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Modular Approaches to Cyclopentanoids and their Heteroanalogs

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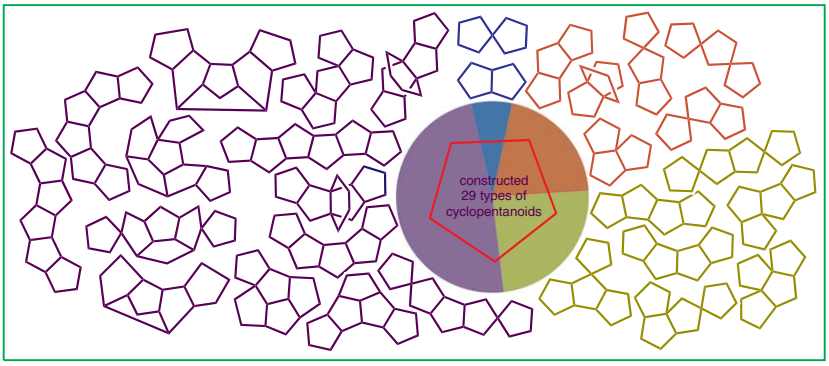

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Abstract Cyclopentanoids and their derivatives are interesting targets in synthetic organic chemistry due to their extensive applications in various branches of chemical sciences like pharmaceuticals, natural and non-natural products. In view of these applications, several synthetic strategies have been developed in the past three to four decades. In this article, we describe our work towards the synthesis of cyclopentanoids and their heteroanalogs involving diverse synthetic strategies during the past two decades. Among these, photo-thermal olefin metathesis, ring-closing metathesis, ring-rearrangement metathesis, cyclopentane annulation, [2+2+2] cycloaddition and Diels–Alder reactions have been used to assemble cyclopentane rings of diverse architecture.

Key words cyclopentanoids, metathesis, cycloaddition, allylation, Grignard reaction, Fischer indolization, Claisen rearrangement

1 Introduction

Polyquinanes consist of fused cyclic compounds containing three or more cyclopentane rings. Cyclopentanoids are considered as privileged structures, present in numerous natural (Figures 1–3, **N1**–**N101**) and non-natural products (Figure 4), and they are core structures of several drug-related molecules. After the structure elucidation of the first cyclopentanoid natural product, i.e., hirsutic acid C (Figure 2, **N54**) in 1966, several cyclopentanoid natural products were isolated from a wide range of plant, microbial, and marine sources. Since then, synthesis of natural and non-natural products containing cyclopentane rings has become a vibrant area of chemical research. Hirsutic acid C is a linearly fused triquinane based sesquiterpene with potent antibiotic and antitumor properties, isolated from basidiomycetes *Stereum hirsutum* in 1946.[1] Similarly, coriolin (Figure 2, **N55**) is a linear triquinane with eight asymmetric centers, that displays prominent antibacterial and antitumor activities,[2] hirsutene (Figure 2, **N56**) is a known fungal metabolite isolated from basidomycete *Coriolus consors*,[3] and cucumins A–C (Figure 2, **N57**–**N59**) were isolated from mycelial cultures of the agaric *Macrocystidia cucumis* and found to display promising antimicrobial and antitumor activities.[4] Subergorgic acid (Figure 2, **N71**) is an angularly fused triquinane with cardiotoxic activity, isolated from the Pacific gorgonian coral *Subergorgia subeross*[5] and its derivatives act as a promising antifouling agents.[6] Likewise, retigeranic acid (Figure 2, **N83** and **N84**) is an angularly fused sesterterpenoid that exhibits a wide range of pharmacological properties.[7]

Presilphiperfolanol belongs to cyclohexane fused diquinane sesquiterpenes with modest biological activity. In this category, presilphiperfolan-8α-ol (Figure 1, **N8**) was the first member to be isolated from *Eriophyllum staechadifolium* and *Flourensia heterolepis*.[8] The later presilphiperfolan-9α-ol (Figure 1, **N9**) was isolated from *Artemisia lacina-*

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ta and *Artemisia chamaemelifolia*, which possesses toxicity to the peripheral and central nervous system of insects as well as antifeedant properties, and application as a fragrance compound.[9] Finally, presilphiperfolan-1β-ol (Figure 1, **N10**), which was isolated from the fern *Anemia tomentosa var. anthriscifolia* and characterized, exhibits potent antimycobacterial properties.[10] Crinipellin A (Figure 3, **N89**) contains angularly and fused linear triquinane hybrid tetraquinane and was found to exhibit potent antibiotic activity; it was first isolated from the strain of basidiomycetes fungus *Crinipellis stipitaria* (Agaricales).[11]

Spiro compounds are prevalent structures in medicinal chemistry due to their occurrence in nature; they exhibit intrinsic complexity, conformational rigidity, and their structural features display several biological properties and impressive applications in various fields.[12] Among spiro compounds, fredericamycin A (Figure 1, **N48**) is a well-known antibiotic and antitumor agent, isolated from a strain of *Streptomyces griseus*, which contains a hexacyclic ring system featuring two spiro cyclopentane rings.[13] Interestingly, indane and its derivatives are important structural motifs found in a large number of medicinally useful natural products and therapeutic agents.[14] For example, pallidol (Figure 1, **N49**) is a dimer of resveratrol, initially isolated form *Cusses pallida* and later from red wine, and it shows strong antioxidant and antifungal activities.[15] Furthermore, some of these compounds are useful as catalysts and chiral ligands with significant applications in organic syntheses and also suitable in designing numerous metallocene complexes.[16]

Cyclopentane fused with arenes and hetero-arenes are also interesting targets in drug discovery programs due to their presence as core units in several bioactive natural products and pharmaceuticals. For instance, roseophilin (Figure 1, **N53**) is a cyclopentane fused pyrrole macrocycle with significant antibiotic and anticancer properties that was isolated from *Streptomyces griseoviridis*.[17] Nakadomarin A (Figure 1, **N47**) is a cyclopentannulated furan alkaloid with potential antimicrobial and cyclin-dependent kinase 4 inhibitory activities.[18] Among the hetero-quinanes, the cyclopenta[*b*]indole core is a good scaffold due to its occurrence in a large number of natural products with diverse biological activities, medicinally important compounds and drugs.[19] For example, Fischerindole L (Figure 1, **N50**), which shows good cytotoxic activity against lung cancer cell line HCl-H460, was isolated from *Fischerella muscicola*.[20] Yuehchukene (Figure 1, **N31**) is a cyclopentannulated bis-indole scaffold, isolated from *Murraya paniculata*, that possesses estrogenic and anti-fertility activities.[21] Spiroindimicins B–D (Figure 2, **N86**-**N88**) feature spiro bis-indole frameworks with moderate cytotoxicity against several cancer cell lines.[22] Other biologically interesting natural products bearing fused/spiro cyclopentane ring systems like ramipril (Figure 1, **N2**), paxilline (Figure 1, **N18**), (–)-agelastatin A (Figure 1, **N3**), variecolol (Figure 1, **N16**) and spiroapplanatumine K (Figure 1, **N22**) and some other natural products are shown in Figures 1–3.[23]

In addition, cyclopentannulated thiophenes and benzothiophenes are an interesting class of heterocycles because of their significant applications in pharmaceutical chemistry and materials science.[24a–c] Hence, several syn-

Biographical Sketches

Prof. Sambasivarao Kotha received his M. Sc. degree in Chemistry from the University of Hyderabad (UoH) and then obtained a Ph.D. in Organic Chemistry from UoH in 1985. He continued his research at the UoH as a postdoctoral fellow for one and a half years. Later, he moved to UMIST Manchester, UK, and the University of Wisconsin, USA, as a research associate. Subsequently, he was appointed as a visiting scientist at Cornell University and as a research chemist at Hoechst Celanese Texas before joining IIT Bombay in 1994 as an Assistant Professor. In 2001, he was promoted to Professor. He has published 295 publications in peer-reviewed journals and was elected as a fellow of various academies (FNASc, FASc, FRSC, and FNA). He was also associated with the editorial advisory board of several journals. His research interests include organic synthesis, green chemistry, unusual amino acids, peptide modification, cross-coupling reactions, and metathesis. Currently, he occupies the Pramod Chaudhari Chair Professor in Green Chemistry (Praj Industries).

Dr. Yellaiah Tangella was born in Telangana, India. He obtained the master degree in Organic Chemistry from SR&BGNR College, Kakatiya University and received his Ph.D (2019) in chemical sciences from CSIR-Indian Institute of Chemical Technology, Hyderabad under the supervision of Dr. Bathini Nagendra Babu and co-supervision of Dr. Ahmed Kamal. He is currently a postdoctoral researcher under the guidance of Prof. S. Kotha at Department of Chemistry, Indian Institute of Technology Bombay, and Mumbai, India. His research interests include the development of novel strategies to access diverse medicinally interesting heterocycles.

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thetic approaches have been explored towards the preparation of these privileged structural motifs involving classical and transition-metal mediated approaches. However, as a part of our major research program, we have developed diverse synthetic strategies to various polyquinanes using cycloaddition reactions [e.g., (2+2), (4+2) (Diels–Alder (DA) reaction),[24d,e] retro-Diels–Alder reaction[24f] and (2+2+2)], Claisen rearrangement (CR),[24g] ring-closing metathesis (RCM),[24h,i] ring-opening metathesis (ROM), ring-rearrangement metathesis (RRM),[24j] ring-opening cross-metathesis (ROCM),[24k] ring-closing enyne metathesis (RCEM),[24l] enyne ring-rearrangement metathesis (ERRM), photo-thermal olefin metathesis and Fischer indolization (FI)[24m] as key steps.

There are several theoretically interesting molecules (Figure 4) such as dodecahedrane (**T1**), pagodane (**T2**), trishomocubane (**T3**), [5]prismane (**T4**), [4]peristylane (**T5**), and [4.5]coronane (**T6**) and trinorbonane (**T7**), which contain fused five-membered rings. Heptacyclotetradecane (**T8**) contains a heptacyclic system, which is considered a rich repository of five-membered rings.[25a,b]

Even though several reviews have been reported,[7c] to our knowledge none of these reviews cover the synthetic approaches that deal with a broad range of polyquinanes that are described here. The current review includes a detailed account of various synthetic transformations developed in our group over the last few decades. Here, we covered the synthesis of a variety of linear, angular, fused, and

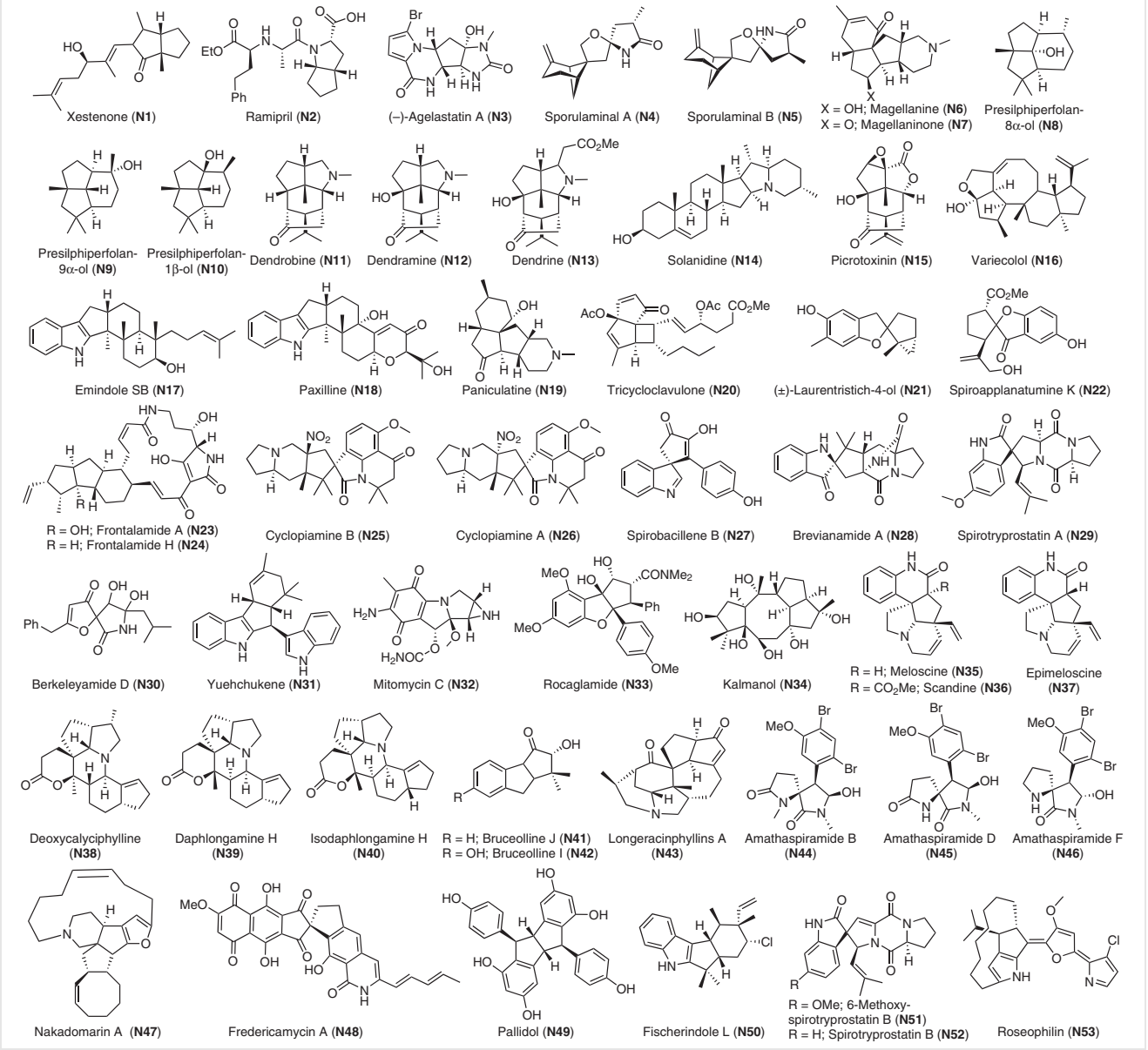

Figure 1 Medicinally interesting natural products containing at least two five membered rings.

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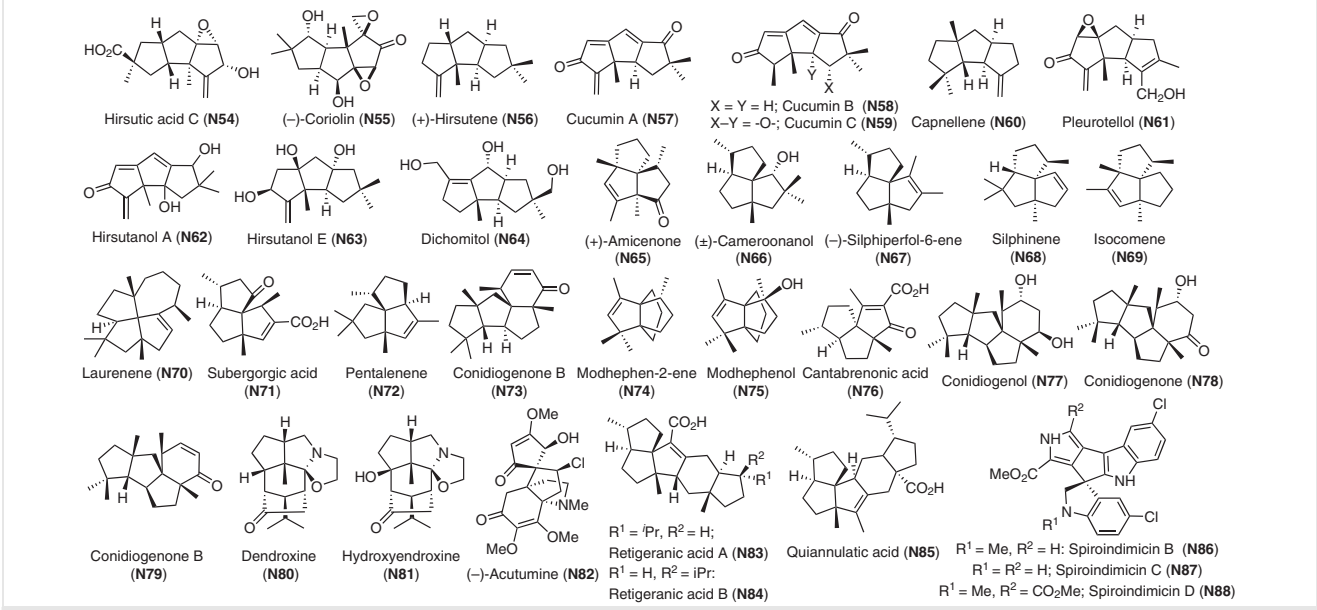

Figure 2 Medicinally interesting natural products containing three cyclopentane rings

spiro polyquinane derivatives and their hetero analogs from our work. We have shown all major possible arrangements of various cyclopentanoids up to four five-membered rings (Figure 5). For example, when two five-membered rings are involved, two possible arrangements are shown in Figure 5(i). Similarly, in case of three five-membered rings, eight possible arrangements are shown in Figure 5(ii). Figure 5(iii) shows some of the possible arrangements of four five membered rings. We did not show all the possible stereochemical arrangements at the ring junction. During our discussion we have mentioned most of the synthetic schemes that we reported from our group. By no means does Figure 5 contain all the possible arrangements. However, most of the major possible arrangements are included.

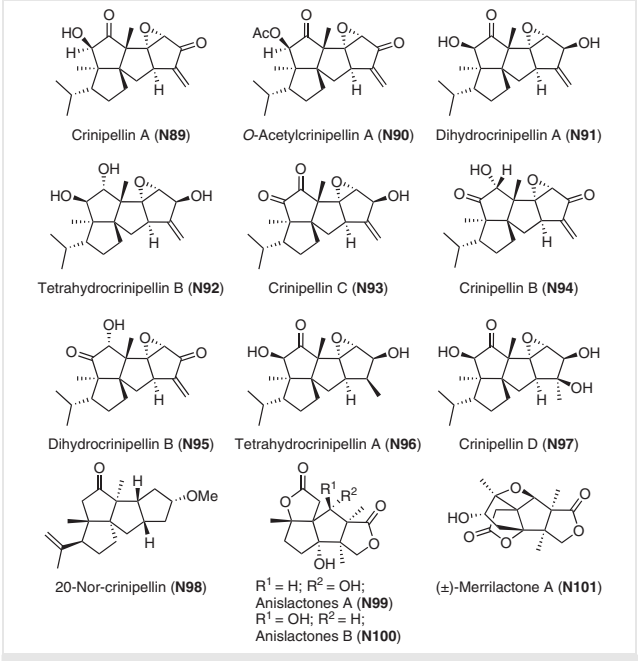

Figure 3 Medicinally interesting natural products containing four five-membered rings

2 Synthesis of Spiro[4.4]nonane (A1) Derivatives

Spirocyclic [4.4] scaffolds containing a carbo framework or heteroatom containing unit are widely represented in natural products. Figure 6 demonstrates the variety of [4.4] spirocyclic scaffolds present in diverse natural product domains.[25c] Several such combinations were prepared in our study. In 1999, our group reported an efficient two-step method for the synthesis of spiro derivatives in good to excellent yields from commercially available compounds con-

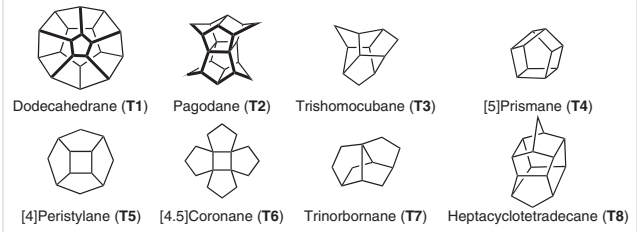

Figure 4 Theoretically important molecules containing five-membered rings

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taining a β-diketone moiety such as **1** through metathesis. Initially, we prepared the RCM precursor **2** through a Pd-catalyzed diallylation of 1,3-carbonyl compounds **1**. Later on, treatment of diallyl dione **2** with a catalytic amount of ruthenium catalyst generated the spiro derivatives **3** in good yields (Scheme 1).[25d,e]

