, allylic alcohol **39** was acylated using the anhydride **40** in the presence of LDA to produce the ester derivative **41** (85%). Next, exposure of the cyclobutene derivative **41** to G-I catalyst in the presence of benzoquinone **42** and then treatment with G-II catalyst in ethylene atmosphere gave the rearranged product **43** (81%). It is interesting to note that benzoquinone usage prevents olefin migration during metathesis [13]. Later, the key precursor **43** was used in the synthesis of (−)-clavilactone B (**44**) and (+)-clavilactone A (**45**), which involve eight-step synthetic sequence (Scheme 8).

Nanda and co-workers demonstrated a simple synthetic strategy to linear triquinane **53** [14], a key precursor in assembling hirsutene analogue **54**. Here, the RRM precursor **47** was designed starting with tricyclic anhydride **46**. To this end, the bicyclic compound **47** was treated with G-II catalyst under ethylene to give the enone **48** (88%). A chemoselective reduction of the enone **48** was achieved in an efficient manner with copper hydride in the presence of hydrogen. Methylation of ketone **49** with methyl iodide gave the compound **50** (78%), which was converted into a RCM precursor **51** by employing a four-step synthetic sequence. Next, di-olefin **51** was exposed to HG-II catalyst to produce a ring-closure product **52** (80%). Finally, tricyclic compound **52** was subjected to reduction with H_2, Pd/C conditions followed by PCC oxidation furnished the dione derivative **53**, a useful precursor for the synthesis of hirsutene analogue **54** (Scheme 9).

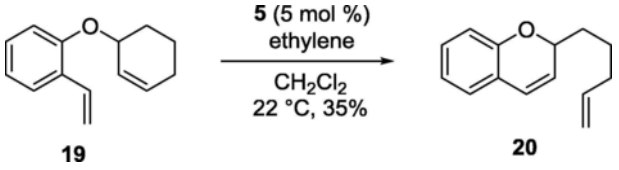
Ghosh and co-workers [15] reported an efficient protocol for the construction of tetracyclic compound **60** by employing a ring-opening/ring-closing enyne metathesis sequence followed by the DA reac-



Scheme 1. RRM using Tebbe's reagent.



Scheme 2. Tandem ring closing-ring opening metathesis.



Scheme 3. Synthesis of chromene *via* RRM.

tion. To this end, the norborene derivative **55** was treated with Grignard reagent to deliver the diol **56**, which was further protected with TBS silyl protecting group to afford the RRM precursor **57**. Later, it was treated with G-I catalyst under ethylene to deliver the diene **58**. Finally, the diene was subjected to DA reaction with DMAD (**59**) to produce the tetracyclic compound **60** (Scheme 10).

Synthesis of carbocycles *via* RRM

As part of our major research programme to design new strategies based on metathesis in the last two decades, non-traditional synthetic routes to various polycyclic compounds by employing RRM protocol [2e] using various ruthenium catalysts were demonstrated (Fig. 2).

To expand the utility of RRM in organic synthesis, new methods to construct a variety of carbocyclic and heterocyclic scaffolds have been designed [16]. To this end, alkenylated enones **62** and **65** were derived by Grignard addition followed by PCC oxidation starting with the enone **21**. Next, these enones **62** and **65** were subjected to RRM with either G-II or GH-II catalyst under ethylene, yielding the rearranged tricyclic enones **63** and **66** respectively (Scheme 11).

Similarly, we also studied RRM process starting with the *exo* isomer **69**. In this context, the *exo*-enone **67** [17a] was subjected to Grignard addition with 3-butenylmagnesium bromide (**61**), which led to the formation of addition product **68**. Later, the hydroxy derivative **68** was treated with PCC to deliver the 1,3-transposed product **69**. Finally, the enone **69** was reacted with G-II catalyst under ethylene atmosphere delivered a mixture of the ROM product **70** and the rearranged product **71**, respectively. It is interesting to note that the rearranged product **71** is core structural unit of longeracinphyllin A (**72**) natural product with appropriate stereochemistry at the ring junction (Scheme 12) [17b].

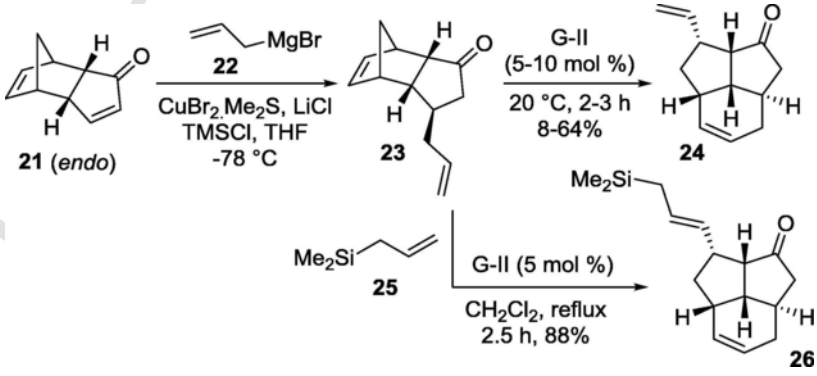
In another event, a simple protocol to tricyclic molecule **77** containing nitrogen atom involving RRM as a key step have been demonstrated [18]. In this regard, the norbornene derivative **73** was treated with $NaBH_4$ in the presence of I_2 to give the alcohol **74** (99%). Subsequently, treatment of the alcohol derivative **74** with allyltrimethylsilane (**25**) in the presence of $BF_3{\cdot}Et_2O$ gave allyl derivative **75** (46%). Later, the alkene **75** was subjected to metathesis *via* Ru-catalysts to produce only ROM product **76**. Finally, the resulting trialkene**76** was exposed to G-II catalyst to deliver the tricyclic ring closure product **77** (86%) (Scheme 13).

In view of brevity of RRM process, we have conceived a new synthetic strategy to assemble propellane **82** and triquinane **83** frameworks [19]. An easily accessible *exo*-norbornene derivative**78** was treated with aniline **79** in the presence of Et_3N to produce *N*-phenyl derivative **80**, which on *C*-allylation with allyl bromide (**14**) gave the diallyl compound **81**. Then, the RRM of the diallyl derivative **81** did not give the rearranged product **85** under G-I catalyst conditions. However, exposure of the diallyl compound **81** to G-I catalyst under ethylene atmosphere delivered a mixture of propellanes **82** (60%) and **83** (37%). Alternatively, the compound **80** was subjected to ROM followed by diallylation gave the precursor **84** (75%) suitable for triquinane synthesis. The compound **84** was subjected to RCM with the aid of G-II catalyst under ethylene atmosphere to produce the triquinane derivative **85** (Scheme 14).

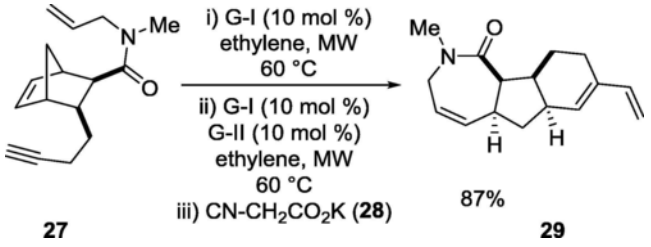
Moreover, this approach was also extended to the bis-triquinane and the bis-propellane derivatives starting with the *exo*-anhydride **78**, which on condensation with 4,4′-diaminodiphenylmethane **86** in the presence of Et_3N under sealed tube conditions (toluene, 160 °C) furnished the compound **87** (96%). Next, bicyclic system **87** was exposed to G-I catalyst to produce the tetraene derivative **88** (94%) by ROM. Next, treatment of compound **88** with allyl bromide (**14**)/ NaHMDS conditions produced the tetraallyl substrate **89** (89%). Finally, reaction of the tetraallyl derivative **89** with G-II catalyst under ethylene delivered a mixture of products containing bis-triquinane**90** (35%), triquinane-propellane **91** (37%), and *bis*-propellane derivative **92** (22%) (Scheme 15).

In another occasion, a pentacyclic ketone **93** was subjected to the RRM process to construct the tetracyclic compound **96** [20]. The endo enone **21** was subjected to DA reaction with freshly cracked cyclopentadiene to deliver the known DA product *endo-anti-endo* isomer **93** [21]. Next, Grignard addition with allylmagnesium bromide (**22**) to ketone **93** generated the allyl alcohol **97** (82%). Finally, exposure of the substrate **97** to G-II catalyst under ethylene produced the rearranged product **96** (40%) yield. Alternatively, the DA adduct **93** was treated with G-I catalyst under ethylene to provide ROM product **94** (71%), which on Grignard addition with allylmagnesium bromide (**22**) furnished the required allyl alcohol **95** (89%). Eventually, exposure of the tricyclic alkene derivative **95** to G-II catalyst under ethylene atmosphere provided the expected tetracyclic compound **96** in 89% yields, which contain tricyclic core of presilphiperfolanol (**98**) (Scheme 16).

Along similar lines, ROM product **94** was alkylated with allyl bromide (**14**) to give alkene derivative **99** (89%), which on treatment



Scheme 4. Synthesis of tricylic framework **24** and **26** *via* RRM.



Scheme 5. Synthesis of tricyclic compound **29** *via* a RRM sequence.

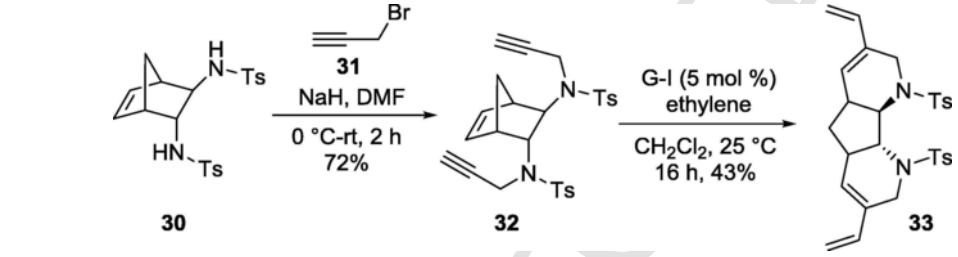
with G-II catalysts afforded the tetraquinane **100** (82%). It is interesting to note that a complex tetracyclic moiety such as **100** was assembled in a three-step sequence from commercially available enone **60**, which constitute the core of crinepellin (**101**) (Scheme 17). To the best of our knowledge, this approach delivered a short route to tetraquinane ring system.

