Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 5597

www.rsc.org/obc

PERSPECTIVE

A synergistic approach to polycyclics *via* a strategic utilization of Claisen rearrangement and olefin metathesis

Sambasivarao Kotha,* Nimita G. Krishna, Somnath Halder† and Shilpi Misra

Received 16th March 2011, Accepted 10th May 2011
DOI: 10.1039/c1ob05413a

Olefin metathesis promoted by a well-defined metal carbene complex has evolved into an efficient method for the construction of a broad range of carbocyclic and heterocyclic rings of varying size. The synthetic potential of the olefin metathesis has been further increased by combining various other C–C bond forming processes either in tandem or in sequence. Herein, application of Claisen rearrangement and olefin metathesis to prepare various intricate and/or biologically important targets has been described.

1. Introduction

Olefin metathesis, a useful chemical transformation, has changed the landscape of organic synthesis for C–C bond formation. Combining metathesis with other C–C bond forming strategies is a powerful way to construct polycyclic compounds. This review focuses on the new synthetic strategies, based on the application of different Claisen rearrangement (CR) processes and metathesis protocols to design diverse synthetic targets; some selected examples from individual groups have been chosen to describe various themes. Due to space limitation, all the known examples in this aspect could not be included here. Before describing the main theme, a brief introduction to CR and olefin metathesis has been included as background information, so that the reader can fully appreciate the diversity of synthons available for further synthetic manipulation.

Department of Chemistry, Indian Institute of Technology-Bombay, Powai, Mumbai, 400 076, India. E-mail: srk@chem.iitb.ac.in; Fax: +91-22-2572 3480

† **Current Address**: Medicinal Chemistry Division, Piramal Life Sciences Ltd. 1A, Nirlon Complex, Goregaon East, Mumbai 400 063, India.

1.1 Claisen rearrangement

The CR was first reported by the German Chemist Ludwig Claisen in 1912.[1a] CR and related [3,3]-sigmatropic rearrangements

Sambasivarao Kotha

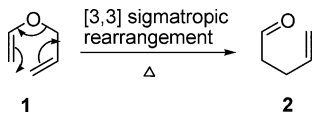
Sambasivarao Kotha was born in 1957 in Amarthalur, AP, India. He received his Ph.D. degree under the supervision of Professor G. Mehta at the University of Hyderabad in 1985. After spending some time in the UK and USA, he joined IIT-Bombay in 1994 as an Assistant Professor and was promoted to Professor in 2001. He is a recipient of the B. M. Birla prize in Chemical Sciences (1996), the Professor N. S. Narasimhan endowment award (2000), CRSI bronze medal (2004) and Bhagyatara National Award (2006). He is a member of various editorial boards (Indian Journal of Chemistry, Section B, J. Chem. Sciences, J. Amino Acids and Catalysis Journal) and also elected as a Fellow of the National Academy of Sciences and Indian Academy of Science. Recently, he received J. C. Bose Fellowship from DST and Y. T. Thathachari award from Mysore. His current research interests include development of new synthetic methods.

Nimita G. Krishna

Nimita G. Krishna was born in New Delhi, India. She graduated in Chemistry from Fergusson College, University of Pune, Maharashtra and obtained her Masters degree in Organic Chemistry from University of Pune in 2004. Presently, she is pursuing her doctoral studies in the Department of Chemistry, IIT-Bombay, Mumbai under the guidance of Professor S. Kotha. Her research interests are related to the development of new synthetic methods and medicinal chemistry.

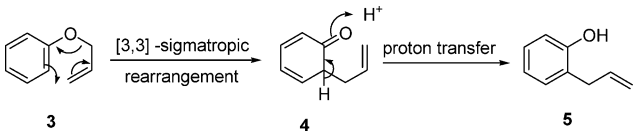
generate molecular complexity from simple starting materials. Since its discovery, CR and its variants delivered synthetically useful and densely functionalized molecules. Moreover, CR allows the conversion of an easily accessible carbon–hetero atom bond into a new C–C bond, making this rearrangement a versatile method for the construction of complex molecules. The CR is an atom economic process and it can be carried out under mild conditions in a chemo-, regio- and/or stereoselective manner to furnish useful polyfunctional molecules.[68] Recently, several reports have been published where it can be performed under microwave irradiation conditions.[1b–f] Several variations of CR are reported, and some of them are described here.

1.1a Aliphatic Claisen rearrangement. Aliphatic CR involves the thermal [3,3]-sigmatropic rearrangement of vinyl allyl ethers to furnish a γ,δ-unsaturated carbonyl compound (Scheme 1). CR is one of the most used [3,3]-sigmatropic rearrangements due to the ease of generation of the intermediate allyl or vinyl system. Moreover, the product formation is smooth and irreversible, and the choice of carbonyl compounds depends on the nature of the allyl vinyl ether moiety. A large number of reviews are available in the literature for the aliphatic CR.[2]



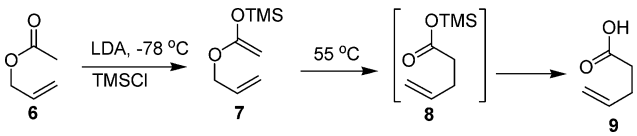
Scheme 1

1.1b Aromatic Claisen rearrangement. Aromatic CR involves thermal [3,3]-sigmatropic rearrangement of allyl phenyl ether, the allyl group shifts to the ortho-position on the aromatic nucleus (where 'ortho' indicates the position of the allyl group relative to the oxygen atom after rearrangement) (Scheme 2). This reaction is useful for the preparation of ortho-substituted phenol derivatives.[3]



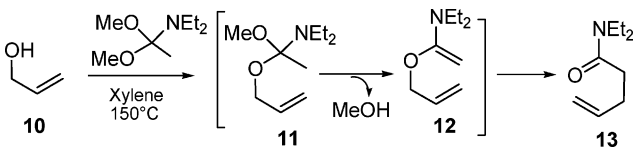
Scheme 2

1.1c Ireland–Claisen rearrangement. In this CR, the allyl ester of a carboxylic acid is converted to its silyl-enolate (silyl ketene acetal) **7** which upon heating (below 100 °C) undergoes CR to deliver the chain extended carboxylic acid **9** (Scheme 3). The main advantage of this CR is that the reaction takes place at lower temperature.[4]



Scheme 3

1.1d Eschenmoser–Claisen rearrangement. Another significant advancement of CR was reported during 1964 by Eschenmoser and co-workers. They found that the condensation of an allyl alcohol with amide acetals results in the formation of *N*,*O*-ketene acetals, which subsequently undergo rearrangement to provide an amide Claisen product (Scheme 4).[5]



Scheme 4

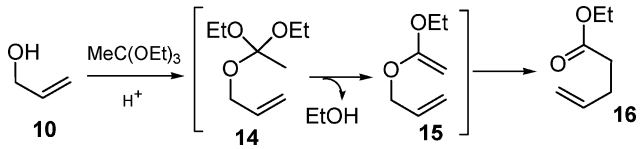
1.1e Johnson–Claisen rearrangement. This type of CR involves the reaction of an allylic alcohol with trimethyl orthoacetate to deliver a γ,δ-unsaturated ester (Scheme 5).[6]

Somnath Halder

Somnath Halder was born in Bankura, West Bengal. He obtained his B.Sc. degree in Chemistry with honours from Bankura Christian College, Burdwan University, West Bengal and M.Sc. degree in Organic Chemistry from Burdwan University. He obtained his Ph.D. degree under the guidance of Professor S. Kotha from the Department of Chemistry, Indian Institute of Technology-Bombay. He worked with Professor Jean-Luc Décout as a Postdoctoral fellow in the Département de Pharmacochimie Moléculaire (DPM) at Université Joseph Fourier-Grenoble, France. Currently he is working as a Senior Scientist in medicinal chemistry division, Piramal Life Sciences Ltd. Mumbai. His research interests are related to new synthetic methods and medicinal chemistry.

Shilpi Misra

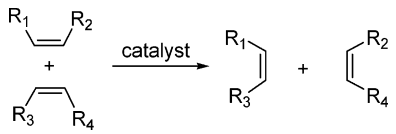
Shilpi Misra was born in Hardoi, Uttar Pradesh (India). She obtained her B.Sc. degree from Kanpur University, Uttar Pradesh and M.Sc. degree from Dayal Bagh Educational Institute, Agra. She is a recipient of a CSIR research fellowship. She has been pursuing her Ph.D. degree under the guidance of Professor S. Kotha from the Department of Chemistry, IIT-Bombay since 2005.



Scheme 5

1.2 Olefin metathesis

Olefin metathesis involves the redistribution of the olefinic bonds in the presence of metal carbene complexes. Among various types of metathesis protocols, ring-closing metathesis (RCM) has emerged as one of the most powerful tools for the construction of C–C bonds (Scheme 6).[7]



Scheme 6

Olefin metathesis involves both the cleavage as well as the formation of C–C double bonds under neutral reaction conditions. A variety of homogeneous and heterogeneous catalysts based on transition-metal complexes are known to effect the olefin metathesis reaction and have many varied chemical applications. Advances in catalyst design have contributed to the increased functional group tolerance, which in turn has expanded the scope of the olefin metathesis reaction.

1.2a Cross metathesis (CM). The cross metathesis reaction is a metal carbene catalyzed intermolecular coupling between two different olefins to afford a new alkene. This methodology has not found many applications because of the unwanted alkenes which are formed due to self-metathesis and also the lack of stereocontrol of the newly formed double bond.[7]

1.2b Ring-closing metathesis (RCM). The catalytic RCM reaction has emerged as an effective strategy in organic synthesis. A wide range of olefin metathesis protocols in organic synthesis have been significantly expanded mainly due to the introduction of alkylidene metal complexes **17** and **24** (Fig. 1). Several reports involving modifications of these catalysts are beyond the scope of this review.

Alkoxy imido molybdenum complex **24** is one of the most important catalyst systems developed by Schrock and co-workers. The major advantage of this system is its high reactivity towards a broad range of substrates with many steric or electronic variations. The alkoxy groups present in the [Mo] system can readily be altered to tune its activity. The drawback of this catalyst is its high sensitivity towards air, moisture and impurities present in the solvent.[8]

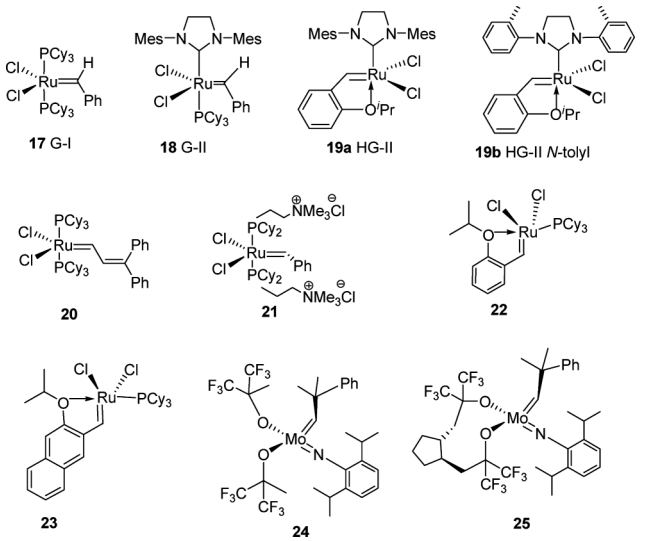


Fig. 1 Commonly used metathesis catalysts.

In the early 1990's, Grubbs and co-workers reported well-defined ruthenium carbene catalysts such as **17** and **20**. The advantages of these catalysts include their easy preparation, reasonable stability towards storage and ease of handling without any special equipment.[9,10]

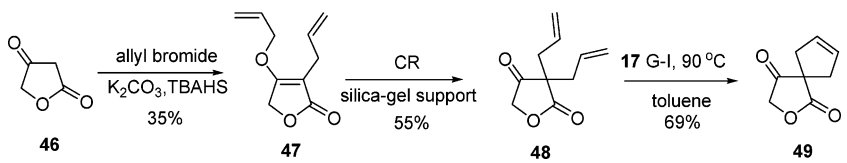
1.3 Biologically active molecules or ring skeletons synthesized by CR and olefin metathesis protocols

The CR–metathesis manifold is a powerful tool for the synthesis of functionalized carbocycles and heterocycles exhibiting biological activity. Various important ring skeleton assemblies using this synthetic protocol (*i.e.*, CR followed by metathesis) are included in Fig. 2. Although one can classify these methodologies by different ways, we decided to categorize them according to the type of CR and metathesis methodology used.

2. Application of simple aliphatic/aromatic CR and RCM to design carbocyclics, heterocyclics and spirocyclics

Tetronic acid and related β-dicarbonyl compounds were dialkenylated to generate diallylated product **47** under phase-transfer catalyst (PTC) conditions. CR of *O*-allylated product **47** gave diallyl tetronic acid **48**. RCM of the diallylated product **48** delivered the corresponding spiro-annulated derivative **49** (Scheme 7) as reported by Kotha and co-workers.[11]

Along similar lines, Schobert and co-workers synthesized 3,3-diallyldihydrofuran-2, 4-dione **51** and 4-*O*-allyl-3-allyltetronate **52** from 3-allyltetronic acid **50** either by Pd(0) catalyzed Tsuji–Trost allylation or by CR conditions according to Scheme 8.[12]



Scheme 7

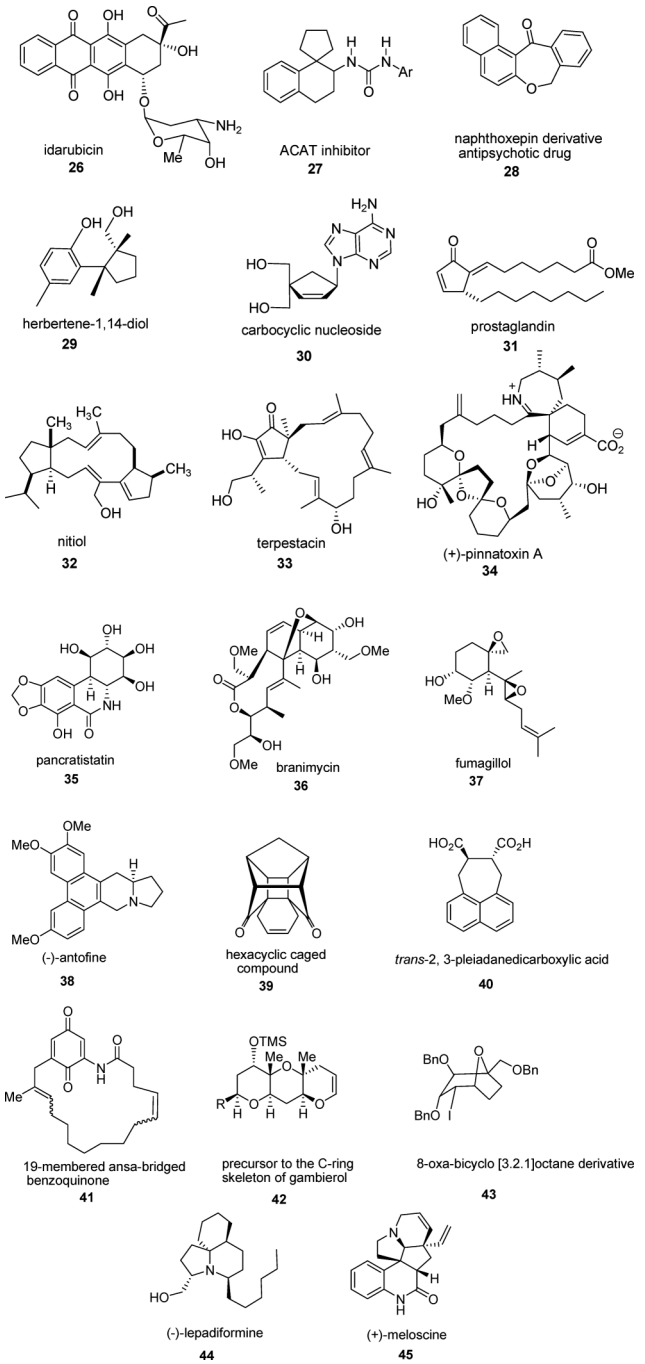
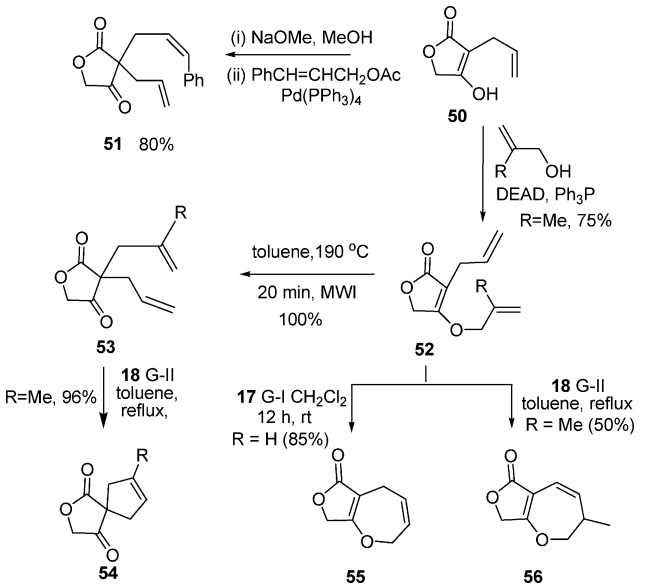


Fig. 2 Skeleton or targets synthesized *via* CR and olefin metathesis.

RCM with bis-allyl tetronates such as **51** and **52** gave the structural motifs of butanolides such as 3,3-spiro-cyclopentenyl, 4,4-spiro-oxacycloalkanyl and 3,4-cycloalkanyl annulation. CR of **52** followed by metathesis of various 3,3-diallylfurandiones **53** with Grubbs second generation catalyst gave 3-spirocyclopentenyldihydrofuran-2,4-dione **54** in good to excellent yields (Scheme 8).