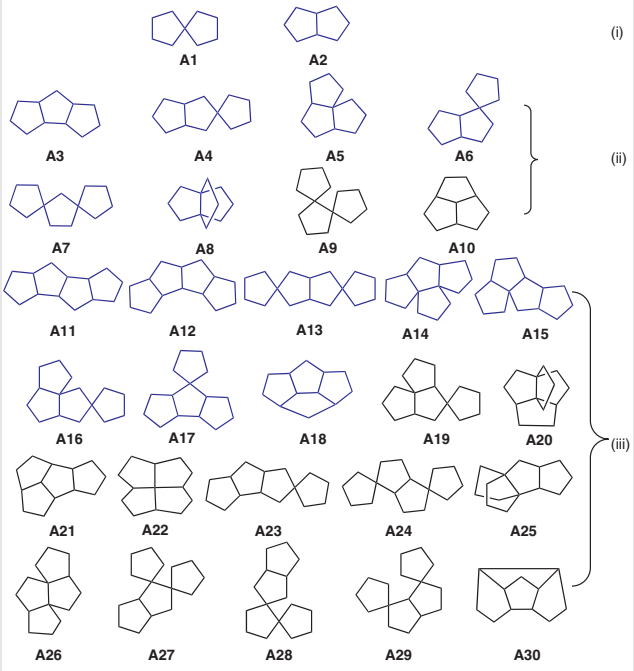


Figure 5 Possible assemblies of cyclopentanoids containing two, three, and four cyclopentane rings

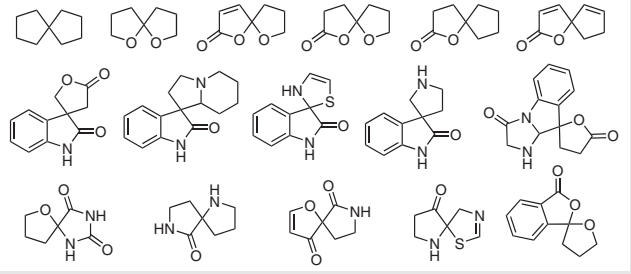
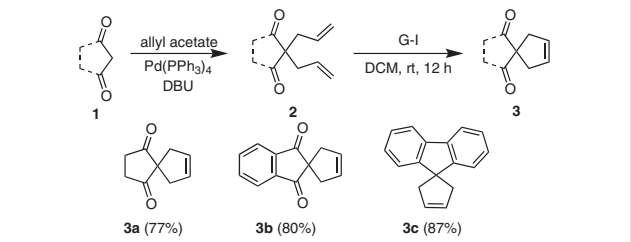


Figure 6 Diverse [4.4.0] spirocyclic scaffolds present in the natural products



Scheme 1 Synthesis of spiro derivatives **3a–c** by RCM

In 2015, we reported an efficient strategy to generate diverse spirocycles through a [2+2+2] cycloaddition and DA reaction sequence starting with readily available substrates. We begin our journey with the propargylation of active methylene compounds (AMCs) such as **4** containing carbonyl or β-dicarbonyl functionality with propargyl bromide (**5**) under basic conditions to generate the dipropargyl derivative **6** (Scheme 2). The cycloaddition sequence of **6** with 2-butyne-1,4-diol (**7**) in the presence of a catalytic amount of Wilkinson's catalyst [$Rh(PPh_3)_3Cl$] and titanium isopropoxide [$Ti(O^iPr)_4$] provides the spiro diol **8**, which was further utilized in the next step without any purification. These diols were converted into the dibromo compounds **9** by treating with PBr_3. The dibromo compounds on reaction with rongalite produced spiro-sultine derivatives **10** in good yields. Further, treatment of sultines with various dienophiles **11** generated the corresponding cycloadducts through a DA sequence, which was aromatized using DDQ to give **12**. Aromatic bromo derivatives are useful substrates to generate a library of new compounds using the cross-coupling reactions (Scheme 2).[26]

Recently, we demonstrated an efficient synthetic protocol for the construction of the ABCD ring fragment of the natural product, fredericamycin A (Figure 1, **N48**), from commercially available inexpensive starting materials utilizing CR, DA reaction and RCM as key steps. To this end, we started our journey with a known indanone derivative **13** (Scheme 3). Later, the key RCM precursor **15** was prepared by the treatment of the indanone **13** with allyl bromide (**14**) in the presence of sodium hydride (NaH). Then, the RCM of diallyl compound **15** with Grubbs' second-generation (G-II) catalyst furnished the desired BCD ring system **16** of the fredericamycin A in 89% yield. Finally, sequential transformations consisting of oxidation, DA reaction, CR and RCM generated the ABCD fragment **17** of the fredericamycin A, involving seven steps (Scheme 3).[27]

Carbon-rich polycyclic aromatic hydrocarbons (PAHs) have been attracting a great deal of interest due to their unique photophysical properties. We envisioned a new approach to truxene **18** and spirotruxene such as **21**, as important building blocks for the preparation of aromatic dendrimers. The truxene **18** was prepared by acid-mediated cyclotrimerization of 1-indanone in 70% yield. Nitration of **18** followed by allylation at three active methylene sites provided the corresponding hexaallyl precursor **20**, which undergoes G-II catalyzed metathesis to generate the spirotruxene **21** in 80% yield (Scheme 4). This strategy has also been extended to synthesize spirofluorene derivatives in good yield.[28]

Kotha and Ali reported a diversity-oriented approach to spiro diquinanes bearing α-amino acids (AAAs), and sulfones starting from easily accessible AMCs. Treatment of AMCs **22** with tetrabromo derivative **23** in the presence of potassium carbonate (K_2CO_3) gave the key precursor spiro dibromo derivatives **24** (Scheme 5). Later, K_2CO_3 mediated alkylation reaction of dibromo compound **24** with diethyl

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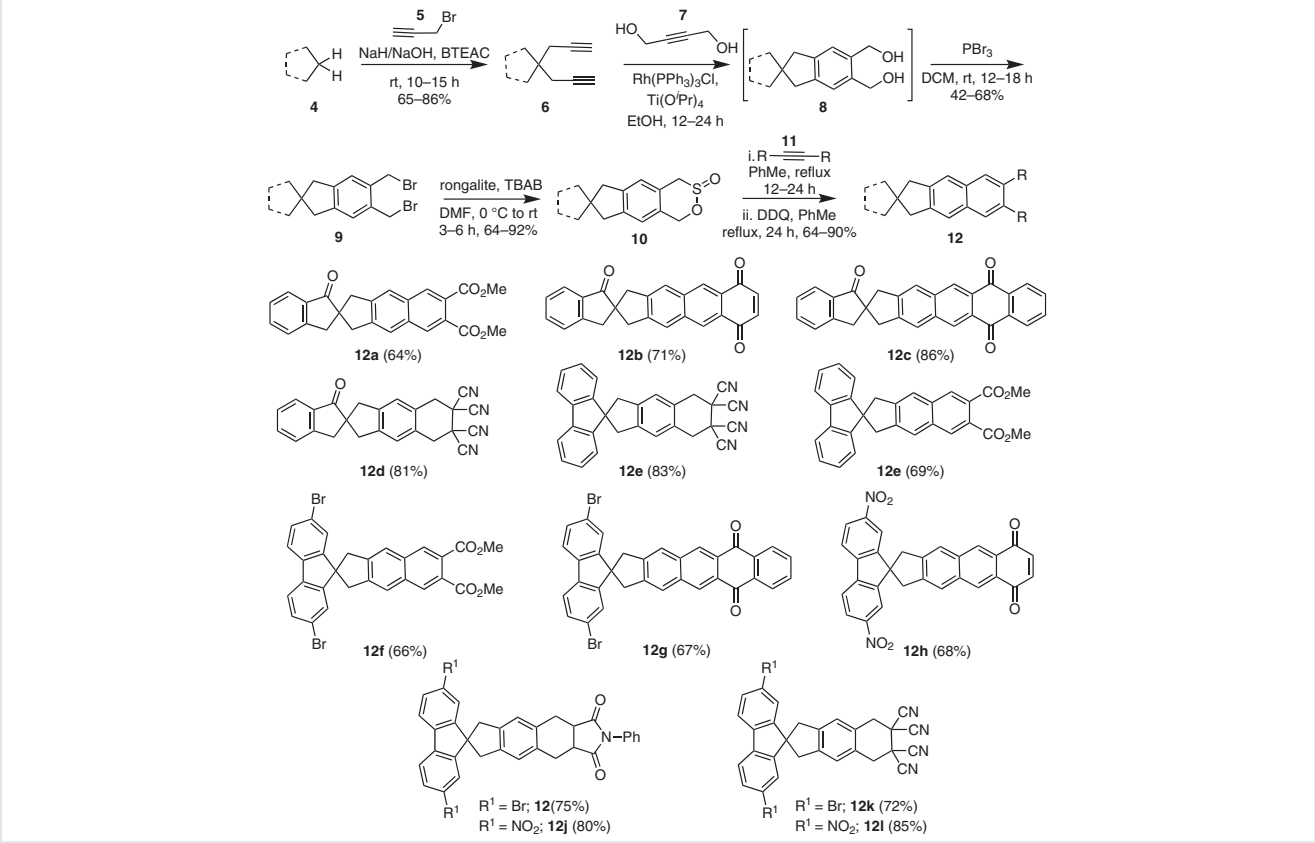
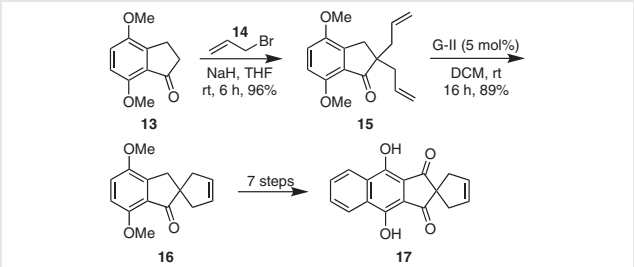


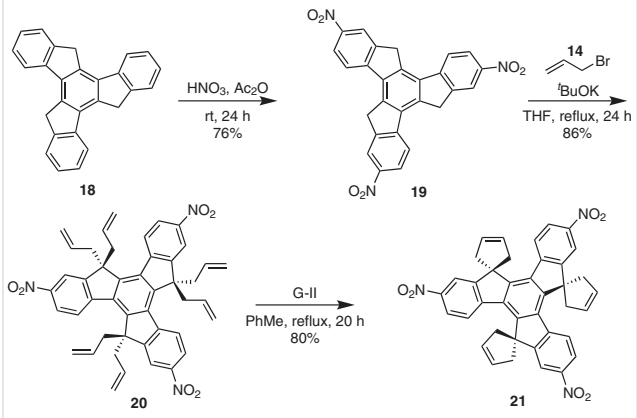
Scheme 2 Synthesis of diverse spirocycles containing two five-membered rings

acetamidomalonate (DEAM) furnished the spiro 1,2,3,4-tetrahydroisoquionline-3-carboxylic acid (Tic) derivatives **25** in good yields. Likewise, the same reaction with ethyl isocyanoacetate (EICA)[29a] instead of DEAM followed by hydrolysis with conc. HCl/EtOH provided the corresponding constrained AAA derivatives **26**.[29b,c] Afterwards, treatment of compound **24** with EICA followed by hydrolysis and acetylation with acetic anhydride led to the formation of spiro *N*-acetyl AAA derivative **27** in 66% yield. Finally, the dibromo building blocks **24** were treated with rongalite to generate the sultine derivatives, which then rearranged to the spirosulfones **28** in good yields under thermal conditions (Scheme 5).[29d]



Scheme 3 Synthesis of the ABCD ring system of fredericamycin A (**N48**)

We have successfully demonstrated the RCEM and DA strategy for the synthesis of indan-based spiroquinanes in good to moderate yields. A selective monopropargylation of indan-1,3-dione (**29**) with propargyl bromide (**5**) was accomplished with 10% KOH and catalytic amounts of copper powder (Scheme 6). Subsequently, allylation of **30** was realized under the phase-transfer catalysis (PTC) conditions to



Scheme 4 Synthesis of spirotruxene **21**

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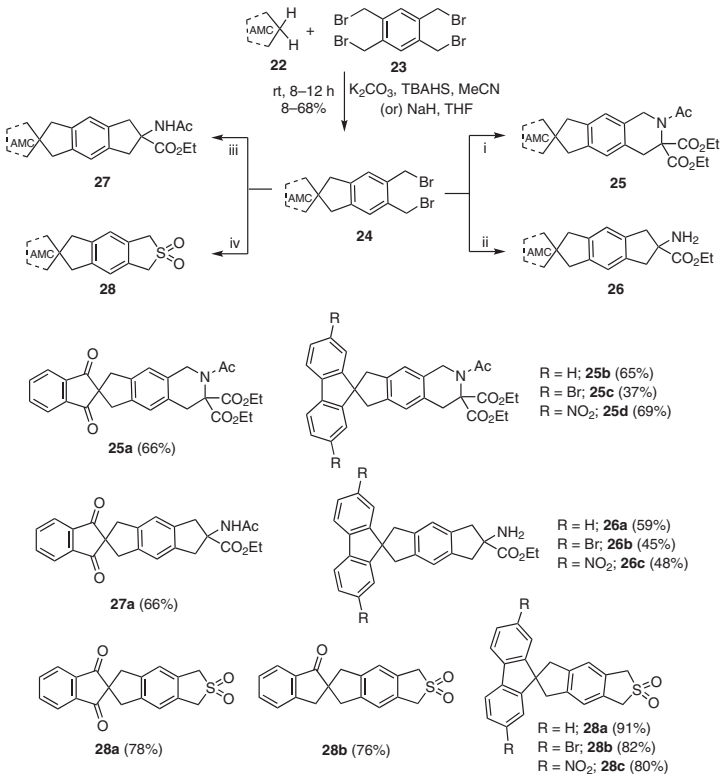
provide the corresponding RCEM precursor **31**. The RCEM of **31** gave the desired diene **32** in the presence of G-II catalyst and a catalytic amount of $Ti(OiPr)_4$. Finally, the DA cycloaddition of diene **32** with a variety of dienophiles (**11**) followed by MnO_2 aided aromatization yielding the corresponding indan-based spiro derivatives **33** (Scheme 6). Subsequently, the key intermediate indane-based diene **34** was obtained from the commercially available indan-1,3-dione (**29**) through a multi-step synthetic sequence. The diene **34** was treated with diverse alkyne partners **11** followed by the DDQ oxidation to deliver the corresponding spiro-indane derivatives **35** in good yields (Scheme 7). This strategy produced a library of interesting spiro-indanes **35a–d**.[30]

In addition, we also constructed the indan-based spiro compounds in good to moderate yields by utilizing the [4+2] and [2+2+2] cycloaddition strategies. To this end, we synthesized two key intermediates **37** and **38** through the alkylation of indan-1,3-dione (**29**) under PTC conditions with propargyl bromide (**5**) and 2,3-bis(iodomethyl)buta-1,3-diene (**36**) respectively (Scheme 8). The [2+2+2] cycloaddition of **37** with various acetylene derivatives **11** furnished the corresponding spiro derivatives. Similarly, DA reaction of **38** provides intricate spiro compounds containing quinone moiety in good yields (Scheme 8). Higher yields were obtained in [4+2] cycloaddition than [2+2+2] cycloadditions.[31]

We have successfully assembled complex spiroindane derivatives **46** by employing the DA cycloaddition and ROCM as key steps. For this purpose, cyclopentadiene (**41**) was treated with 1,2-bis(bromomethyl)benzene (**40**) in the presence of potassium hydroxide (KOH) under the PTC conditions to generate the sprirodiene **42**, which, upon DA cycloaddition with quinone derivatives **43**, provided the corresponding DA adducts **44**. Finally, spiroindane derivatives **46** were produced in good yields by the ROCM with G-II catalyst form DA adducts **44** and 1,4-diacetoxybut-2-ene **45** (Scheme 9).[32]

The synthesis of norbornene fused spiro diquinane **49** was realized starting with the key precursor *endo*-dicyclopentadiene-1-one (**47**), which was obtained from the commercially available dicyclopentadiene based on the known protocol. Reduction of **47** with Zn-AcOH followed by the allylation with allyl bromide (**14**) in the presence of NaH gave the diallyl compound **48**. Later, the diallyl derivative **48** was treated with G-II catalyst to produce the corresponding unsaturated spiro diquinane **49** in 82% yield (Scheme 10). Spiro norbornene **49** was further utilized to assemble a li-



Scheme 5 A diversity-oriented approach to spiro aromatic compounds. *Reagents and conditions*: i. DEAM, K_2CO_3, TBAHS, MeCN, rt, 15–20 h, 37–69%; ii. (a) EICA, K_2CO_3, TBAHS, MeCN, rt, 14–17 h; (b) HCl/EtOH, rt, 1–2 h, 45–59%; iii. (a) EICA, K_2CO_3, TBAHS, MeCN, rt, 14–17 h; (b) acetic anhydride (Ac_2O), MeCN, 30 h, 66%; iv. (a) rongalite, TBAB, DMF, 0 °C–rt, 3–6 h, 64–92%, (b) PhMe, reflux, 10–15 h 76–91%.

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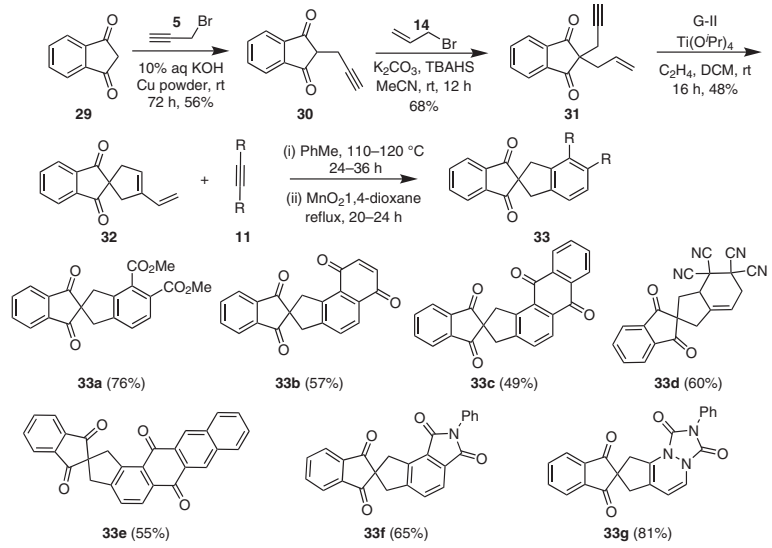
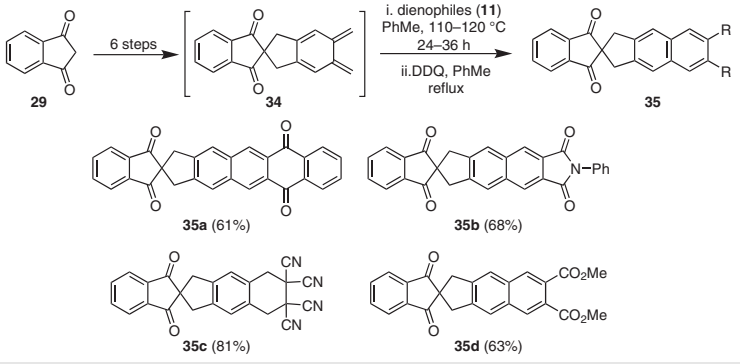
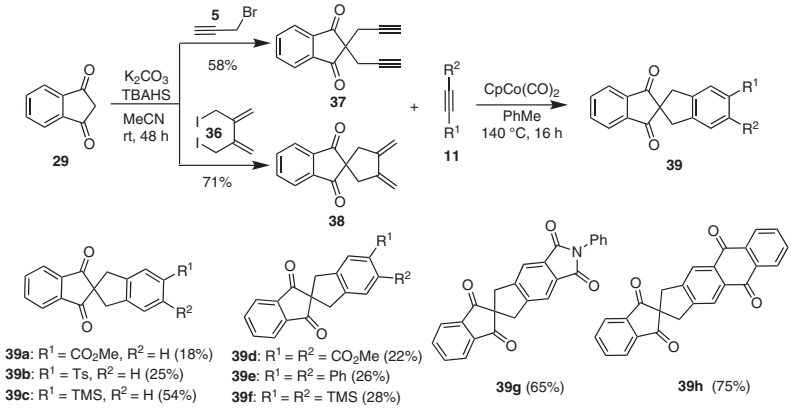