Synthesis of azacycles *via* RRM

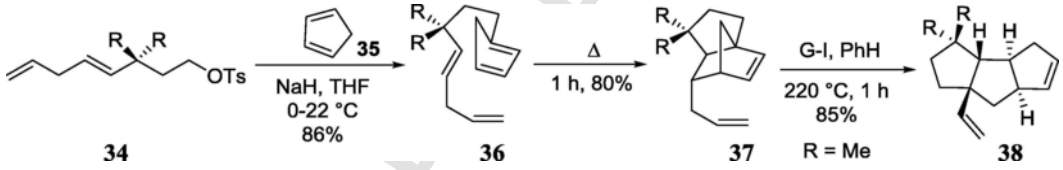
In another instance, a new synthetic strategy to assemble tricyclic amide **106** have been established [22]. The required RRM precursor **105** was prepared by employing the Beckman rearrangement followed by *N*-allylation protocol using allyl bromide (**14**) and NaH. Later, the *N*-allyl derivative **105** was exposed to G-II catalyst under ethylene to create the tricyclic product **106** in 90% yield (Scheme 18).

A simple route to construct azacycles by employing a sequential usage of Overman rearrangement and RRM protocol was demonstrated [23]. Our journey begins with the selective reduction of the enone **60** using DIBAL-H. Next, treatment of the alcohol derivative **107** with trichloroacetonitrile in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave the trichloroacetimidate **108**. Subsequently, treatment of the intermediate **108** with K_2CO_3 in refluxing toluene delivered the rearranged amine derivatives **109** (41%) and **110** (27%). Additionally, amino compound **110** was also prepared by reacting the compound **109** with NaOH in EtOH. Later, these compounds **109** and **110** were *N*-allylated separately with allyl bromide (**14**) to deliver the allyl building block **111**. Finally, *N*-allyl derivative **111** was subjected to RRM with G-I catalyst to yield the azacycle **112** (98%) (Scheme 19).

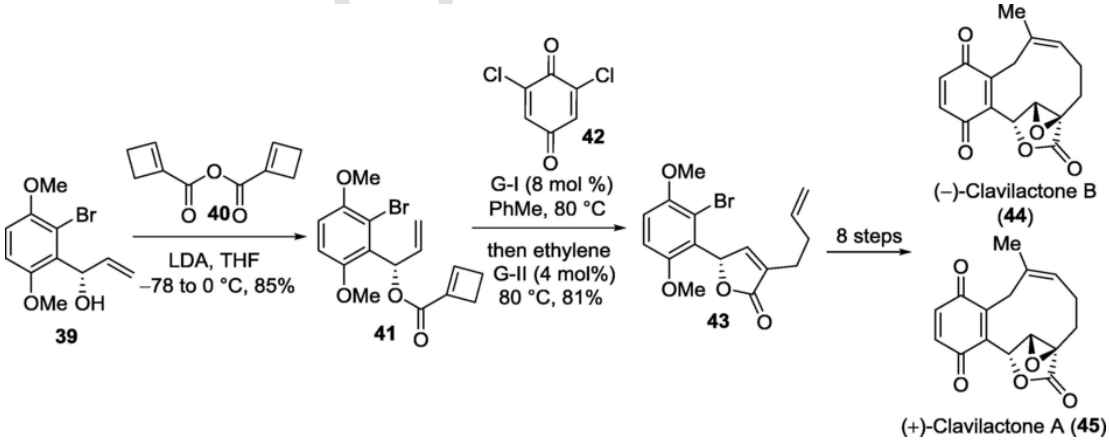
We introduced a new protocol involving the oxidative C—H activation process in combination with RRM to construct the tetracyclic framework **116** [24]. A readily available *N*-methoxybenzamide (**113**) was subjected to oxidative C—H activation involving norbornadiene (NBD) with the aid of Ru catalyst to provide the tetracyclic amide



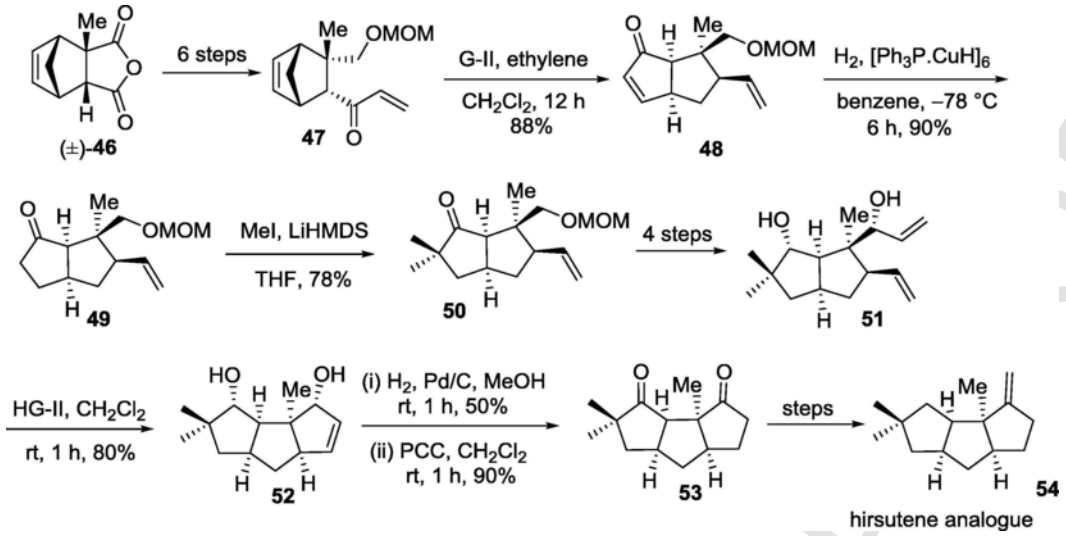
Scheme 6. Synthesis of tricyclic framework **33** *via* RRM strategy.



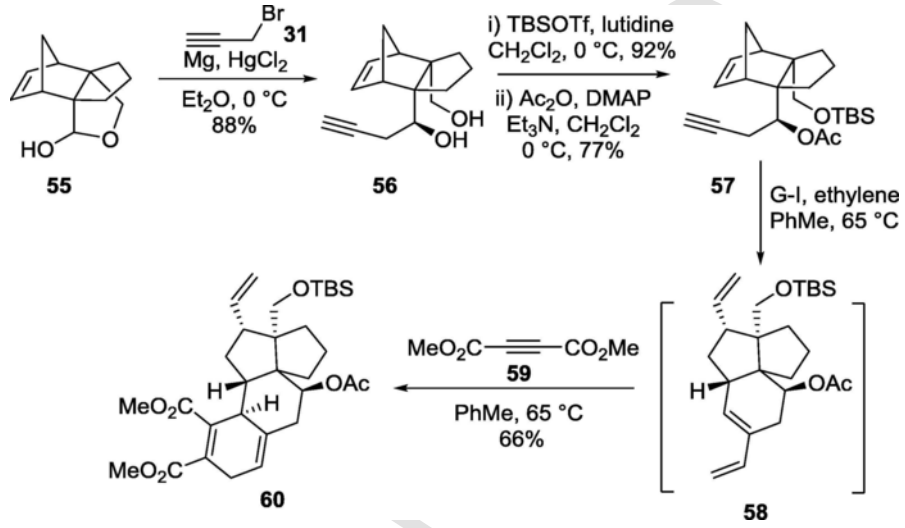
Scheme 7. Synthesis of linear triquinane by RCM-ROM-CM sequence.



Scheme 8. Total synthesis of clavilactones through a sequential usage of ROM/RCM protocol.



Scheme 9. A sequential use of RRM and RCM to linear triquinane **52**.



Scheme 10. Synthesis of tetracycle **60** *via* domino metathesis and Diels–Alder strategy.

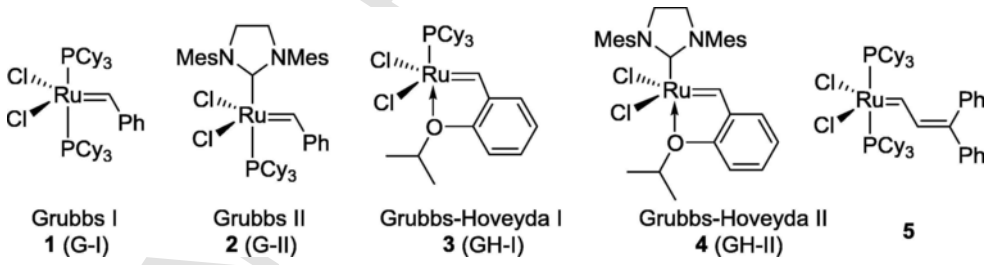
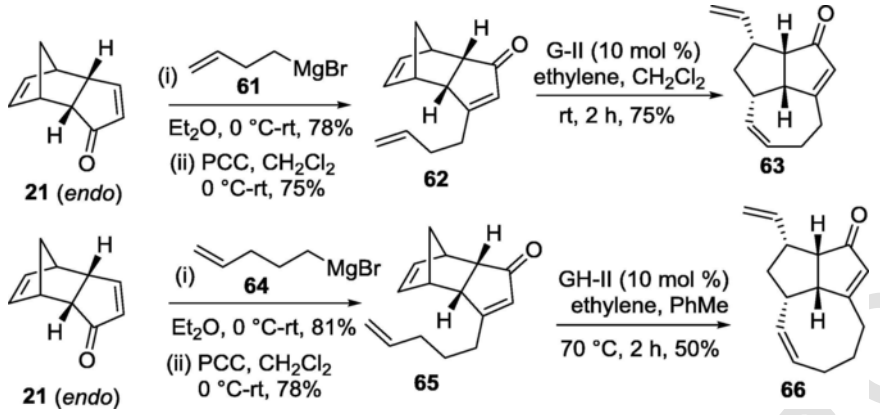


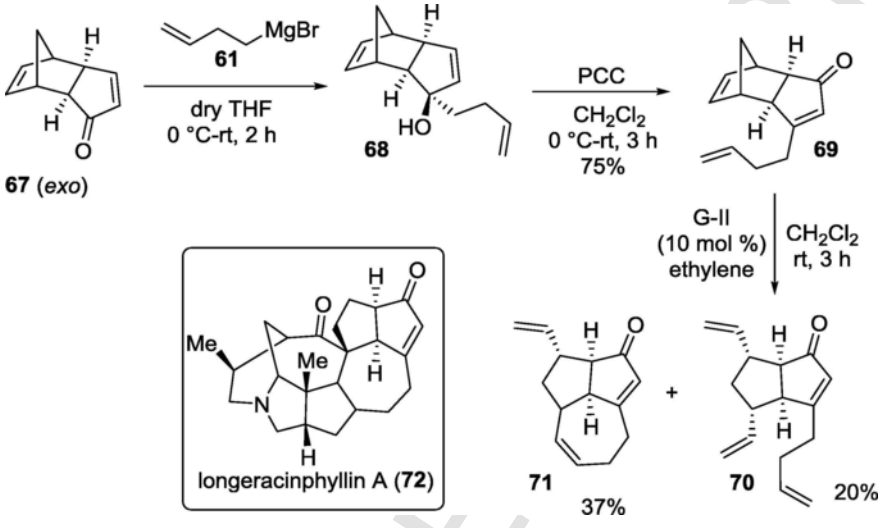
Fig. 2. Ruthenium alkylidene catalysts used in RRM processes.