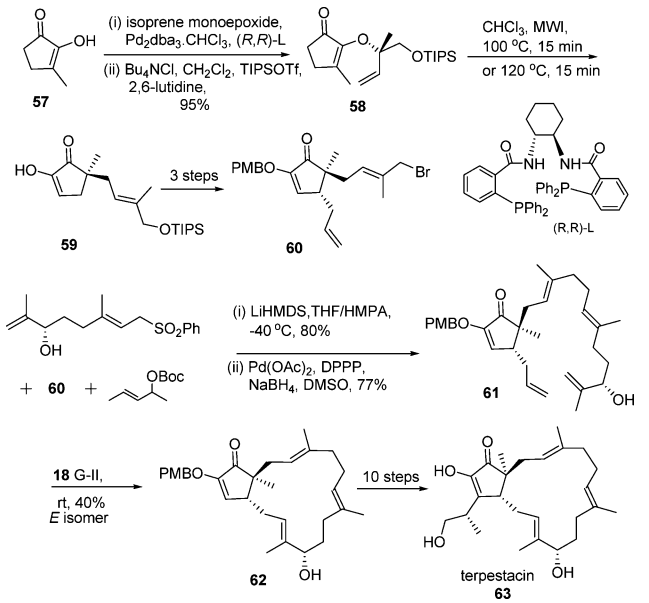
Grubbs second generation catalyst and harsh conditions were required in some cases due to steric hindrance. Thus, RCM of allyl-methallyl derivative **52** (when R = Me) required Grubbs second generation catalyst **18** and forcing conditions resulting



Scheme 8

in concomitant shift of the double bond into a conjugated position delivering the bicyclic compound **56** (Scheme 8). Alkene isomerization, especially with allylic alcohols and allyl ethers, is a common side reaction in metathesis processes initiated with Grubbs catalysts. The choice of catalyst depends on the degree of substitution in the olefin substrate.[12]

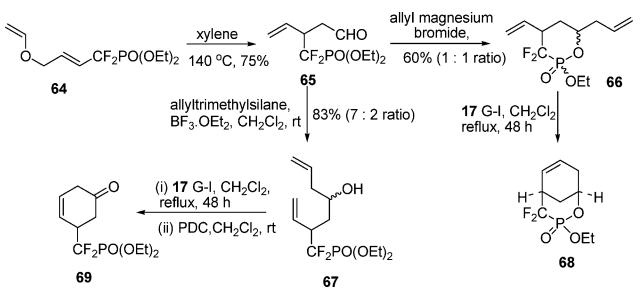
Trost and co-workers have reported a diosphenol-based strategy for the total synthesis of (−)-terpestacin (**63**), a fifteen membered macrocycle, which could be a potential drug for cancer. It possesses an enol form of an α-diketone with three geometrically defined trisubstituted olefins. These features have been incorporated by using a Pd catalyzed Claisen protocol and a highly selective RCM as key steps (Scheme 9).[13]



Scheme 9

Percy and co-workers have reported the application of CR and RCM tactics to design the functionalized cyclohexenone derivative

69. Thus, application of CR and RCM allowed the conversion of a readily available allylic difluorophosphonate **64** to an inositol phosphate analogue (Scheme 10).[14]



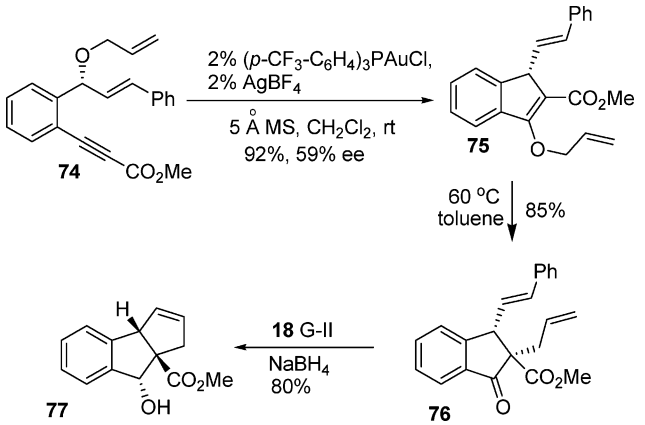
Scheme 10

Profound changes in reactivity and conformation can be achieved by replacing the ring oxygen of a pyranose with a $-CF_2$ group. Percy and co-workers have devised a flexible route towards the synthesis of direct precursors to analogues of pentapyranoses, 6-deoxyhexoses and hexoses from trifluoroethanol, in which a CF_2 centre replaces the pyranose oxygen. They have prepared cyclohexene diols (**72** & **73**) *via* fluorine-assisted [3,3]-sigmatropic rearrangement and subsequent application of RCM (Scheme 11).[15]

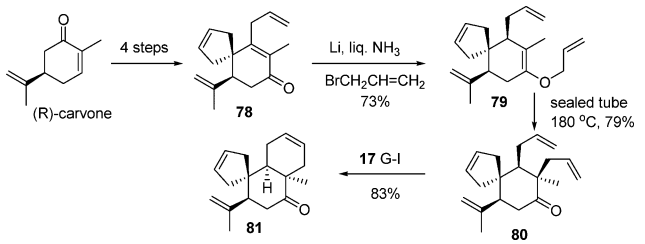
Gold(I)-catalyzed carboalkoxylation of alkynes has been shown to proceed with chirality transfer, providing a rapid entry into functionalized enantio-enriched indenyl ether **75** from readily available benzylic ether **74**. Further, these enol ethers can be manipulated *via* a gold(I)-catalyzed carboalkoxylation–CR sequence, wherein a quaternary carbon centre has been introduced in a diastereoselective manner. Thus, allyl ether **74** underwent gold(I)-catalyzed rearrangement to the indene derivative **75**, which upon CR gave the indanone derivative **76** with excellent chirality transfer and good chemical yield. The RCM of indanone **76** in the presence of a Grubbs second generation catalyst (**18** G-II) followed by reduction delivered the indane derivative **77** (Scheme 12).[16]

Srikrishna and co-workers have reported a short and efficient enantiospecific approach to a functionalized ABC ring system of tetranortriterpene dumsin and its analogs. The *O*-allyl compound **79** on CR at 180 °C in a sealed tube furnished the stereoisomer **80** in 79% yield. The bis allyl compound **80** underwent RCM with Grubbs first generation catalyst (**17** G-I) at rt affording the spiroenone **81** in 83% yield, bearing the ABC ring skeleton of dumsins (Scheme 13).[17]

Rainier and co-workers have demonstrated an efficient route for the total synthesis of gambierol, a neurotoxin which shows the ability to bind to ion channels. It possesses an octacyclic core



Scheme 12



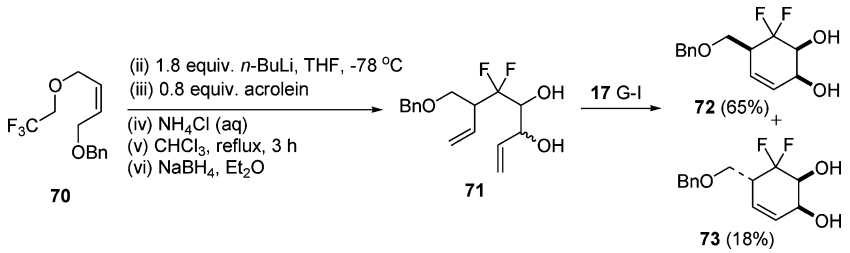
Scheme 13

and eighteen stereocentres. They have employed a C(10) allyl vinyl ether in a CR to generate the C(11) ketoside controlled by subtle conformational issues. Subsequently, an enol ether-olefin RCM provided a tetrasubstituted enol ether **85** as the precursor to the C ring skeleton of gambierol (Scheme 14).[18,19]

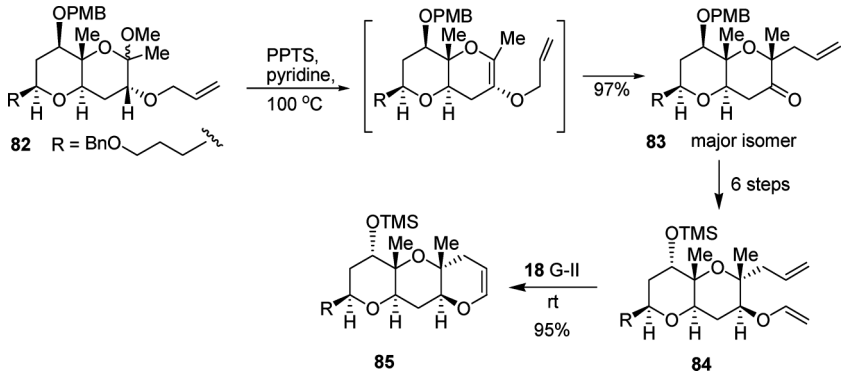
Indenol and indenone are the important structural motifs for the synthesis of several natural products. Otterlo and co-workers have used CR and RCM as the key steps for the synthesis of indenol **89** from **88** as depicted in Scheme 15. A noteworthy feature of this reaction is that when an internal alkene is involved in the metathesis step, the reaction proceeded unusually well.[20]

Wang and co-workers have reported the synthesis of benzoheterocyclics such as substituted benzofurans like 7-acetylbenzo[b]furan **94** and 8-allyl-4-methyl-2*H*-chromene **96** from 2-hydroxyacetophenone **90** *via* the application of CR and RCM protocol (Scheme 16).[21]

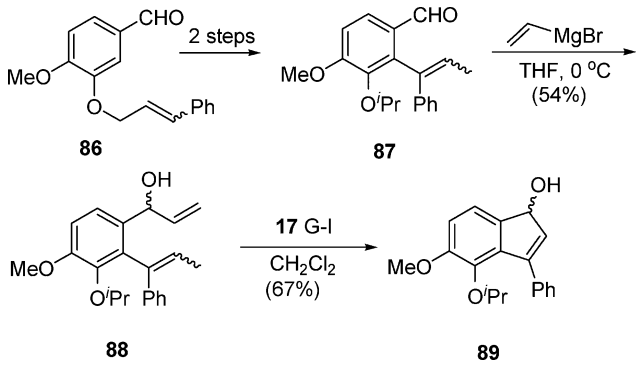
Otterlo and co-workers have demonstrated the application of CR and RCM towards the synthesis of a number of benzo-fused bicyclic compounds, such as 4*H*-chromenes, naphthols and indenols. These molecules with bicyclic skeletons are ubiquitous



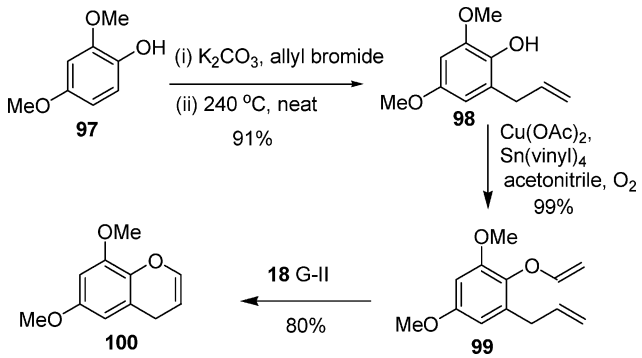
Scheme 11



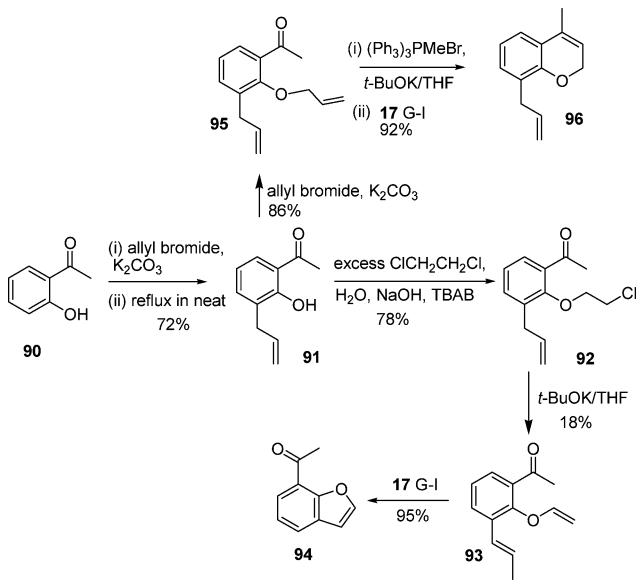
Scheme 14



Scheme 15



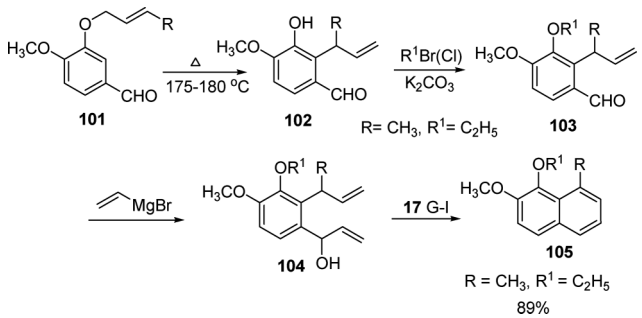
Scheme 17



Scheme 16

in nature and often show interesting biological activities. Thus, *O*-allylation of substituted phenol **97**, followed by CR furnished the corresponding substituted phenol in a moderate yield (Scheme 17). Later, vinylation with tetravinyl tin gave the bis-alkene **99** which underwent RCM with Grubbs second generation catalyst **18** G-II to deliver the 4*H*-chromene **100** (also known as 4*H*-1-benzopyran) in excellent yields.[20,22]

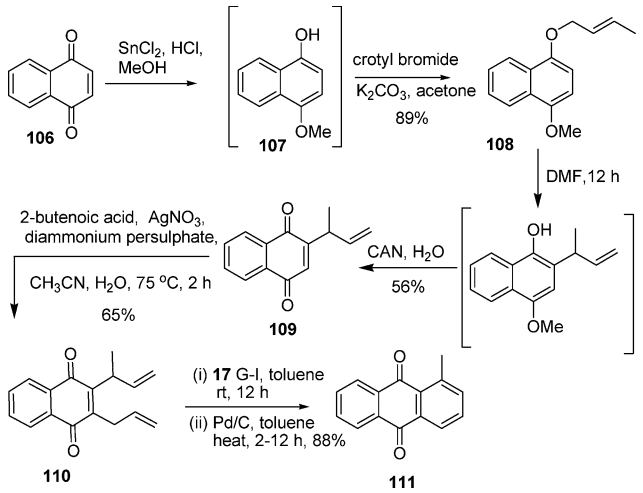
Wang and co-workers reported a practical and efficient route to highly functionalized naphthalene derivatives starting with isovanillin **101** based on CR and RCM protocol (Scheme 18).[23]



Scheme 18

Anthraquinones display attractive biological properties. CR in combination with RCM has been applied to furnish 1-substituted anthraquinone **111** (Scheme 19). This methodology has also been extended to the regiocontrolled synthesis of substituted anthraquinones in an elegant manner by Kimpe and co-workers.[24]

Angelicin displays potent antifungal activity and exhibits an inhibitory effect on the biotransformation of aflatoxin B_1 to aflatoxin B_1-8,9-epoxide. Several approaches are reported for the synthesis of angelicin and have some disadvantages such as low yield and lengthy synthetic sequence. In an attempt to develop more efficient synthetic routes to angelicin, a combination of the CR and RCM reaction has been reported by Wang and co-workers (Scheme 20).[25] Thus, the 8-allyl-7-hydroxycoumarin

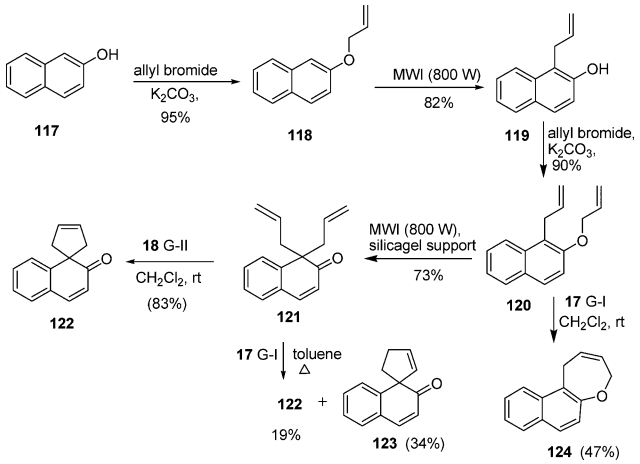


Scheme 19

(**113**) was prepared from 7-hydroxycoumarin (**112**) *via* allylation and CR. Chloro olefin **114** on treatment with ^{t}BuOK at ambient temperature underwent isomerization of the double bond of the allyl group with concomitant elimination of HCl and generation of the diolefin **115**. Reaction with Grubbs first generation catalyst **17** G-I gave the RCM product, angelicin **116**.

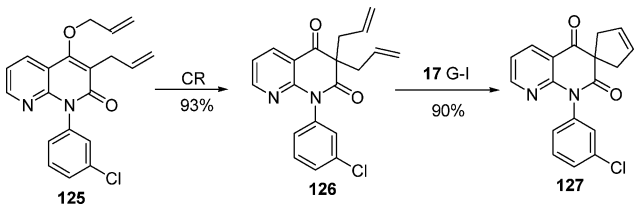
The spirocyclic cyclopentanoid core is present in a variety of pharmacologically active terpenoids such as stemaranes and scopadulanes. Moreover, the naphthoxepin derivatives **28** and **40** (Fig. 2) are clinically important targets. Kotha and co-workers have reported the application of CR and RCM protocol to several medium size ring heterocycle and carbocycle fused naphthalene derivatives of potential medicinal importance.[26]

An interesting approach based on microwave-assisted CR and ruthenium catalyzed RCM as key steps to naphthoxepin was reported by Kotha and co-workers starting from readily available β-naphthol **117**. Thus, *O*-allylation of the β-naphthol followed by CR under microwave-irradiation involving solvent free conditions afforded the compound **121**. Ruthenium catalyzed RCM of enone derivative **121** using G-II gave the corresponding spirocyclic compound **122**. With the aid of **18** G-II, the yield of the RCM product was found to increase substantially and also no double bond isomerized product was obtained. It was observed that in the presence of **17** G-I, isomerization of the double bond is feasible due to prolonged heating conditions. Ruthenium catalyzed RCM of compound **120** in presence of **17** G-I at RT gave the corresponding naphthoxepin skeleton **124** in 47% yield (Scheme 21).[27]



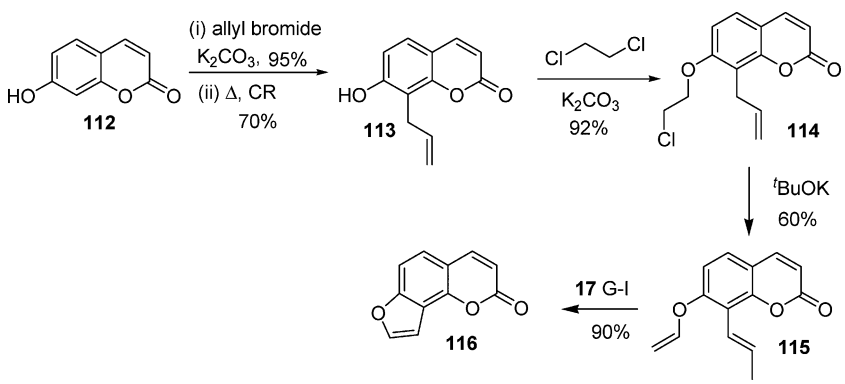
Scheme 21

Substituted 1,8-naphthyridine derivatives are potential diagnostics and also useful candidates for therapy of human diseases such as AIDS, Alzheimer's disease and for combating exo-and endo-parasites in agriculture. Based on the above approach, Majumdar and co-workers have developed an efficient route to 1,8-naphthyridinone-fused polyheterocycles **127** (Scheme 22).[28]

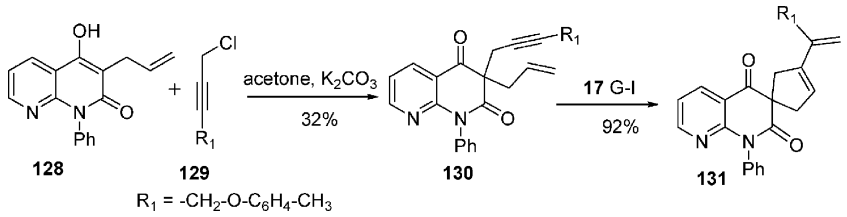


Scheme 22

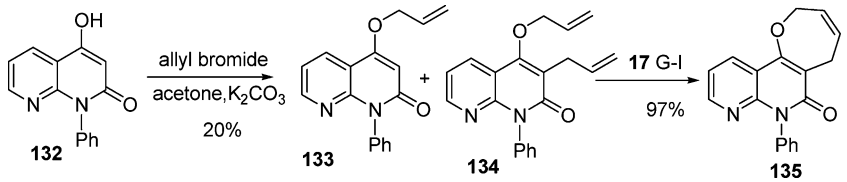
Substituted naphthyridines and spiro-naphthyridinones are potential candidates for suppressing the immune response and in the treatment of autoimmune and other types of immune disorders. The same authors have also demonstrated a useful strategy for the preparation of spiro-naphthyridinone derivatives **131** *via* a combined CR and ring-closing enyne metathesis (RCEM) protocol (Scheme 23).[28]



Scheme 20



Scheme 23

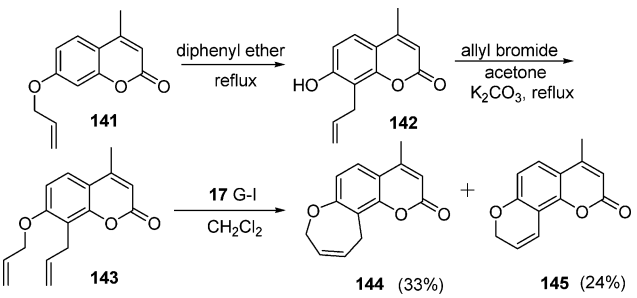


Scheme 24

They also used the same methodology for the synthesis of unsubstituted oxepine annulated 1,8-napthyridin-2(1*H*)-one derivative **135** from naphthyridione **132** (Scheme 24).[29]

Langer and co-workers have reported the synthesis of oxepin- and oxocin-annulated quinolines *via* the CR and RCM reaction as key steps (Scheme 25).[30] It was observed that the quinoline moiety is compatible with the metathesis reaction despite the presence of the nitrogen atom containing a lone pair of electrons and it was not necessary to protect the nitrogen atom as the hydrochloride salt, as in the case of a pyridine moiety.