Scheme 6 Synthesis of angularly fused bis-indane derivatives



Scheme 7 Synthesis of spiro-indane derivatives by DA approach



Scheme 8 Spiroindane derivatives through [4+2] cycloaddition strategy

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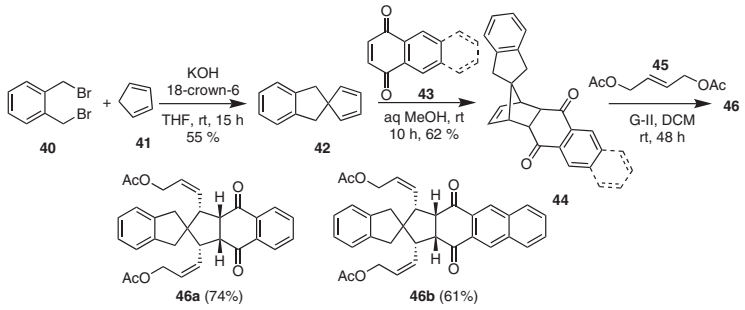


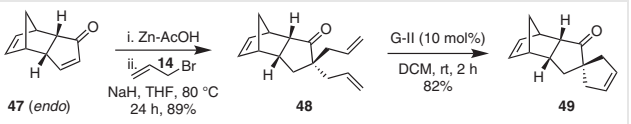
Scheme 9 Synthesis of complex spiroindane derivatives by cross-metathesis (CM)

brary of quinane derivatives by allylation/metathesis sequence.[33]

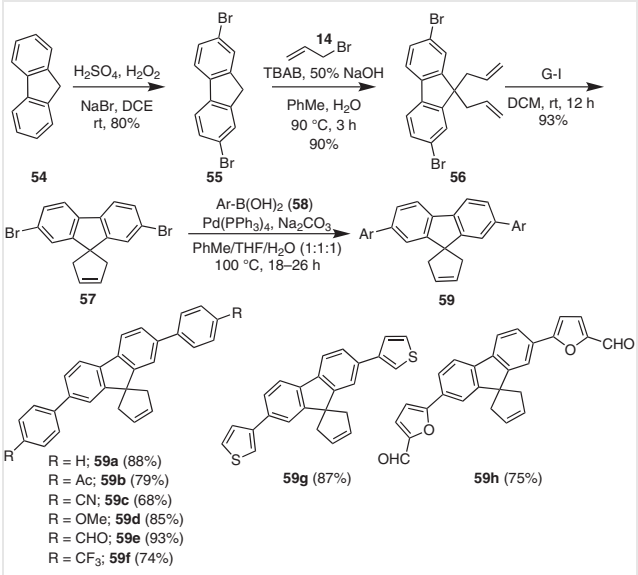
It is worth mentioning that the alkylation reaction between indan-1,3-dione (**29**) and tetra-bromo compound **23** in the presence of a base led to the formation of the dibromo spiro-oxepine **51** (39%) along with the spiro dimer **50** (14%) through an unusual rearrangement (Scheme 11). The compound **51** was treated with the rongalite ($Na^+HOCH_2SO_2^-$), followed by the DA reaction with naphthoquinone (**43**) to produce the corresponding DA adduct **52** in good yield. The spiro compound **53** was generated by rearrangement followed by aromatization using the MnO_2 (Scheme 11).[34]

A simple approach to diverse spirofluorenes from easily accessible starting materials through RCM and SM cross-coupling reactions has been reported. The synthesis began with the generation of dibromofluorene **55**, prepared by the acid-mediated bromination of fluorene **54** (Scheme 12). Further, treatment of compound **55** with an excess amount of allyl bromide (**14**) in the presence of tetrabutylammonium bromide (TBAB) under basic conditions gave the diallyl compound **56**. RCM of diallyl derivative **56** with the aid of Grubbs' first-generation (G-I) catalyst yielded the dibromo substituted spirofluorene **57**. The SM reaction of compound **57** with commercially available aryl/heteroaryl boronic acids **58** in the presence of $Pd(PPh_3)_4$ and sodium carbonate (Na_2CO_3) resulted a library of new spirofluorene derivatives **59** in good to excellent yields (Scheme 12).[35]

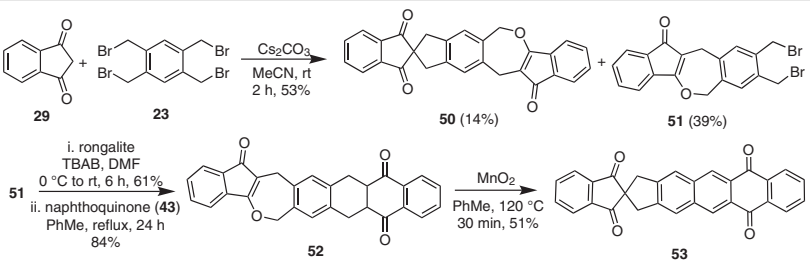
Along similar lines, we accomplished the assembly of spirocyclic indanone derivatives through a RCM sequence. The spiro-indanones were successfully accessed by a two-



Scheme 10 Synthesis of norbornene fused spiro diquinane



Scheme 12 Synthesis of diverse spirofluorene derivatives by RCM



Scheme 11 Synthesis of spiro derivatives by cyclization strategy

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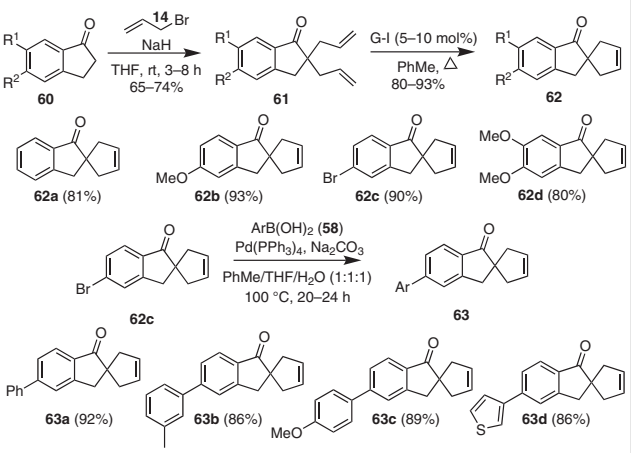
step protocol starting with 2,3-dihydro-1*H*-inden-1-one (**60**), which was treated with allyl bromide (**14**) in the presence of NaH to obtain the diallyl indanones **61** (Scheme 13). The RCM sequence of diallyl indanones **61** with the aid of G-I catalyst gave the corresponding spiro-indanones **62a–d** in good yields. Further, a library of new spiro compounds **63a–d** have been prepared in good to excellent yields through a SM cross-coupling of bromo-spirocycle **62c** with diverse arylboronic acids **58** using Pd catalyst (Scheme 13).[36]

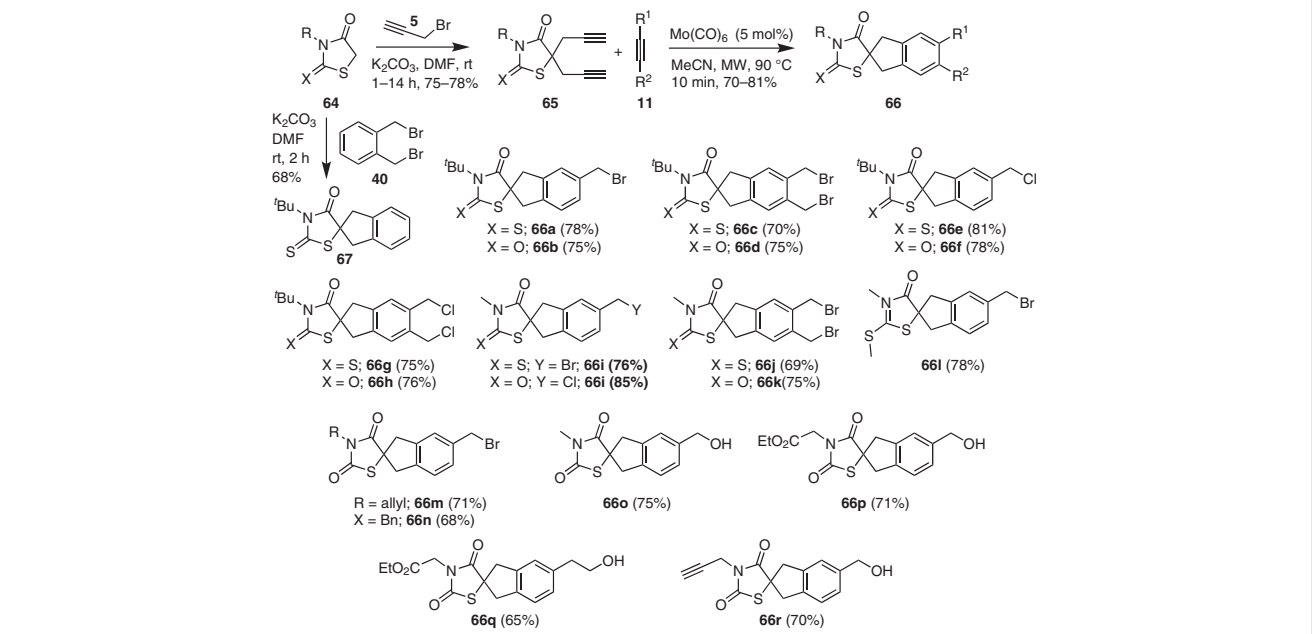
Rhodanines and thiazolidinediones are five-membered heterocycles that are privileged structures in medicinal chemistry due to their inherent hydrophobic interactions,



Scheme 13 Synthesis of spiro-indanone derivatives by RCM

hydrogen bonding, and metal ionic interactions at the ligand binding site of proteins. In view of the interesting biological and pharmacological properties of rhodanines, we have investigated a new route for the preparation of spirorhodanine/thiazolidinedione derivatives through molybdenum catalyzed [2+2+2] cyclotrimerization sequence. The substituted rhodanines/thiazolidinediones **64** (x = S/O; Scheme 14) were synthesized using inexpensive starting materials by known chemical transformations. Treatment of compound **64** with propargyl bromide (**5**) in the presence of K_2CO_3 delivered the dipropargyl synthons **65**. A metal-mediated [2+2+2] cyclotrimerization of compounds **65** with substituted alkyne partners **11** under the microwave irradiation (MWI) conditions provided the corresponding halo substituted spiro-rhodanines/thiazolidinediones **66**. Furthermore, benzene ring fused spiro-rhodanine **67** was successfully synthesized by the reaction of *N*-*tert*-butyl substituted rhodanine **64** with 1,2-bis(bromomethyl)benzene (**40**) in the presence of K_2CO_3. In addition, some of these compounds have been utilized to generate a library of new rhodanines/thiazolidinediones through a sequence of established chemical transformations (Scheme 14).[37]

Spirooxindole and its derivatives are found in numerous natural products, and medicinally interesting molecules such as spirotryprostatin A, elacomine, horsfiline, antibacterial agent and antimalarial drug NITD609.[38] There is thus a need for the development of novel approaches to their syntheses. In this regard, we have disclosed a facile route to functionalized spirooxindole derivatives via the DA reaction. Bromination of durene (**68**) with *N*-bromosuccinimide (**69**) under photochemical conditions gave the tetrabromo



Scheme 14 Synthesis of spiro-rhodanines/thiazolidinediones by a [2+2+2] cycloaddition strategy

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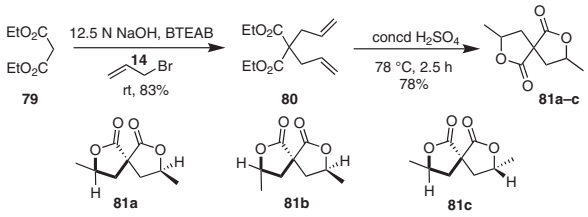
derivative **23**, which, on treatment with *N*-protected oxindoles (**70**), gave the corresponding dibromo spirooxindoles **71** (Scheme 15). An isomeric mixture of sultine derivatives **72** and **73** was obtained by treating the oxindoles **70** with rongalite in the presence of TBAB. The sultine derivatives **72** and **73** obtained were subjected to a DA reaction with various dienophiles (**11**) to yield diverse spirooxindole derivatives **74a–g**. In addition, we synthesized sulfones containing spirooxindole **75** through the rearrangement of a mixture of sultine derivatives **72** and **73** under thermal conditions (Scheme 15).[39]

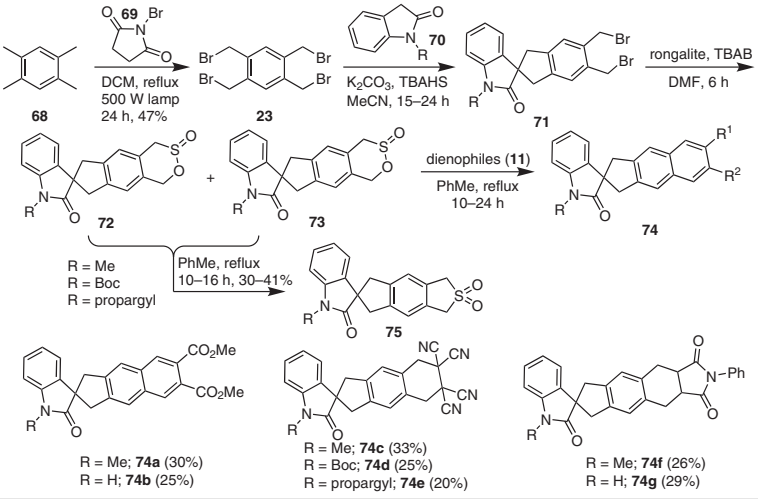
We explored a simple [2+2+2] cyclotrimerization approach to the spiro hydantoins using easily accessible starting material **76** (Scheme 16). The propargylation reaction was carried out in the presence of lithium bis(trimethylsilyl)amide (LiHMDS) to generate the di-propargyl hydantoin **77**, which underwent a molybdenum catalyzed cyclotrimerization with various acetylenes **11** to afford the corresponding spiro hydantoins **78a–d** in good yields (Scheme 16).[40]

Spirolactones are attractive targets due to their occurrence in several natural products and medicinally and pharmaceutically important targets. Our group successfully reported a practical approach for the preparation of 3,8-dimethyl-2,7-dioxaspiro[4.4]nonane-1,6-dione (**81**) in good yield. The diastereomeric mixture of spirolactones **81a–c** were obtained by the diallylation of ethyl malonate (**79**) followed by the acid-mediated hydrolysis and subsequent cyclization. The structures of diastereomers **81a–c** were confirmed by the NMR spectral data and further supported by the X-ray diffraction studies (Scheme 17).[41]

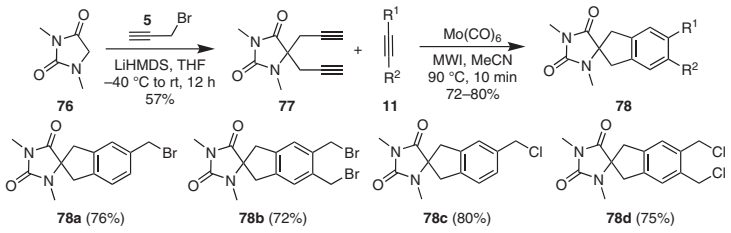


Scheme 17 Synthesis of spirolactones by acid-catalyzed cyclization

Spiro diquinanes **85** have been assembled by our group from 1,3-dicarbonyl compounds such as tetronic acid (**82a**) and thiotetronic acid (**82b**) by utilizing CR and RCM strategy. Allylation of acids **82** with allyl bromide (**14**) in the presence of a base furnished a mixture of allyl derivatives **83** and **84**. Later, the undesired *O*-allyl derivatives **83** were converted into the desired RCM precursors **84** by CR. Finally,



Scheme 15 A concise approach to spirooxindole by a cyclization strategy



Scheme 16 Synthesis of spiro hydantoins by a [2+2+2] cycloaddition strategy

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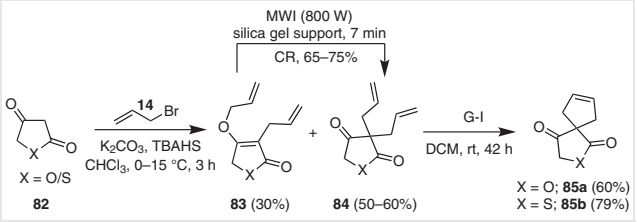
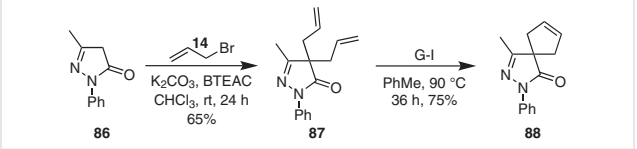
the spiro compounds **85** were obtained in good yields by the RCM of diallyl precursor **84** with the aid of G-I catalyst (Scheme 18).[42]



Scheme 18 Synthesis of spiro diquinanes containing hetero atom by RCM strategy

Pyrazoles are ubiquitous in numerous bioactive natural products, drug-related molecules and agrochemicals.[43] Hence the development of new methods to access these novel heterocycles is a useful exercise to organic chemists. Herein, we applied the same strategy for the construction of spiro-pyrazole derivatives. Allylation of phenyl substituted pyrazole **86** with allyl bromide (**14**) in the presence of benzyltriethylammonium chloride (BTEAC) gave the diallyl pyrazole **87**, which, upon treatment with G-I catalyst, gave the corresponding spiro-pyrazole **88** through the RCM sequence (Scheme 19).[44]

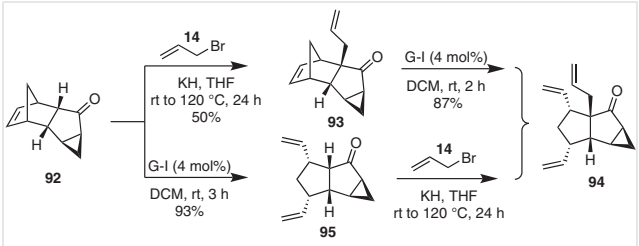


Scheme 19 Synthesis of spiro-pyrazole by RCM

3 Synthesis of Octahydropentalene (A2) Derivatives

In view of the importance of fused cyclopentanoids in natural and non-natural products synthesis, a new approach for the preparation of linear diquinanes starting with *endo*-enone **47** was investigated (Scheme 20). The saturated dimethyl compound **89** was generated by reduction followed by the methylation of key intermediate **47**. The allylation of compound **89** with allyl bromide (**14**) in the presence of potassium hydride (KH) provided the monoallyl compound **90**, which was then subjected to RRM with G-II catalyst under ethylene atmosphere. Unfortunately, we obtained the diquinane **91** through ROM instead of the expected triquinane via RRM (Scheme 20).[45]

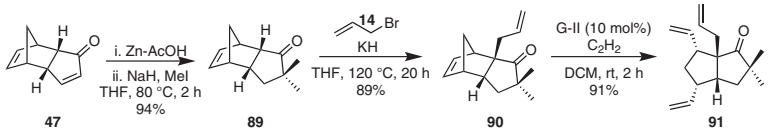
Recently, our group described a new approach to diquinane **94** containing a cyclopropane moiety from a key intermediate **92**, which was obtained by the reaction of **47** with sulfur ylide.[45] Allylation of the keto compound **92** followed by metathesis with G-I catalyst provides the cyclopropanated diquinane **94**. Additionally, the same diquinane **94** was also synthesized from compound **92** through the ROM process of **92** followed by the allylation sequence of compound **95** (Scheme 21).[33]



Scheme 21 Synthesis of linear diquinane containing cyclopropane by a ROM strategy

Kotha et al. reported a new approach to the construction of monoalkyl derivatives of *cis*-bicyclo[3.3.0]octane derivative **100** using alkyl halides (Scheme 22). Initially, several reaction conditions were attempted to synthesize monoalkyl derivatives of *cis*-bicyclo[3.3.0]octane-3,7-dione, but unfortunately all met with little success. The bicyclic derivative **98** has been obtained by performing the Weiss–Cook reaction between *t*-butyl ester of ketoglutarate **96** and glyoxal **97**. The bis-enol ether **99** was prepared by treating the tetra ester **98** with diazomethane. The monoalkyl diones **101** were prepared by KH mediated alkylation with different alkyl halides at low temperature followed by the acid hydrolysis and decarboxylation. By applying this strategy, various monoalkyl *cis*-bicyclo[3.3.0]octane-3,7-diones **101** have been synthesized in 78–93% yield (Scheme 22).[46]

In connection with polyquinanes syntheses, an advanced protocol has been developed to prepare diallyl *cis*-bicyclo[3.3.0]octane-3,7-diones **104** and **105** via the Weiss–Cook reaction involving two paths as shown in Scheme 23. Reaction of tetra ester **99** with allyl bromide (**14**) in the presence of a base followed by subsequent hydrolysis provided the corresponding diallyl diones **104** and **105**. Preparation of **99** involves the use of diazomethane, which is not