114 (50%). Subsequently, allylation was accomplished with allyl bromide (**14**) to offer the required RRM precursor **115** (95%). Treatment of the *N*-allyl derivative **115** with G-II catalyst under ethylene afforded the rearranged product **116** (77%). Further, structure of the tetracyclic compound was determined by single crystal X-ray diffraction data (XRD) (Scheme 8). It is worth noting that the tetracyclic product **116** contain a tricyclic framework of annotinolide A alkaloid (**120**) (Scheme 20).

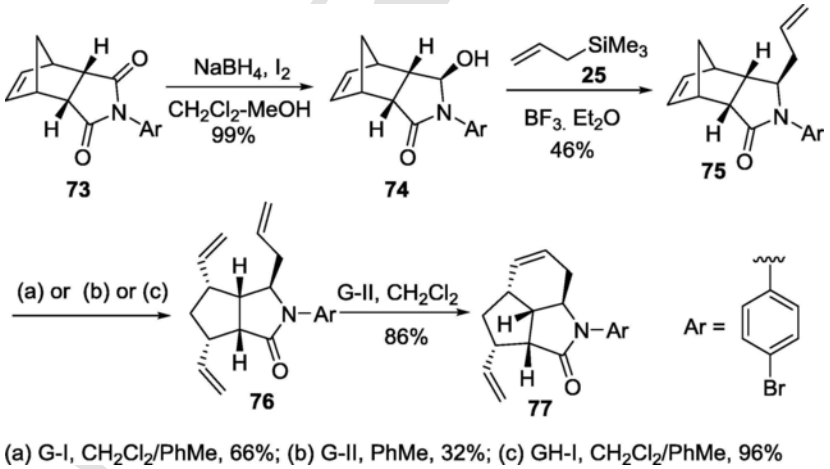
Along similar lines, treatment of tetracyclic amide **114** with propargyl bromide (**31**) gave the enyne derivative **117** (98%). Next, the enyne building block **117** was treated with G-I catalyst under ethylene to produce only CEM product **118** in 24% yield. However, the ERRM product **119** (45%) was obtained with G-II catalyst condi-



Scheme 11. Synthesis of the tricyclic enones **63** and **66** *via* RRM.



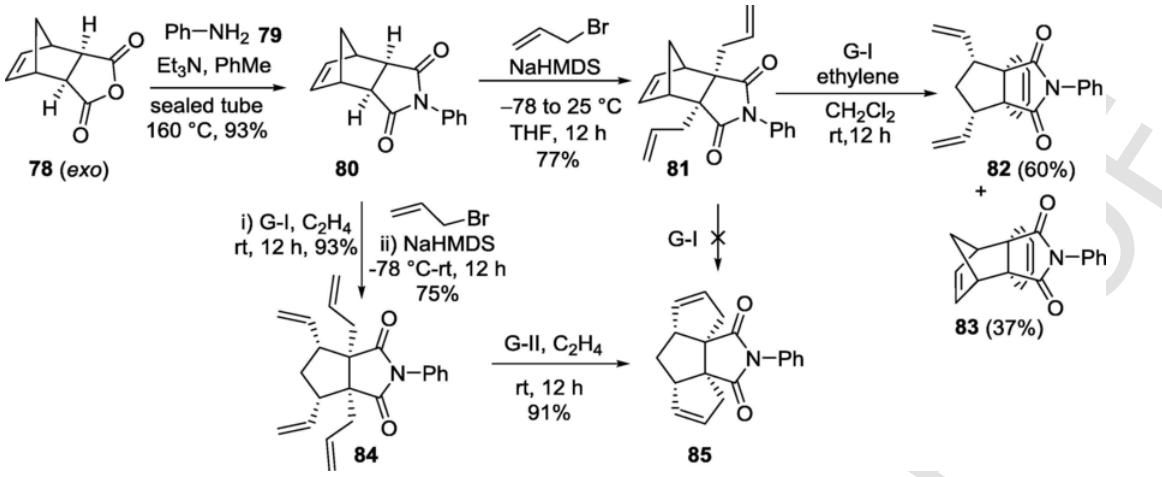
Scheme 12. Synthesis of tricyclic carbocycles **71** *via* a RRM strategy.



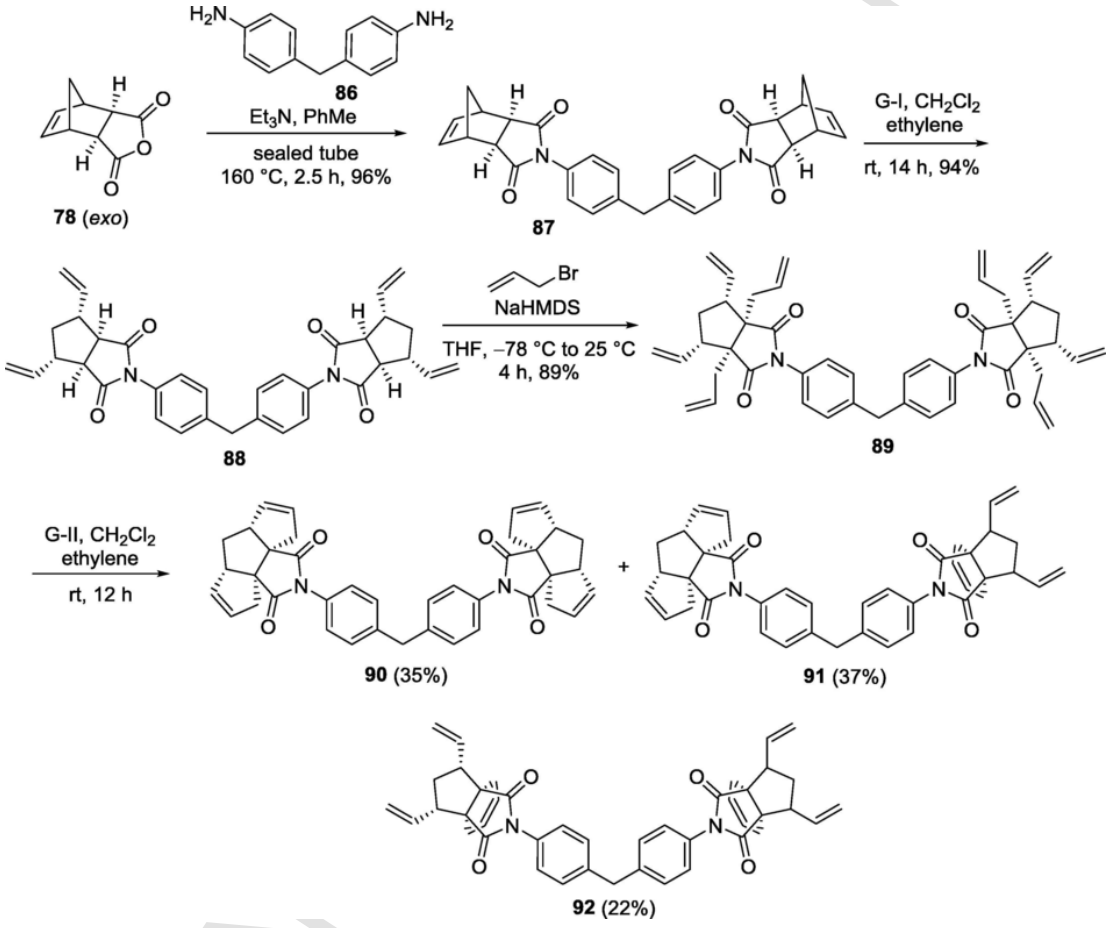
Scheme 13. Synthesis of tricyclic amide derivative *via* RRM as a key step.

tions. Unfortunately, the DA reaction of the diene **119** with various dienophiles like tetracyanoethylene (TCE) and *N*-phenylmaleimide in refluxing toluene was found to be futile. The diene **119** seems to be unstable during prolonged heating (Scheme 21).

Allyl indole derivative **122** is a useful substrate for the RRM process. It was prepared from the 2-bromo-*N*-allylaniline (**121**) by palladium-catalyzed annulation with NBD in the presence of Cs_2CO_3 using tri-*tert*-butylphosphoniumtetrafluoroborate (t-Bu_3PHBF_4) lig-



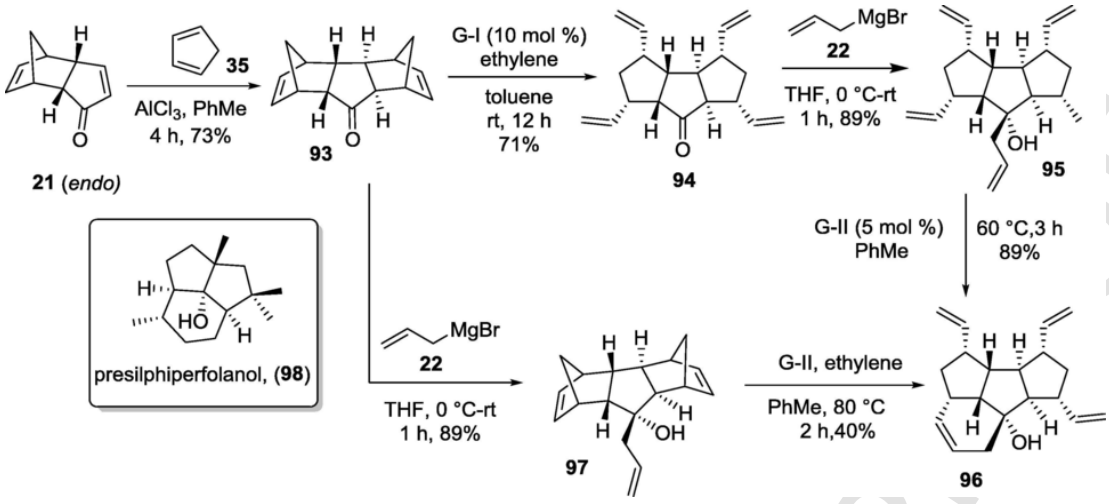
Scheme 14. RRM approach to synthesis of triquinane and propellanes.



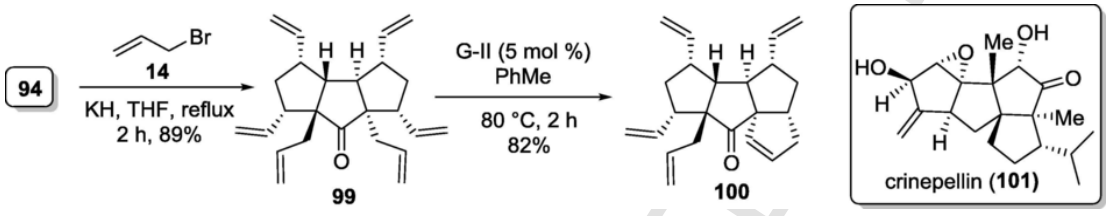
Scheme 15. Synthesis of bis(triquinane) and propellanes *via* ROM followed by RCM.

and in 70% yield. Next, treatment of the compound **122** with G-I catalyst under ethylene delivered a mixture of the RRM product **123** (52%) and ROM product **124** (35%) (Scheme 22).