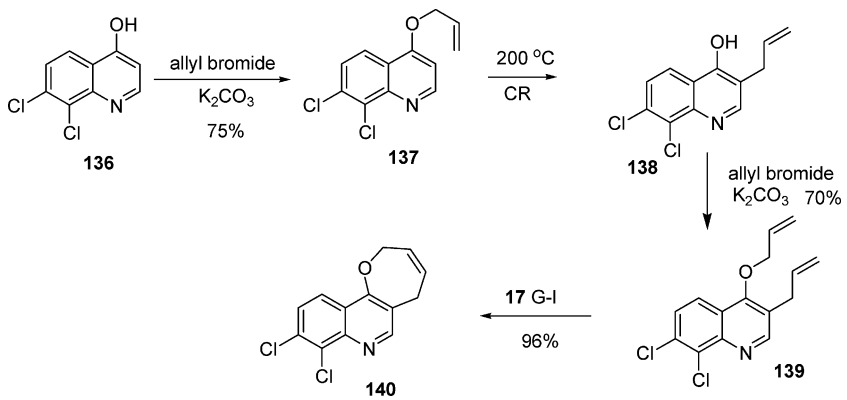
Coumarins containing fused heterocycles show interesting biological and photodynamic properties. A number of methodologies have been reported for the synthesis of various 3,4-, 6,7-, and 7,8-fused furocoumarins and pyranocoumarins. However, limited information is available for assembling medium ring oxacycle fused coumarins. A nice method for the formation of medium sized rings by tandem CR and RCM as key steps was reported by Chattopadhyay and co-workers as depicted in Scheme 26.[31] They have synthesized compound **143** by the conventional alkylation and CR method in good yield. RCM of **143** with Grubbs first generation catalyst (**17** G-I) in refluxing dichloromethane gave two products **144** and **145**. Formation of the new pyran ring in pyranocoumarin **145** resulted due to selective isomerization of the double bond before the RCM sequence.



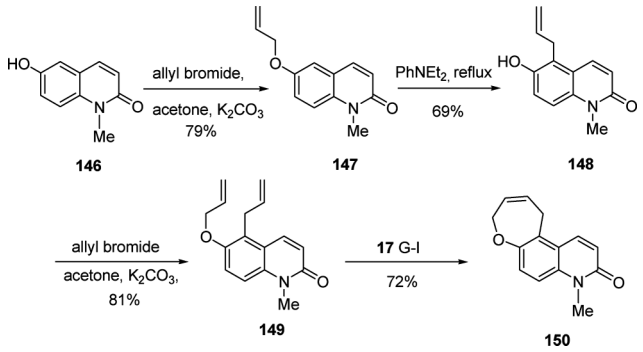
Scheme 26

Various quinolone derivatives have been used extensively for the treatment of a broad range of clinical infections. A new methodology based on tandem CR and RCM has been developed by the same group for the regioselective synthesis of oxepin- and oxocin-annulated 2-quinolones. The key intermediate **149** was prepared by straightforward alkylation and CR from 6-hydroxy-*N*-methyl-2-quinolone **146**. RCM reaction of **149** in the presence of **17** G-I catalyst gave the angularly-fused oxepinoquinolone **150** (Scheme 27).[32]

Venkateswaran and co-workers have reported a total synthesis of heliannuol B by employing CR and RCM as key steps. Heliannuol B is an allelopathic sesquiterpene comprised of a



Scheme 25



Scheme 27

unique benzoxepin ring system. The ether **152** obtained by alkylation of **151** with crotyl bromide underwent thermal CR to give styrenol **153** in 82% yield. The styrenol derivative **153** was alkylated with 2-bromobutyrolactone followed by ring opening and alkene formation to provide the RCM precursor **155**. RCM of **155** by **18** G-II gave benzoxepane carboxylate(s) **156** in 87% yield as a 1 : 1 mixture which subsequently yielded the target compound heliannuol B **159** (Scheme 28).[33]

3. Design and synthesis of biologically interesting and theoretically important frameworks by utilizing CR and cross metathesis

Garsubellin A (**160**) (Fig. 3) is a polyprenylated phloroglucin natural product which has highly oxygenated and densely functionalized bicyclo[3.3.1]nonane system which is a core unit for several therapeutic agents for Alzheimer's disease. Stoltz and co-workers have reported successful synthesis of semifunctionalized garsubellin A (**166**) using CR and CM as key steps. They have prepared bicyclic compound **162** from vinylogous ester **161**, and later, condensation of the bicyclic compound **162** with allyl alcohol followed by CR and treatment with diazomethane gave the allyl ether derivative **164**. Installation of the prenyl unit has been accomplished by CM using **18** G-II in the presence of 2-methyl-2-butene to furnish **165** in 88% yield. Saponification of

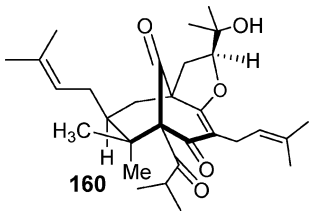


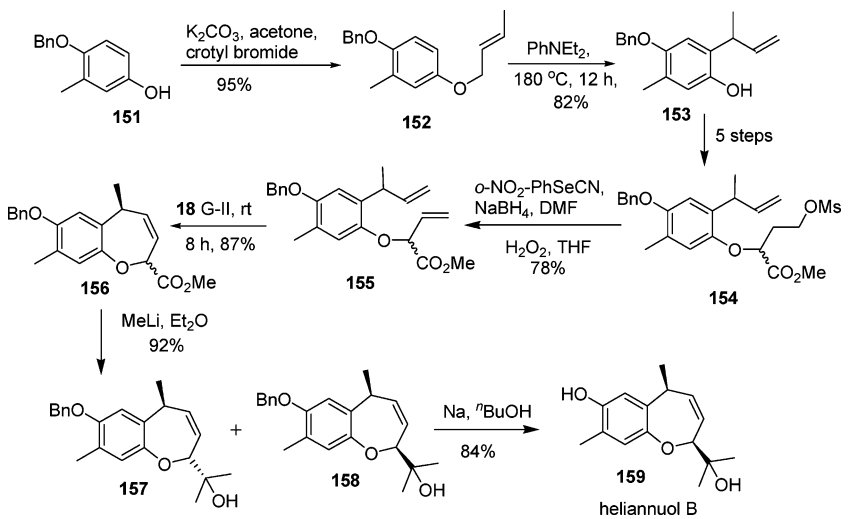
Fig. 3 Garsubellin A

this vinylogous ester **165** proceeded in good yield to provide the semifunctionalized garsubellin A core system **166** (Scheme 29).[34]

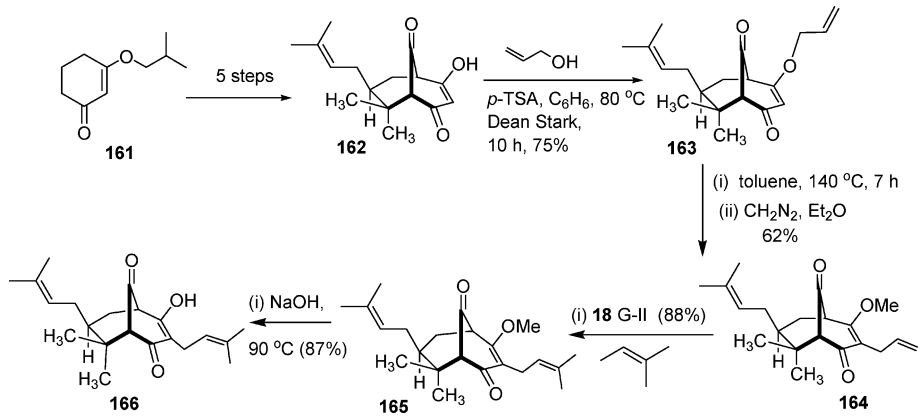
Ditopic 8-hydroxyquinoline ligand systems are useful building blocks for luminescent helicates and find useful applications in supramolecular chemistry. Albrecht and co-workers have reported the synthesis of homo- and heteroditopic 8-hydroxyquinoline-based receptors through a sequential use of CR and olefin metathesis homodimerization (Scheme 30).[35] These receptors posses an amide or a carboxylate moiety at the tridentate coordination site for the complexation of Ln^{3+} ions or an 8-hydroxyquinoline unit as an alternative to bidentate segment for addressing transition- or *p*-block metal ions.

Metz and Tischer have reported[36] an efficient strategy for regioselective C-6 prenylation of various flavone derivatives starting from readily available parent flavonoids. They have employed a sequence of europium(III)-catalyzed CR followed by CM as key steps (Scheme 31). These prenylated flavonoids **174** have attracted considerable interest in the field of nutrition, health and medicine. It was observed that europium(III) catalysis during the CR step was essential to stop the rearrangement of allyl ether **172** at the C-6 allyl stage. This is because purely thermal activation afforded a 1 : 1 mixture of the desired compound **173** and the C-8 allylated diacetate **175** resulting from a domino Claisen–Cope process. The CR–CM strategy could be extended towards the preparation of other flavonoid derivatives with cytotoxic activity against human oral tumor cell lines as well.

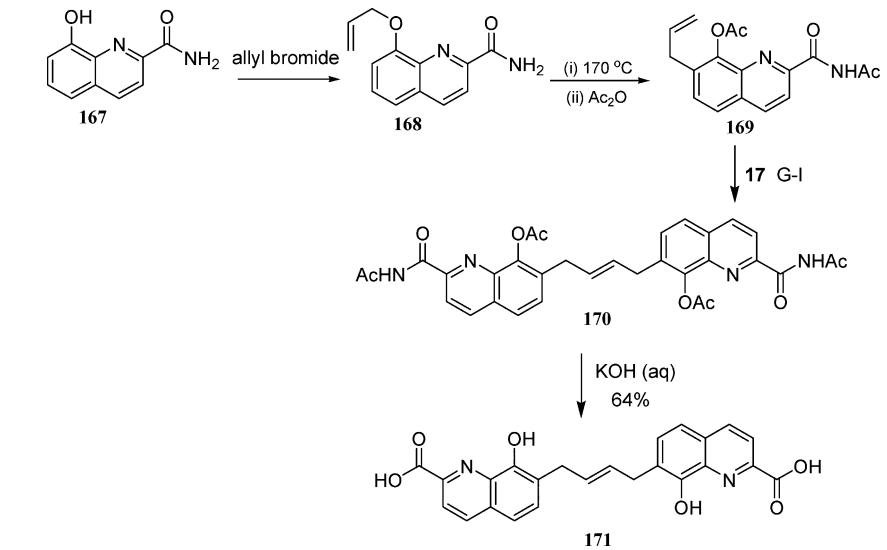
Palmer and co-workers have utilized a CR–CM approach for the synthesis of imidazo[1,2-α]pyridines (such as pyranoimidazopyridine **181**) which act as potassium-competitive acid blockers for the treatment of gastroesophageal reflux diseases (Scheme 32).[37]



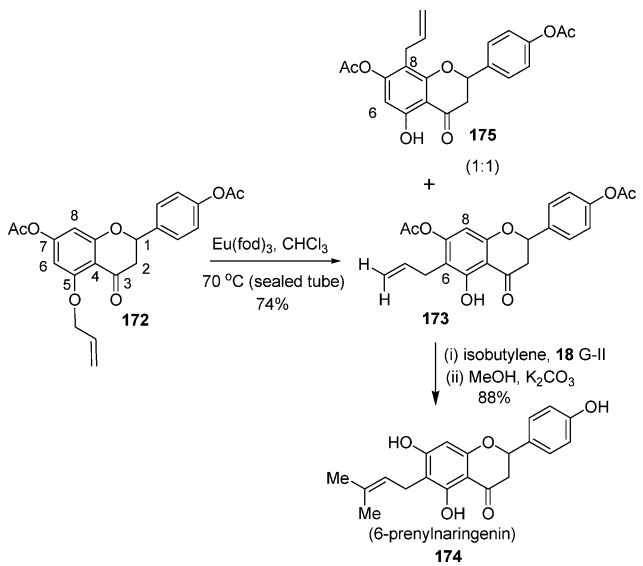
Scheme 28



Scheme 29



Scheme 30



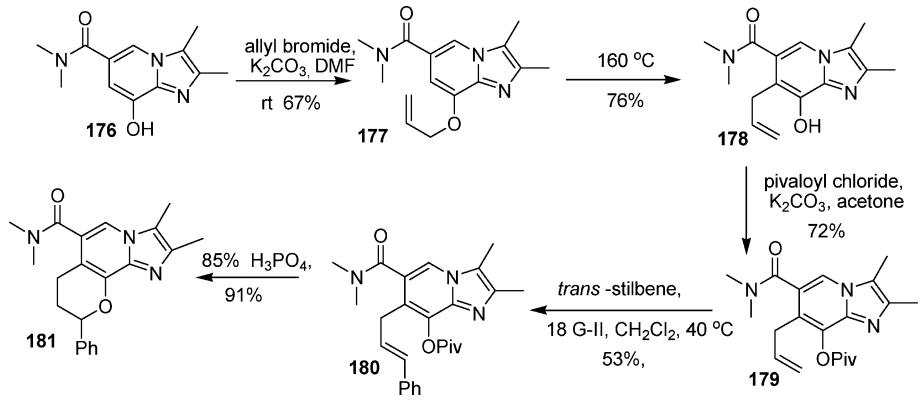
Scheme 31

Kotha and co-workers have reported the preparation of highly functionalized cage compound(s) **188** through the combination of CR and CM by using a modified Grubbs–Hoveyda *N*-tolyl catalyst (**19b**) (Scheme 33).[38]

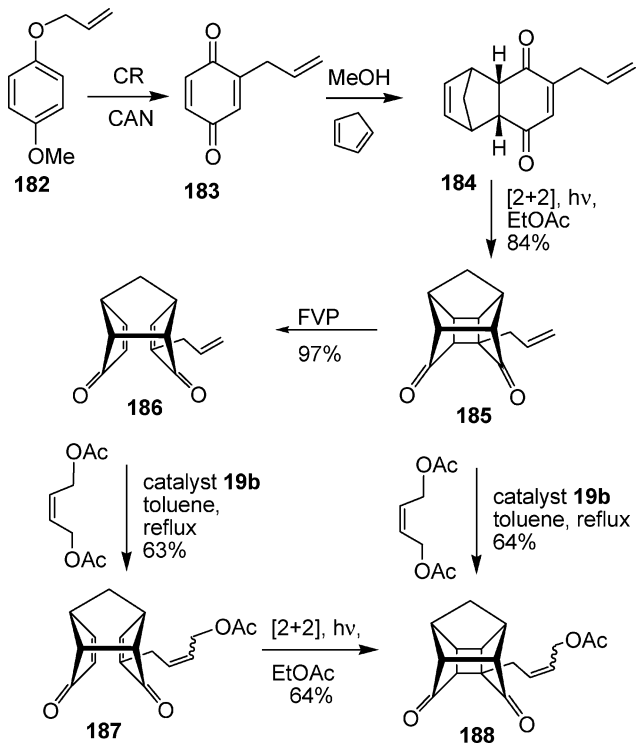
4. Synthesis of polycyclic compounds *via* double CR and RCM

The benzoannulation[39] reaction is useful for appending an aromatic ring to a pre-existing polycyclic structure. In this regard, benzoannulated quinones are useful candidates for the treatment of a wide variety of disorders. Examples include anthracycline antibiotics such as idarubicin, doxorubicin and daunorubicin which have been widely used as clinically effective anti-tumor agents against acute leukemia, Hodgkin's disease, lymphomas, breast carcinomas and sarcomas. Therefore, there is a pressing need to design new approaches capable of adding an aromatic moiety for the synthesis of polycyclic compounds.

In this regard, Kotha and co-workers have demonstrated a new methodology based on double CR followed by a one-pot RCM and DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) oxidation sequence. Thus, *O*-allylation of 1,4-dihydroxyanthracene-9,10-dione derivative **189** afforded the required diallyl precursor **190** suitable for the double CR. Treatment of the bis-allyloxy anthraquinone



Scheme 32



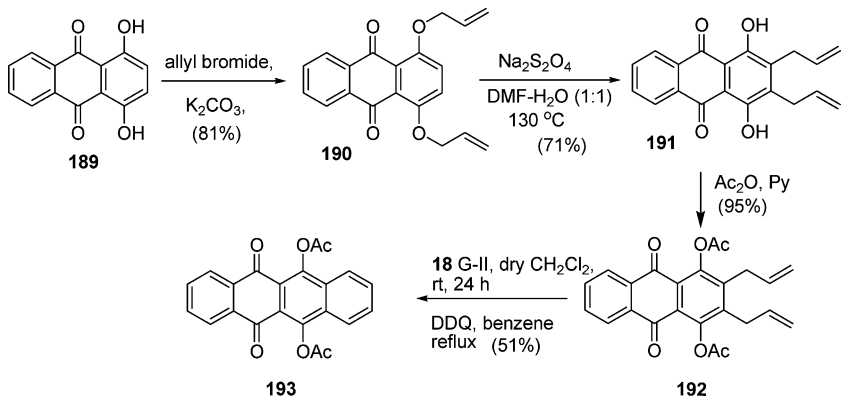
Scheme 33

190 with sodium dithionate in the presence of sodium hydroxide in dimethylformamide–water (1 : 1) under thermal conditions furnished the desired double rearranged product **191** in 71% yield. Protection of the hydroxyl group followed by RCM and aromatization sequence with DDQ gave the benzoannulated product **193** (Scheme 34).[40] Chattopadhyay and co-workers independently reported the same approach to generate various naphthalene derivatives.[41]

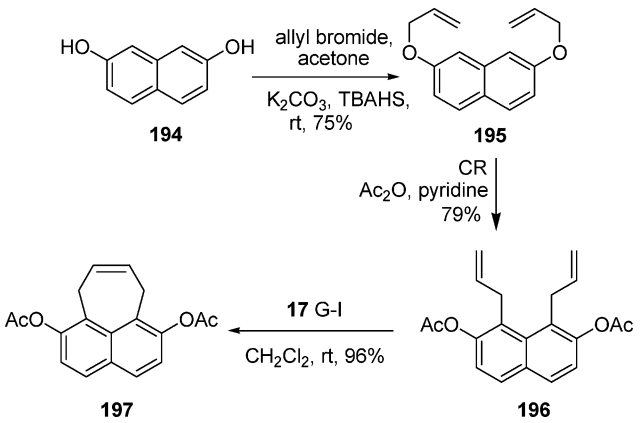
The Kotha group has reported the preparation of the cycloheptanaphthalene skeleton which is present in the important enzyme inhibitor *trans*-2, 3-pleiadanedicarboxylic acid. In this connection, double allylation of commercially available 2,7-dihydroxynaphthalene **194** gave the diallyl ether **195**, which in the presence of pyridine and 4-dimethylaminopyridine (DMAP) under refluxing acetic anhydride condition gave the diacetate **196**. Compound **196** underwent smooth RCM to furnish the pleiadene derivative **197** (Scheme 35).[26] Later on, Chattopadhyay and co-workers reported the same compound by following the same strategy.[42]

Kotha and co-workers [43] have reported the preparation of novel hexacyclic caged compound **204** by a combination of CR and RCM sequence (Scheme 36). The intricate molecular structure along with the lack of conformational mobility and associated molecular symmetry was the main motivation for investigation of caged polycyclics. Here, Diels–Alder (DA) and [2 + 2] photocycloaddition reactions are used to generate the required precursor **203** suitable for RCM. Novel hexacyclic propellane derivative **204** has been realized with **17** G-I.