Scheme 20 Synthesis of linear diquinane by ROM

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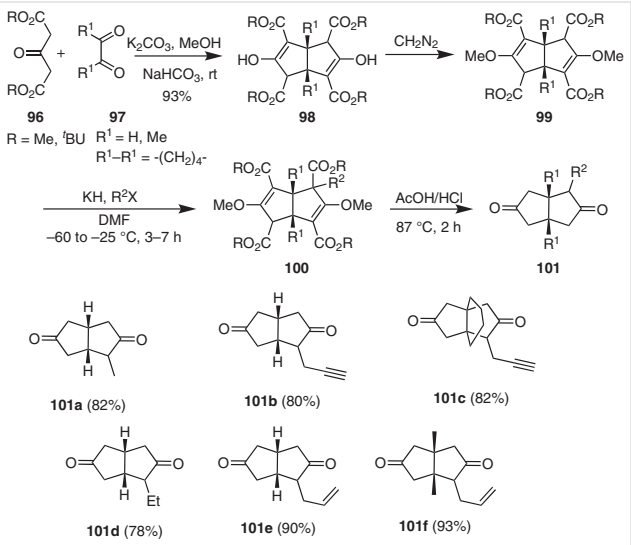
desirable on a large scale. Alternatively, an efficient route involved the construction of an important dione **102** via the Weiss–Cook reaction followed by hydrolysis of glyoxal and β-ketoglutarate. Dione **102** is a key building block to generate various fused cyclopentanoids. CR route involving the dione **102** and allyl alcohol (**103**) in the presence of PTSA provided diallyl diones **104** and **105** in 50% and 32% yields, respectively (Scheme 23).[47]

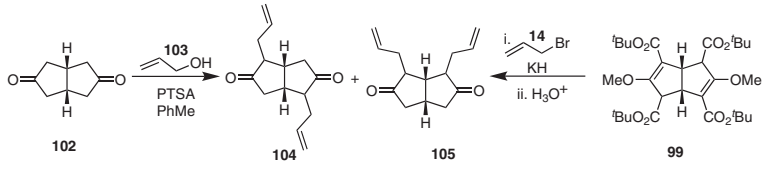


Scheme 22 Synthesis of diverse monoalkyl diquinanes by Weiss–Cook reaction

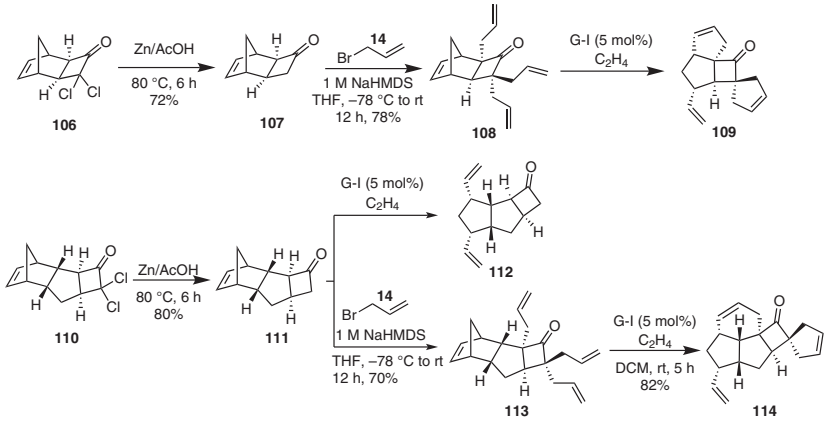
In another occasion, our group has performed studies for the building of another natural product core, namely tricycloclavulone, which contains a linear diquinane derivative fused with spirocyclobutanone.[48] To this end, compound **107** was prepared by Zn/AcOH mediated dechlorination of **106**. Further, synthesis of triallyl derivative **108** was achieved by the reaction of **107** with allyl bromide, which then undergoes ROM and RCM with the aid of G-I catalyst to provide the fused diquinane **109** in good yield. Likewise, diquinanes **112** and **114** were constructed in good yields via ROM of compound **111** and RRM-RCM of compound **113**, respectively (Scheme 24).[49]

Recently, we established a new route to substituted diquinanes form tetracyclic precursor **115**, obtained from the commercially available starting materials. To generate the target quinanes, initially, compound **115** was treated with allyl bromide (**14**) in the presence of NaH to obtain the *O*-allyl compound **116**. RRM of the latter with the aid of G-II catalyst delivered the corresponding pyran fused diquinane **117** in 75% yield. Afterward, metathesis of the tetracyclic compound **115** with G-II catalyst generated the tetravinyl diquinane **118** in good yields through ROM process (Scheme 25).[49]

Propellanes are a unique class of compounds that are present as core structural units in a variety of bioactive natural products. In this regard, we reported a new synthetic strategy to indane-based propellanes by using RCM as a key step (Scheme 26). The key indane-dione (**121**) was prepared from commercially available ethyl phenylacetate (**119**). Condensation of **119** followed by intramolecular cy-



Scheme 23 Synthesis of allyl diquinanes via CR



Scheme 24 Synthesis of cyclobutane fused linear diquinane by ROM

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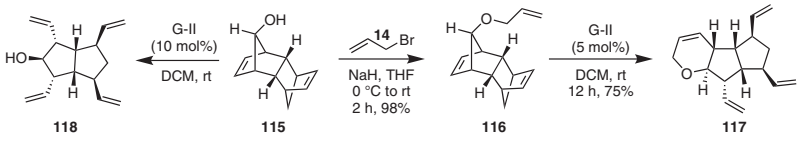
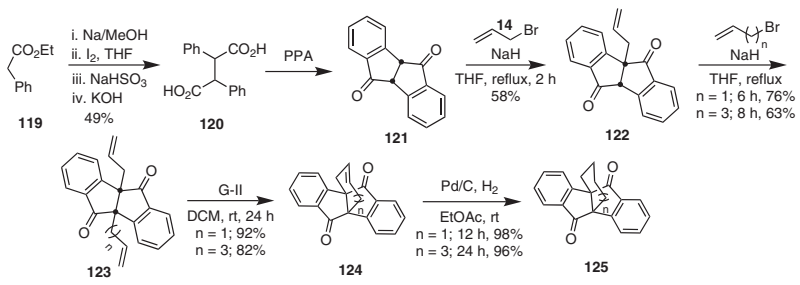
clization gave the dione **121**. The latter was converted into monoallyl indane derivative **122** by reacting with allyl bromide (**14**) in the presence of NaH. This allyl dione **122**, on reaction with alkyl bromides, gave **123**, which undergo RCM to produce **124**. Compounds **124** were hydrogenated to provide the corresponding propellane derivatives **125** (Scheme 26).[50]

A diversity-oriented approach has been investigated for the construction of several linear diquinanes in good yields using a simple building block such as dicyclopentadiene. The key precursor **126** was prepared by SeO_2 oxidation of dicyclopentadiene under reflux conditions (Scheme 27).[51] Treatment of the compound **126** with allyl bromide (**14**) in the presence of NaH generated the *O*-allyl compound **127**, which, upon RRM with G-I catalyst, yielded the resulting diquinane bearing oxacycle **128** in 78% yield. Subsequently, *O*-propargylation of compound **126** followed by the RRM provided the corresponding diene **130**, which, on treatment with different types of dienophiles (**11**) under the DA reaction conditions, generated the annulated diquinane **131** bearing oxacycle (Scheme 27).[51]

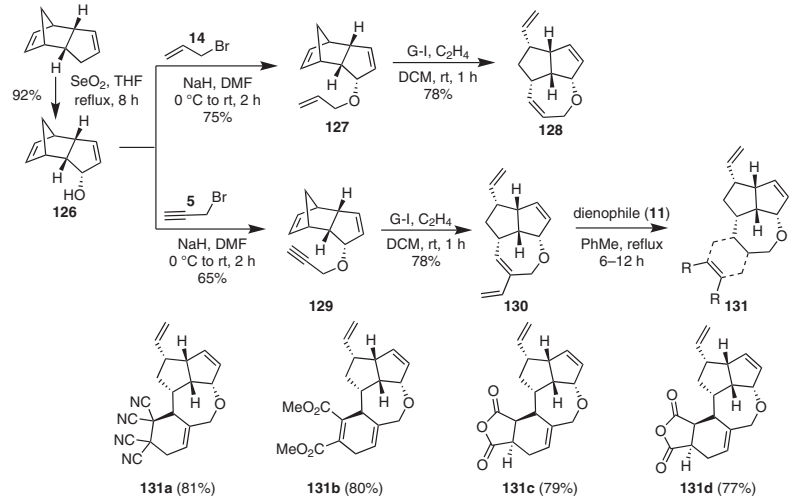
The cyclic ether moiety is widespread in a number of bioactive natural products like isosorbide, inostamycins and polyether antibiotics, and some of these derivatives exhibit significant biological activity.[52] FDA-approved therapeutic drugs like idarubicin (antitumor antibiotics) and floxuridine (antimetabolite) contain a cyclic ether linkage and it is evident that these are interesting structural motifs for the discovery of useful drugs. Hence, we developed a new protocol to assemble spirocyclic ether **136** using dione



Scheme 25 Facile approaches to substituted linear diquinanes by metathesis



Scheme 26 Synthesis of propellane bearing linear diquinane derivatives involving RCM



Scheme 27 A diversity oriented approach to polycycles bearing linear diquinanes by RRM

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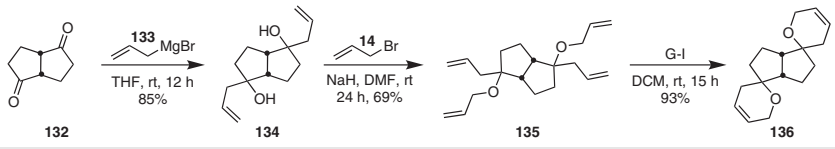
132 via a Grignard addition and RCM as key steps (Scheme 28). The dione **132** was obtained in good yield from an easily accessible 1,5-cyclooctadine through a three-step sequence.[53] The Grignard addition between dione **132** and allylmagnesium bromide (**133**) provided the diallyl diol **134**, which, on treatment with allyl bromide (**14**), gave the RCM precursor **135**. Finally, the tetra allyl compound **135** was subjected to the metathesis with the aid of G-I catalyst to generate the pyrano-spirocyclic ether **136** in excellent yield (Scheme 28).[54]

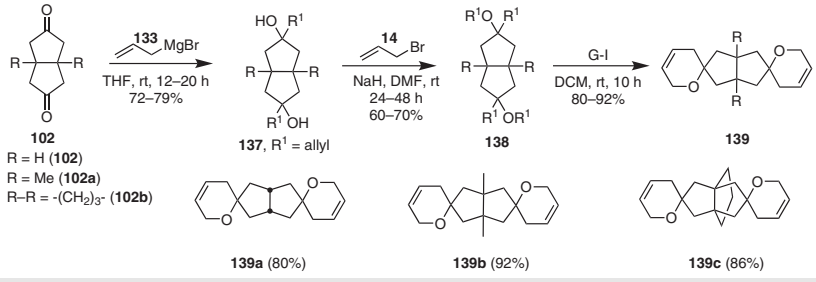
Subsequently, the same sequence of steps has been applied to the construction of other spirocyclic ethers **139a** and **139b** and propellane containing pyrano spirocyclic ether **139c** in good yields starting with substituted *cis*-bicyclo[3.3.0]octane-3,7-diones **102** (Scheme 29).[54,55]

We have reported a simple synthetic protocol to produce oxa-bowls starting with the tricyclic enone **140**, which was prepared by following known procedures.[51] Reduction of the ketone **140** with diisobutylaluminum hydride (DIBAL-H, **141**) and subsequent allylation with allyl bromide (**14**) under basic conditions generated *O*-allyl tricyclic compound **143** (Scheme 30). Later, *O*-allyl compound **143** was subjected to RRM with the aid of G-I catalyst under ethylene atmosphere to yield the oxa-bowl **144** in excellent yield. Along similar lines, oxa-bowl **147** was generated through the propargylation of compound **142**, and subsequent RRM of **145** followed by the DA reaction of **146** with *N*-phenyl maleimide (Scheme 30).[56]

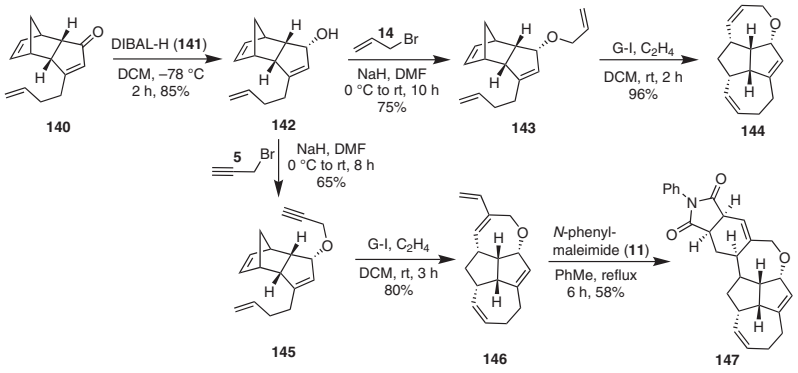
In 2017, we reported a concise approach for the construction of intricate aza-diquinanes bearing an indole moiety by employing C–H activation and RRM/ERRM as key steps from a commercially available inexpensive simple building block such as 2-bromoaniline (**148**). To this end, the key precursor, indole derivative **149** was prepared from aniline derivative **148** by utilizing known procedures involving C–H activation as a key step (Scheme 31). The indole derivative **149** was subjected to RRM with the aid of G-I catalyst under ethylene atmosphere, which generated a mixture of RRM product **150** along with the ROM product **151** in 52% and 35% yield, respectively.[57]



Scheme 28 Synthesis of pyrano-spirocycle by RCM



Scheme 29 Synthesis of linear diquinane containing pyrano-spirocyclic ether



Scheme 30 Synthesis of extended diquinanes by RRM

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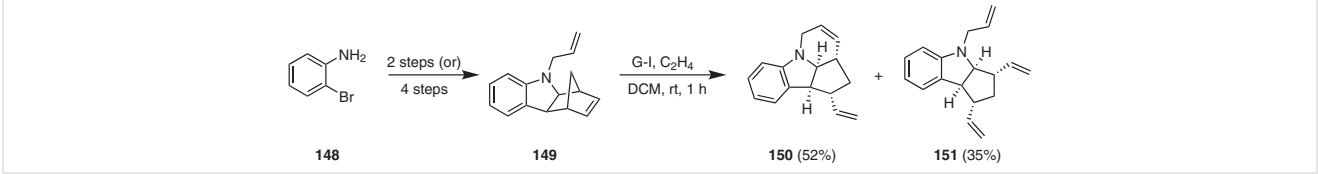
Subsequently, the other key starting material, *N*-propargyl indole derivative **152** was synthesized from the 2-bromoaniline by slightly altering the reaction sequence. Then, indole derivative **152** was treated with G-I catalyst under ethylene atmosphere to deliver the ERRM product **153** in 22% yield and ROM product **154** in 69% yield. Furthermore, the ROM product was subjected to RCM with G-II catalyst to furnish the diene **154**. Finally, the DA reaction between diene **154** and tetracyanoethylene (**11**) under the sealed tube conditions generated the resulting DA adduct **155** in moderate yield (Scheme 32).[57]

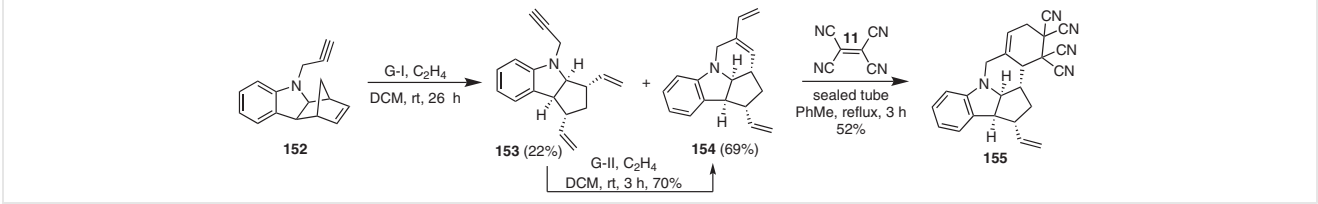
An easy entry to the core structure of dendrobine[58] was developed starting with the key precursor **156**, obtained by a two-step sequence from commercially available starting materials (Scheme 33). A selective reduction of **156** with $NaBH_4$-I_2 at room temperature led to the formation of alcohol derivatives **157**, which, upon treatment with allyltrimethylsilane (**158**) under the acidic conditions, provided the corresponding allyl derivative **159**. Next, these allyl compounds **159** were subjected to ROM with aid of Grubbs and Hoveyda–Grubbs catalysts in ethylene atmosphere under different reaction conditions. Unfortunately, we obtained the ROM products **160** instead of the expected RRM products **161**. Finally, compounds **160** were treated with G-II catalyst to generate the core of dendrobine **161** through RCM sequence (Scheme 33).[58d]

In recent years, C_3-symmetric frameworks have gained significant interest due to their applications in various fields of chemical sciences, especially for their optoelectronic applications. So, development of new synthetic methods are a worthy exercise. Moreover, some of these derivatives are potential ligands for catalysis.[59] Furthermore, there are limited synthetic approaches available for the construction of propellane containing C_3-symmetric molecules. Here, we have developed a new strategy for the first time to construct N-containing star-shaped molecules bearing a propellane moiety from easily accessible substrates. To this end, we started with *endo*-DA adduct **162**, obtained from the DA reaction between cyclopentadiene and maleic anhydride (Scheme 34). The DA adduct **162** was treated with 4-aminoacetophenone (**163**) in the presence of a base under heating conditions to generate the amide product **164**, which was then subjected to ROM with the aid of G-I catalyst to yield the divinyl compound **165**. Trimerization of the compound **165** in the presence of ethanol and silicon tetrachloride resulted in the corresponding C_3-symmetric compound **166** in moderated yield. Further, a sequence of allylation followed by RCM with G-II catalyst provided the N-containing C_3-symmetric molecule **167** bearing a propellane moiety in 87% yield (Scheme 34).[60]

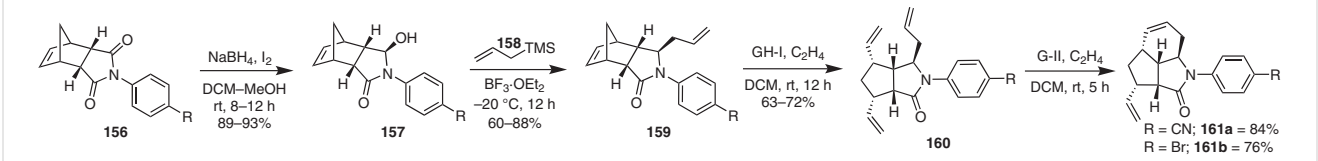
Very recently, Kotha and Pulletikurti developed a facile protocol for the diastereoselective synthesis of azadiquinane containing indolizidine derivatives via ROM (Scheme 35). For instance, the hydroxyl compound **168** was prepared by a well-established procedure and reacted with benzofuran (**169**) in the presence of an excess amount of $BF_3{\cdot}OEt_2$ (70–80 equiv) to provide the corresponding cyclized indolizidine derivative **170**. Further, indolizidine **170**



Scheme 31 Synthesis of benzene fused heterodiquinanes involving RRM



Scheme 32 Synthesis of heterodiquinane by enyne metathesis



Scheme 33 A new approach to the dendrobine core by olefin metathesis

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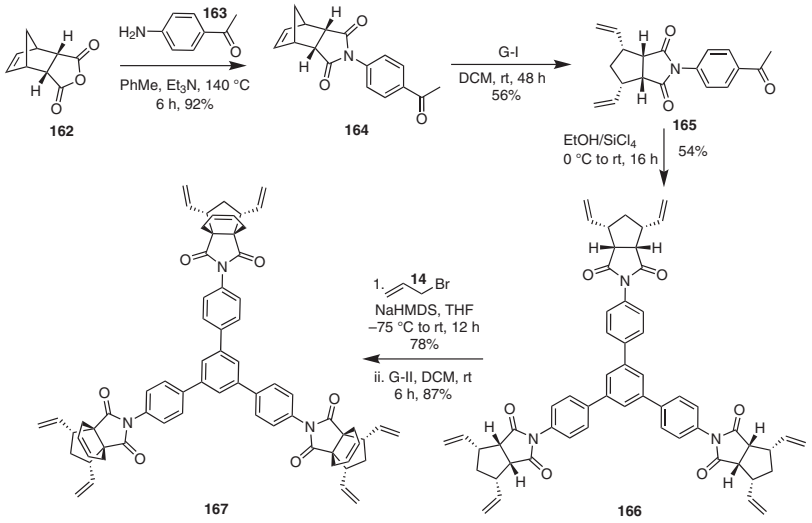