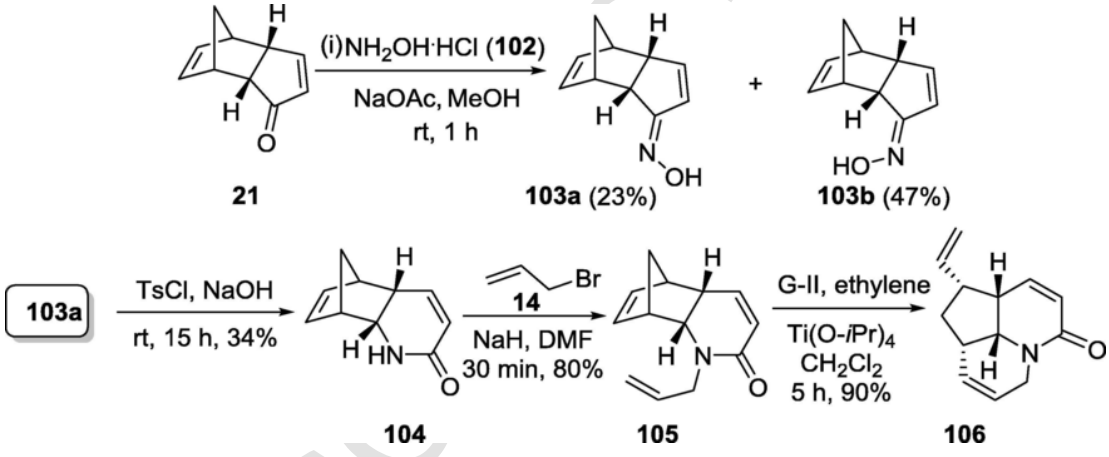
To extend the scope of RRM process, the propargyl derivative **126** was prepared. To this end, Indole derivative **125** was subjected to *N*-alkylation with propargyl bromide (**31**) to provide enyne building block **126** (69%). Then, enyne building block **126** was exposed to G-I catalyst under ethylene to deliver a mixture of the ERRM product **127** (69%) and the ROM product **128** (22%). Interestingly, 1,3-diene **127** (69%) was obtained *via* EM of ROM product **128** with the aid of G-II catalyst under ethylene atmosphere. Next, the DA reaction of the diene **127** was realized with TCE **129** in refluxing toluene to produce the DA adduct **130** (52%) (Scheme 23). Interestingly, the *N*-heterocycles **123**, **127** and **130** bear the tricyclic core of the alkaloids



Scheme 16. Various metathetic processes to assemble tetracycle **97**.



Scheme 17. Synthesis of tetraquinane **100** *via* a sequential ROM and RCM strategy.



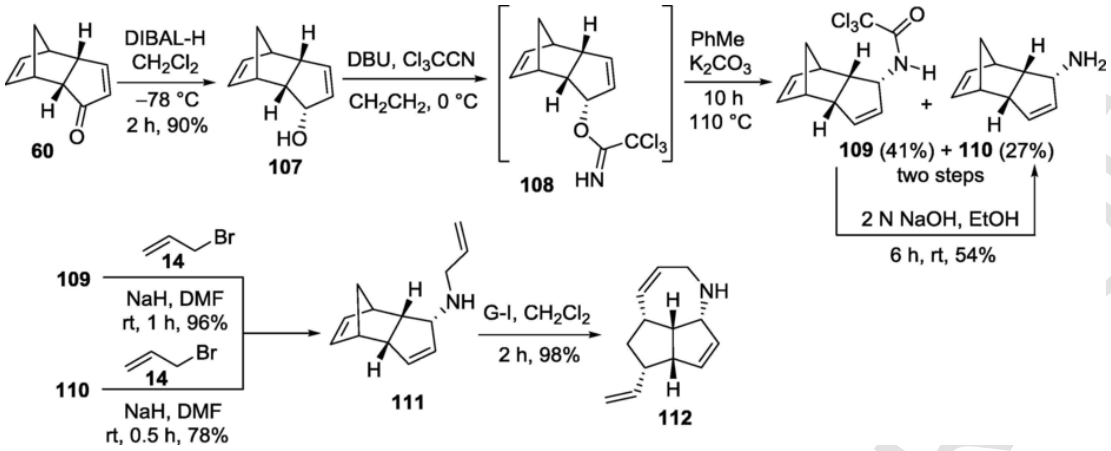
Scheme 18. Synthesis of fused tricyclic compound**106** *via* RRM protocol.

epimeloscine (**131**), deoxycalyciphylline B (**132**), and daphlongamine H (**133**) (Fig. 3).

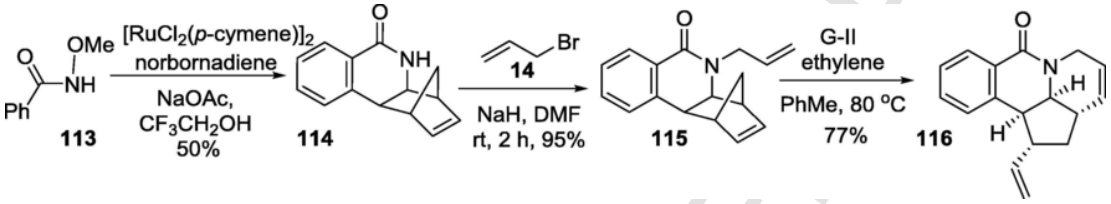
In another event, Fischer indolization was used to construct the azatriquinane derivative **138** starting with the dicyclopentadienone **60** [16]. For this purpose, reduction of the *endo*enone **60** with Zn in AcOH/EtOH produced the saturated ketone **134** (90%), which was subjected to Fischer indolization (FI) with phenylhydrazine (**135**) in the presence of L-(+)-TA/DMU gave the indole derivative **136** (79%). Subsequently, the *N*-allylation of the compound **136** with allyl bromide (**14**) produced the allyl derivative **137**. Finally, *N*-allyl indole **137** was exposed to G-I catalyst to produce the rearranged pentacyclic system **138** (97%) (Scheme 24).

Similarly, a simple route to assemble indole containing pentacyclic system**142** starting with enone isomer **67** also been demonstrated [25]. To this end, *exo*-enone **67** on reduction with Zn in AcOH and ethanol mixture gave the tricyclic keto derivative **139**. Next, compound **139** was subjected to Fischer indolization (FI) with phenylhydrazine (**135**) in the presence of L-(+)-TA/DMU to deliver the indole derivative **140**.

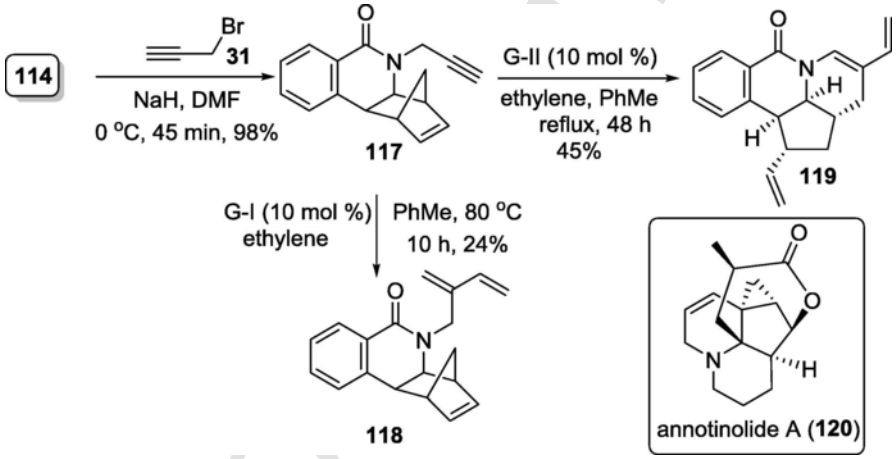
Subsequently, alkylation of indole nitrogen with various alkenyl bromides gave the respective *N*-alkenyl derivatives **141a–d**. To study the RRM of *N*-alkenyl derivatives such as **142a–d**, initially, treatment of the *exo* compound **141a** with G-I catalyst in the presence of ethylene did not give the rearranged product **142a**; however, ROM product **143a** (81%) was observed. Alternatively, exposure of *N*-butenyl de-



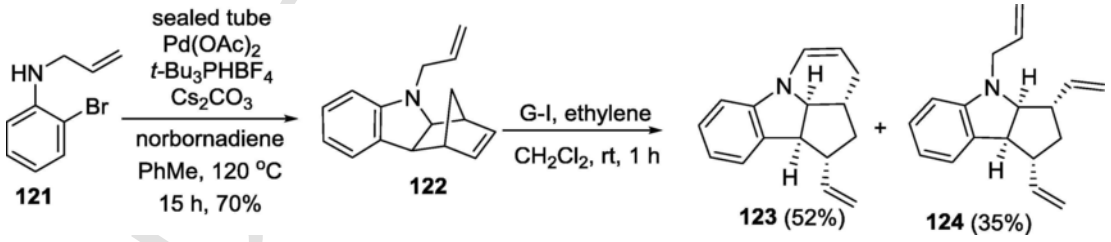
Scheme 19. Synthesis of aza tricyclic system **112** *via* RRM as a key step.



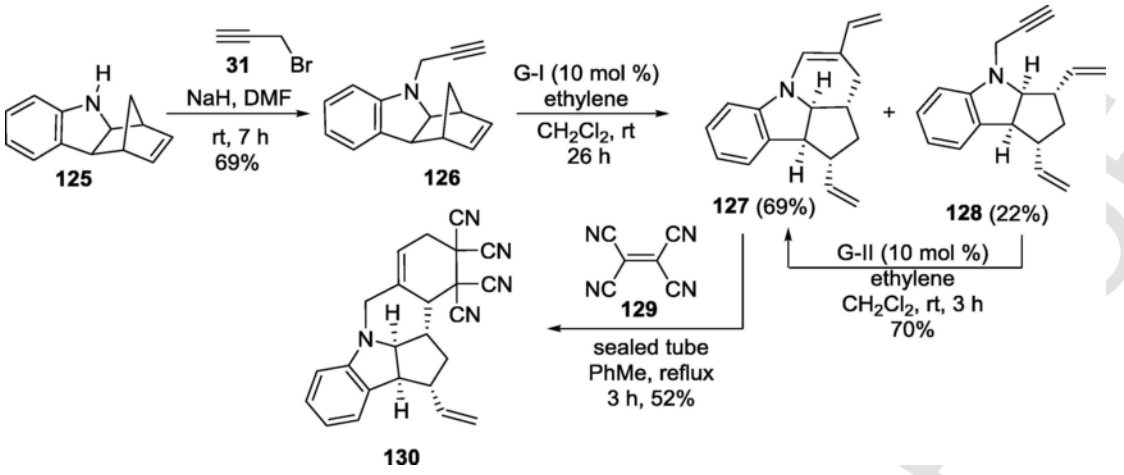
Scheme 20. RRM approach to synthesis of tetracyclic amide **116**.