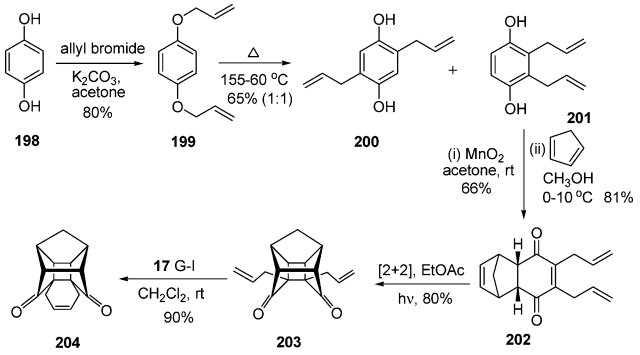
Various benzo-fused bisoxepin and bisoxocin derivatives have been assembled with the aid of double CR by utilizing



Scheme 34



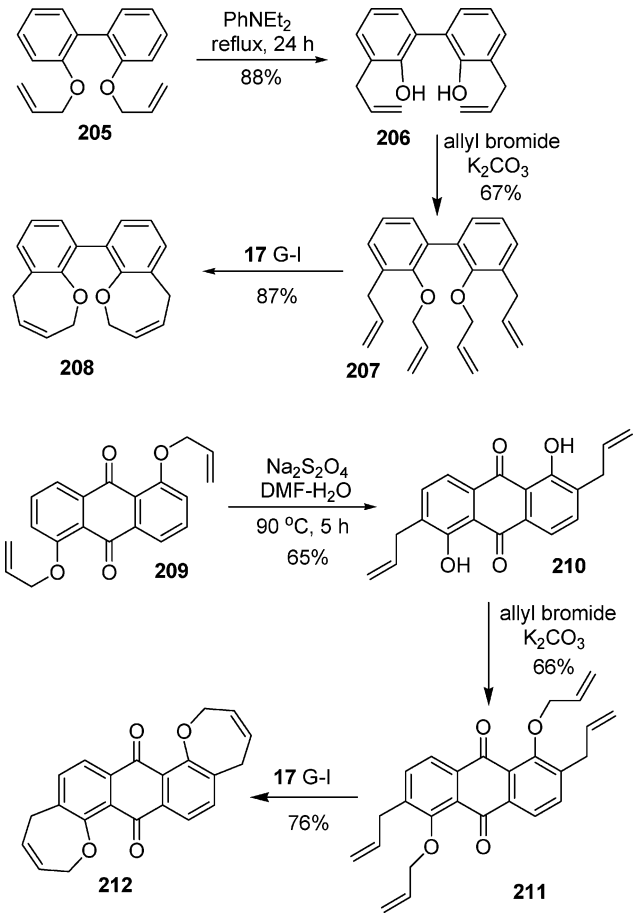
Scheme 35



Scheme 36

two-directional RCM. Chattopadhyay and co-workers have shown that a double CR of 2,2′-bis(allyloxy)biphenyl proceeds better when conducted in dilute solutions of *N*,*N*-diethylaniline at reflux and a consistent and improved yield (>85%) could be realized under these conditions. The biphenol **206** underwent a smooth double allylation to deliver the corresponding bisallyl ether **207**.

RCM of **207** attempted with Grubbs first generation catalyst (**17** G-I) led to the formation of only bisoxepin derivative **208** in 87% yield. In an analogous manner, the bisoxocin derivative was prepared using 4-bromobutene in a modest yield of 48% as the only isolable product along with some unchanged starting material (15%). Using a similar reaction strategy the authors also reported the synthesis of bisoxepin-fused anthraquinone derivative **212** starting from **209** with good yields (Scheme 37).[44]

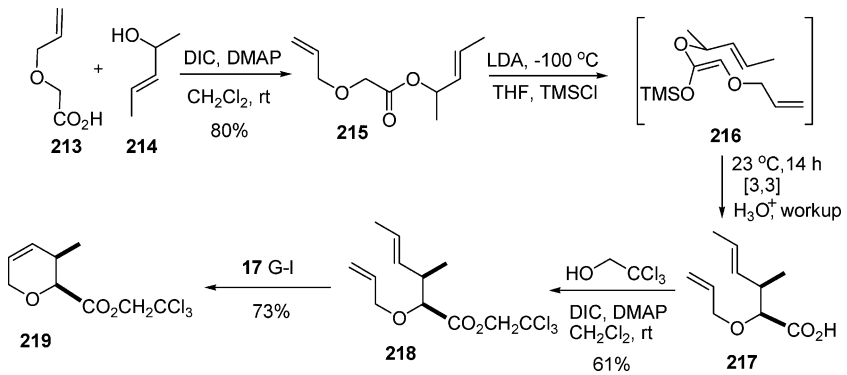


Scheme 37

5. Application of Ireland CR and RCM towards the synthesis of complex bioactive targets

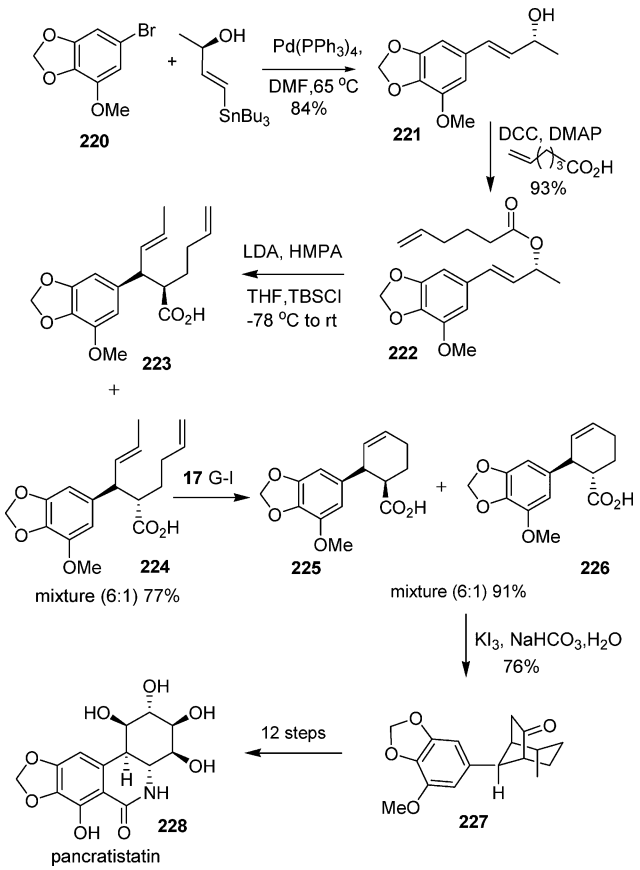
Burke and co-workers reported a general methodology to produce functionalized dihydropyran-2-carboxylate **219** by a combination of tandem glycolate CR and RCM as key steps (Scheme 38).[45] This approach is among the early examples involving CR and RCM.

Kim and co-workers have demonstrated the synthesis of pancratistatin, an antitumor alkaloid which exhibits high levels of *in vitro* and *in vivo* cancer cell growth inhibitory activity and antiviral activity. They used the Ireland CR as a key step to construct the



Scheme 38

A and C ring with appropriate stereochemistry. The B ring of the phenanthridone skeleton has been realized by employing the Bischler–Napieralski reaction. The overall yield of the reaction sequence is 5.8% from the readily available starting material **220** (Scheme 39).[46]

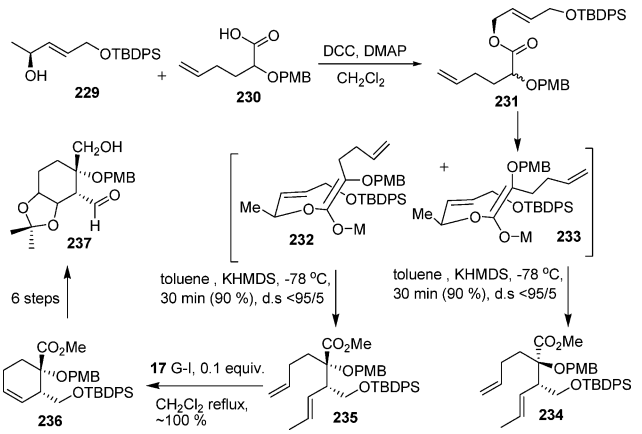


Scheme 39

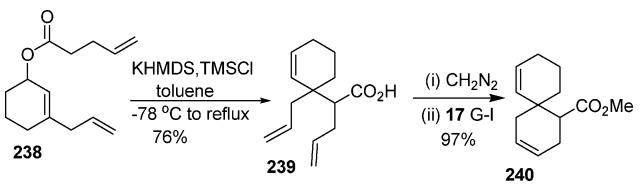
The sesquiterpenes such as fumagillin and ovalicin exhibit interesting biological activity like inhibition of angiogenesis. Langlois and co-workers reported a highly stereoselective route using CR followed by metathesis to afford a key precursor suitable for the synthesis of fumagillin and ovalicin. The synthesis starts with the hydroxyl derivative **229**, which undergoes esterification to generate **231**. Having compound **231** in hand, Ireland CR in combination with RCM gave the desired precursor **236** suitable for further side chain modification (Scheme 40).[47]

Ogilvie and co-workers reported[48] a rapid and reliable route for assembling spirocycles.[49] The formation of the quaternary centre is engineered *via* the Ireland CR. The allylic oxygen centre in **238** would dictate the confirmation of quaternary centre present in **239**. Esterification and RCM sequence of **239** afforded the spirocyclic system **240** (Scheme 41).

Zakarian and co-workers have reported[50] the enantioselective total synthesis of (+)-pinnatoxin A **248**, a calcium channel activator comprised of a 27-membered carbocycle incorporating a unique A,G-spiroimine and B,C,D-spirotricyclic bis-ketal fragments. The challenging quarternary stereogenic center at C-5 and the adjacent tertiary stereocenter at C-31 were assembled *via* the Ireland CR. The 27-membered macrocycle frame of the target



Scheme 40



Scheme 41

molecule (+) pinnatoxin A was accomplished by RCM sequence of the intermediate **246** (Scheme 42).

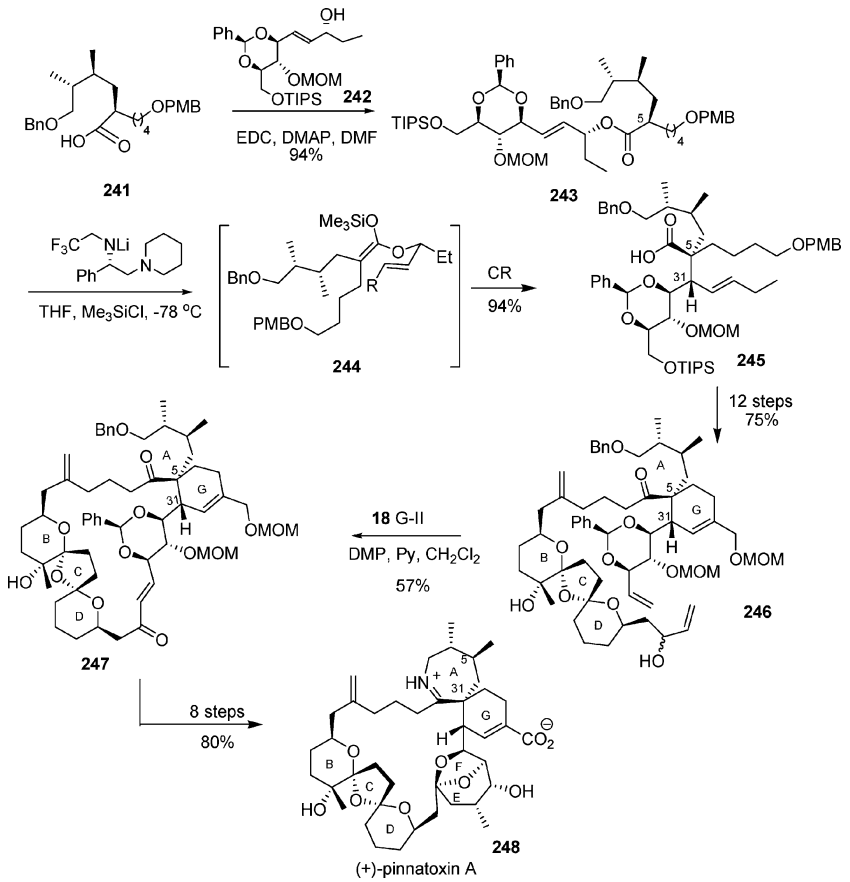
Srikrishna and Ramesh Babu have reported[51] an efficient total syntheses of spiro sesquiterpenes such as acorenols. The spiro[4.5]decane skeleton present in the acorenols was efficiently assembled by a combination of an Ireland CR and RCM. Starting from cyclohexane-1,4-dione **249**, a key precursor of the acorenols, the spiro[4.5]decanecarboxylate **254** was obtained in seven steps with an overall yield of 67% (Scheme 43).

A combination of Ireland CR and RCM has been employed for an efficient formal total syntheses of herbertane class of sesquiterpenes **262** containing two vicinal quaternary carbon atoms on a cyclopentane ring (Scheme 44).[52] Construction of vicinal quaternary carbon atoms on a cyclopentane ring is not a trivial task. These sesquiterpenes possess a sterically crowded 1-aryl-1,2,2-trimethylcyclopentane moiety. The significant biological properties of the phenolic herbertanes qualify them as important synthetic targets.

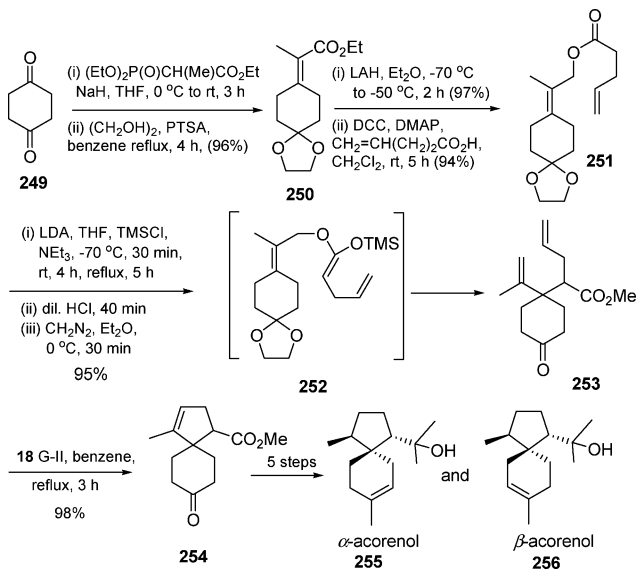
Barrett and co-workers[53] have reported a useful route to bicyclic β-lactam derivatives (**267–270**) *via* tandem Ireland CR and RCM as key steps. They have shown that polyfunctional β-lactam dienes are excellent substrates for metathesis; but suitable substrates could not be designed due to a lack of strategies. To address this issue, a carboxylic acid motif was incorporated adjacent to the lactam nitrogen *via* Ireland CR and subsequently they were subjected to RCM. This approach represents a powerful strategy to generate novel β-lactam pharmacophores (Scheme 45).

Towards the total synthesis of nitiol, Dake and co-workers have synthesized 1,22-dihydroxynitianes **272** (Fig. 4). The stereochemistry of the synthetically challenging C-ring fragment of **272** has been accomplished using an Ireland CR and RCM as key steps.[54]

The well-accepted chair conformation in the transition state of the Ireland CR offered excellent transmission of stereochemical information from the starting material leading to enantioselective



Scheme 42



Scheme 43

synthesis of **272**. The protocol outlined in Scheme 46 was adopted to construct the *trans*-disubstituted diastereomer of **277** starting with the (*Z*)-diastereomer of **273**, which ensures minimum epimerization.[54]

Kim and co-workers have synthesized the *cis*-disubstituted cyclohexene ring by a diastereoselective Ireland CR and a RCM

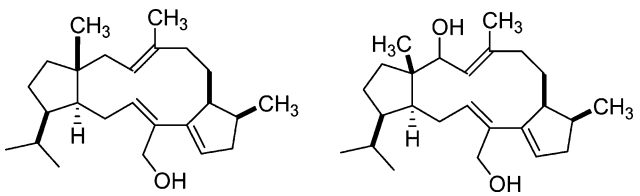


Fig. 4 Nitiol (**271**, left) and 1,22-dihydroxynitianes (**272**, right)

reaction which paves way for the first stereoselective total synthesis of the dibenzyl *cis*-tetrahydrocannabinol, (−)-perrottetinene (Fig. 5). The stereogenic centers present in **278** were created by Ireland CR. The required CR product **279** was obtained from 3,5-dimethoxybenzaldehyde. The synthetic sequence involving CR followed by RCM is briefly outlined in Scheme 47.[55] It was observed that during the RCM sequence, protection of the *O*-phenolic hydroxyl group was not required, despite the *O*-phenol groups in **283** having the potential to inhibit the Grubbs catalyst by coordinating with the ruthenium centre. This constitutes one

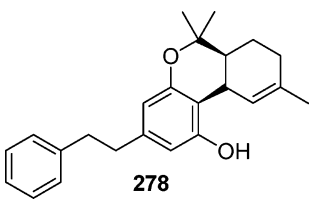
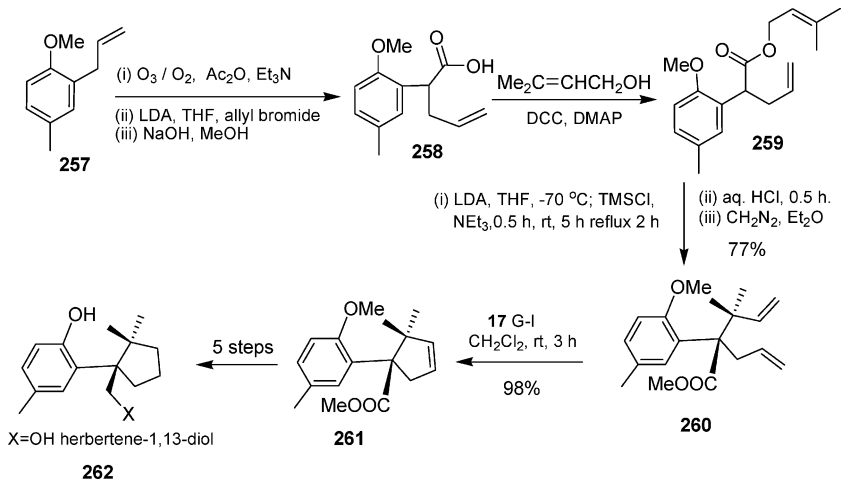
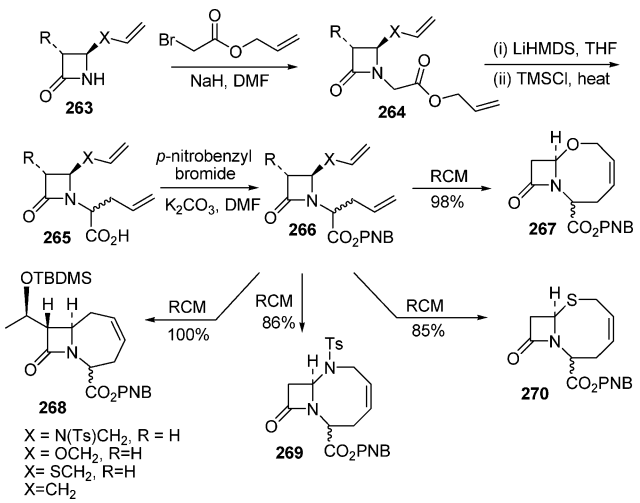


Fig. 5 Perrottetinene (**278**)

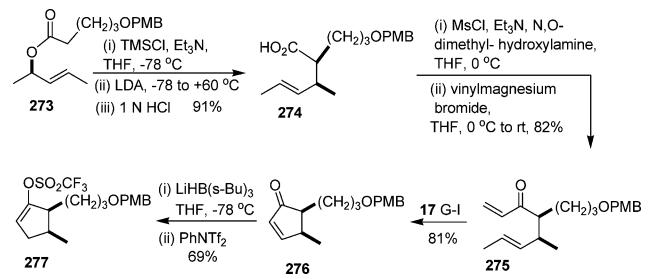


Scheme 44



Scheme 45

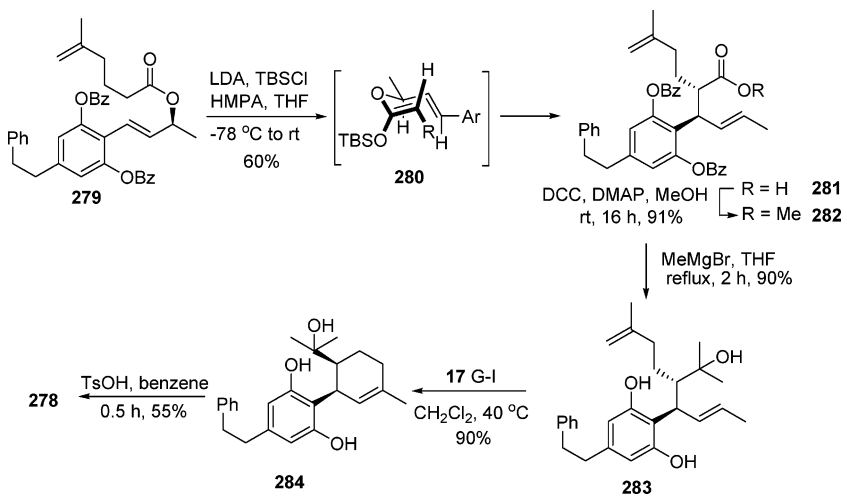
of the first successful examples of olefin metathesis involving the proximal *O*-phenolic group.