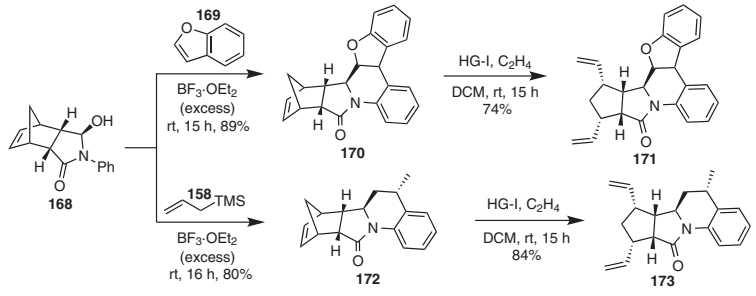
Scheme 34 A new approach to C_3-symmetric heterodiquinane by ROM as a key step

was subjected to ROM sequence by HG-I catalyst to deliver the divinyl compound **171**. Similarly, an excess Lewis acid mediated reaction of **168** with allyltrimethylsilane (**158**) provided compound **172**, which, under the optimized ROM conditions, gave a single diastereomer of indolizidine **173** in good yield (Scheme 35).[61]

Sulfone and its derivatives are ubiquitous structural motifs that are widely used in diverse biologically interesting molecules and also marketed as drugs and agrochemicals. Most importantly, the sulfone moiety is a versatile building block in organic synthesis.[62] In this context, we have developed a simple approach to diquinanes containing sulfonyl group through DA reaction and RRM. The key intermediate sulfide **174** was prepared through a sequence of known protocols in good yields (Scheme 36).[63a] Then, sulfide **174** was oxidized using Oxone® to get sulfone **175**. Later, sulfone **175** was treated with various alkyl bromides in the presence of *n*-BuLi to produce the dialkylated sulfone derivatives **176a–d**. Next, the compounds were subjected to RRM by treatment with the ruthenium catalyst under the ethylene atmosphere. Starting with two substrates (where n = 1 and n = 2), we obtained the RRM products **177** and **178** in 48% and 97%, respectively. However, with the other substrate (n = 3), the reaction delivered the cyclic RRM product **179** along with other products **180** and **181**. Whereas, with a lengthy alkyl chain (n = 4) we obtained only the ROM product **182** rather than the RRM product (Scheme 36).[63b]

4 Synthesis of Linear Triquinanes (A3)

The development of simple approaches for the construction of linear triquinanes has attracted a great deal of attention of synthetic groups due to their potential applications in natural and non-natural products synthesis. In 1984, a concise synthetic approach to linear triquinanes from pentacyclic system **183** via flash vacuum pyrolysis (FVP) and metal promoted cleavage was disclosed (Scheme 37). The FVP of **183** at a higher temperature (560 °C) furnished the corresponding linear triquinane **184** in 78% yield, which was further subjected to catalytic hydrogenation using Pd/C to furnish triquinane **185** through the 1,4-reduction of conjugated diene system. Alternatively, a



Scheme 35 Synthesis of diquinane containing indolizidine derivatives by ROM

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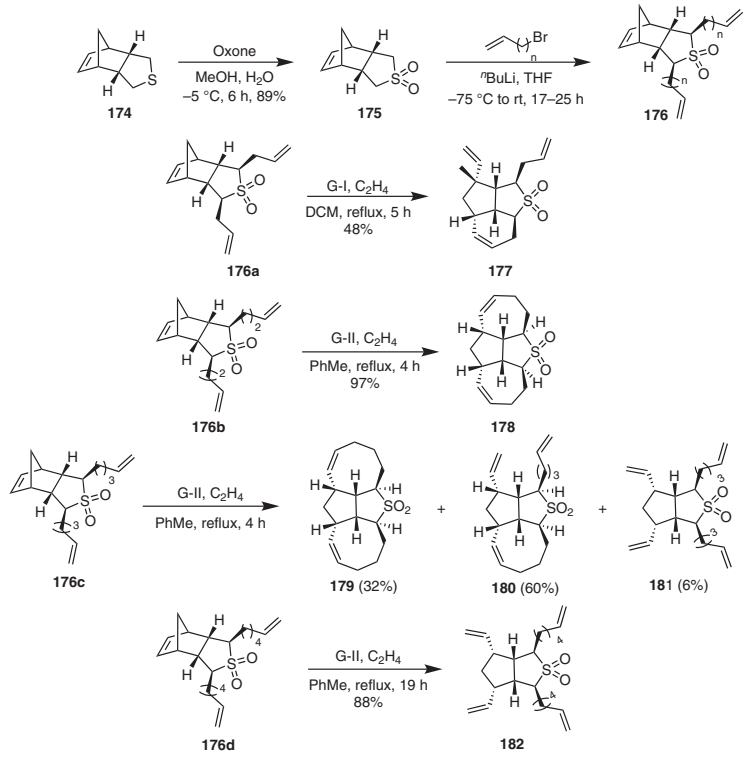
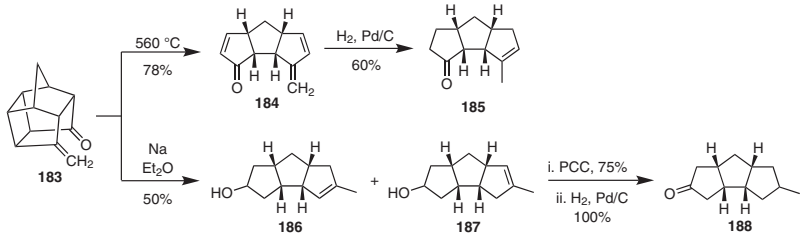


Scheme 36 Synthesis of diquinanes containing SO_2 group via olefin metathesis

slightly different approach has been designed to synthesize an important triquinane derivative **188**. For instance, alkali metal-mediated reduction of **183** provided a mixture of tricyclic alcohols **186** and **187** in 50% yield. The oxidation of compounds **186** and **187** with PCC followed by hydrogenation with Pd/C afforded the corresponding saturated triquinane **188** (Scheme 37).[64]

Additionally, a facile procedure for the construction of a linearly fused tricyclopentanoid framework by using the reductive C–C bond cleavage of commercially available Cookson's dione **189** was reported. In this strategy, the Zn-dust-mediated reaction of **189** in acetic acid under sonication yielded the corresponding tetracyclic dione **190** in 90% yield through C1–C7 bond reduction. The reaction of **190** with an excess amount of Na-K alloy in the presence of trimethylsilyl chloride gave the tricyclic dione **191** via C9-C10 bond reduction along with the pentacyclic diol **192**. The yields of these compounds **191** and **192** were dependent on the nature of solvent used for quenching. Subsequently, dione **193**, under similar reaction conditions, delivered the corresponding triquinane **195** along with the byproduct **196** (Scheme 38).[65] These triquinanes **191** and **195** are important synthons to develop a library of polycycles through a variety of chemical transformations. For example, FI sequence is used to synthesize fused indole derivatives from these compounds. Along similar lines, linear triquinanes **191** and **199** were synthesized in good yields from the corresponding cage diones **197** (Scheme 39).[66] In case of methyl group substitution, we observed another minor product **200**.

We also described a facile Lewis acid catalyzed rearrangement of the substituted pentacyclic diones to the cor-



Scheme 37 Synthesis of linear *cis-syn-cis* triquinanes via FVP and C–C bond cleavage

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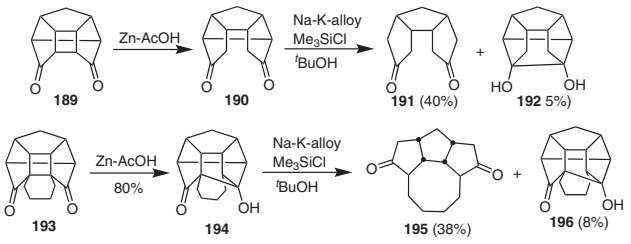
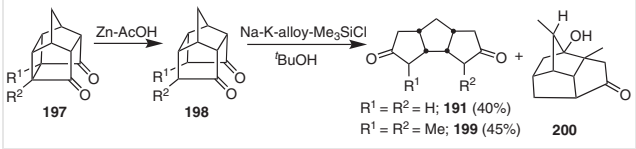


Scheme 38 Synthesis of linear triquinane by reductive C–C bond cleavage

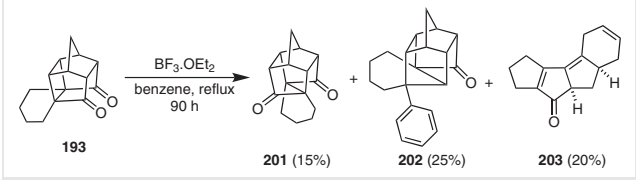
responding linear triquinanes. To this end, treatment of **193** with $BF_3{\cdot}OEt_2$ resulted in a mixture of products **201** and **202** along with a linear triquinane **203** in 15%, 25% and 20% yields, respectively. The structures of these compounds were determined by NMR spectroscopic studies. The hexacyclic propellane derivative **201** was formed through a Cargill-type rearrangement of compound **193** (Scheme 40). The hydrogenation of **203** with Pt_2O gave the corresponding saturated triquinane derivative.[67]

Kotha and Manivannan successfully synthesized functionalized linear triquinanes starting with the known substrate 6,7-dimethyl methanoanthracene derivative **204**. In this regard, the intramolecular cycloaddition of **204** under photochemical irradiation leads to the generation of the required compound **206** in 54% yield along with the formation of aromatized compound **205** in 11% yield. This may be due to the over-oxidation during the preparation of **205**. Ruthenium-catalyzed C–C bond cleavage of dione **206** affords the corresponding pentacyclic derivative **207**. Later, FVP of **207** followed by hydrogenation with Pd/C yielded the saturated dione **209** in 64% yield (Scheme 41).[68]

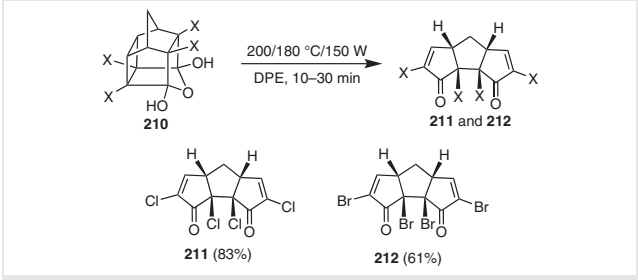
We subsequently reported a simple synthetic approach to *cis-syn-cis* triquinane frameworks starting with the cage diones under MWI conditions. Cage diones were generated from easily accessible inexpensive materials such as 1,3-cyclopentadiene and *p*-benzoquinone derivatives through a DA reaction and [2+2] photocycloaddition. The halogen-substituted cage dione **210** was subjected to a photothermal olefin metathesis reaction under MWI conditions in diphenyl ether (DPE) to generate the corresponding halotriquinanes **211** and **212** in good yields (Scheme 42). Whereas, non-halogenated cage diones (**197a**; $R^1 = R^2 = Me$ and **197b**; $R^1 = H$, $R^2 = Me$) under similar reaction conditions provided a mixture of triquinanes (**213a**, **214a** and **213b**, **214b**, Scheme 43). Interestingly, other diones **197** generated selectively *cis-syn-cis* triquinanes **213c–e** under these conditions (Scheme 43). It is worth mentioning that a photothermal olefin metathesis of cage diones under conventional heating/FVP conditions led to the generation of *cis-syn-cis* triquinanes selectively. Whereas under MWI conditions, double bond isomerized products were obtained along with normal products. Afterward, a photothermal olefin metathesis of cage diones **215** and **219** bearing spiro center at the bridgehead position under MWI conditions delivered a mixture of triquinanes **216–218**, and **220** and **221** as shown in Scheme 44 and Scheme 45.[69]



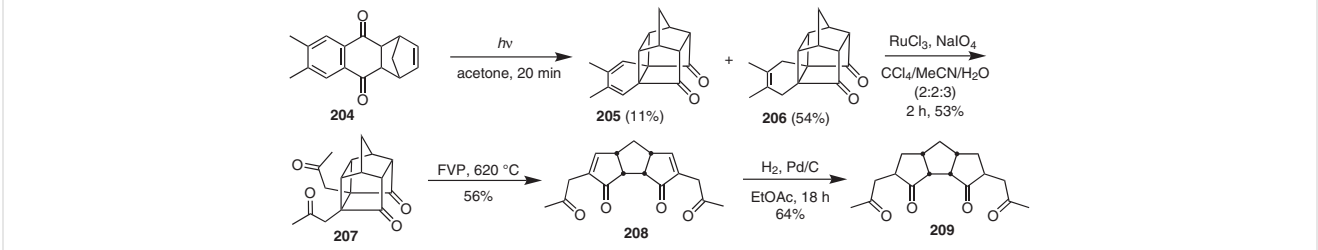
Scheme 39 Synthesis of linear triquinanes from Cookson's dione



Scheme 40 Synthesis of linear triquinane **203** by rearrangement approach



Scheme 42 Synthesis of halotriquinanes by photothermal metathesis under MWI conditions



Scheme 41 Synthesis of linear triquinane by photothermal olefin metathesis

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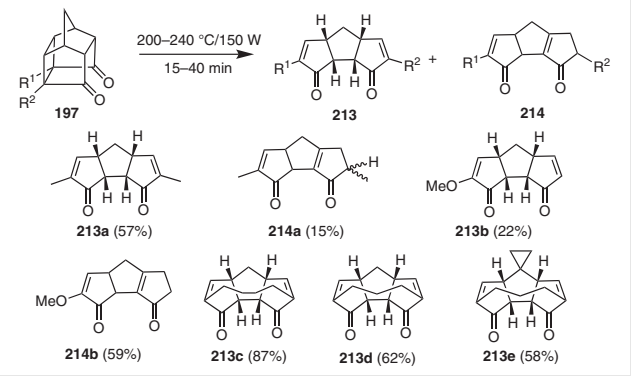
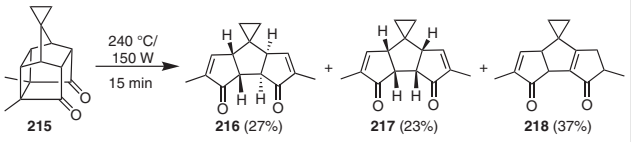
Cage polycyclic compounds are useful synthons to assemble various biologically interesting triquinane containing natural and non-natural products. In this context, functionalized linear triquinanes were generated by utilizing photothermal olefin metathesis and CM from easily accessible substrates. The photothermal olefin metathesis reaction of cage compound **222** under MWI conditions gave the linear *cis-syn-cis* triquinane compound **223** in 43% yield, which, on treatment with *cis*-1,4-diacetoxy-2-butene (**224**) with the aid of modified Grubbs catalyst **225**, provided the corresponding acetyl triquinane **226** through CM sequence. A similar strategy was realized to generate monoallyl triquinanes **230** and **231** prepared from a known DA adduct **227** through a FVP followed by CM sequence with the aid of modified Grubbs catalyst **225**. Moreover, the cage compound **229** was prepared through the CM and [2+2] photocycloaddition of compounds **231** and **228**, respectively (Scheme 46).[70]

Recently, we investigated a versatile approach to construct a variety of linear triquinanes using stereochemically defined DA adduct **232** as a starting material, obtained from the *endo*- and *exo*-dicyclopentadiene-1-one.[71] Treatment of **232** with allyl bromide (**14**) in the presence of NaH/KH provided monoallyl compound **233**, which, upon the metathesis sequence with G-II catalyst, gave the corresponding ROM product **234** in moderate yield rather than the expected RRM product. Later, ROM of compound **232** generated the tetravinyl derivative **235**, which, upon the Grignard reaction with allylmagnesium bromide (**133**), furnished the allyl substituted hydroxy derivative **236**. Subsequent RCM with G-II catalyst in toluene under heating conditions led to the formation of cyclohexane fused triquinane **237** in 89% yield. Similarly, Grignard addition followed by RCM of linear triquinane **238** provided the corresponding cyclohexane fused triquinane **240** in good yield (Scheme 47).[72]

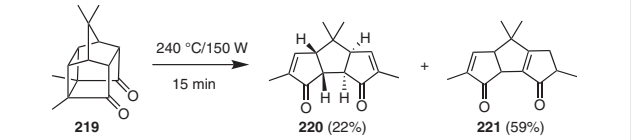
Along similar lines, we prepared the triquinane **243** starting with a key precursor **241**, which was obtained by a sequence of known chemical transformations starting with readily available basic materials. Grignard addition of compound **241** with allylmagnesium bromide (**133**) generated the corresponding allyl alcohol **242**, which, upon treatment with G-II catalyst, delivered the triquinane derivative **243** through RRM sequence along with the ROM product **244** (Scheme 48).[49]



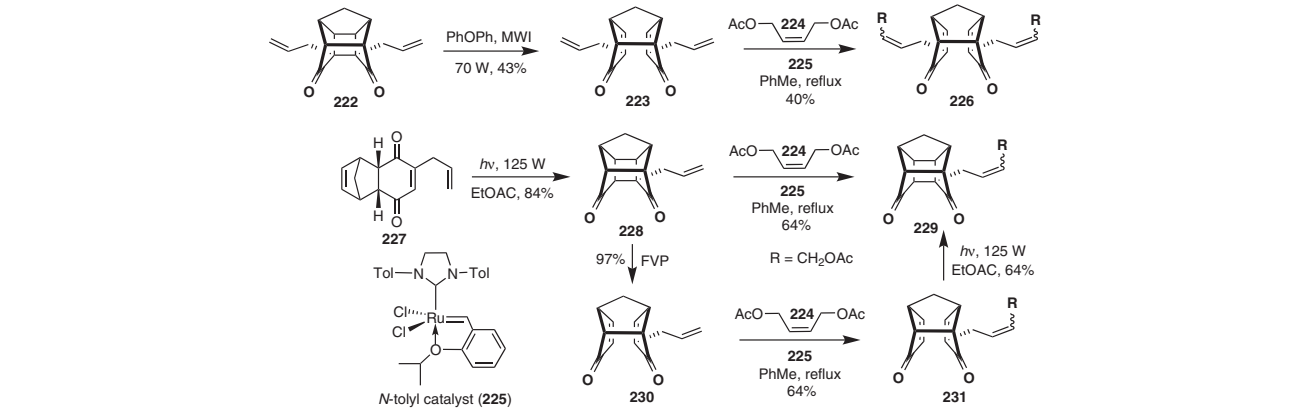
Scheme 43 Synthesis of triquinane derivatives under MWI conditions



Scheme 44 Synthesis of linear triquinanes containing a cyclopropane unit



Scheme 45 Synthesis of tetramethyl linear triquinanes under MWI conditions



Scheme 46 Synthesis of *cis-syn-cis* triquinanes by photothermal olefin metathesis and CM