Scheme 21. CEM and ERRM approach to polycyclic amides.



Scheme 22. Synthesis of tetracyclic indole **123**.



Scheme 23. ERRM-DA approach to pentacyclic scaffold **130**.

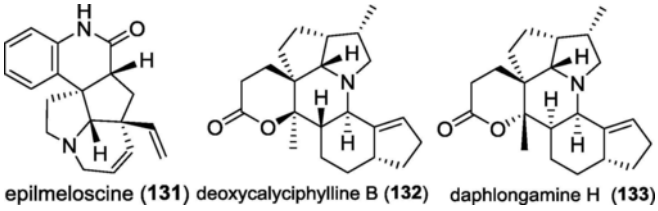


Fig. 3. Melodin*us* alkaloids (**131**–**133**).

rivative **141b** to G-I catalyst gave a mixture of RRM product **142b** (32%) and the ROM product **143b** (62%). When, the alkenyl chain length was increased as in **141c**, RRM product **142c** was obtained exclusively in 90% yield (Scheme 25).

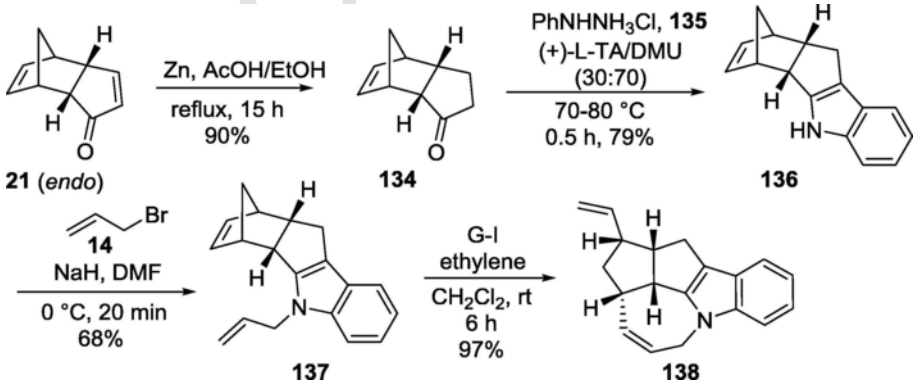
Synthesis of oxacycles *via* RRM

A simple and an atom-economic process involving RRM for the construction of fused and spirooxacyclic compounds**147** and **149** starting with norbornene diol **144** have been established [26]. RRM precursors **146** and **148** were derived from **144** by Swern oxidation, Grignard reaction followed by allylation and propargylation sequences. Next, the triallyl compound **146** was subjected to RRM in the presence of G-I catalyst to afford the spirooxacycle **147** (75%). Similarly, on exposure of dipropargyl derivative **148** to G-I catalyst produced the rearranged spiro system **149** (65%) (Scheme 26).

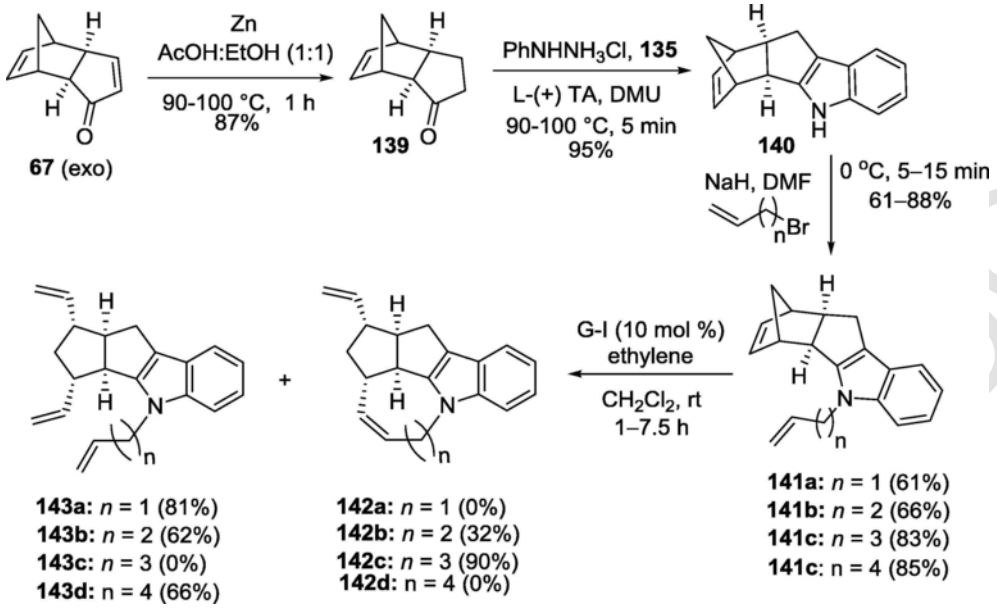
To study RRM sequence in strained systems, we conceived a unique molecule, containing both cyclobutene and norbornene rings such as **151**. The RRM of such system can generate intricate molecules, which are otherwise difficult to synthesize by conventional approaches. To this end, bicyclic diol **144** was treated with 3,4-dichlorocyclobut-1-ene (**150**) under basic reaction conditions a mixture of coupling products **151** and **152** were produced in 1:1 ratio. Further, exposure of the olefin **152** to HG-II catalyst gave the RRM product **153** (59%). However, the treatment of **151** with G-II catalyst produced only ring opening product in 45% yield. Alternatively, the diol **144** was *O*-diallylated by using allyl bromide (**14**) to generate the diallyl derivative **154** (92%). Finally, the diallyl derivative **154** underwent RRM sequence to generate a tricyclic compound **155** (90%) (Scheme 27) [7a].

The synthesis of oxatricycle **158** was accomplished *via* RRM of *O*-allyl derivative **157** using the G-I catalyst in the presence of ethylene. In addition, the *O*-propargyl building block **159** was obtained by using *O*-propargylation of endo alcohol **107**. Later, the propargyl derivative **159** was exposed to G-I catalyst under similar reaction conditions to give the diene **160**. Subsequently, treatment of the diene **160** with dimethyl acetylenedicarboxylate (DMAD) in refluxing toluene afforded the tetracyclic DA adduct **161** (Scheme 28) [16].

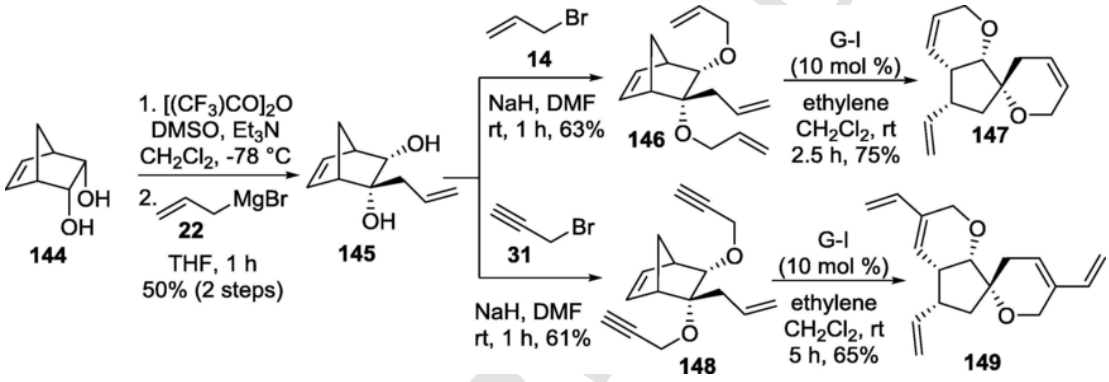
A simple route to oxygen-containing tricyclic amide **165** by employing the *O*-allylation followed by RRM sequence was also conceived. However, the RCM of compound **164** was not realized to produce the tricyclic system **165** (Scheme 29) [18].



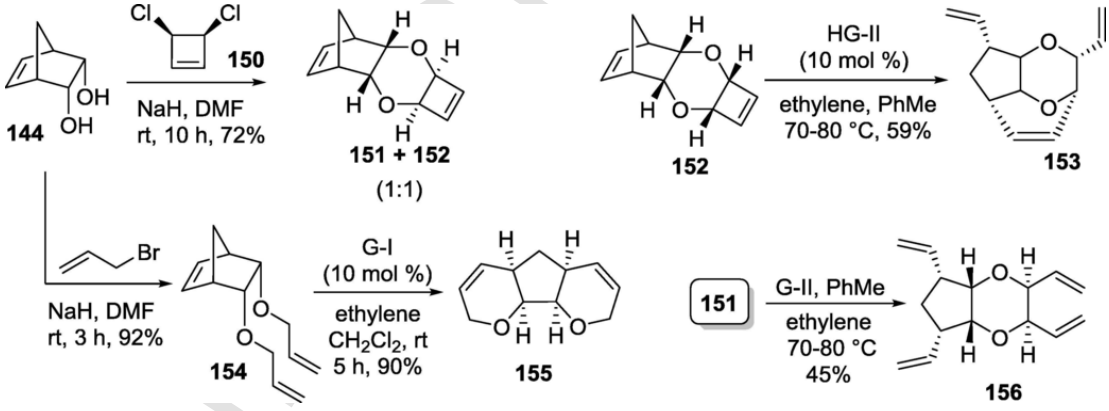
Scheme 24. Synthesis of azatriquinane derivative **138** through a RRM protocol.



Scheme 25. Synthesis of indole derivatives *via* RRM protocol.

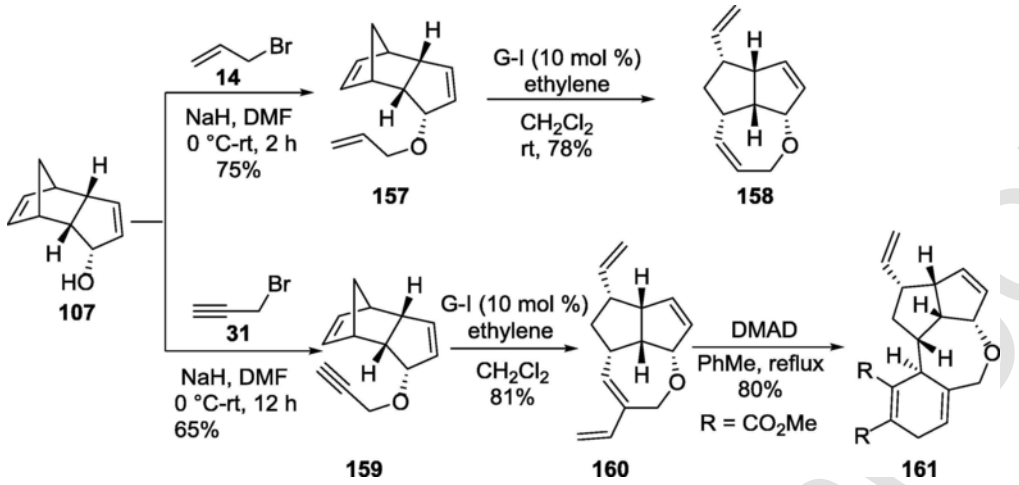


Scheme 26. Synthesis of spirocycles *via* a RRM protocol.