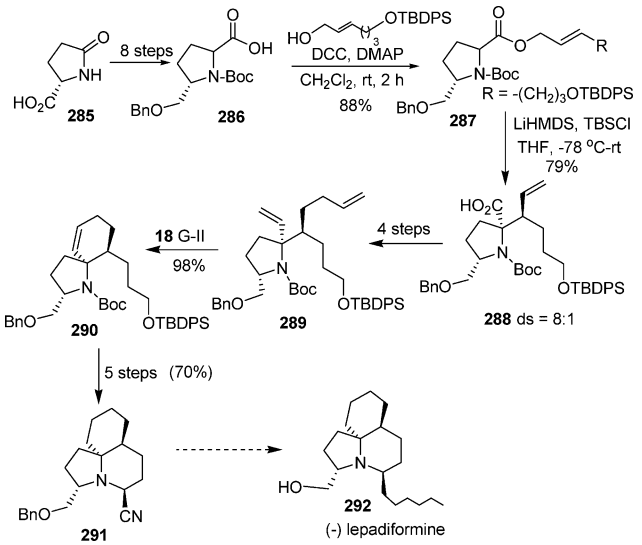
Scheme 46

Kim and co-workers have reported a formal total synthesis of (–)-lepadiformine **292** and in this regard, the azaspirocyclic skeleton has been created involving a sequence of cyclic amino acid ester-enolate CR and RCM starting from (*S*)-pyroglutamic acid **285**. Chelation control between the enolate oxygen atom and the heteroatom of the *N*-Boc group might have influenced the stereochemical outcome of the CR (Scheme 48).[56]

Quartromicins exhibit a broad spectrum of anti-viral activity and the junction between diastereomeric spirotetronate subunits A and B leads to a highly symmetrical structure. Bedel and



Scheme 47



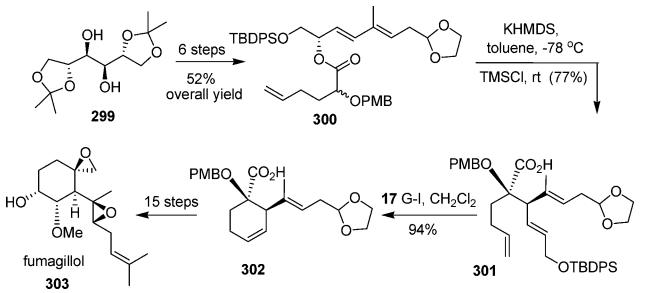
Scheme 48

co-workers have synthesized the spirotetronate subunit B **297** of quartromicins using a highly enantioselective sequential Ireland CR-enyne metathesis approach allowing the synthesis of cycloalkenes bearing two contiguous highly functionalized asymmetric centers. The diastereoselectivity of the Ireland CR dropped when the acetylenic moiety was unprotected due to presence of a double-metallated species generated before the Ireland CR process (Scheme 49).[57]

Bedel and co-workers also reported a stereoselective formal synthesis of (–)-fumagillol **303** which is a direct precursor of the anti-angiogenic sesquiterpene fumagillin. They have applied a sequence of stereoselective Ireland CR and RCM as key steps using diisopropylidenemannitol **299** as the starting material (Scheme 50).[58]

Ariza and co-workers have synthesized (–)-phaseolinic acid (**311**) *via* a sequential RCM and Ireland CR (Scheme 51).[59] The synthesis was completed in eight steps with 40% overall yield from commercially available (*S*)-oct-1-yn-3-ol (**304**) as the source of chiral synthon.

Stereoselective synthesis of medium size ring ethers has significant interest because they are often viewed as potent bioactive natural products. Fujiwara and co-workers have reported stereoselective synthesis of *cis*-2,3-disubstituted eight-membered medium-



Scheme 50

ring ethers *e.g.* **316** based on Ireland CR of 3-alkoxy-2-propenyl glycolate ester **314** followed by RCM (Scheme 52).[60] Stereoselective construction of these branched ethers is a challenging task due to the difficulty involved in their synthesis.

Fujiwara and coworkers have developed a process for the stereoselective synthesis of chiral *cis*-3-alkoxy-2-carbomethoxy medium-ring oxacyclic compound **320** from (*R*)-3-(3-butenyl)-4-propynoyloxazolidin-2-one **317** which was synthesized from L-serine. They have employed a combination of chirality-transferring Ireland CR of 3-alkoxyallyl glycolate ester **318** to provide a *syn*-2,3-dialkoxy carboxylate ester **319** and a relay RCM to form a medium-ring ether **320** (Scheme 53)[61] along with **321**. Along similar lines, seven- and eight-membered cyclic ethers were also synthesized.

Branimycin **322** (Fig. 6) is an unusual member of the nargenicin antibiotic family[62] which exhibits activity against *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus*, and *Streptomyces viridochromogenes*. The structure **322** contains *cis*-fused decalin core, the 1,4-oxygen bridge, and the 9-membered macrolide ring which makes it attractive for total synthesis. The required

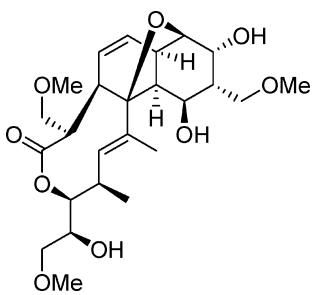
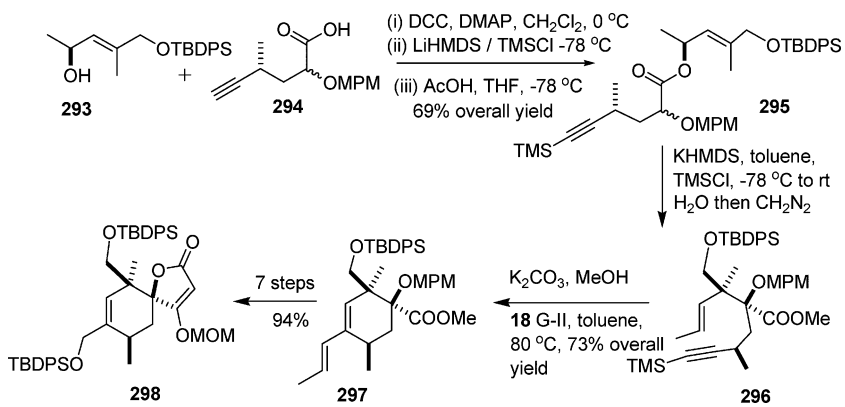
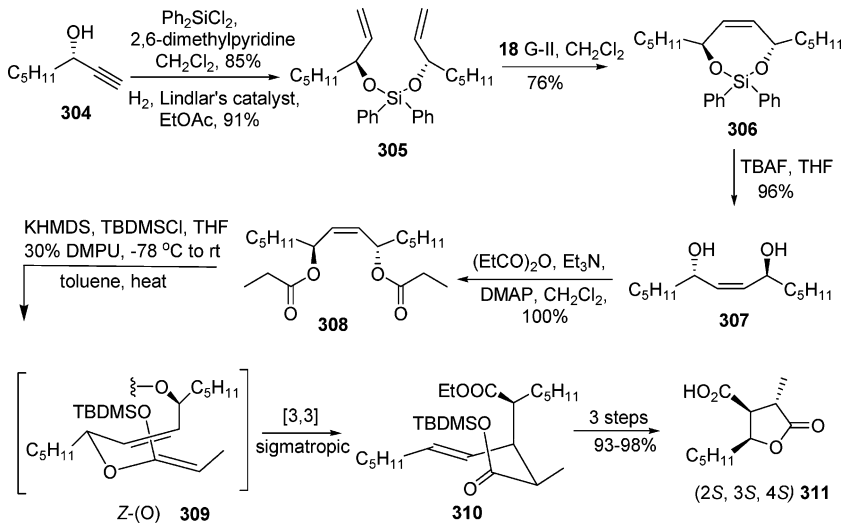


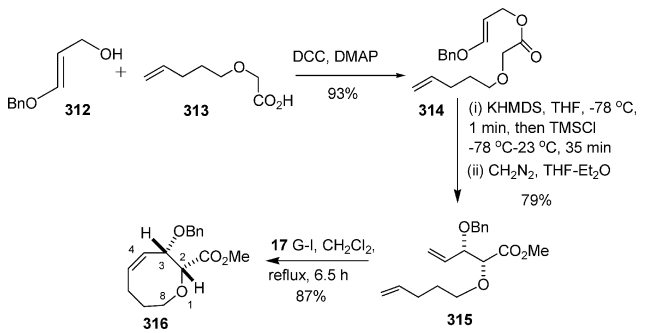
Fig. 6 Branimycin (**322**)



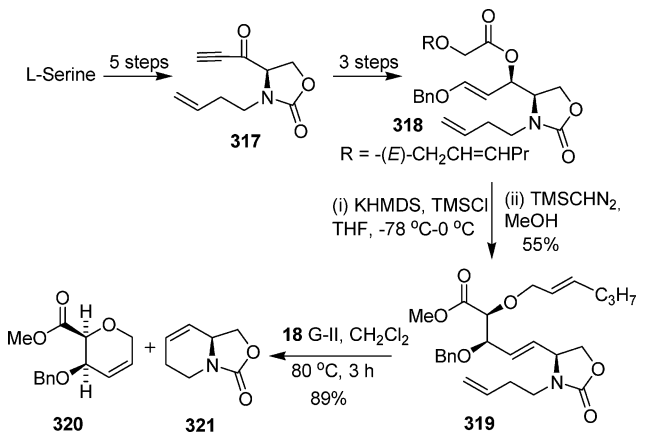
Scheme 49



Scheme 51



Scheme 52



Scheme 53

monosubstituted double bonds in the second ring were installed *via* two successive Ireland CR, from protected diol precursor **323** (Scheme 54), which was prepared from (–)-quinic acid in a seven-step sequence, reported by Mulzer and co-workers.[63] The RCM reaction of **328** was carried out with Hoveyda-Grubbs catalyst since the Grubbs second generation catalyst **18** G-(II) was unstable at the required temperature.

6. Design of heterocyclics and carbocyclics by chelated CR and RCM

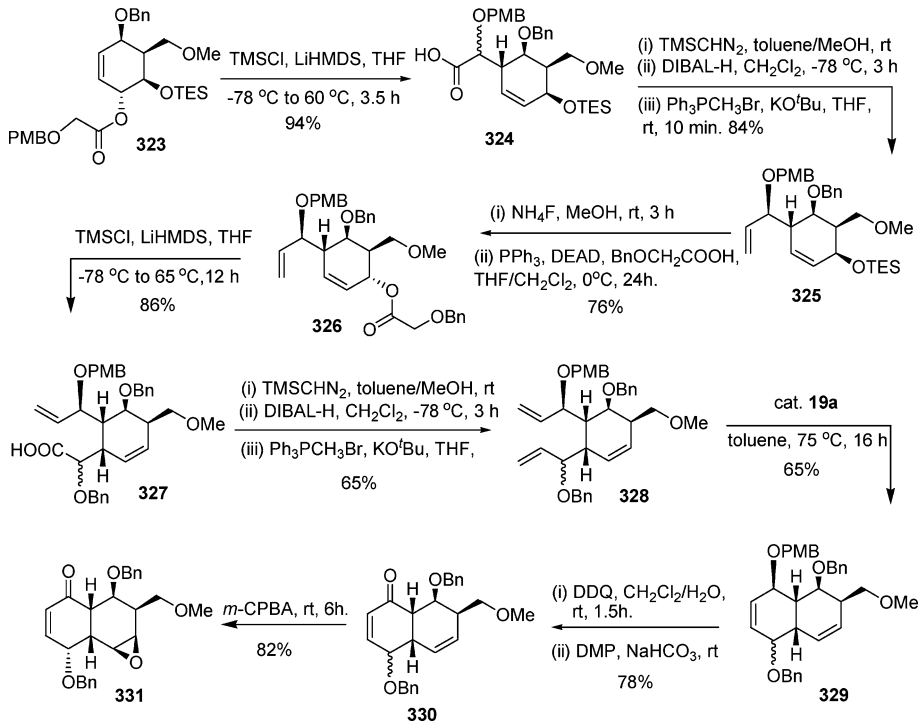
Kazmaier and Maier described the synthesis of pharmaceutically important cyclic peptides suitable for peptidomimetics. To this end, peptide ester **332** undergoes CR in the presence of tin chloride. A RCM sequence of **334** with **17** G-I gave the desired cyclic product **335** (15 membered ring) in 77% yield as shown in Scheme 55.[64] The same group extended this methodology for the syntheses of non-proteinogenic amino acids and polyhydroxylated amino cyclopentanes, an interesting class of glycosidase inhibitors.[65]

Hong and co-workers explored the stereoselective synthetic route for 6′(α)-hydroxy carbovir analogues **347** from an acyclic precursor such as solketal **336**. The required stereochemistry was successfully installed using a chelation-controlled glycolate CR followed by RCM (Scheme 56).[66]

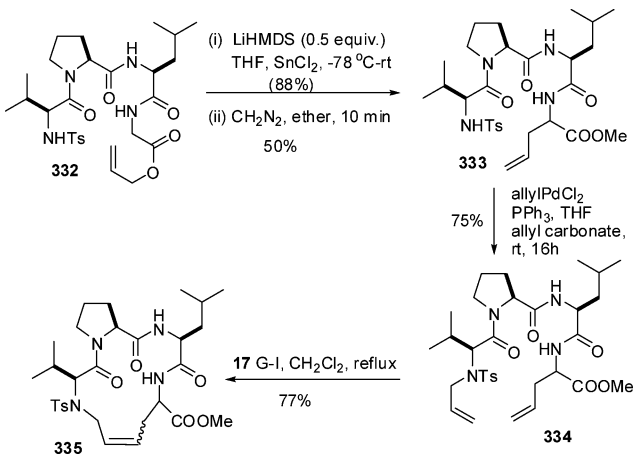
A formal synthesis of (–)-perhydrohistrionicotoxin *via* Ireland CR and RCM as key steps has been reported by Kim and co-workers.[67] The interesting feature of this sequence is the creation of stereogenic centres for the construction of the azaspirocyclic skeleton. The CR product has been obtained under the Kazmaier conditions ($ZnCl_2$ coordination) in a highly regioselective manner. Later, the key RCM precursor **352** was assembled by reduction, oxidation and Grignard addition sequence. RCM has been realized with **17** G-I. Further functional group manipulation gave the key intermediate **354** required for the target compound, (–)-perhydrohistrionicotoxin (Scheme 57).

Piscopio and co-workers demonstrated the Ireland CR and RCM protocol for the synthesis of pipecolinic acid derivatives. The key synthetic sequence adopted in this strategy is shown in Scheme 58.[68] This methodology has also been extended to spirocyclic systems. This approach is among the early examples involving CR and RCM.

The asymmetric version of Ireland CR and RCM sequence has been employed to synthesize various cyclic quaternary α-alkoxy acids/esters with excellent diasteroselectivity by choosing appropriate starting substrates. In this regard, Ple and co-workers reported[69] a diastereoselective synthesis of cyclic quaternary



Scheme 54



Scheme 55

α-hydroxy and α-amino acid derivatives. Synthesis began with coupling of isobutyraldehyde and alkyne to give substituted alkyne **358** which on partial reduction under Lindlar catalyst conditions followed by Ireland CR and RCM respectively gave cyclopentene derivative **362** (Scheme 59).

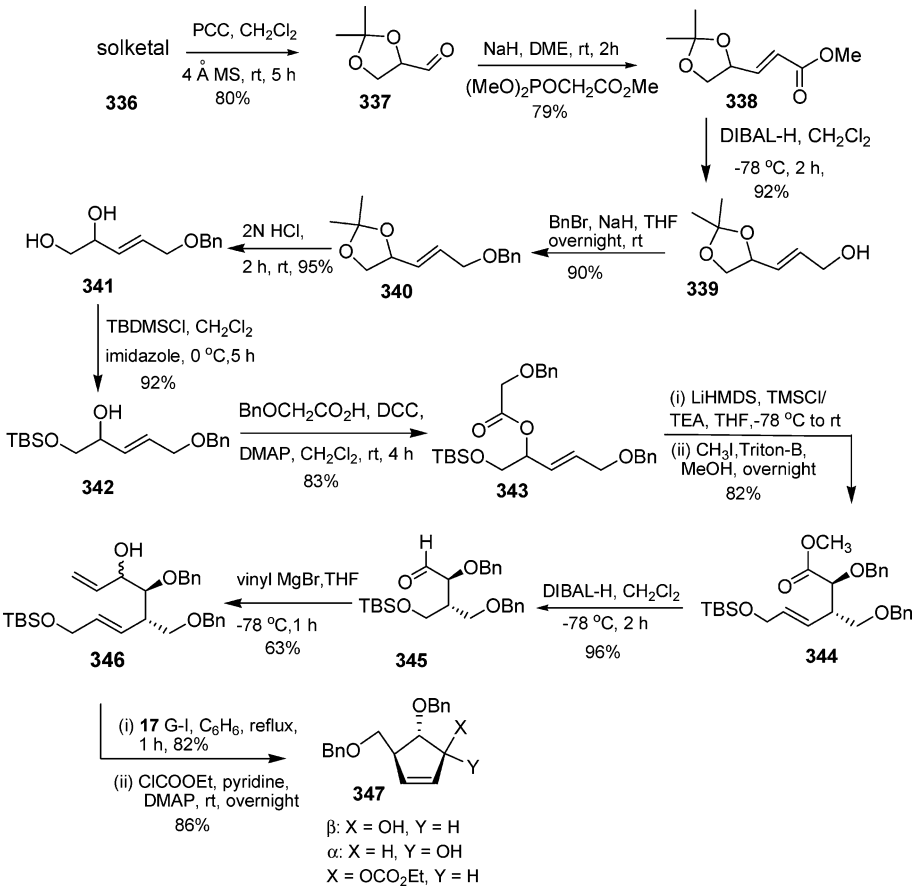
Polyhydroxylated piperidines and pipecolinic acid derivatives are interesting candidates for the inhibition of various glycosidases. Mues and Kazmaier have employed an asymmetric chelated CR–RCM protocol for the synthesis of non-proteinogenic amino acids. The chelated enolates undergo facile CR to give γ,δ-unsaturated amino acid with high diastereomeric purity and high enantiomeric excess by employing a chiral ligand such as the cinchona alkaloid. A palladium catalyzed allylic alkylation of the *N*-terminus of the amino acid followed by RCM gave the amino acid derivative **367** (Scheme 60).[70]

(–)-Ecklonialactone B (**369**) is a carbocyclic C_{18}-oxylipin of marine origin, isolated from the brown algae *Ecklonia stolonifera* and *Egregia menziessi*. Hiersemann and co-workers have demonstrated the power of the catalytic asymmetric CR (CACR) combined with RCM sequence for the enantioselective synthesis of the C10-C18 segment of ecklonialactone B. The CACR offers access to stereoisomerically pure acyclic α-keto esters. The strategic positioning of the double bonds allows easy access to cyclic building blocks suitable for the total synthesis of enantiomerically pure natural products. The CACR of the allyl vinyl ether (*E*, *Z*) **371** in presence of the chiral Lewis-acid {Cu[(*S*,*S*)-*tert*-Bu-box]} $(H_2O)_2(SbF_6)_2$ **370** furnished the α-keto ester (3*R*, 4*R*)-**372** as a single stereoisomer. Reduction of **372** with K-selectride provides the α-hydroxy ester **373** as a single diastereomer. The RCM reaction of **373** in the presence of Grubbs second generation catalyst **18** G-II provides the cyclopentenoid derivative **374** which was converted to the C10-C18 segment of (–)-ecklonialactone B (**369**) (Scheme 61).[71]

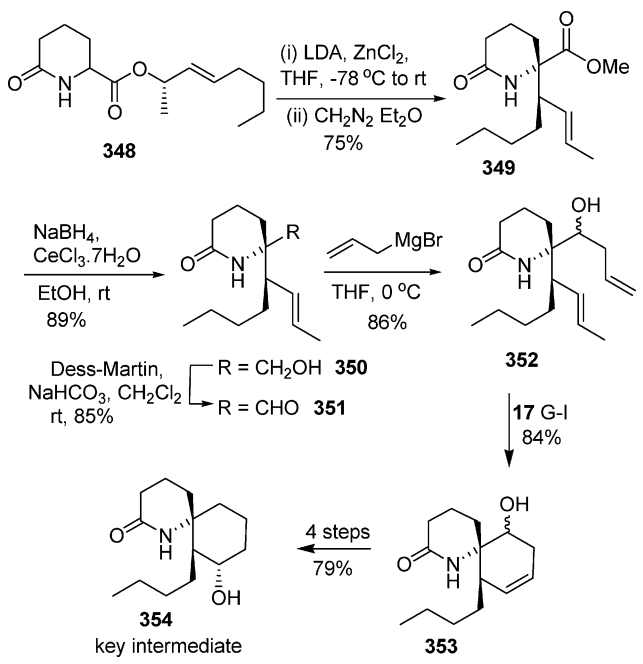
Kazmaier and co-workers reported the synthesis of allylated peptides from allylic esters of peptides *via* CR, *N*-allylation and RCM providing access to cyclic peptides (Scheme 62).[72] Frequently occurring loops and turns in peptides and proteins are responsible for their biological activity. Therefore, these structures are interesting targets from a pharmaceutical point of view.