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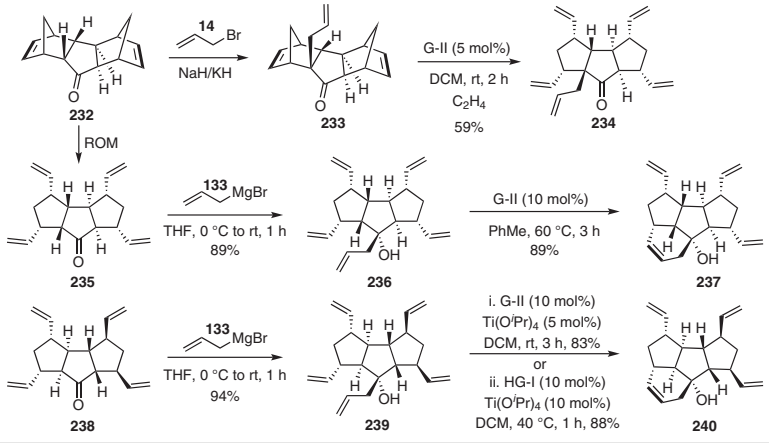
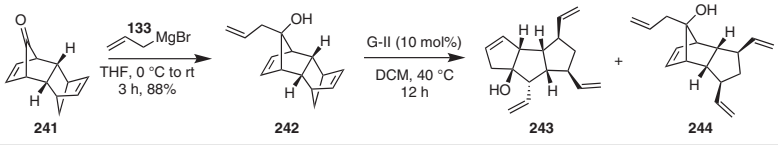
Heteropolyquinanes involve a fused cyclopentane system containing at least one heteroatom such as N/O/S in their structure. These honored structures are found in numerous drug-related molecules and natural products. In view of their proven utility, there is a need to develop more efficient synthetic strategies to access hetero-polyquinanes for 'drug discovery'. One of the most popular synthetic approaches to introduce a nitrogen atom in the molecule is by FI sequence as key step starting with keto substrates. It is well known that the indole unit is a privileged scaffold in drug discovery due to its presence in several bioactive natural products and drugs. To this end, to expand heteropolyquinanes library, our group envisioned a systematic approach to indole based aza-triquinanes from readily available carbonyl synthons via FI and RRM as key steps. The Zn-AcOH mediated selective reduction of a conjugated double bond of *exo*-tricyclic enone **245** produced the saturated ketone **246**. FI of **246** with phenylhydrazine hydrochloride (**247**) in the presence of L-(+)-tartaric acid (TA) and *N*,*N*′-dimethylurea (DMU) furnished the corresponding fused indole derivative **248**. The indole derivative **248** was then treated with allyl bromide (**14**) and propargyl bromide (**5**) with NaH to generate the corresponding *N*-allyl and *N*-propargyl indole derivatives **249** and **251**, respectively, in good yields. Metathesis reaction of indole derivatives **249** and **251** with G-I catalyst under the ethylene atmosphere selectively gave the corresponding ROM products **250** and **252** rather than the expected RRM products. Further, treatment of the compound **252** with the aid of G-II catalyst furnished the enyne metathesis (EM) product **253** in good yield without new ring formation (Scheme 49).[73]

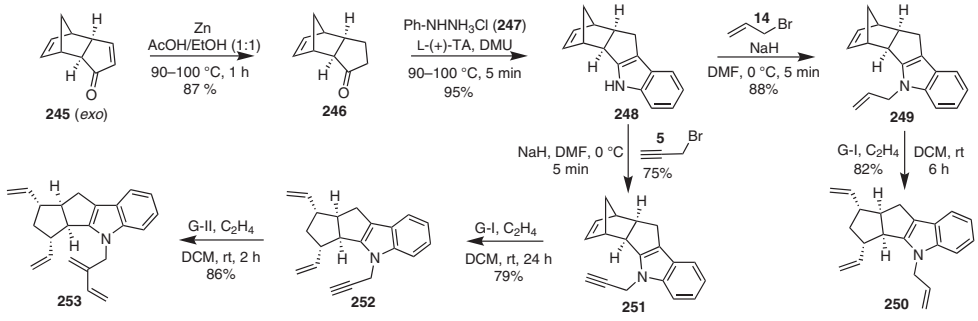
To expand the scope of this methodology, several indole derivatives containing longer *N*-alkyl chains were prepared and subjected to ruthenium-catalyzed metathesis under



Scheme 47 A ROM approach to triquinane **234** and beyond



Scheme 48 Synthesis of triquinane derivative **243** by tandem metathesis



Scheme 49 New approach to aza-triquinanes by ROM

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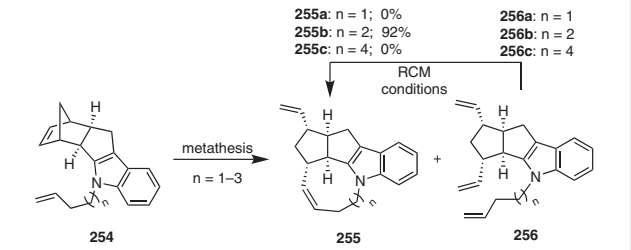
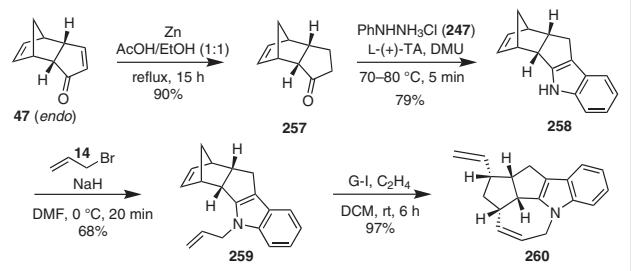
different conditions. Interestingly, RRM product **255b** was obtained selectively when n = 2. Surprisingly, when n = 1, we observed both RRM and ROM products **255a** and **256a**, and with substrate when n = 3, we obtained ROM product **256b** selectively. Subsequently, the RCM reaction was carried out with longer chain *N*-alkenyl ROM indole derivatives **256**. It is worth mentioning that the RCM product **255b** was obtained only when the allyl chain length is suitable (n = 2), which was confirmed by single-crystal X-ray studies (Scheme 50).[73]



Scheme 50 Synthesis of aza-triquinane fused macrocycles

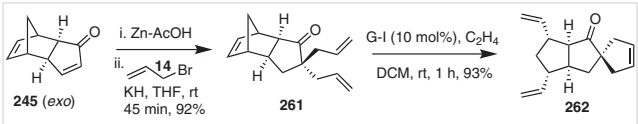
Later, we successfully synthesized aza-triquinane **260** starting with the key *endo* precursor **47** through a four-step sequence. The reduction of compound **47** using Zn-AcOH under reflux conditions furnished the corresponding saturated ketone **257**, which was then subjected to FI cyclization with phenylhydrazine hydrochloride (**247**) in the presence of a low-melting mixture of TA and DMU to generate the indole derivative **258**. The indole derivative **258** was treated with allyl bromide (**14**) to generate the *N*-allyl indole **259**. The RRM of compound **259** with G-I catalyst under ethylene atmosphere provided the aza-triquinane derivative **260** in excellent yield (Scheme 51).[51]



Scheme 51 Synthesis of aza-triquinane **260** by RRM

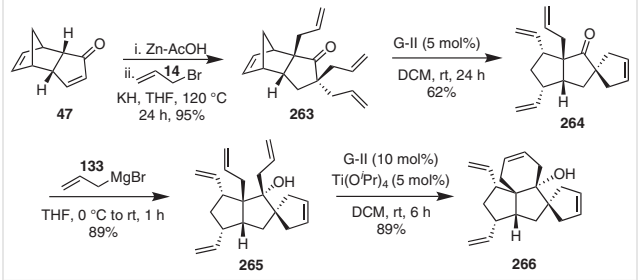
5 Synthesis Spiro Triquinanes (A4)

By extension of this metathesis strategy an unsaturated spiro diquinane **262** was produced from a key precursor *exo*-dicyclopentadiene-1-one **245**. The reduction of key precursor **245** with Zn-AcOH followed by allylation delivered the corresponding diallyl norbornene derivative **261**. Later, the diallyl compound **261** was subjected to RCM with the aid of G-I catalyst to yield the unsaturated spiro triquinane **262**, which was further utilized to generate a library of new polyquinanes (Scheme 52).[33]



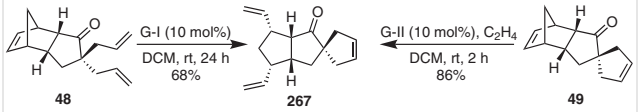
Scheme 52 Synthesis of vinyl substituted spiro triquinane by RCM and ROM

Next, the same strategy was extended to assemble cyclohexane fused with spiro triquinane derivative **266**, which resembles the core structure of natural products magellanine (**N6**) and magillaninone (**N7**).[26] To begin with, Zn-AcOH reduction of *endo*-dicyclopentadiene-1-one **47** gave the saturated keto derivative, which, on treatment with allyl bromide (**14**) in the presence of KH, delivered the triallyl compound **263**. The metathesis sequence of compound **263** with G-II catalyst produced the cyclized compound **264** through RCM followed by ROM. Incorporation of one more allyl group on compound **264** was archived by Grignard addition with allylmagnesium bromide (**133**). Spiro compound **265** was subjected to RCM with the aid of G-II catalyst to yield the corresponding cyclohexene derivative **266** in 89% (Scheme 53).[33]



Scheme 53 Synthesis of spiro triquinane by metathesis

The key RCM precursor **48** was obtained from compound **47** through reduction followed by diallylation. Metathesis of **48** with the G-I catalyst gave the corresponding unsaturated spiro derivative **267** involving RCM and ROM. Further, the same triquinane **267** was produced by the ROM of norbornene derivative **49** with G-II (Scheme 54).[33]



Scheme 54 Synthesis of spiro triquinane **267** by RCM and ROM

Alternatively, vinyl substituted triquinanes **271** and **272** were synthesized from a key precursor *exo*-dicyclopentadiene-1-one **245** by applying the metathesis sequence. For

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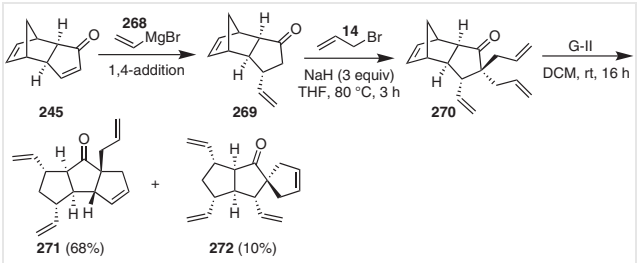


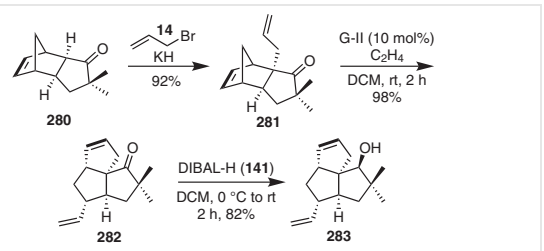
Scheme 55 Synthesis of linear and spiro triquinanes via RCM

this purpose, 1,4-addition of compound **245** with vinylmagnesium bromide (**268**) gave vinyl compound **269**, which, upon allylation in the presence of NaH using allyl bromide (**14**), furnished the diallyl compound **270**. The norbornene derivative **270** was treated with G-II catalyst delivered a mixture of linear and spiro triquinanes **271** and **272**, respectively, through RCM and ROM sequence (Scheme 55).[33]

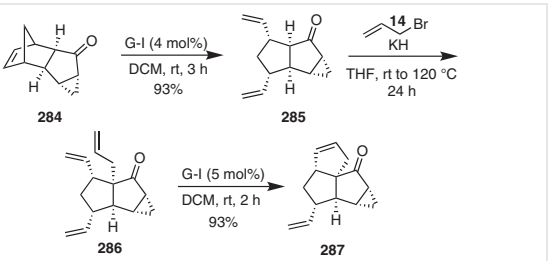
A convenient approach to spiro and linear triquinanes was developed by employing *endo*-tricyclic vinyl ketone **273** through RCM as a key step. The vinyl compound **273** was obtained from the *endo*-intermediate **47** via 1,4-addition of vinylmagnesium bromide (**268**). Allylation of vinyl compound **273** with allyl bromide (**14**) in the presence of NaH gave diallyl compound **274** and with KH gave triallyl compound **277**. RCM of compound **274** with G-II catalyst furnished a mixture of unsaturated spiro- and linear-triquinanes **275** and **276** in 10% and 68% yields, respectively. Similarly, RCM of compound **277** with G-II catalyst provides a mixture of spiro- and linear-triquinanes **278** and **279** in 33% and 46% yield, respectively. Further, a library of new compounds were prepared by utilizing these final structures through hydrogenation as well as RCM sequence (Scheme 56).[33]

6 Synthesis of Angular Triquinane (A5) Systems

Another interesting application of metathesis shown here is the synthesis of basic skeletons of natural products subergorgic acid and cameroonanol.[74] As described with



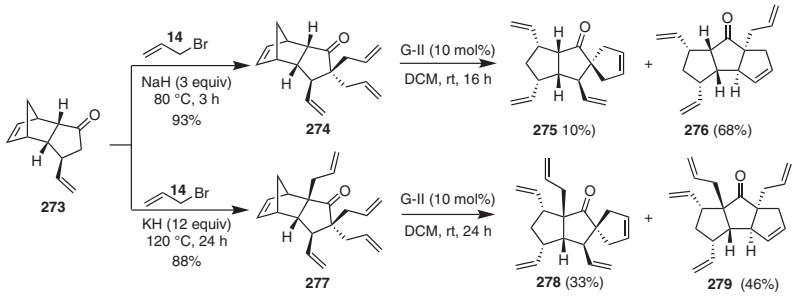
Scheme 57 Synthesis of angular triquinane via tandem metathesis



Scheme 58 A simple strategy to access the natural product subergorgic acid (**N71**) core

the *exo* substrate **245**, reduction followed by methylation of *exo*-enone **245** gave the corresponding dimethyl keto derivative **280**, which was treated with allyl bromide (**14**) in the presence of KH to produce allyl compound **281**. RRM of **281** with the G-II catalyst under ethylene atmosphere yielded the angular triquinane **282** in 82% yield, which is similar to the core structure of natural product subergorgic acid.[73] Further, reduction of angular triquinane **282** with DIBAL-H (**141**) provided the corresponding alcohol **283**, which resembles the core structure of natural product cameroonanol (Scheme 57).[33]

As previously described, the keto derivative **284**, containing cyclopropane, was obtained by the a reported procedure starting with *exo*-enone **245**.[45] The tetracyclic compound **284** was treated with G-I catalyst to deliver the ROM product **285**, which, on allylation with allyl bromide (**14**) in the presence of KH, provided the allyl precursor **286**. The RCM of unsaturated compound **286** with the G-I catalyst



Scheme 56 A simple approach to linear and spiro triquinanes via tandem metathesis

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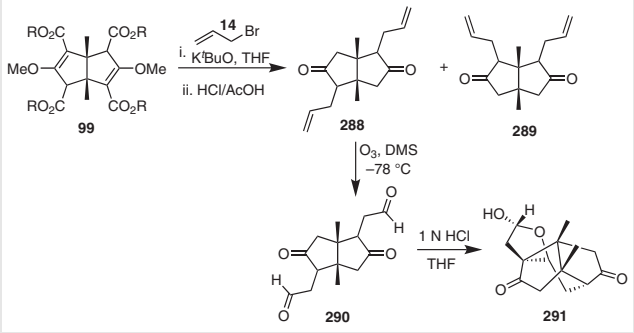
gave the angular triquinane **287** in good yield (Scheme 58).[33]

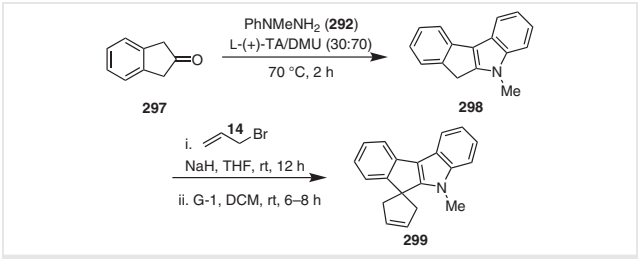
7 Synthesis of Hexahydro-2′H-spiro[cyclopentane-1,1′-pentalene] (A6) Ring System

The bis-enol ether **99**, synthesized through Weiss–Cook reaction, was then reacted with allyl bromide (**14**) in the presence of potassium *tert*-butoxide followed by the acid-catalyzed ester hydrolysis and decarboxylation to give non-separable diallyl quinanes **288** and **289**. The ozonolysis of diallyl compound **288** provided the stereoisomeric mixture of *exo*/*endo* bis-aldehyde **290** in 98% yield. Later, diketo diol was intended to be accessed by bisaldolization of **290** through cyclization under acidic conditions. Unfortunately, bis-aldehyde **290** provided the transannular product **291** rather than the expected diketo diol (Scheme 59).[75]

Based on our experience on FI, the spiro-indole derivatives **294**–**296** and **299** were synthesized in good yields in a three-step sequence through FI and RCM. The FI of substituted 1-indanones **60** with *N*-methylphenylhydrazine (**292**) provided the corresponding indole derivatives **293**. Subsequently, allylation of indole derivatives **293** with allyl bromide (**14**) followed by RCM with the aid of G-I catalyst yielded the target spiro-indole derivatives **294**–**296** (Scheme 60). The same method has been applied for the generation of an isomeric spiro-indole derivative **299** from 2-indanone (**297**, Scheme 61).[76]

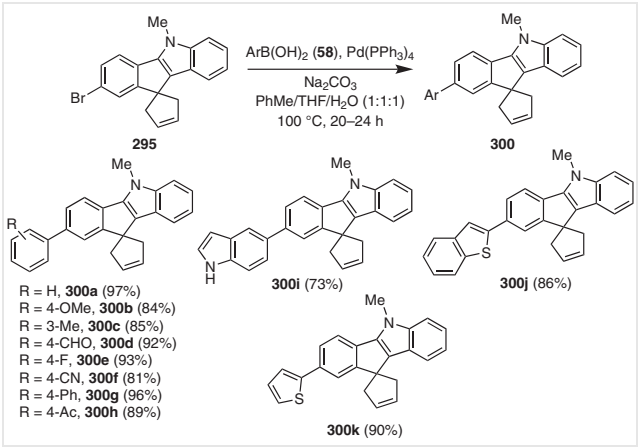


Scheme 59 Synthesis of spiro triquinane via Weiss–Cook reaction



Scheme 61 Synthesis of spiro indole derivative **299**

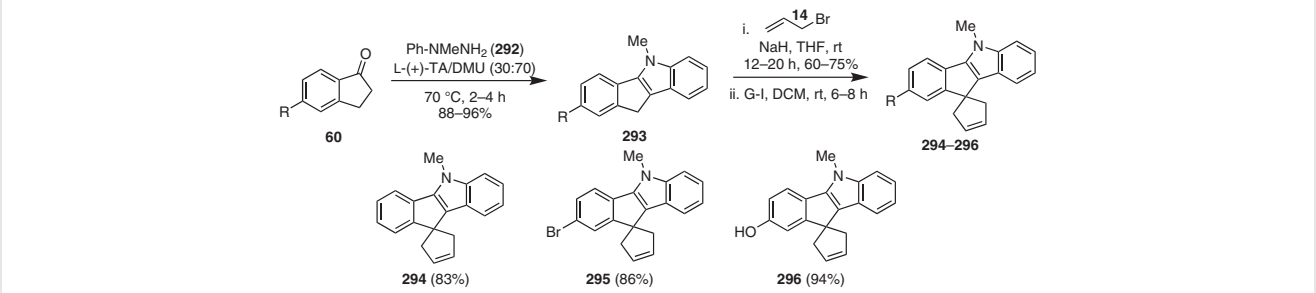
Furthermore, the bromo compound **295** was subjected to SM coupling with diverse aryl/heteroaryl-boronic acids **58** to synthesize a library of indole derivatives **300a–k** in good to excellent yields (Scheme 62). Such compound libraries offer potential candidates for drug discovery programs.[76]



Scheme 62 A facile approach to spiro indole derivatives **300a–k**

8 Synthesis of Dispiro[4.1.4^7.2^5]tridecane (A7) Ring System

A conceptually different strategy has been devised to construct various complex bis-armed spiro-triquinanes by employing a two-directional [2+2+2] co-trimerization and



Scheme 60 Synthesis of spiro indole derivative **294–296**

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[4+2] cycloaddition reaction as key steps. In this context, the building block 301 was synthesized from carbonyl compounds by tetrapropargylation (Scheme 63). Tetra-ol derivatives 302 were synthesized by the reaction of 301 with 2-butyne-1,4-diol (7) in the presence of Wilkinson's catalyst and a catalytic amount of titanium isopropoxide, which, on treatment with phosphorus tribromide, gave 303. The structural isomers of sultine derivatives 304–306 were obtained with rongalite from the corresponding bromo derivatives 303. The aromatized products 307 were obtained through a sequential DA reaction of 304–306 with different dienophiles (11) followed by DDQ oxidation. In this event, we also observed the formation of rearranged sulfone derivatives 308 as minor products. This observation prompted us to investigate the selective synthesis of sulfone derivatives due to their biological and drug-like properties. The bis-armed spirosulfone derivatives 308 were generated in good yields from 304–306 by using a two-directional [2+2+2] co-trimerization under reflux conditions in toluene (Scheme 63).[77]

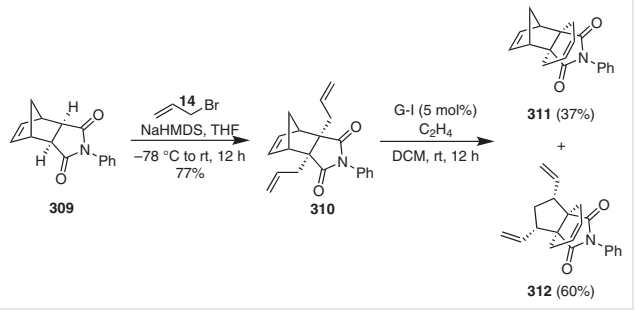
9 Synthesis of Hexahydro-1*H*-3*a*,7*a*-propanoindene Ring System