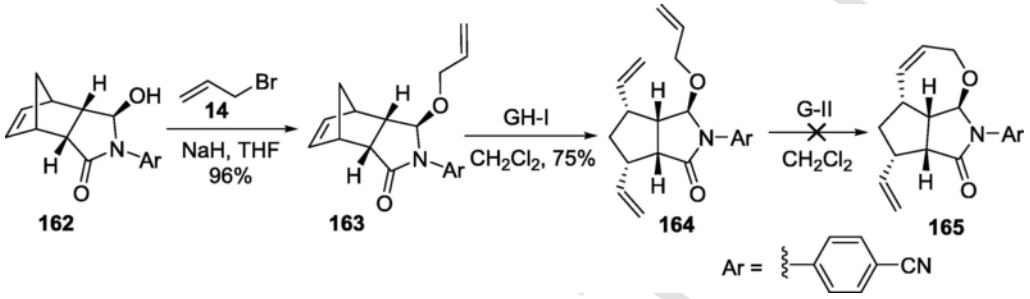


Scheme 27. Synthesis of tricyclic compounds **153** and **155** *via* RRM protocol.

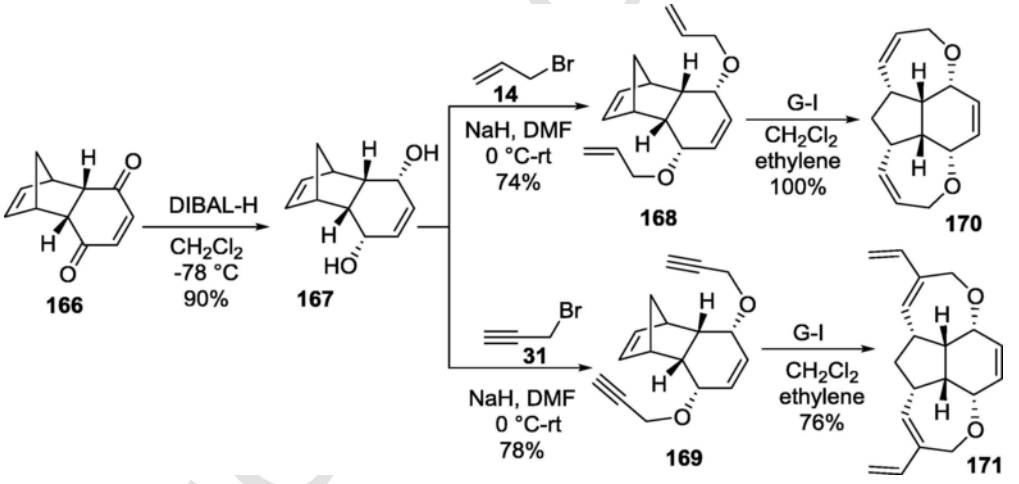
Interestingly, we used [27] norbornene derivative **166** to construct the tetracyclic oxa derivatives involving RRM. The required RRM precursors such as **168** and **169** were assembled by employing allylation and propargylation sequence respectively starting with a readily accessible diol **167** in a two-step sequence. To this end, the DA adduct **166** was obtained from cyclopentadiene (**35**) and 1,4-benzoquinone, which was further converted into diol **167** by using DIBAL-H reduction. Later, the resulting allyl and propargyl com-



Scheme 28. Construction of tricyclic **158** and tetracyclic **161** systems using RRM.



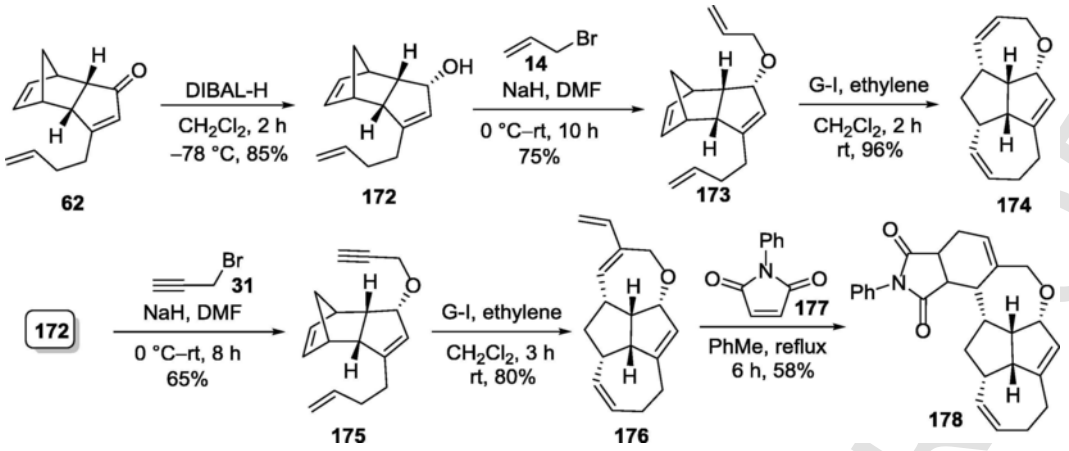
Scheme 29. Attempted synthesis of tricyclic amide derivative**165** *via* RRM.



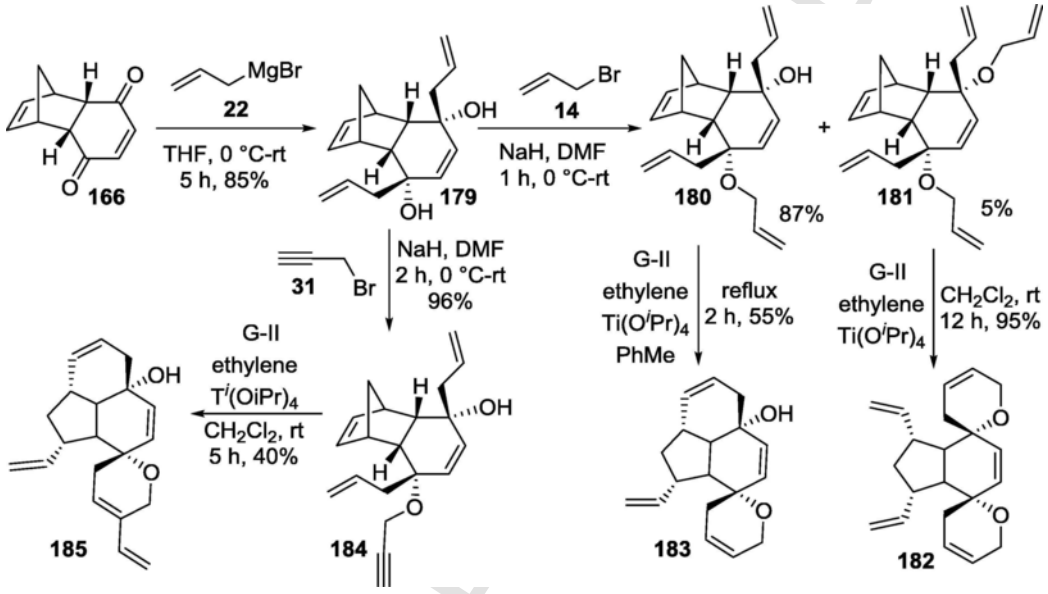
Scheme 30. Synthesis of tetracyclic systems (**170** and **171**) by using RRM.

pounds **168** and **169** were subjected to RRM and enyne ring-rearrangement metathesis (ERRM) processes with the aid of G-I catalyst under ethylene to deliver the tetracyclic systems **170** (100%) and **171** (76%), respectively (Scheme 30). This strategy to generate higher analogues starting with 1,4-naphthoquinone DA adduct was also extended.

Similarly, we have demonstrated RRM strategy to synthesize oxa-bowls **174** and **178**. In this regard, the RRM strategy starting with bicyclic building block **172** was studied to assemble oxabowls. Reduction of tricyclic enone **62** was accomplished with DIBAL-H to give the allyl alcohol **172** (85%). Then, the alcohol **172** was subjected to *O*-allylation with allyl bromide (**14**) in the presence of NaH to generate the *O*-allyl derivative **173**(75%). Exposure of *O*-allyl compound**173**to G-I catalyst under ethylene atmosphere furnished the rearranged product **174** (96%). Similarly, propargylation of alcohol **172** with propargyl bromide (**31**) produced the enyne building block **175** (65%). Next, ERRM of compound **175** with G-I catalyst under ethylene provided the rearranged product **176** (80%). Finally, the diene



Scheme 31. Synthesis of oxa-bowls through a RRM process.



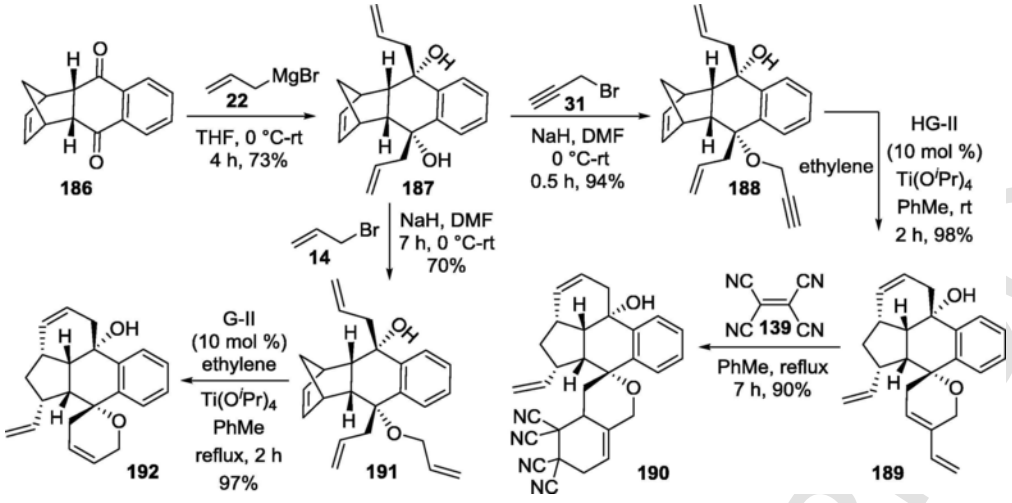
Scheme 32. Synthesis of oxa-spirocycles *via* RRM.

176 was treated with *N*-phenylmaleimide (**177**) to produce the hexacyclic DA adduct **178** (58%) (Scheme 31).