7. Application of Reformatskii–CR and RCM to design fluorinated carbocyclic nucleotides

Qing and co-workers have reported the synthesis of 3′,3′-difluoro-2′-hydroxymethyl-4′,5 unsaturated carbocyclic nucleoside **385** starting from an ester derivative **380** by a stereoselective silicon-induced Reformatskii–CR followed by RCM sequence (Scheme 63).[73]



Scheme 56



Scheme 57

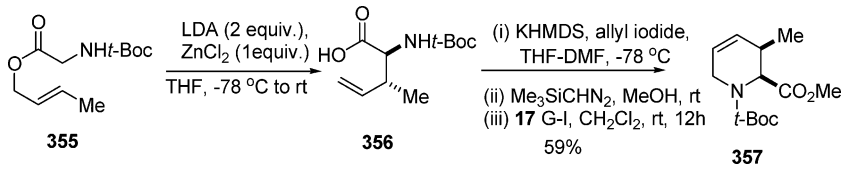
The same author has reported the synthesis of *gem*-difluoromethylenated carbocyclic nucleoside(s) (**392**) from (*Z*)-but-2-ene-1,4-diol (**386**) in 14 steps. The *gem*-difluoromethylene group was incorporated by silicon-induced Reformatskii–CR of chlorodifluoroacetic ester and the carbocyclic ring was then constructed by RCM protocol (Scheme 64).[74]

8. Synthesis of heterocycles by aza–Claisen rearrangement and RCM as key steps

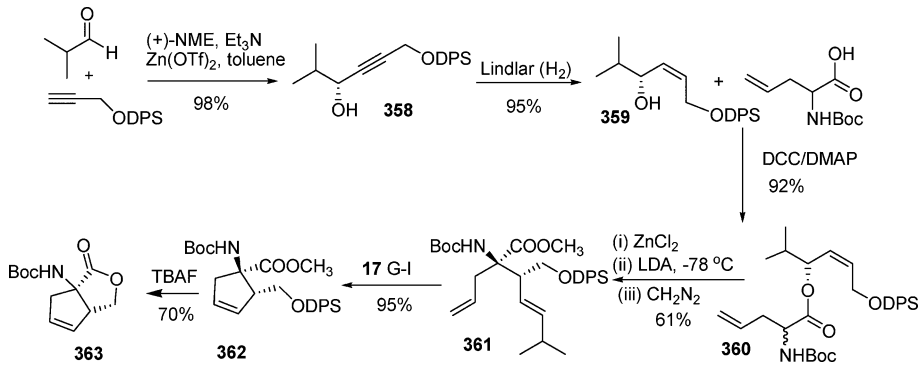
Kim and co-workers described the total synthesis of (–)-antofine and (–)-cryptopleurine by using an efficient route combining Overman rearrangement (aza–CR) and RCM. The required starting material was prepared by coupling phenanthryl bromide **394** with a tin derivative. Next, application of an Overman rearrangement generated (*E*)-allylic trichloroacetamidate **397**. At the end, *N*-allylation of **398** followed by RCM provided the precursor **400** suitable for synthesis of (–)-antofine **401** (Scheme 65).[75]

Van Boom and co-workers illustrated the synthesis of highly functionalized carbocycles by use of Vasella rearrangement followed by an Overman rearrangement and RCM (Scheme 66).[76] The same group reported that this methodology could be extended to the synthesis of the acetonide derivative of (3*S*,4*R*,5*S*)-(+)-4,5-dihydroxycyclopent-l-en-3-ylamine, a key compound to hyper modified nucleoside Q.[77]

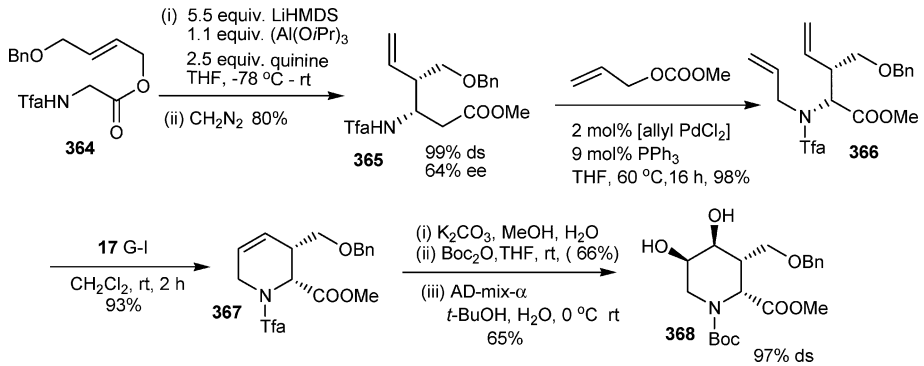
Kotha and co-workers have described the synthesis of 1-benzazepine derivative(s) **415** using aza-CR–RCM as shown in Scheme 67.[78] This simple methodology was realized for the synthesis of 7-substituted 2,3,4,5-tetrahydro-1-benzazepine derivatives



Scheme 58



Scheme 59



Scheme 60

with Suzuki–Miyura cross-coupling, aza–CR and RCM as the key steps.

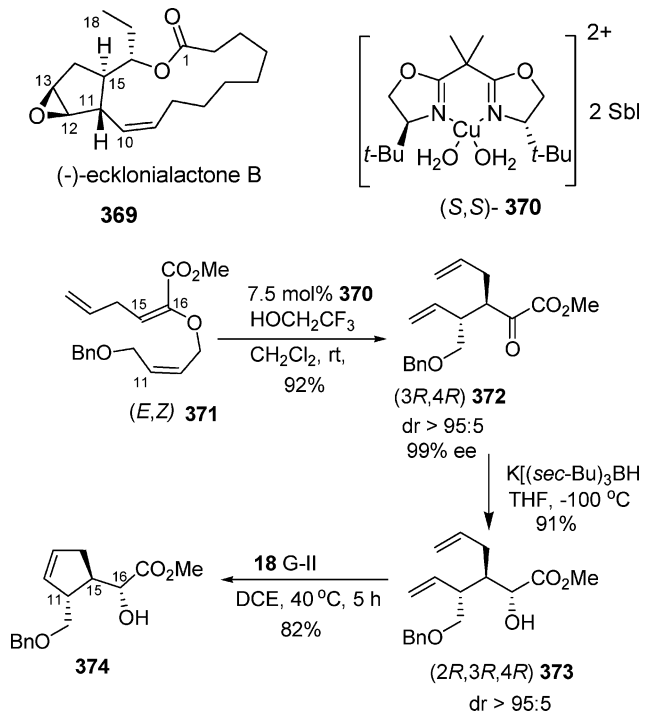
Jamieson and Sutherland have developed a simple and direct route for the synthesis of (+)-α-conhydrin **422** and its pyrrolidine analogue using a palladium(II)-catalyzed, MOM-ether-directed aza–CR to generate the second stereogenic center and subsequent RCM protocol. It was observed that both oxygen atoms of the MOM group were utilized in directing the Pd(II) catalyst to one face of the allylic trichloroacetimidate, resulting in a highly diastereoselective reaction (Scheme 68).[79]

Nubbemeyer and co-workers have synthesized various functionalized (*R*)- and (*S*)-*C*-allylglycine derivatives *e.g.* **425** by employing a chiral auxiliary directed diastereoselective aza CR. High stereoselectivity has been achieved (de > 15 : 1) without loss of chiral information. These derivatives are useful for the synthesis of enantiopure phenanthridine, cyclohexene and alkaloid synthesis. The (*S*)-configured auxiliary pyrrolidine substituent derived from L-proline, always gave (α *R*)-γ,δ-unsaturated amides **425** with high diastereoselectivities *via* a zwitterionic aza-CR as a key step (Scheme 69).[80] The amide derivative **425** was converted to the isoquinolone derivative **426** by iodolactonization and aryl lithium addition reaction without loss of chirality. A second allyl chain was introduced by allyllithium reaction of **426** to deliver the diallylquinoline **427**. Acid hydrolysis of **427** followed by RCM reaction afforded the phenanthridine derivative **429** in 68% yield.

9. Design of miscellaneous targets *via* Johnson orthoester CR and RCM

2′,3′-Nucleosides, such as carbovir and abacavir which are potent anti-HIV agents, have fuelled the growth of new nucleoside research. To this end, Hong and co-workers have demonstrated a convenient procedure for making 4′-cyclopropylated carbovir analogues (**440**) using a sequential Johnson's orthoester CR and RCM protocol (Scheme 70).[81]

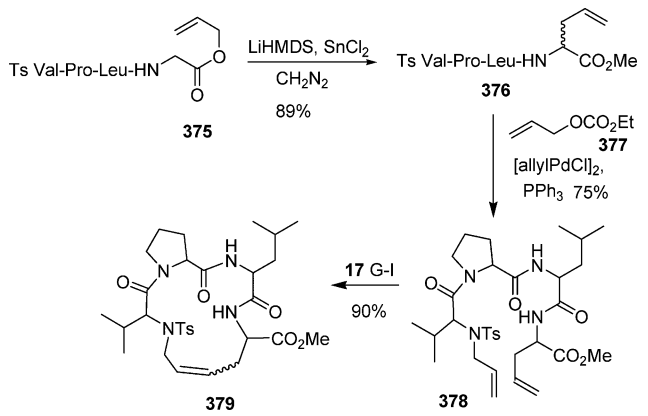
Srikrishna and co-workers reported the total synthesis of (±)-1,14-herbertenediol **449** through (±)-11-*epi*-herbertenolide **448** *via* a simple and efficient methodology based on Johnson CR and RCM as key steps. The starting compound 2-methoxy-5-methylphenyl acetate **441** has been transformed to cinnamyl alcohol **442** and orthoester rearrangement of **442** with triethylorthoacetate and propionic acid followed by RCM furnished (±)-11-*epi*-herbertenolide **448**. Reduction of **448** with LAH gave (±)-1,14-herbertenediol **449** as shown in Scheme 71.[82]



Scheme 61

Sequosempervirin A belongs to the taxodiaceae family that exhibits useful bioactivity. Surprisingly, their biological properties have not been explored. The first step of the syntheses is Horner–Wadsworth–Emmons olefination of the cyclohexanone derivative followed by Johnson CR and RCM sequence leading to *iso*-sequosempervirin A in 81% yield, reported by Maity and Ghosh (Scheme 72).[83]

Florent and co-workers have designed a stereospecific route to the alkylidene cyclopentenone prostaglandin **463** with an unnatural and more stable C-12 configuration. Compound **463** has been reported to be very active *in vivo* against *cis*-platin resistant tumors. The synthesis involved the preparation of the chiral 1,5-



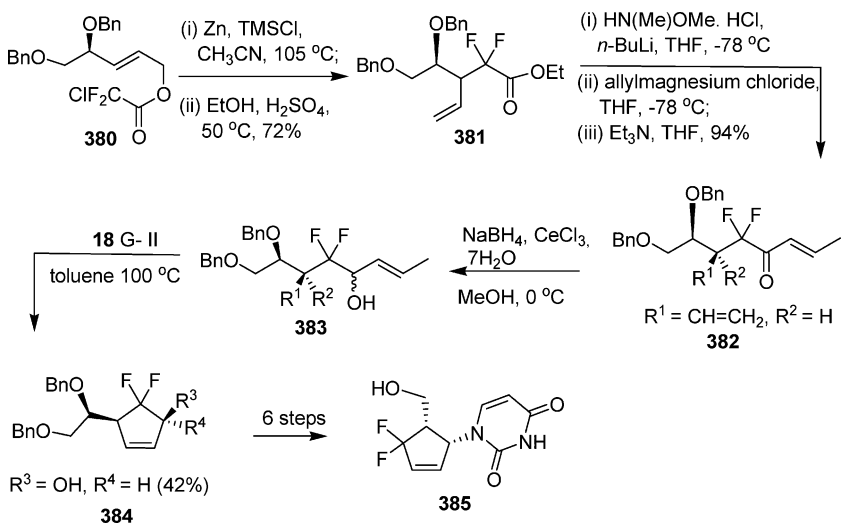
Scheme 62

diene **461** using a stereoselective CR from the allylic alcohol **459** which after vinylation gave the ester derivative **460**. The RCM sequence generated the key cyclopentenol derivative **462** which, after oxidation, gave the cyclopentenone precursor suitable for the prostaglandin synthesis (Scheme 73).[84]

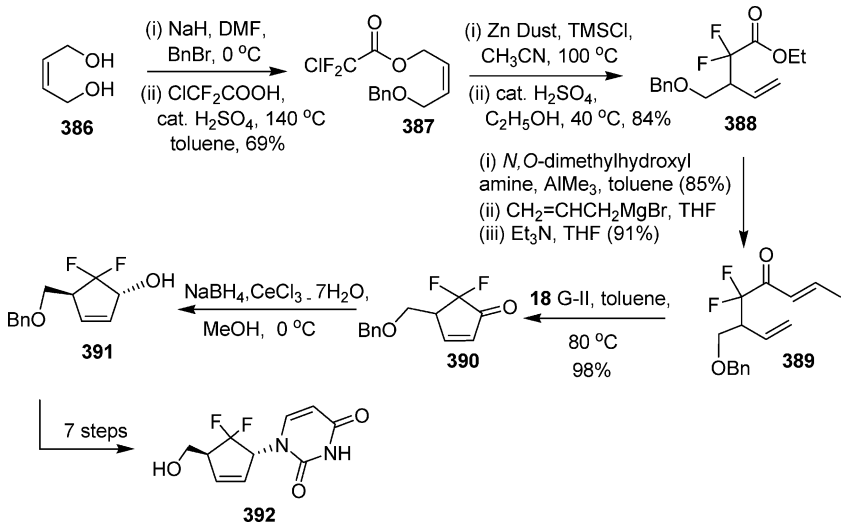
To address drug resistance and toxicity problems in antiviral chemotherapeutics, a number of structurally modified nucleosides have been synthesized. Among them, carbocyclic nucleosides have attracted great attention owing to their interesting chemical and metabolic features. Carbocyclic nucleosides comprise of a unique class wherein a methylene group replaces the oxygen in the furan ring resulting in metabolic stability to endogenous phosphorylase.

Ko and Hong have reported the stereocontrolled synthesis of target nucleosides by Johnson CR and RCM, starting with 1,3-dihydroxy acetone. Nucleoside bases such as adenine and cytosine were coupled with the aid of Pd(0)-catalyzed alkylation in a highly regiocontrolled manner leading to the synthesis of novel 4′α-*C*-hydroxymethyl branched carbocyclic nucleosides such as **470** (Scheme 74).[85]

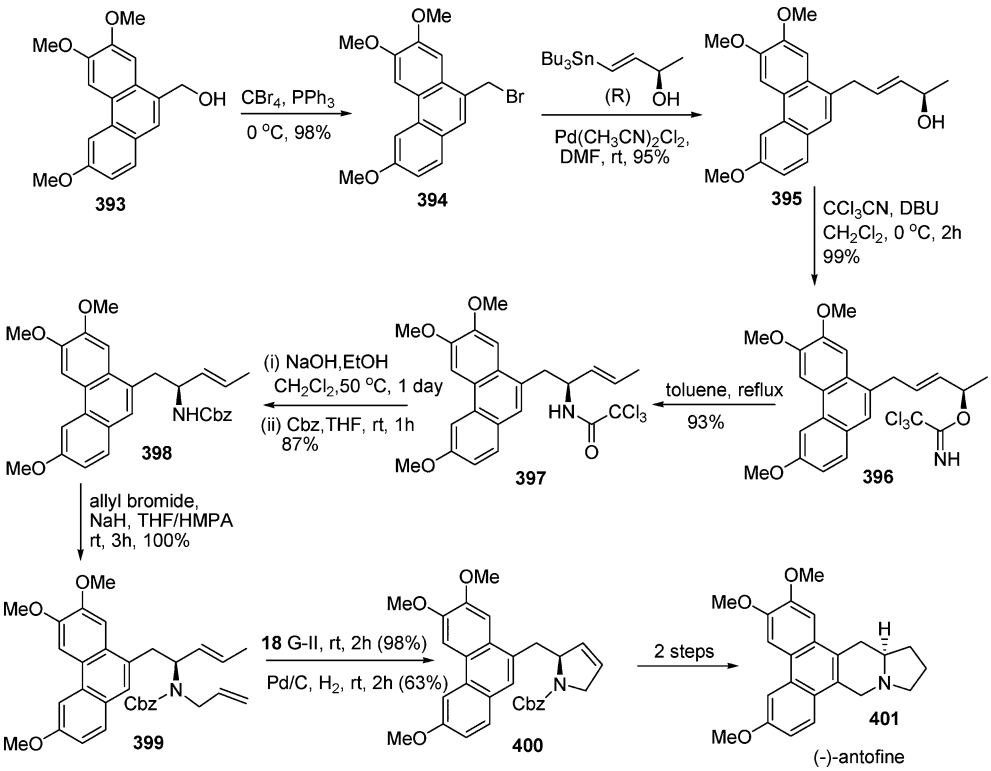
Selig and Bach have demonstrated the first enantioselective total synthesis of (+)-meloscine (**475**), a monoterpenoid indole alkaloid, starting from quinolone derivative **471** in 15 steps with