A facile synthetic approach has been reported to access the triquinane derivative from *exo*-nadic anhydride **309**, easily obtained by a reported procedure. Next, it was subjected to allylation with allyl bromide (**14**) in the presence of NaHMDS to furnish the diallyl compound **310** with retention of configuration at the ring junction. Later, the diallyl compound **310** was treated with G-I catalyst under the ethylene atmosphere to produce the propellane derivative **312** in 60% yield through ROM and RCM process along with a minor amount of RCM product **311** (Scheme 64).[78]

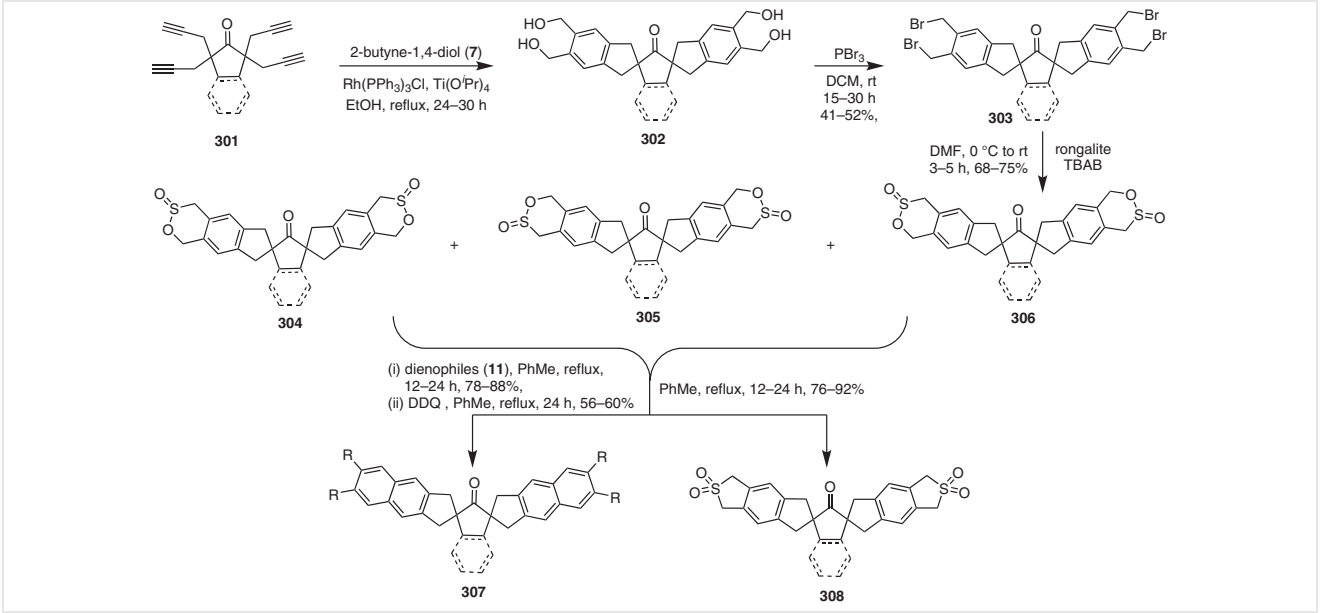
10 Synthesis of Linear Tetraquinanes (A11 and A12)

In 1988, an efficient approach was reported for the preparation of tetraquinane **317** using the Weiss–Cook reaction as a key step. The reaction of 2,6-diallyl tetraester **104** with hydrobromic acid (**313**) gave the dibromo derivative **314** in 68% yield. Finally, the SmI_2 (**315**) and HMPA (**316**) mediated cyclization of dibromo compound **314** gave a mixture of stereoisomeric tetracyclic diol **317** in an approximate ratio of 15:2. Among these, the *cis-cisoid-cis-cisoid* isomer formed as a major product (Scheme 65).[79]

The tricyclic keto olefin **318**, on reaction with dichloroketene, derived from trichloroacetyl chloride (**319**) in the presence of zinc, delivered the corresponding regioiso-



Scheme 64 Synthesis of propellane derivative **312**



Scheme 63 Synthesis of bis-armed spiro derivatives

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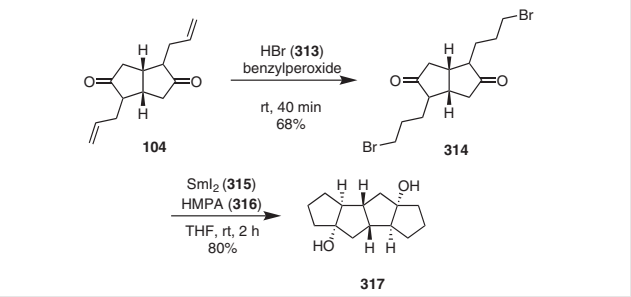
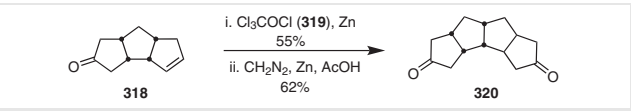


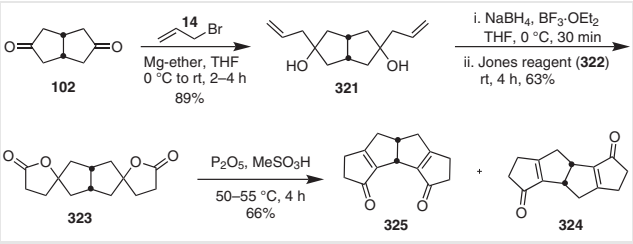
Scheme 65 Synthesis of tetraquinane derivative **317**



Scheme 66 Synthesis of tetraquinane **320**

mers in 1:1 ratio, which, on ring expansion with diazomethane followed by the dechlorination with Zn-AcOH, gave the diketo-tetraquinane **320** (Scheme 66).[65]

We reported a concise approach to several polyquinanes via cyclopentane annulation using inexpensive starting materials. In this regard, readily accessible bicyclo[3.3.0]octane

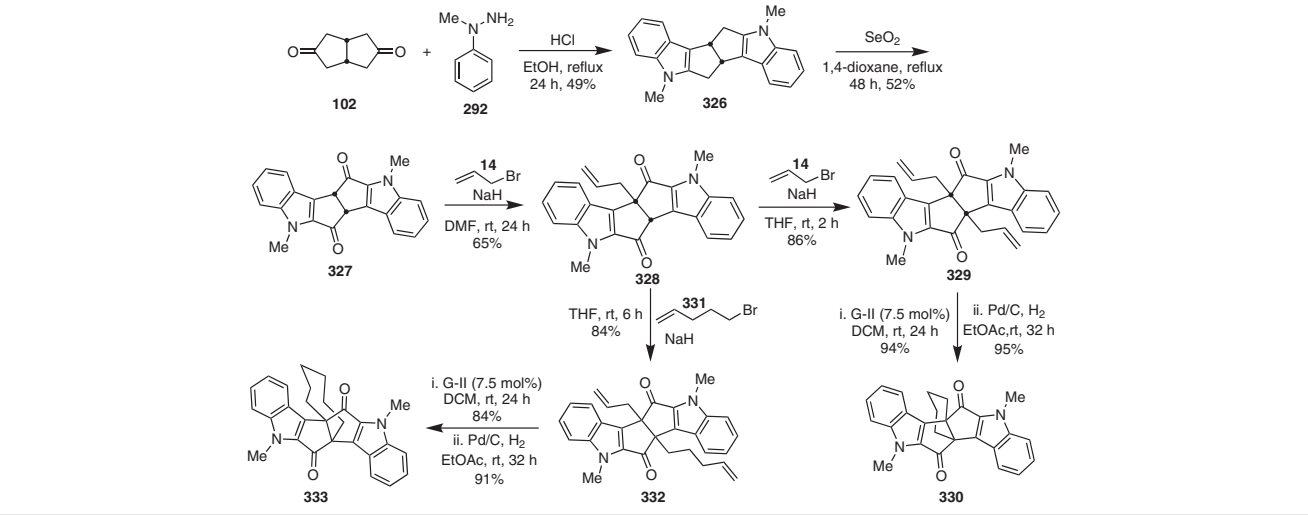


Scheme 67 Synthesis of tetraquinane derivatives **324** and **325**

derivative **102** was converted into diallyl diol **321** by the Grignard reaction involving allyl bromide (**14**) and magnesium. Later, the diol **321** underwent a hydroboration-oxidation sequence with $NaBH_4$ and Jones reagent (**322**) to furnish the lactone **323**, which underwent rearrangement with methanesulfonic acid/P_2O_5 to produce a mixture of tetracyclic enones **324** and **325** (Scheme 67). Finally, Pd/C mediated hydrogenation gave the corresponding saturated tetraquinanes.[80]

In 2013, we developed a simple protocol for the construction of synthetically challenging indole-based [*n*.3.3] propellanes through a two-fold FI and RCM as key steps. The cyclopentane-fused bis-indole **326** was synthesized via FI of diketone **102** with *N*-methylphenylhydrazine (**292**), which further oxidized with SeO_2 to afford diindole derivative **327**. Later, RCM precursors **329** and **332** were generated by alkylation reaction with alkenyl bromides such as **14** and **331**. Next, these alkene derivatives **329** and **332** underwent a metathesis sequence with the aid of the G-II catalyst followed by hydrogenation to provide the indole-based propellanes **330** and **333** in excellent yields (Scheme 68).[81a] Alternatively, indole-based propellanes **334** and **335** were prepared by a different approach through FI of propellane **102b** with **292** (Scheme 69).[81b]

Diindole-fused quinanes were successfully synthesized by using a combination of Weiss–Cook reaction and FI, starting with easily available synthons. Diindole-fused diquinane **337** was synthesized through the acid mediated FI of *cis*-bicyclo[3.3.0]octane-3,7-dione (**102**) with phenylhydrazine (**336**). The dimethyl diindole derivative **326** was prepared in good yield by methylation of free N-H of diindole **337**. Alternate approach has been developed to construct a mixture of *cis*- and *trans*-diindole-fused diquinanes **326** and **338**. This approach involves the FI of **102** with *N*-methylphenylhydrazine (**292**) using L-(+)-TA and DMU. In-



Scheme 68 Synthesis of indole-based [*n*.3.3] propellanes

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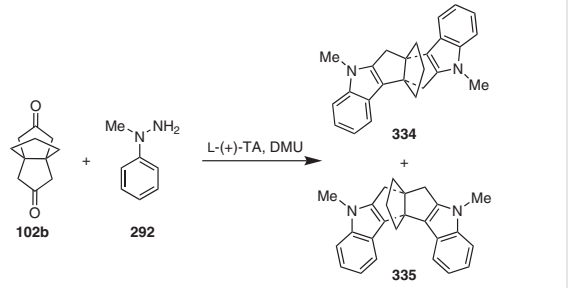


Scheme 69 Synthesis of indole-based propellanes **334** and **335**

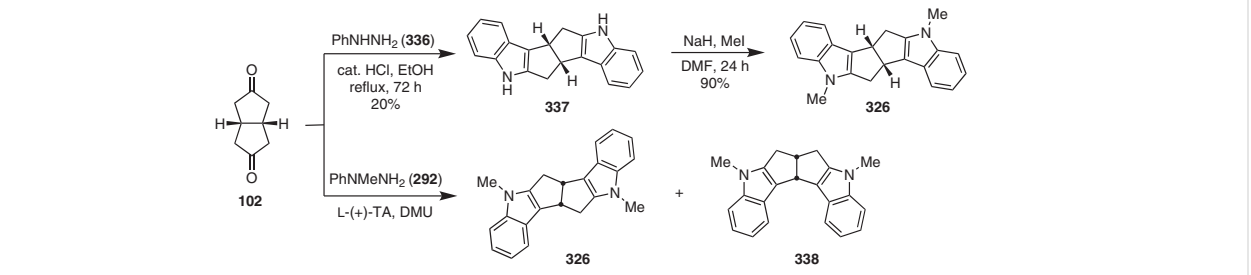
terestingly, the deep eutectic mixture gave thermodynamically less favorable product **338**, which could not be obtained by conventional FI sequence (Scheme 70).[81a,82]

11 Synthesis of Tetrahydro-1′*H*,3′*H*-dispiro[cyclopentane-1,2′-pentalene-5′,1′′-cyclopentane] (A13) Ring System

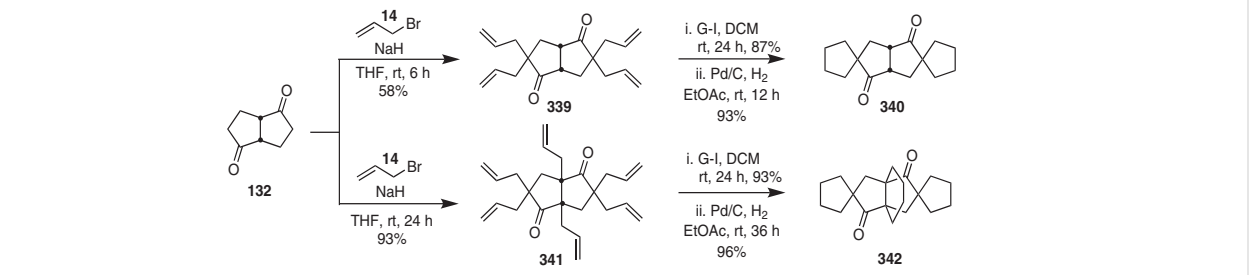
An efficient and simple strategy was disclosed to construct the bis-spiro tetraquinane and bis-spiro propellane derivatives by our group in 2014 from commercially available starting materials. The pivotal diketo compound **132** was prepared from (1*Z*,5*Z*)-cycloocta-1,5-diene through a known procedure. A carefully controlled allylation of **132** with allyl bromide (**14**) in the presence of NaH provided the corresponding RCM precursors, tetraallyl compound **339** and hexaallyl compound **341** in 6 and 24 hours, respectively. Interestingly, metathesis sequence of compounds **339** and **341** with the help of G-I catalyst followed by hydrogenation with Pd/C afforded the saturated bis-spiro tetraquinane **340** and bis-spiro propellane derivative **342** in good yields, respectively (Scheme 71).[83]

12 Synthesis of Decahydro-1*H*,8*H*-dicyclopenta[*a*,*h*]pentalene (A14) Ring System

A useful synthetic approach has been established to access tetraquinanes and propellanes in good yields through a ROM and RCM. The construction of fused heterocyclic tetraquinane derivatives **345** begins with *exo*-nadic anhydrides **309**, which is easily obtained by a known sequence. To this end, we performed the key ROM reaction initially with various substituted *exo*-nadic anhydrides **309** by using G-II catalyst to afford the divinyl compounds **343**. Allylation of **343** followed by RCM with the aid of G-II catalyst provides the desired tetraquinanes **345** as the major product along with minor amounts of propellane derivatives **312** and **346**. The RCM reaction was optimized by studying several reaction conditions, including changing catalysts under different conditions. In this regard, screening revealed that the use of G-II catalyst in DCM is a better choice to generate the hetero-tetraquinanes as major products (Scheme 72).[78] Another interesting example of this approach is illustrated in the synthesis of hetero-bis-tetraquinane **348**, tetraquinane-propellane **349** and bis-propellane **350** (Scheme 73).[78]



Scheme 70 Synthesis of diindole-fused diquinanes



Scheme 71 A facile approach to bis-spiro tetraquinane **340** and bis-spiro propellane **342**

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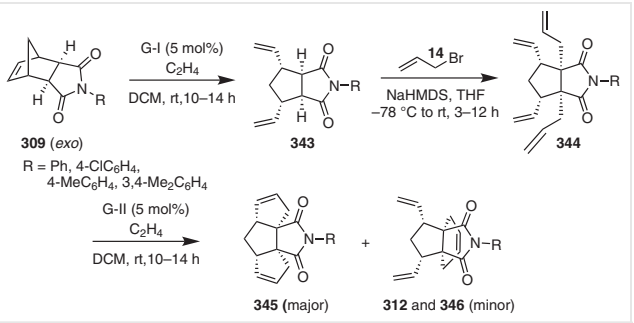
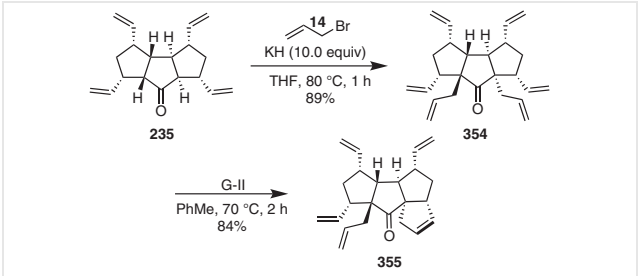


Scheme 72 Synthesis of hetero-tetraquinanes **345** and hetero-propellanes **312** and **346**

13 Synthesis of Dodecahydro-1*H*-dicyclopenta[*a*,*d*]pentalene (A15) Ring System

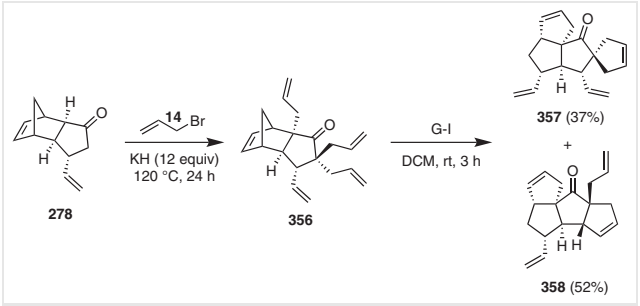
Another synthetically intricate approach to fused tetraquinane derivative **353** was envisioned from stereochemically well-defined DA adduct **351**. Alkylation of **351** with allyl bromide (**14**) in the presence of KH led to the generation of monoallyl compound **352** in 46% yield. Next, monoallyl derivative **352** was subjected to RRM by exposure to the G-II catalyst to obtain the tetraquinane **353** in excellent yields. The catalyst loading had not much influence on the reaction efficacy (Scheme 74).[72] Late-stage manipulation of allyl derivative **352** by one-step metathesis process to generate a meaningful and densely functionalized natural product like cyclopentane core (i.e., **353**) is not a trivial exercise. This work highlights the power of RRM and the value of simple building blocks available by DA chemistry.