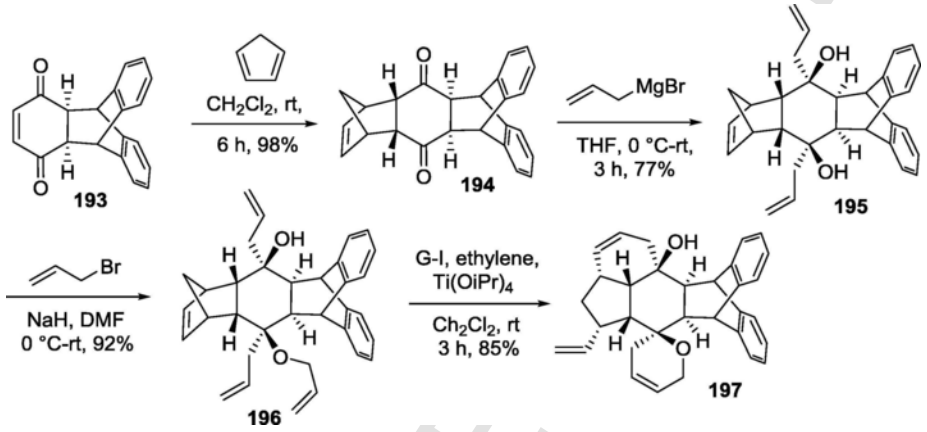
Later, RRM strategy was also extended to assemble complex spirocycles such as **182**, **183**, and **185** starting with norbornene derivative **166** [28]. In this regard, the DA adduct **166** on Grignard addition with allylmagnesium bromide delivered the diallyl product **179** (85%). Subsequent allylation of the diol **179** with allyl bromide (**14**) gave a mixture of a triallyl compound **180** (87%) as a major product and tetraallyl compound **182** (5%) as a minor product. Next, the triallyl and tetraallyl derivatives were separately subjected to RRM with G-II catalyst to generate the corresponding rearranged products **183** (55%) and **182** (95%) respectively. The diol **179** was converted into *O*-propargyl derivative **184** (96%) using propargyl bromide (**31**). The enyne building block **184** was exposed to G-II catalyst, which led to the formation of the spirodiene **185** (40%) (Scheme 32).

Similarly, we have demonstrated the synthesis of oxacycles such as **189** and **192** starting with norbornene derivative **186** containing naphthoquinone moiety by RRM strategy. To this end, the DA adduct **186** was treated with allylmagnesium bromide (**22**) followed by *O*-allylation to afford the *O*-allyl building block **191**. Next, RRM of compound **191** was attempted with G-II catalyst (10 mol%) in the presence $Ti(O^iPr)_4$ to deliver the rearranged product **192** (97%). Along similar lines, RRM/EM cascade also been studied [29]. To this end, diol **187** was subjected to *O*-propargylation to give the enyne building block **188**, which on treatment with HG-II catalyst (10 mol %) produced the expected diene **189**. Finally, the resulting diene **189** was reacted with TCE **129** to generate the corresponding [4+2] cycloaddition product **190** (90%, Scheme 33).

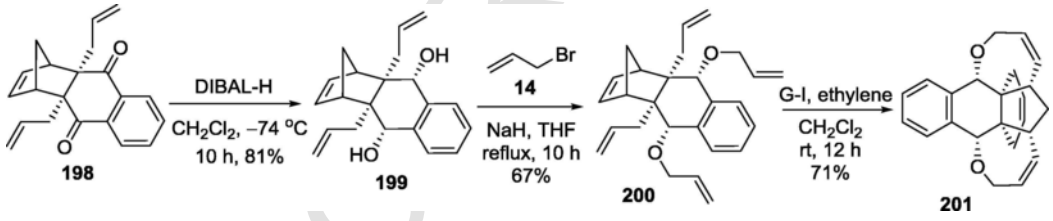
The above strategy to construct the polycyclic compound **197** containing bicyclo[2.2.2] unit was also extended. To this end, the known DA adduct **193** [30] was subjected to a [4+2] cycloaddition with cyclopentadiene to produce DA adduct **194** (98%). The resulting DA adduct **194** was treated with allylmagnesium bromide to deliver the diol **195** (77%). Next, the diol **195** was treated with an excess amount of allyl bromide (**14**) in the presence of NaH to furnish the mono-*O*-allyl derivative **196** (92%). Exposure of the triallyl compound **196** to G-I catalyst under ethylene atmosphere gave the RRM product **197** (Scheme 34). It is interesting to note that the stereochemistry of hydroxyl group in **195** is opposite to that of hydroxyl present in **187** due to presence of bulky bicyclo[2.2.2] unit.



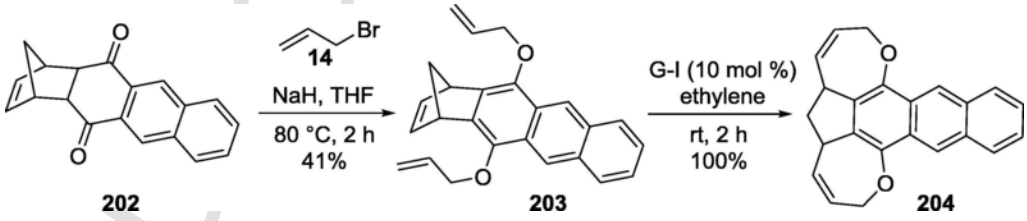
Scheme 33. Synthesis of oxa-spirocycles *via* a RRM strategy.



Scheme 34. Synthesis of polycycle **197** through a RRM strategy.

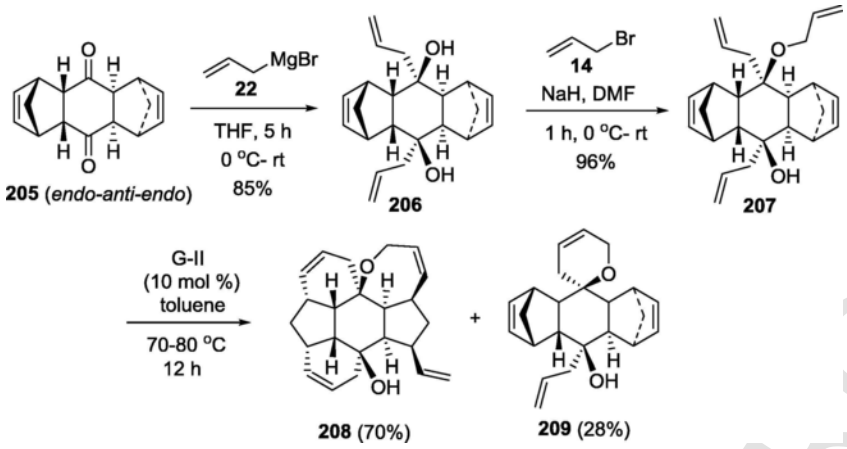


Scheme 35. Synthesis of oxabowl-propellane hybrid by using RRM sequence.

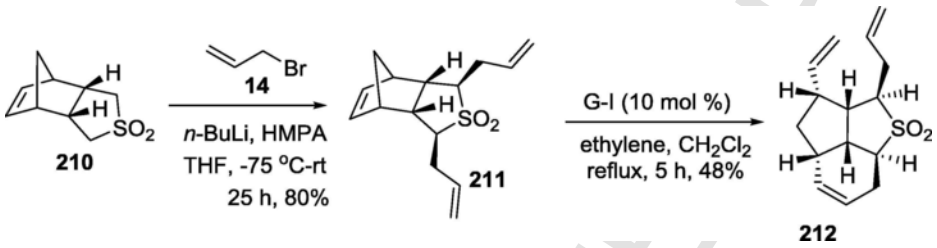


Scheme 36. Synthesis of oxacycle **204** *via* RRM.

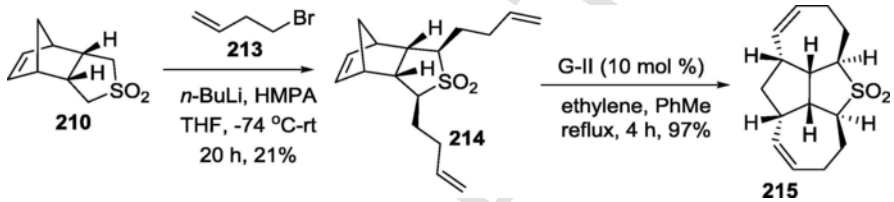
In another event, we have established a useful protocol to design the hexacyclic hybrid molecule **201**containing propellane system and oxabowl involving RRM as a key step [31]. The tetraallyl derivative **200** was prepared from a readily accessible diallyl compound **198** by employing DIBAL-H reduction followed by *O*-allylation. Then, the tetraallyl derivative **200** was subjected to RRM with G-I catalyst to



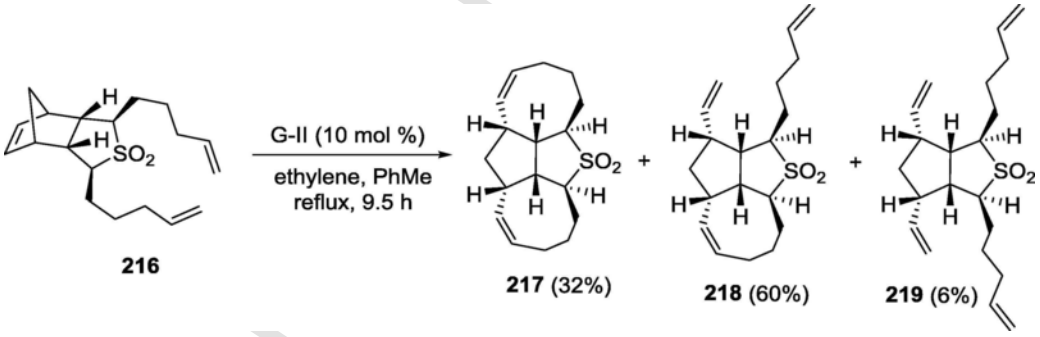
Scheme 37. Synthesis of hexacycle through a RRM strategy.



Scheme 38. Synthesis of sulphone-containing tricyclic system *via* a RRM protocol.



Scheme 39. Synthesis of tetracyclic compound through a RRM strategy.

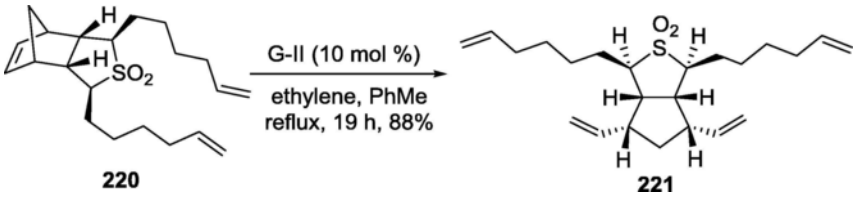


Scheme 40. RRM of bicyclic sulphone derivative **217**.

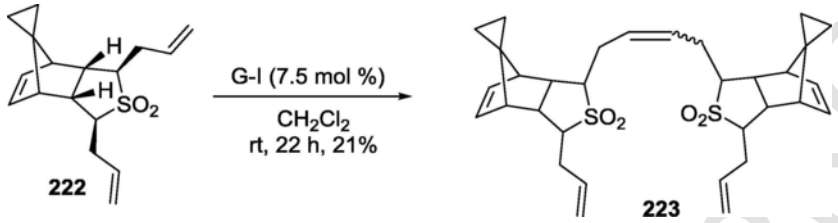
produce the propellane derivative **201** (71%) (Scheme 35). Moreover, this strategy to generate higher propellane analogues was also extended.