Scheme 63



Scheme 64

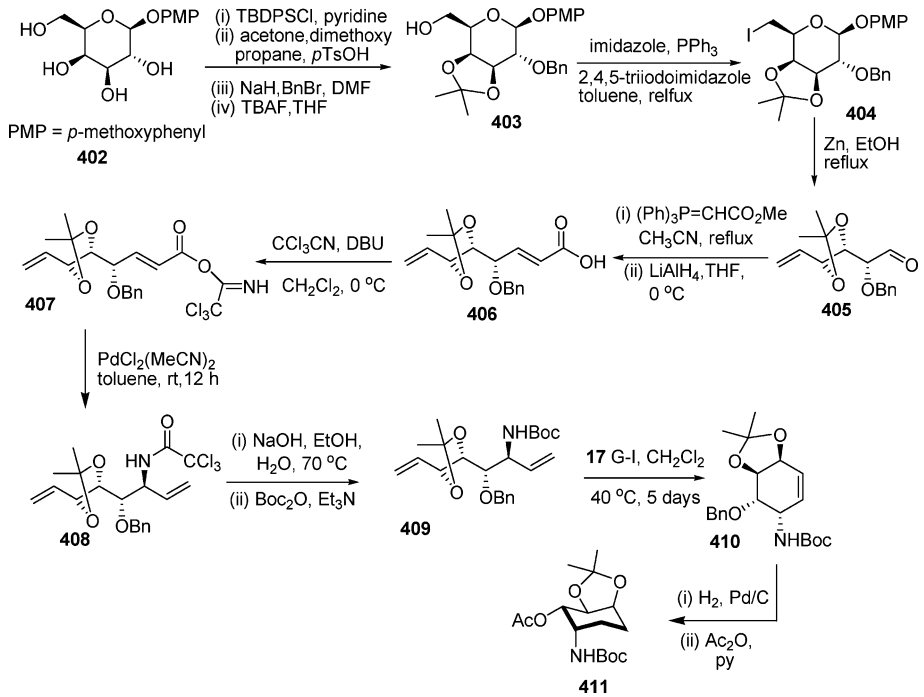


Scheme 65

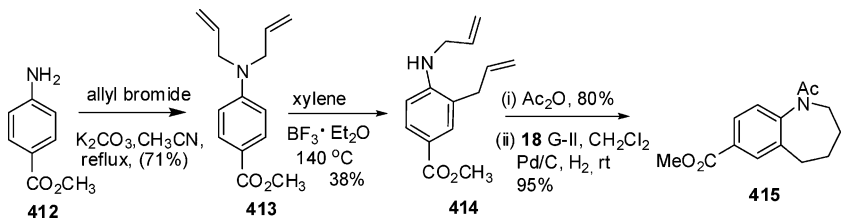
7% overall yield. They have employed Johnson CR followed by RCM to construct the pentacyclic meloquinoline skeleton (Scheme 75).[86]

10. Synthetic utility of ring expansion CR in combination with RCM

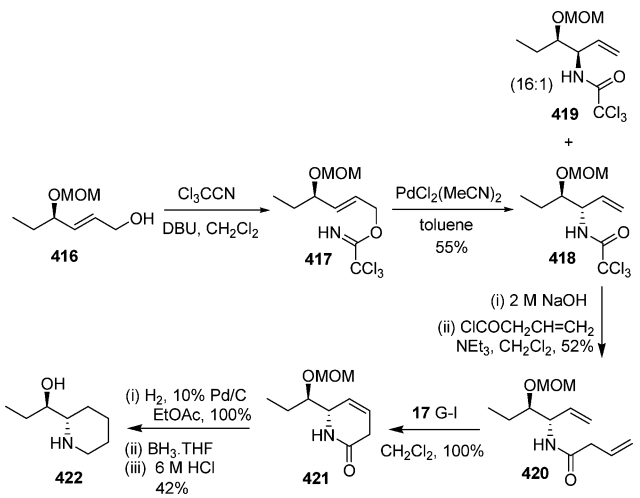
Eleutherobin is an important cytotoxic compound which possesses microtubule stabilizing properties similar to that of paclitaxel.[87] Holmes and co-workers demonstrated the formation of the nine-membered medium ring lactone **478** through Claisen ring expansion methodology.[88] The ring expansion of **477** into the nine-membered lactone **478** was affected through the intermediate ketene acetal generated by selenoxide elimination. The intermediate **477** was prepared from 2-deoxy-D-ribose, the lactone **478** is an important intermediate in the enantioselective synthesis of a simplified analogue of a useful cytotoxic compound eleutherobin. The strategy developed to avoid the formation of bis-cyclopentene from **479** was to protect the interfering endocyclic double bond with an epoxide group and then perform the RCM reaction. Compound **485** constitutes the core bicyclic building block towards the enantioselective synthesis of eleutherobin (Scheme 76).[88]



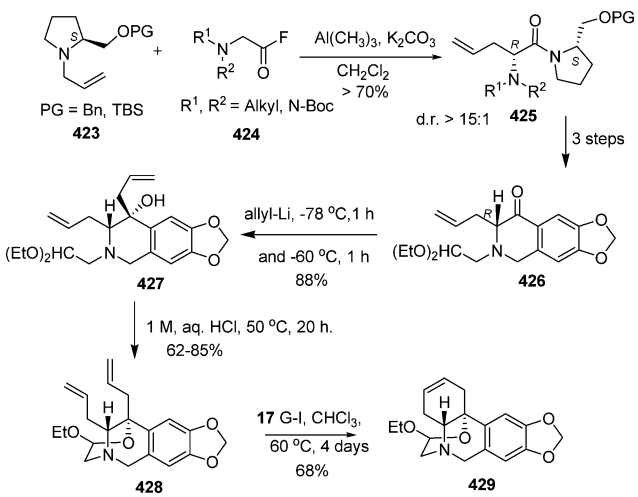
Scheme 66



Scheme 67

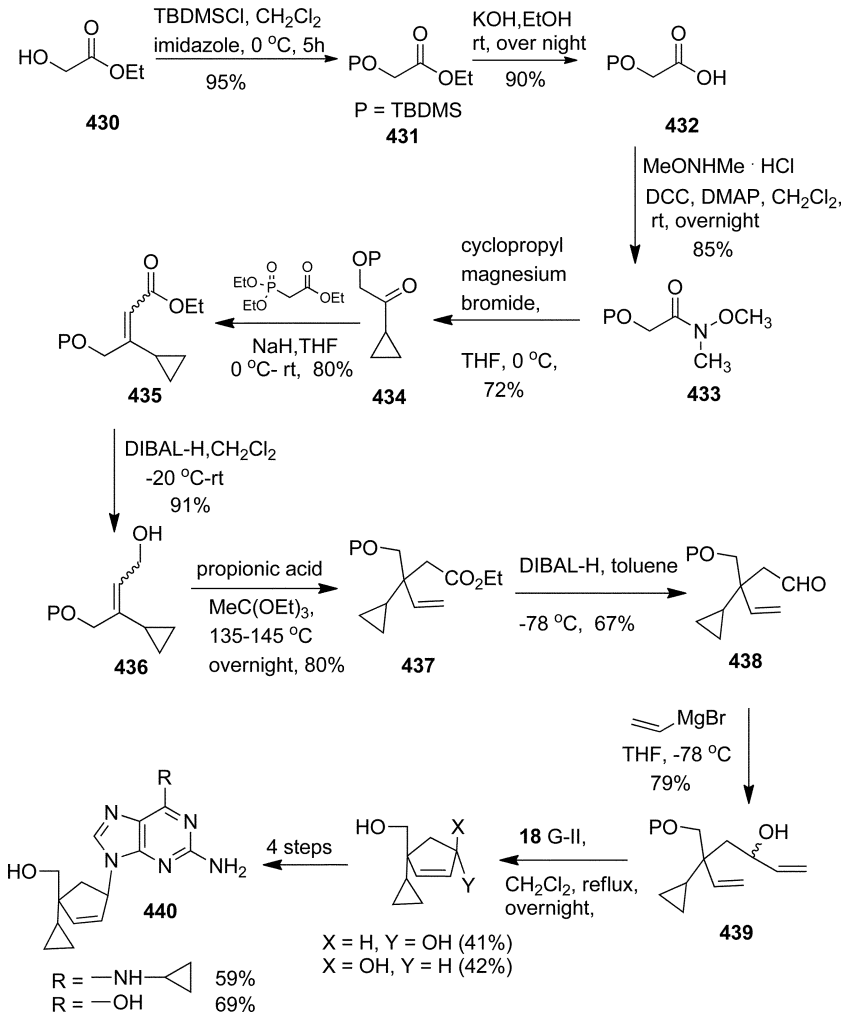


Scheme 68

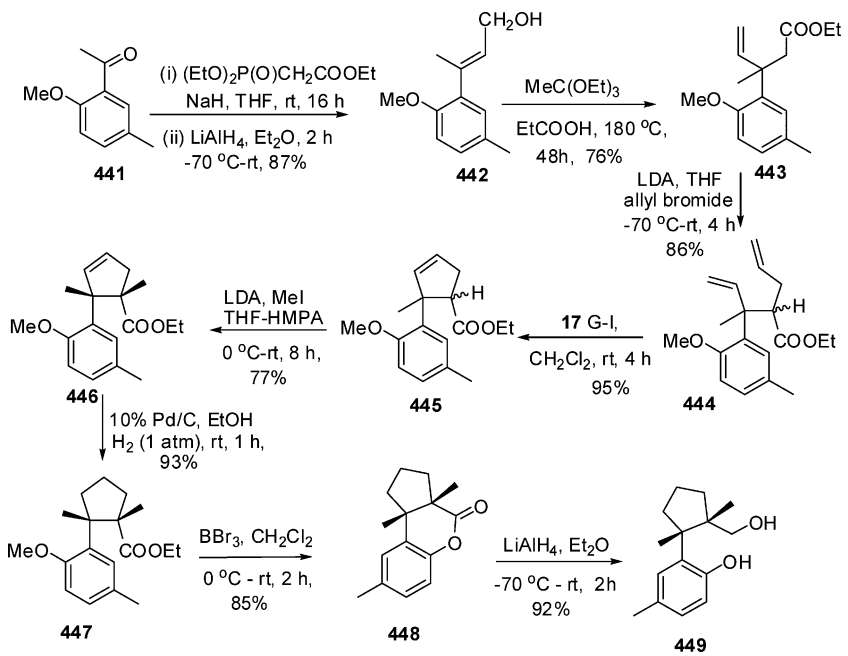


Scheme 69

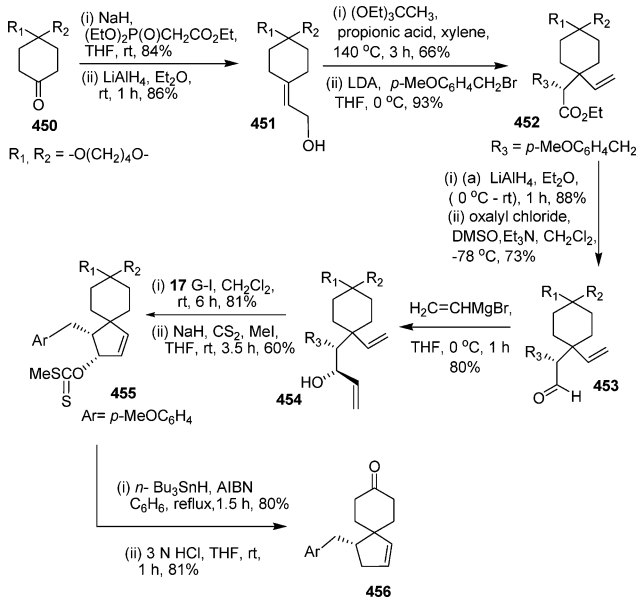
Quinone derivatives constitute an important group of natural pigments and they also participate in a range of biological redox processes. For instance, ubiquinones serve as essential electron transfer agents in the respiratory chain and adriamycin (doxorubicin) and mitomycin C serve as anticancer quinones. A simple and versatile route to benzoquinones based on CR in combination with RCM to form the 19-membered ring **491** has been reported by Davis and Moody.[89] 2-Methyldodeca-1,11-dien-3-ol **486**, prepared by addition of isopropenyl magnesium bromide to 9-decenal, underwent Mitsunobu reaction with 2-nitrophenol.



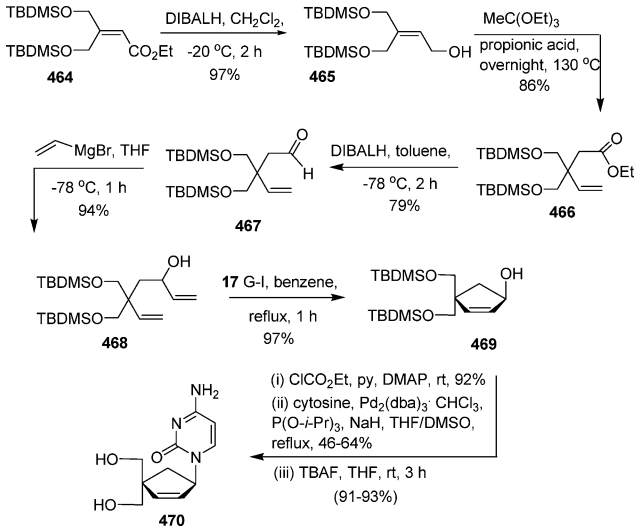
Scheme 70



Scheme 71



Scheme 72



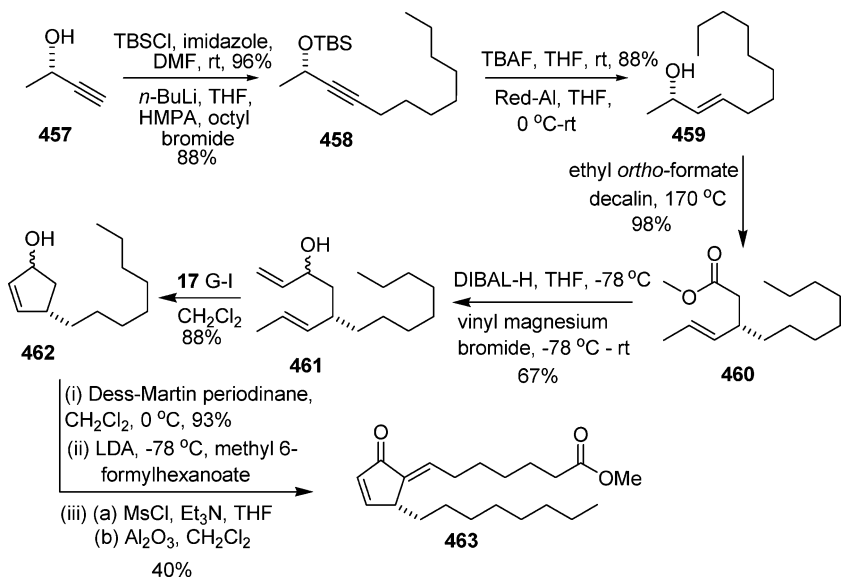
Scheme 74

Reduction of the nitro group followed by reaction with 4-pentenoic acid in the presence of dicyclohexylcarbodiimide (DCC) gave the key substrate **487** (Scheme 77). CR of compound **487** has been accomplished by heating in xylene in the presence of sodium carbonate to deliver the *E*-isomer **489**, which on treatment with **17** G-I gave the 19-membered macrocycle **490** as a 1 : 1 mixture of *E*/*Z*-isomers in 76% yield. Alternatively, RCM reaction of **487** resulted in the formation of 17-membered macrocycle **488** again as a mixture of *E*/*Z*-isomers at the 4–5 double bond in good yield.

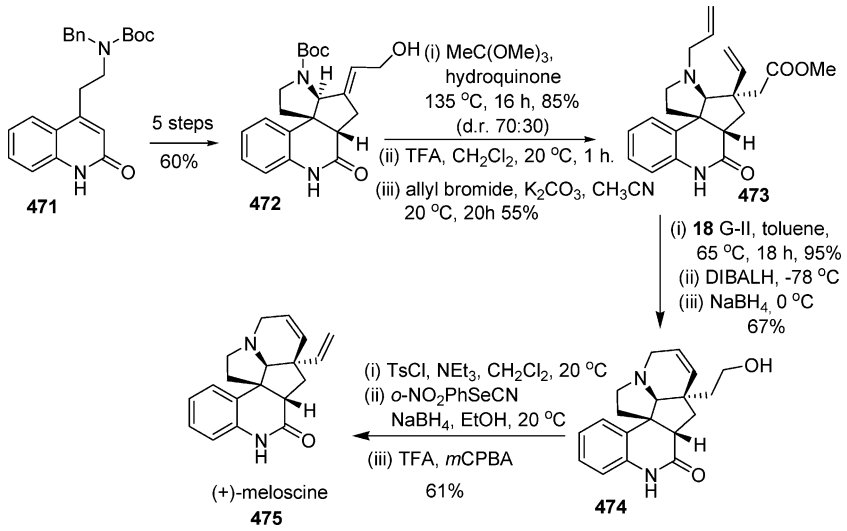
CR of **488** resulted in ring expansion to 19-membered ring **490** followed by oxidation of the phenol moiety with Fremy's salt gave the ansa-bridged benzoquinone **491** as a mixture of *E*/*Z*-isomers.

11. Conclusions

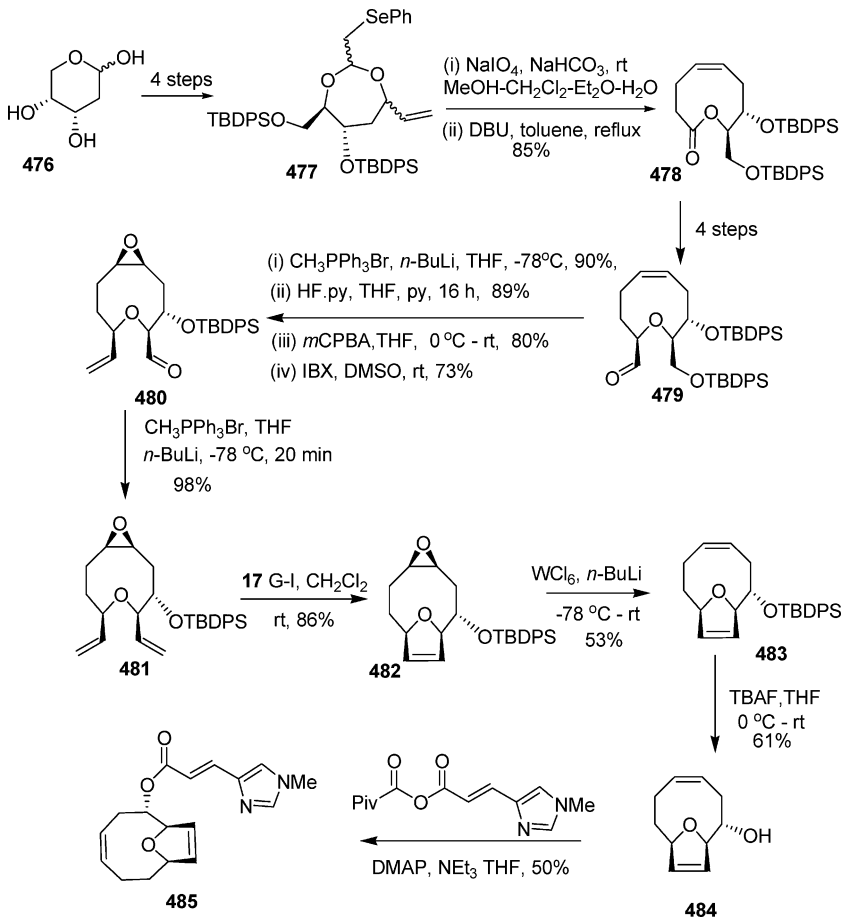
With the advent of new catalysts that can tolerate a variety of functional groups, olefin metathesis has emerged as a powerful strategy and has been employed in the design of a wide variety of complex molecules with multiple functionalities. CR is a well established process and it takes place through a highly ordered six-membered transition state and therefore the stereochemical outcome can easily be predicted. With the availability of several variations of CR a diverse range of carbonyl compounds with an olefinic appendage can be produced. Since carbonyl compounds are central in C–C bond formation protocol, a combination of CR and olefin metathesis can provide an efficient synthetic route to many intricate targets with a reduced number of synthetic steps. Here it was shown that a combination of CR and olefin metathesis has grown into an important method of choice. We anticipate that several such advances will appear in the future at an increasing



Scheme 73



Scheme 75

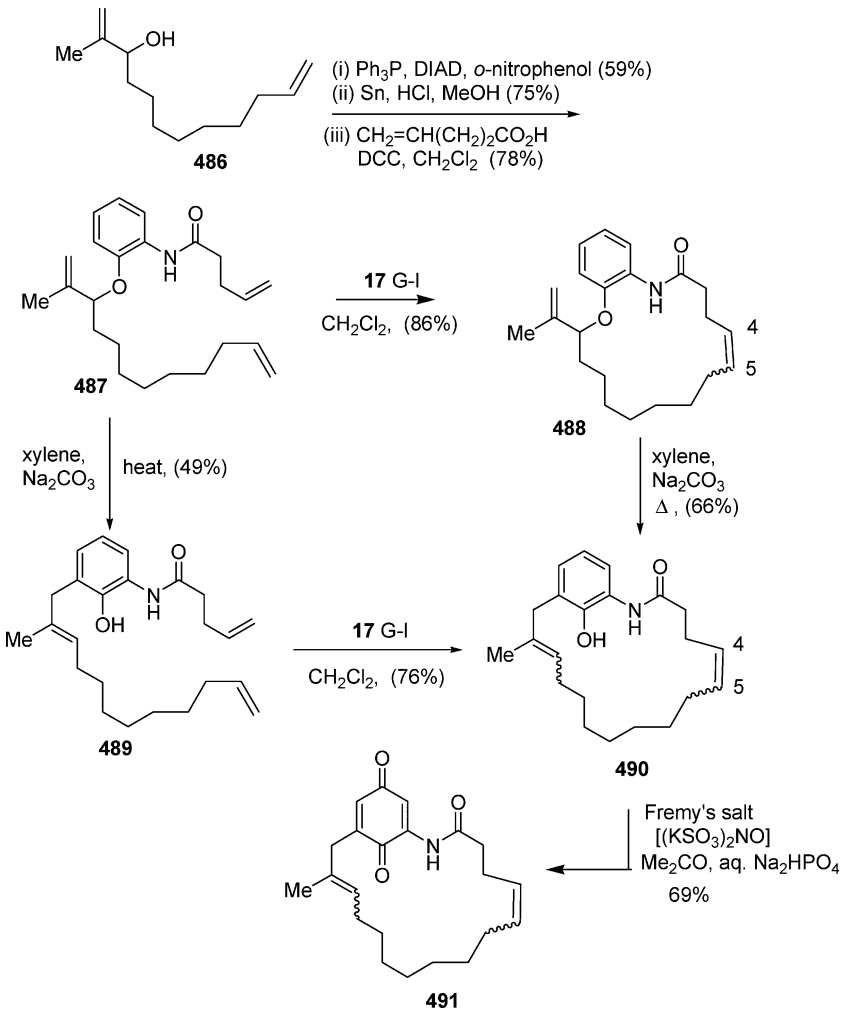


Scheme 76

rate. We hope that this review may inspire the development of new strategies based on CR in combination with olefin metathesis. CR in alliance with olefin metathesis may provide practical solutions to biologically important targets which in turn broaden their structural diversity.