Along similar lines, the anthraquinone DA adduct **202** was subjected to diallylation and aromatization to deliver the *O*-allyl derivative **203**. Later, the diallyl compound **203** was treated with G-II catalyst to yield the RRM product **204** in quantitative yield (Scheme 36).

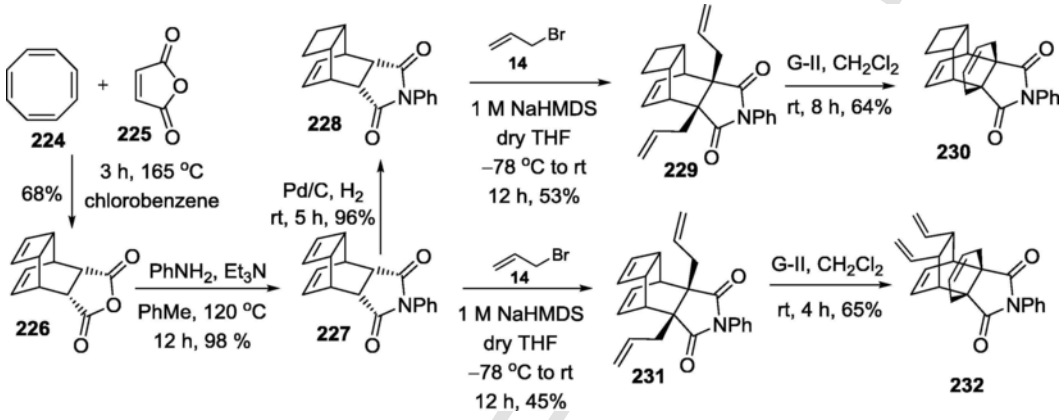
We have also demonstrated a RRM strategy to construct the fused polycycles starting with bis-norbornene derivative **205** [32]. For this purpose, the known bis-adduct **205** [33] was treated with allylmagnesium bromide to generate the diol **206** (85%). Subsequently, treatment of the diol **206** with an excess amount of allyl bromide (**14**) gave only the mono-*O*-allyl compound **207** (96%). Next, the triallyl derivative **207** was reacted with G-II catalyst to accomplish RRM se-



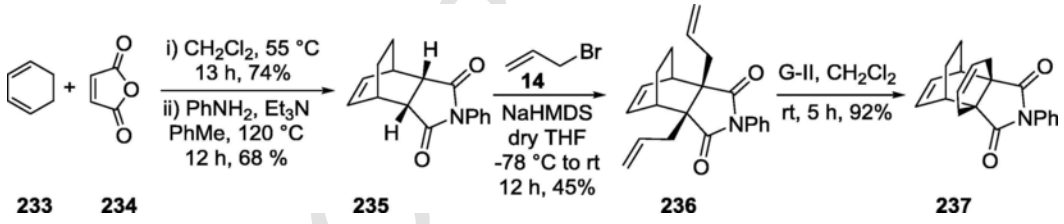
Scheme 41. ROM of bicyclic sulphone derivative **221**.



Scheme 42. Dimerization of sulphone derivative **222**.



Scheme 43. Synthesis of propellanes **230** and **232** through a RCM protocol.



Scheme 44. Attempt of RRM of bicyclic compound **236**.

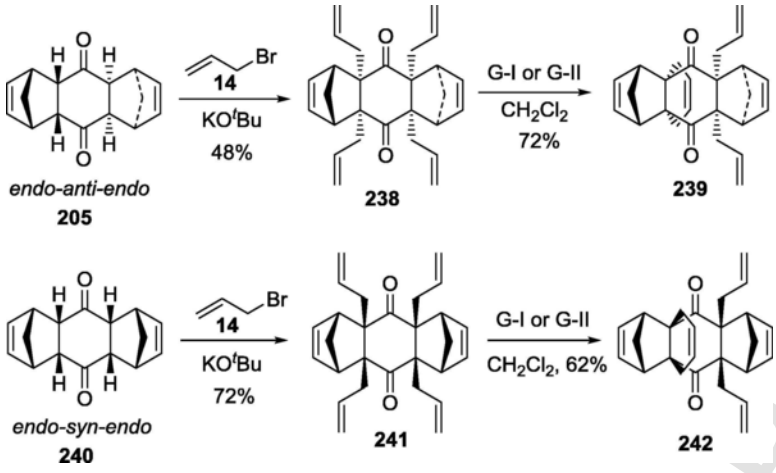
quence, which led to the formation of a mixture of the rearranged product **208** (70%) and the RCM product **209** (28%). Gratifyingly, an atom-economic approach have been shown, which can deliver six fused rings-containing 10 stereocenters through a RRM process involving a five-step synthetic sequence (Scheme 37).

Synthesis of sulphur containing polycycles *via* RRM

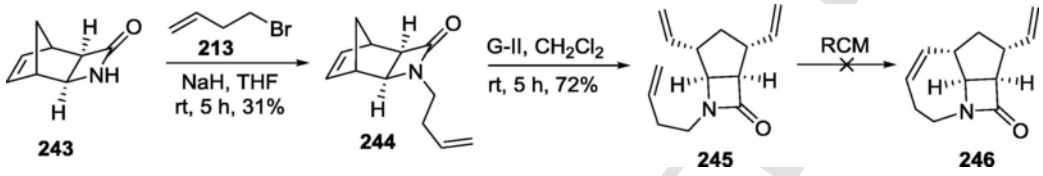
In this section, we describe application of RRM approach to assemble several polycycles containing sulfone moiety [34]. To this end, the sulphone derivative **210** was allylated with allyl bromide (**14**) under basic conditions to deliver the diallylsulphone **211** (80%), which on exposure with G-I catalyst completed the RRM at one side to give the rearranged product **212** (48%). Due to strain involved in the formation of *trans* C—C bond in six membered ring, only one side ring closure product was observed (Scheme 38).

Similarly, the sulfone **210** was subjected to alkenylation using 4-bromo-1-butene (**213**) under similar reaction conditions to furnish the required dialkenylated compound **214** (21%) along with monoalkenylated product. Later, the exposure of dialkenylated substrate **214** to G-II catalyst led to formation of the tetracyclic compound **215** in 97% yield. Interestingly, the butenyl chain in the sulphone **214** assisted the ring-closure, which led to the formation of the tetracyclic system **215** exclusively (Scheme 39).

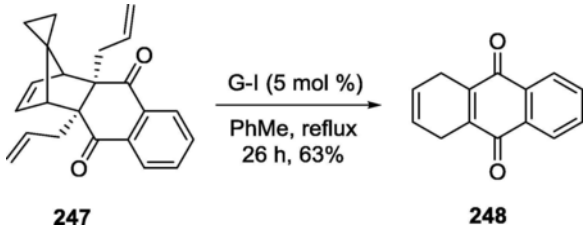
To expand this strategy, the dipentenyl sulphone derivative **216** was exposed to G-II catalyst under ethylene, a mixture of products **217** (32%), **218** (60%), and **219** (6%) were produced (Scheme 40).



Scheme 45. Synthesis of propellanes **239** and **242** *via* RCM protocol.



Scheme 46. Attempted RRM of *N*-alkenylated lactam **244**.



Scheme 47. Attempted RRM of compound **247**.

Surprisingly, when RRM was attempted with **220**, the rearranged product was not observed, rather ring-opening metathesis product, **221** was realized (Scheme 41). Later, dimerization of the compound **222** was observed to give the compound **223**. The steric hindrance imposed by cyclopropane ring may be responsible for the unreactive nature of norborene system **222** (Scheme 42) [35].

Miscellaneous reactions involving metathesis

In another instance, we studied the RRM process in hybrid systems such as **229** and **231** containing both cyclobutene and bicyclo[2.2.2]octane units. To this end, the required precursors **229** and **231** were synthesized starting with easily accessible cyclooctatetraene (**224**) and maleic anhydride (**225**) involving a short synthetic sequence. Next, exposure of diallyl compound **229** to G-II catalyst gave only RCM product **230** (64%). Similarly, treatment of the olefinic system**231** with G-II catalyst underwent a sequential RCM and ROM, which led to formation of the propellane derivative **232** (65%) [36]. It is noted that, RRM did not happen in strained ring systems such as **229** and **231**. Surprisingly, opening of bicyclo[2.2.2]octene system was not observed to effect ROM process in both of these systems. However, cyclobutene ring was opened in the strained system **231** to produce the divinyl compound **232**, and these vinyl groups did not participate further in ring-closure process with the adjacent allyl moieties (Scheme 43).

Along similar lines, we have designed less hindered RRM building block **236**, which was further treated with G-II catalyst to realize RRM product, however; only RCM product **237**was observed (Scheme 44).

We have also studied the RRM sequence with tetraallyl systems such as **238** and **241**. To this end, the ring-opening of bicyclo[2.2.1]heptene systems in **238** and **241** did not observe [37]. The required RRM precursors **238** and **241** were prepared from readily accessible *endo-anti-endo***205** and *endo-syn-endo***240** bis-adducts *via* allylation sequence using allyl bromide (**14**) in the presence of potassium *tert*-butoxide (KO^{t}Bu). Exposure of the tetraallyl derivatives **238** and **241** to either G-I or G-II catalysts effected only monocyclization to give the respective propellane derivatives **239** (72%) and **242** (62%). Nevertheless, ROM step was not observed in both the cases. Interestingly, Philips and co-workers reported the RRM of bicyclo[2.2.2]octene system, where, the ROM was viable [38]. In Philips system system the initiation may start outside the bicyclic system.

Further, the stereochemistry of propellane derivative **242** was confirmed by single crystal X-ray diffraction data (Scheme 45).

In another instance, RRM of compound **244** with the aid of G-II catalyst also been attempted; however, we did not observe the rearranged product **246**. Rather, ROM product was obtained [39] (Scheme 46).

Along similar lines, the RRM of compound **247** was not realized. Interestingly, when treatment of the compound **247** with G-I catalyst under refluxing toluene, one-pot RCM/*retro*-DA reaction was occurred to generate the anthraquinone derivative **248** [40] (Scheme 47)

Conclusions

Here different synthetic strategies are reported for the construction of polycyclic and heterocyclic scaffolds by employing the RRM as a key step. It is found that in various strained ring-systems, RRM did not occur. In addition, unique systems to understand the role of stereochemical disposition of olefinic moieties in RRM sequence have been designed. Various name reactions such as Grignard addition, Overman rearrangement, Fischer indolization, Beckmann rearrangement and DA reaction to design a variety of intricate molecules have been employed. We hope that, the knowledge gained during these studies can be useful to design complex targets. RRM strategy will provide a short synthetic sequence to complex targets and thereby enhance synthetic economy.

Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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