Acknowledgements

We thank DST (New Delhi) for generous financial support of our research activities over the past decades. SK thanks the DST for the award of J. C. Bose fellowship.



Scheme 77

References

1 (*a*) L. Claisen, *Ber. Dtsch. Chem. Ges.*, 1912, **45**, 3157–3166; (*b*) J. B. Daskiewicz, C. Bayet and D. Barron, *Tetrahedron Lett.*, 2001, **42**, 7241–7244; (*c*) S. Kotha, N. Sreenivasachary and E. Brahmachary, *Tetrahedron*, 2001, **57**, 6261–6265; (*d*) T. Durand-Reville, L. B. Gobbi, B. L. Gray, S. V. Ley and J. S. Scott, *Org. Lett.*, 2002, **4**, 3847–3850; (*e*) A. M. Jacob and C. J. Moody, *Tetrahedron Lett.*, 2005, **46**, 8823–8825.

2 (*a*) P. Wipf, in *Comprehensive Organic Synthesis*, 1991 B. Trost and I. Fleming (ed.) Pergamon Press, New York, Vol. 5; (*b*) F. E. Ziegler, *Chem. Rev.*, 1988, **88**, 1423–1452; (*c*) R. P. Lutz, *Chem. Rev.*, 1984, **84**, 205–247; (*d*) U. Nubbemeyer, *Synthesis*, 2003, 961–1008; (*e*) A. M. M. Castro, *Chem. Rev.*, 2004, **104**, 2939–3002; *The Claisen Rearrangement, Methods and Applications*, 2007 M. Hiersemann and U. Nubbemeyer (ed.) Wiley-VCH, Weinheim.

3 (*a*) D. S. Tarbell, *Org React.*, 1944, **2**, 1–48; (*b*) S. J. Rhoads and N. R. Raulins, *Org. React.*, 1975, **22**, 1–252; (*c*) B. Ganem, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 936–945.

4 (*a*) R. E. Ireland and R. H. Mueller, *J. Am. Chem. Soc.*, 1972, **94**, 5897–5898; (*b*) R. E. Ireland and A. K. Willard, *Tetrahedron Lett.*, 1975, **16**, 3975–3978; (*c*) F. E. Ziegler, *Acc. Chem. Res.*, 1977, **10**, 227–232; (*d*) Y. Chai, S. Hong, H. A. Lindsay, C. McFarland and M. C. McIntosh, *Tetrahedron*, 2002, **58**, 2905–2928.

5 A. E. Wick, D. Felix, K. Steen and A. Eschenmoser, *Helv. Chim. Acta*, 1964, **47**, 2425–2429.

6 W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T-T. Li, D. J. Faulkner and M. R. Petersen, *J. Am. Chem. Soc.*, 1970, **92**, 741–743.

7 (*a*) *Handbook of Metathesis*, R. H. Grubbs (ed) Wiley-VCH, Weinheim, 2003, Vol. 1-3; (*b*) R. H. Grubbs, R. R. Schrock and A. Fürstner, *Adv. Synth. Catal.*, 2007, **349**, 1–265; (*c*) *Metathesis in Natural Product Synthesis*, 2010 J. Cossy, S. Arsencyalis and C. Mayer (ed.) Wiley-VCH, Weinheim; (*d*) S. P. Nolan and H. Clavier, *Chem. Soc. Rev.*, 2010, **39**, 3305–3316; (*e*) A. H. Hoveyda, S. J. Malcolmson, S. J. Meek and A. R. Zhugralin, *Angew. Chem., Int. Ed.*, 2010, **49**, 34–44; (*f*) J. M. Basset, C. Coperet, D. Soulivong, M. Taoufik and C. J Thivolle, *Acc. Chem. Res.*, 2010, **43**, 323–334; (*g*) W. A. van Otterlo and C. B. de Koning, *Chem. Rev.*, 2009, **109**, 3743–3782; (*h*) S. Kotha, M. Meshram and A. Tiwari, *Chem. Soc. Rev.*, 2009, **38**, 2065–2092; (*i*) C. Samojlowicz, M. Bieniek and K. Grela, *Chem. Rev.*, 2009, **109**, 3708–3742; (*j*) S. Kotha and K. Mandal, *Chem.–Asian J.*, 2009, **4**, 354–362; (*k*) S. Kotha and K. Lahiri, *Synlett*, 2007, 2767–2784; (*l*) K. Grela, *Angew. Chem., Int. Ed.*, 2008, **47**, 5504–5507; (*m*) N. Holub and S. Blechert, *Chem.–Asian J.*, 2007, **2**, 1064–1082; (*n*) H. Villar, M. Frings and C. Bolm, *Chem. Soc. Rev.*, 2007, **36**, 55–66; (*o*) B. M. Trost, M. U. Frederiksen and M. T. Rudd, *Angew. Chem., Int. Ed.*, 2005, **44**, 6630–6666; (*p*) K. C. Nicolaou, P. G. Bulger and D. Sarlah, *Angew. Chem., Int. Ed.*, 2005, **44**, 4490–4527; (*q*) A. M. Harned, M. Zhang, P. Vedantham, S. Mukherjee, R. H. Herpel, D. L. Flynn and P. R. Hanson, *Aldrichimica Acta*, 2005, **38**, 3–16; (*r*) S. Kotha and N. Sreenivasachary, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 2001, **40**, 763–780.

8 (*a*) R. R. Schrock, J. S. Murdzek, G. C. Bazan, J. Robins, M. DiMare and M. O'Regan, *J. Am. Chem. Soc.*, 1990, **112**, 3875–3886; (*b*) R. R. Schrock, *Macromolecules*, 1996, **29**, 6114–6125.

9 (*a*) S. T. Nguyen, L. K. Johnson and R. H. Grubbs, *J. Am. Chem. Soc.*, 1992, **114**, 3974–3975; (*b*) P. Schwab, R. H. Grubbs and J. W. Ziller, *J. Am. Chem. Soc.*, 1996, **118**, 100–110.

10 J. L. Herisson and Y. Chauvin, *Makromol. Chem.*, 1971, **141**, 161–176.
11 (*a*) S. Kotha, A. C. Deb and R. V. Kumar, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 1039–1043; (*b*) S. Kotha and A. C. Deb, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 2008, **47**, 1120–1134.
12 R. Schobert and J. M. U. González, *Tetrahedron Lett.*, 2005, **46**, 3657–3660.
13 B. M. Trost, G. Dong and J. A Vance, *J. Am. Chem. Soc.*, 2007, **129**, 4540–4541.
14 A. H. Butt, J. M. Percy and N. S. Spencer, *Chem. Commun.*, 2000, 1691–1692.
15 C. Audouard, J. Fawcett, G. A. Griffith, E. Kerouredan, A. Miah, J. M. Percy and H. Yang, *Org. Lett.*, 2004, **6**, 4269–4272.
16 P. Dubé and F. D. Toste, *J. Am. Chem. Soc.*, 2006, **128**, 12062–12063.
17 A. Srikrishna, V. H. Pardeshi and P. Thriveni, *Tetrahedron: Asymmetry*, 2008, **19**, 1392–1396.
18 U. Majumdar, J. M. Cox, H. W. B. Johnson and J. D. Rainier, *Chem.–Eur. J.*, 2006, **12**, 1736–1746.
19 M. Satake, M. Murata and T. Yasumoto, *J. Am. Chem. Soc.*, 1993, **115**, 361–362.
20 W. A. L. van Otterlo, E. L. Ngidi, E. M. Coyanis and C. B. de Koning, *Tetrahedron Lett.*, 2003, **44**, 311–313.
21 K. S. Huang, S. R. Li, Y. F. Wang, Y. L. Lin, Y. H. Chen, T. W. Tsai, C. H. Yang and E. C. Wang, *J. Chin. Chem. Soc.*, 2005, **52**, 159–167.
22 (*a*) W. A. L. van Otterlo, E. L. Ngidi, S. Kuzvidza, G. L. Morgans, S. S. Moleele and C. B. de Koning, *Tetrahedron*, 2005, **61**, 9996–10006; (*b*) J.-L. Panayides, R. Pathak, H. Panagiotopoulos, H. Davids, M. A. Fernandes, C. B. de Koning and W. A. L. van Otterlo, *Tetrahedron*, 2007, **63**, 4737–4747.
23 K. Huang and E. Wang, *Tetrahedron Lett.*, 2001, **42**, 6155–6157.
24 T. N. Van, M. D'hooghe, S. Pattyn and N. D. Kimpe, *Synlett*, 2004, 1913–1916.
25 T. W. Tsai and E. C. Wang, *J. Chin. Chem. Soc.*, 2004, **51**, 1019–1023.
26 S. Kotha, K. Mandal, A. Tiwari and S. M. Mobin, *Chem.–Eur. J.*, 2006, **12**, 8024–8038.
27 S. Kotha and K. Mandal, *Tetrahedron Lett.*, 2004, **45**, 1391–1394.
28 K. C. Majumdar, R. Islam, H. Rahaman and B. Roy, *Org. Biomol. Chem.*, 2006, **4**, 2393–2398.
29 K. C. Majumdar, H. Rahaman, R. Islam and B. Roy, *Tetrahedron Lett.*, 2006, **47**, 2111–2113.
30 S. Rotzoll, H. Görls and P. Langer, *Synthesis*, 2008, 45–52.
31 S. K. Chattopadhyay, S. Maity and S. Panja, *Tetrahedron Lett.*, 2002, **43**, 7781–7783.
32 S. K. Chattopadhyay, R. Dey and S. Biswas, *Synthesis*, 2005, 403–406.
33 A. Roy, B. Biswas, P. K. Sen and R. V. Venkateswaran, *Tetrahedron Lett.*, 2007, **48**, 6933–6936.
34 S. J. Spessard and B. M. Stoltz, *Org. Lett.*, 2002, **4**, 1943–1946.
35 M. Albrecht, O. Osetska and R. Frohlich, *Eur. J. Org. Chem.*, 2007, 4902–4908.
36 S. Tischer and P. Metz, *Adv. Synth. Catal.*, 2007, **349**, 147–151.
37 A. M. Palmer, B. Grobbel, C. Jecke, C. Brehm, P. J. Zimmermann, W. Buhr, M. P. Feth, W. A. Simon and W. Kromer, *J. Med. Chem.*, 2007, **50**, 6240–6264.
38 S. Kotha, V. Seema, K. Singh and K. D. Deodhar, *Tetrahedron Lett.*, 2010, **51**, 2301–2304.
39 S. Kotha, S. Misra and S. Halder, *Tetrahedron*, 2008, **64**, 10775–10790.
40 S. Kotha and K. Mandal, *Tetrahedron Lett.*, 2004, **45**, 2585–2588.
41 S. K. Chattopadhyay, B. K. Pal and S. Maity, *Chem. Lett.*, 2003, **32**, 1190–1191.
42 S. K. Chattopadhyay, D. Ghosh and K. Neogi, *Synth. Commun.*, 2007, **37**, 1535–1543.
43 S. Kotha and M. K. Dipak, *Chem.–Eur. J.*, 2006, **12**, 4446–4450.
44 S. K. Chattopadhyay, T. Biswas and S. Maity, *Synlett*, 2006, 2211–2214.
45 S. D. Burke, R. A. Ng, J. A. Morrison and M. J. Alberti, *J. Org. Chem.*, 1998, **63**, 3160–3161.
46 H. Ko, E. Kim, J. E. Park, D. Kim and S. Kim, *J. Org. Chem.*, 2004, **69**, 112–121.
47 W. Picoul, R. Urchegui, A. Haudrechy and Y. Langlois, *Tetrahedron Lett.*, 1999, **40**, 4797–4800.
48 P. Beaulieu and W. W. Ogilvie, *Tetrahedron Lett.*, 2003, **44**, 8883–8885.
49 S. Kotha, A. Deb, K. Lahiri and E. Manivannan, *Synthesis*, 2009, 165–193.
50 C. E. Stivala and A. Zakarian, *J. Am. Chem. Soc.*, 2008, **130**, 3774–3776.
51 A. Srikrishna and R. Ramesh Babu, *Tetrahedron Lett.*, 2007, **48**, 6916–6919.
52 A. Srikrishna and B. Vasantha Lakshmi, *Synlett*, 2005, 1173–1175.
53 A. G. M. Barrett, M. Ahmed, S. P. Baker, S. P. D. Baugh, D. C. Braddock, P. A. Procopiou, A. J. P. White and D. J. Williams, *J. Org. Chem.*, 2000, **65**, 3716–3721.
54 M. S. Wilson, J. C. S. Woo and G. R. Dake, *J. Org. Chem.*, 2006, **71**, 4237–4245.
55 Y. Song, S. Hwang, P. Gong, D. Kim and S. Kim, *Org. Lett.*, 2008, **10**, 269–271.
56 M. Lee, T. Lee, E. Y. Kim, H. Ko, D. Kim and S. Kim, *Org. Lett.*, 2006, **8**, 745–748.
57 O. Bedel, A. Français and A. Haudrechy, *Synlett*, 2005, 2313–2316.
58 O. Bedel, A. Haudrechy and Y. Langlois, *Eur. J. Org. Chem.*, 2004, 3813–3819.
59 M. Amador, X. Ariza, J. Garcia and J. Ortiz, *J. Org. Chem.*, 2004, **69**, 8172–8175.
60 K. Fujiwara, A. Goto, D. Sato, H. Kawai and T. Suzuki, *Tetrahedron Lett.*, 2005, **46**, 3465–3468.
61 D. Sato, K. Fujiwara, H. Kawai and T. Suzuki, *Tetrahedron Lett.*, 2008, **49**, 1514–1517.
62 M. Speitling, I. Grün-Wollny, F. G. Hannske and H. Laatsch, *12 and 13 IRSEER Naturstofftage der DECHEMA e. V. Irsee*, 2000 and 2001.
63 S. Marchart, J. Mulzer and V. S. Enev, *Org. Lett.*, 2007, **9**, 813–816.
64 U. Kazmaier and S. Maier, *Org. Lett.*, 1999, **1**, 1763–1766.
65 H. Mues and U. Kazmaier, *Synthesis*, 2001, 487–498.
66 J. H. Hong, C-H. Oh and J-H. Cho, *Tetrahedron*, 2003, **59**, 6103–6108.
67 S. Kim, H. Ko, T. Lee and D. Kim, *J. Org. Chem.*, 2005, **70**, 5756–5759.
68 J. F. Miller, A. Termin, K. Koch and A. D. Piscopio, *J. Org. Chem.*, 1998, **63**, 3158–3159.
69 N. P. Probst, A. Haudrechy and K. Plé, *J. Org. Chem.*, 2008, **73**, 4338–4341.
70 H. Mues and U. Kazmaier, *Synthesis*, 2001, 487–498.
71 Q. Wang, A. Millet and M. Hiersemann, *Synlett*, 2007, 1683–1686.
72 U. Kazmaier, S. Maier and F. L. Zumpe, *Synlett*, 2000, 1523–1535.
73 Y. Y. Yang, J. Xu, Z. W. You, X. H. Xu, X. L. Qiu and F. L. Qing, *Org. Lett.*, 2007, **9**, 5437–5440.
74 Y. Y. Yang, W. D. Meng and F. L. Qing, *Org. Lett.*, 2004, **6**, 4257–4259.
75 S. Kim, T. Lee, E. Lee, J. Lee, G-J. Fan, S. K. Lee and D. Kim, *J. Org. Chem.*, 2004, **69**, 3144–3149.
76 H. Ovaa, J. D. C. Codée, B. Lastdrager, H. S. Overkleeft, G. A. Van Der Marel and J. H. van Boom, *Tetrahedron Lett.*, 1999, **40**, 5063–5066.
77 H. Ovaa, J. D. C. Codée, B. Lastdrager, H. S. Overkleeft, G. A. vander Marel and J. H. van Boom, *Tetrahedron Lett.*, 1998, **39**, 7987–7990.
78 S. Kotha and V. R. Shah, *Eur. J. Org. Chem.*, 2008, 1054–1064.
79 A. G. Jamieson and A. Sutherland, *Org. Lett.*, 2007, **9**, 1609–1611.
80 N. Zhang, W. Münch and U. Nubbemeyer, *Adv. Synth. Catal.*, 2004, **346**, 1335–1354.
81 L. J. Liu, J. C. Yoo and J. H. Hong, *Nucleosides, Nucleotides Nucleic Acids*, 2008, **27**, 1186–1196.
82 A. Srikrishna and M. S. Rao, *Tetrahedron Lett.*, 2002, **43**, 151–154.
83 S. Maity and S. Ghosh, *Tetrahedron Lett.*, 2007, **48**, 3355–3358.
84 R. Weaving, E. Roulland, C. Monneret and J. C. Florent, *Tetrahedron Lett.*, 2003, **44**, 2579–2581.
85 O. H. Ko and J. H. Hong, *Tetrahedron Lett.*, 2002, **43**, 6399–6402.
86 P. Selig and T. Bach, *Angew. Chem., Int. Ed.*, 2008, **47**, 5082–5084.
87 T. Lindel, P. R. Jensen, W. Fenical, B. H. Long, A. M. Casazza, J. Carboni and C. R. Fairchild, *J. Am. Chem. Soc.*, 1997, **119**, 8744–8745.
88 G. C. H. Chiang, A. D. Bond, A. Ayscough, G. Pain, S. Ducki and A. B. Holmes, *Chem. Commun.*, 2005, 1860–1862.
89 C. J. Davis and C. J. Moody, *Synlett*, 2002, 1874–1876.