Subsequently, the triquinane **235**, on reaction with allyl bromide (**14**) in the presence of an excess amount of KH under heating conditions, yielded the diallyl compound **354**. Later, RCM of **354** with the aid of G-II catalyst in dry toluene at 70 °C gave the tetraquinane **355** in 84% yield (Scheme 75).[72]

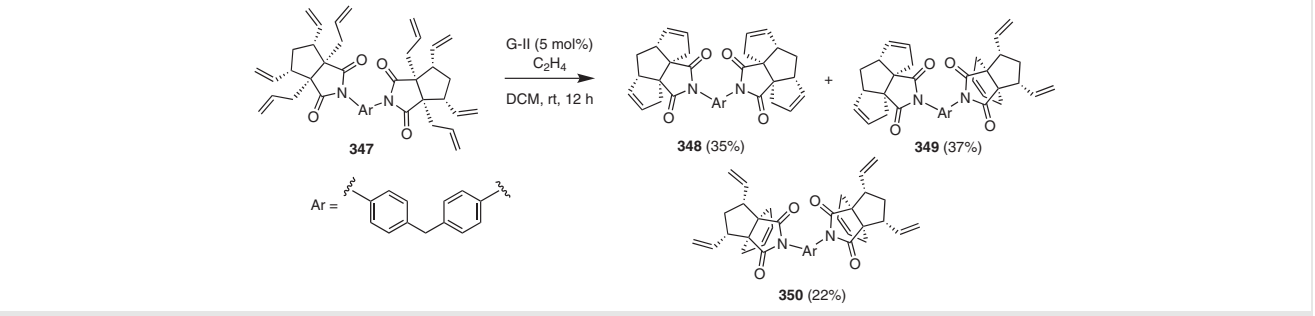


Scheme 75 Synthesis of fused tetraquinane **355**

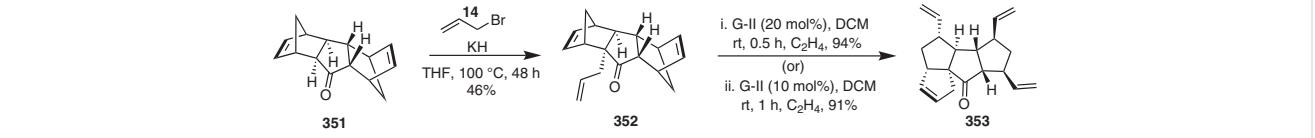
Two unsaturated tetraquinane derivatives were synthesized by our group by performing conjugate addition and allylation followed by RRM using the key precursor *exo*-dicyclopentadiene-1-one (**245**). For this purpose, keto compound **278** was prepared through the 1,4 vinyl Grignard addition of the enone **262**. Next, allylation of the compound



Scheme 76 Synthesis of tetraquinane **358** and spiro tetraquinane **357** by tandem metathesis



Scheme 73 Synthesis of diverse hetero-bis-tetraquinane derivative



Scheme 74 Synthesis of fused tetraquinane derivative **353**

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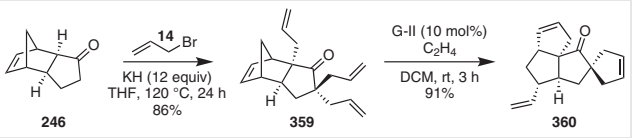
278 with allyl bromide (**14**) in the presence of a large amount of KH delivered the triallyl derivative **356** and it was treated with various ruthenium catalysts, which gave a mixture of unsaturated spiro- and angular-tetraquinanes **357** and **358**. In case of G-I catalyst, we observed a better yield of tetraquinanes **357** (37%) and **358** (52%). It is worth mentioning that the structure of compound **358** resembles the core structure of the natural product crinipellin (Scheme 76).[33]

14 Synthesis of Octahydro-1′*H*-spiro[cyclopentane-1,2′-cyclopenta[*c*]pentalene] (A16) Ring System

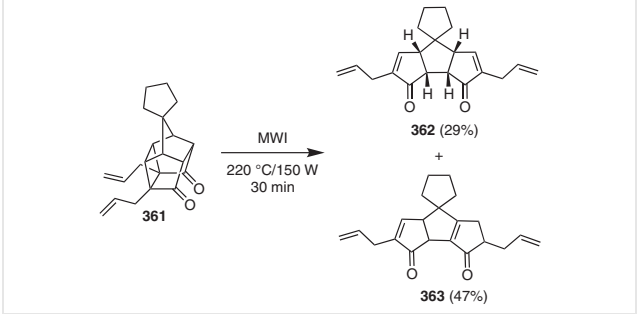
We have also prepared the unsaturated spirotetraquinane **360** from the key precursor **245** by applying the RRM strategy as a key step. The selective reduction of compound **245** in the presence of Zn-AcOH furnished the norbornene fused keto compound **246**, which, upon allylation in the presence of KH at higher temperature, led to the formation of triallyl derivative **359** in good yields. Finally, compound **359** was treated with G-II catalyst under ethylene atmosphere to give the spiro tetraquinane **360** in 91% yield through RRM sequence (Scheme 77).[33]



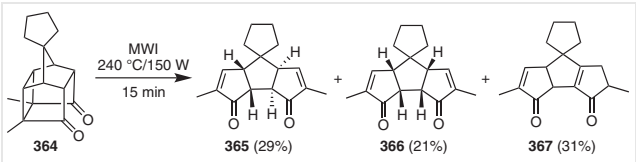
Scheme 77 Synthesis of spiro tetraquinane via tandem metathesis

15 Synthesis of Decahydrospiro[cyclopentane-1,7′-cyclopenta-[*a*]pentalene] (A17) Ring System

We have reported a concise strategy to diverse quinane frameworks from cage diones under green reaction conditions. To this end, several cage diones were prepared from a sequence of known chemical transformations. The cage dione **361** under MWI at 150 W and 180–240 °C provided a mixture of spiro-tetraquinanes **362** and **363** in 29% and 47% yields, respectively (Scheme 78). Subsequently, the same strategy has been applied to generate diverse tetraquinanes and their isomerized products **365–367** in good yields, which are useful precursors for natural product syntheses (Scheme 79).[69]



Scheme 78 Synthesis of diallyl spiro tetraquinanes



Scheme 79 Synthesis of tetraquinanes

16 Synthesis of Compact Tetraquinane (A18)

Triquinacane based tetracyclic compound **371** was efficiently synthesized by using the diastereomeric mixture of 2,6-dially diketo compound **104**. Initially, the diastereomeric mixture **104** was oxidized on a small scale under ozonolysis conditions to deliver the epimeric mixture of dialdehydes **368** in 90% yield. Unfortunately, on large-scale, the reaction was sluggish in nature and the product was obtained in poor yields. To resolve this issue, ozonolysis reaction was performed instead of OsO_4 oxidation by using dimethyl sulfide (DMS) to diminish the oxidative intermediates. However, moderate amounts of other by-products like peracetals or keto acetals were also observed along with the two epimeric aldehydes **368**. Interestingly, the ozonolysis reaction provided a mixture of both epimeric aldehydes **368** cleanly in 90% yield by replacing the DMS with trimethyl phosphite, which presumably reduces the formation of by-products. Further, the mixture of bis-aldehyde **368** underwent intramolecular aldol condensation in the presence of 2N HCl to provide a mixture of tetraquinane **369** in 35%, which, on reduction with borane-THF (**370**) gave the tetraol derivative **371**. Surprisingly, an unprecedented tetraquinane **372** was obtained instead of the expected dehydrative compound when tetraol **371** was reacted with HMPA (Scheme 80).[79]

In connection with our interest in the synthesis of new cyclopentanoids, initially we focused on the construction of an important target pentaquinane. For this purpose, we performed a PTSA catalyzed reaction of dione **373** with the mixture of allyl alcohol (**103**) and 2,2′-dimethoxypropane (**374**) under reflux in toluene to achieve diallylation. Unfortunately, we obtained a mixture of products such as monoallyl triquinane **375** and tetracyclic ether **376** rather than the expected diallyl triquinane (Scheme 81).[68]

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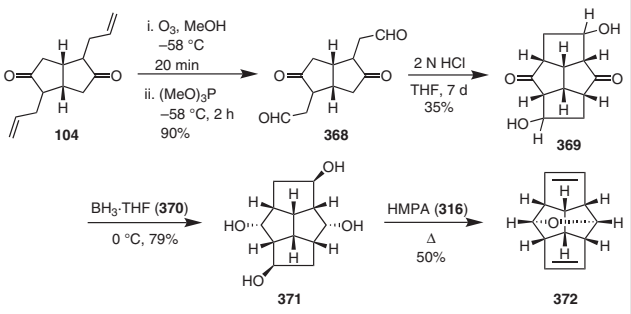
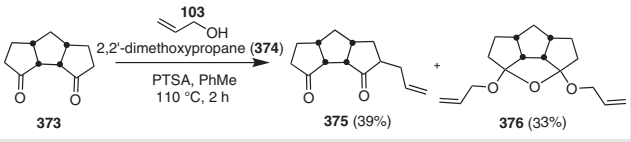
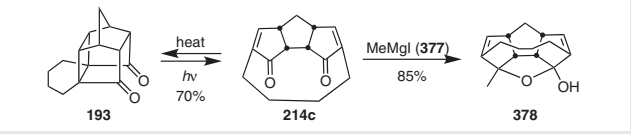


Scheme 80 Synthesis of tetraquinane **371**



Scheme 81 Allylation of triquinane via CR

To further expand the synthetic applicability of the cage dione **193**, 'belted' triquinane bis-enone **214c** was synthesized through [2+2] cycloreversion under FVP conditions at 550 °C in 70% yield, which undergoes a nucleophilic addition with MeMgI (**377**) to provide the oxa-tetraquinane derivative **378** (Scheme 82).[67]

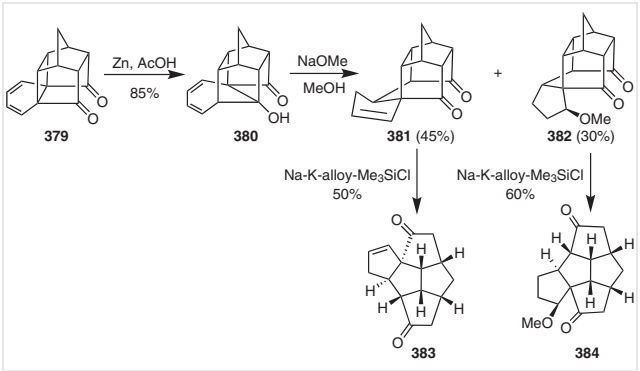


Scheme 82 Synthesis of oxa-tetraquinane **378**

17 Synthesis of Higher Polyquinanes

A new approach for the synthesis of novel C_{15}-pentaquinane was started with the rearrangement of cage compound **379** with Zn-AcOH to provide an annulated trishomocubane derivative **380**. Reaction of **380** with NaOMe-MeOH under reflux conditions provided the mixture of the annulated cages **381** and **382** in 45% and 30% yields, respectively. Reduction of **381** with Na-K alloy-Me_3SiCl in dry toluene led to the formation of expected C_{15}-polyquinane **383** in 50% yield; the structure was unambiguously established from both spectral and single-crystal X-ray diffraction studies (Scheme 83).[84] Along similar lines, a facile approach to the substituted pentaquinane **384** form the cage dione **382** in the presence of Na-K-alloy-Me_3SiCl was reported.

Subsequently, we also investigated the synthesis of pentaquinanes from the DA adduct **351** through RRM/RCM sequence. For this purpose, treatment of compound **351** with allyl bromide (**14**) in the presence of a large amount of KH



Scheme 83 Synthesis of C15-polyquinanes starting with cage compound **379**

in THF at 140 °C provided the diallyl compound **385**, which, upon RRM with G-II catalyst, led to the generation of pentaquinane **387** in excellent yield. Further, ROM of **351** with G-I catalyst gave the triquinane **238**, which, upon allylation with allyl bromide (**14**) in the presence of 12 equivalents of KH, gave the diallyl precursor **386** in 52% yield. The RCM of compound **386** with G-II catalyst furnished the pentacyclic compound **387** in excellent yield (Scheme 84).[72] The architecture of **387** is intriguing. It can be viewed as a fusion of two angular triquinanes with a common cyclopentane ring. Alternatively, it can be considered as a combination of linear triquinane and two angular triquinanes. By any standards it is not an easy task to design such a target by traditional synthetic routes. This example demonstrates the power of the rearrangement approach to design complex targets that contain eight chiral centers.

A convenient strategy to synthesize hexaquinane **393** has been reported by a series of simple chemical transformations from an easily accessible tetraquinane **388**. The Grignard reaction of diketone **388** with allyl bromide and magnesium provided a diastereomeric mixture of homoallylic alcohols **389** and **390** in 1:8 ratio. Later, **391** was subjected to a hydroboration–oxidation with sodium borohydride and Jones reagent (**322**) to give the dilactone **391** in 94% yield. Finally, **391** was treated with methanesulfonic acid and P_2O_5 to provide the rearranged conjugated dienone **392**, followed by hydrogenation of the conjugated double bond, which led to the formation of hexaquinane **393**. The stereochemistry of **393** was established by single-crystal X-ray diffraction studies (Scheme 85).[85]

Along similar lines, the reaction of dione **394** with an excess amount of allylmagnesium bromide (**133**) furnished a diastereomeric mixture of homoallylic alcohol **395**. Then, hydroboration followed by oxidation with Jones reagent (**322**) provided the lactone **396**, which was then treated with methanesulfonic acid/P_2O_5 under heating conditions to afford dienone **397** along with a novel transannular product **398** in equal proportions. The hydrogenation of **397** with Pd/C provided the saturated C_{20}-hexaquinane (Scheme

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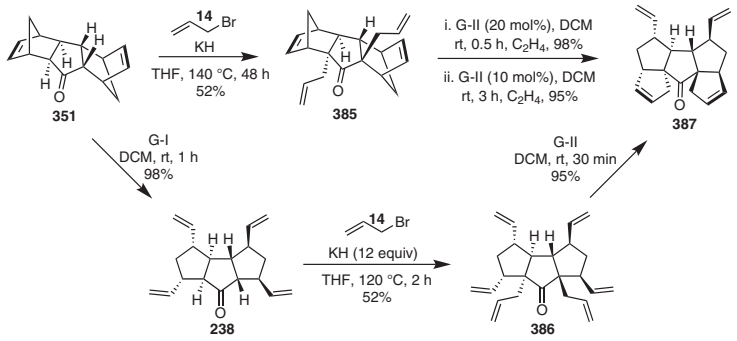
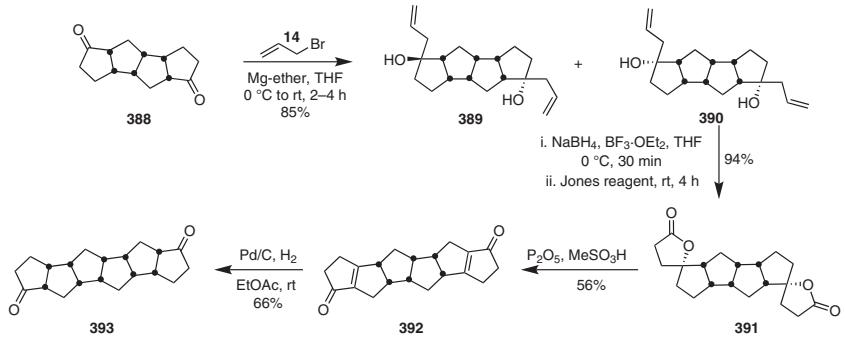


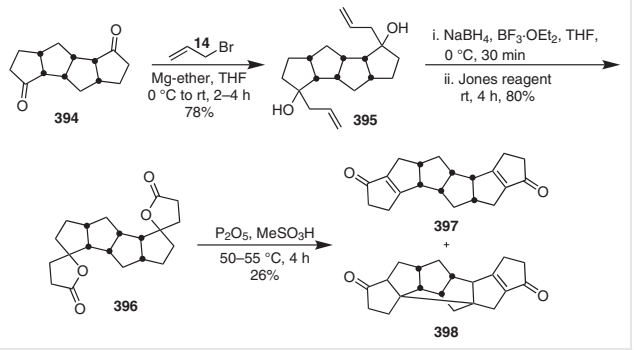
Scheme 84 Synthesis of pentaquinane **387** via olefin metathesis



Scheme 85 Synthesis of hexaquinane **393**

86).[80a] Synthesis of these advanced precursors (e.g. **393**, **397**, and **404**) to dodecahedrane (T1, Figure 4) containing all twenty carbons demonstrate the power of reiterative processes and a 'two-directional functionalization strategy'. Interestingly this is nothing but 'Brevity in Reaction Design'.[80b]

Along similar lines, the allyl Grignard reaction of **133** and tetraquinane **399** afforded a mixture of diallyl diol **400** and transannular product **401** in 45% and 30% yields, respectively. Hydroboration–oxidation sequences of **400** and **401** produced the corresponding rearrangement lactones **402** and **403**. Later, **403** was subjected to rearrangement



Scheme 86 Synthesis of hexaquinanes **397** and **398**

with methanesulfonic acid/P_2O_5 to produce the curved C_{20}-hexacyclic dione **404** (Scheme 87).[86]

Next, we describe an efficient synthetic route to spiro polyquinanes from diketo compounds via RCM. To this end, allylation of dione **373**, in the presence of sodium hydride (NaH), provided the hexaallyl precursor **405**, which underwent RCM with the aid of G-I catalyst followed by hydrogenation to furnish the corresponding saturated bis-spiro polyquinane **406** in good yield. The same approach was applied to construct bis-spiro polyquinane derivatives **409** in good yields starting from the dione **407** (Scheme 88).[87]

A synthetically useful strategy has been investigated to assemble interesting aza-polyquinane/propellane derivatives via FI as a key step starting with Weiss–Cook dione such as **410**. This approach is robust and generated the isomeric mixture of bis-indole derivatives **411** and **412** through two-fold FI of tricyclic [4.3.3]propellane dione (**410**) with *N*-methylphenylhydrazine (**292**; Scheme 89).[88]

Subsequently, to expand the scope of this strategy and to synthesize a variety of polycyclic bis-indole derivatives **413** and **414** in a five-step sequence from easily accessible substrates. The reaction of **383** with *N*-methylphenylhydrazine (**292**) in the presence of a low-melting mixture of TA and DMU produced the bis-indole derivative via twofold FI, which, on hydrogenation, gives the corresponding saturated

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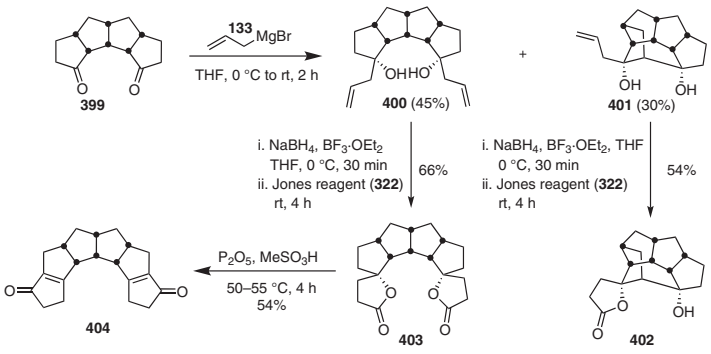
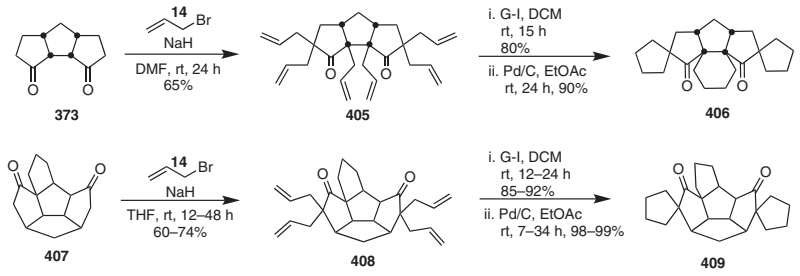
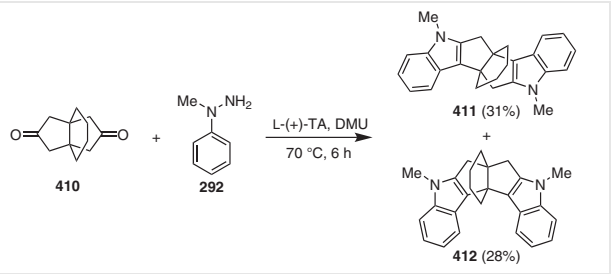


Scheme 87 Synthesis of hexaquinane **404**



Scheme 88 Synthesis of bis-spiro polyquinanes



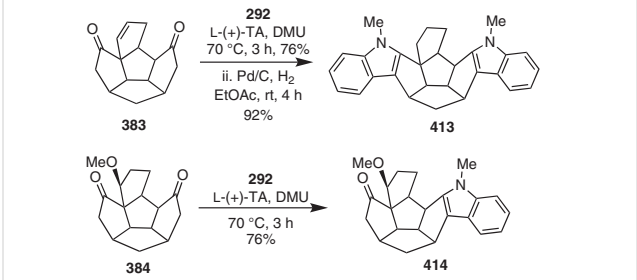
Scheme 89 Synthesis of indole-based propellanes

bis-indole based polyquinane **413**. Surprisingly, FI of methoxy substituted pentacyclic dione **384** provided the unexpected mono-indole derivative **414** instead of bis-indole derivative due to the steric factor induced by methoxy group (Scheme 90).[88]

Another interesting entry to bis-indole derivatives was disclosed using FI and RCM. Starting with *cis-syn-cis*-triquinane-dione **373**, the bis-indole derivative **415** was synthesized through FI with phenylhydrazine (**247**). Reaction of bis-indole **415** with allyl bromide (**14**) in the presence of NaH produced the *N*-allyl derivative **416**, which, on treatment with G-II catalyst, afforded the RCM product **417**. Then hydrogenation with Pd/C led to the bis-indole based macrocycle **418** in 95% yield (Scheme 91).[87]

In connection with our interest in hetero polyquinanes, we also investigated the synthesis of indole-based polyquinanes from readily available carbonyl compounds via FI. To this end, the dione **394** was prepared from Weiss–Cook dione **102** as shown earlier. Later, the FI of dione **394** with *N*-methylphenylhydrazine (**292**) gave the corresponding bis-indole polyquinane **419** in 73% yield. Similarly, the FI of dione **421** with *N*-methylphenylhydrazine (**292**) produced the diaza polyquinane **422** (Scheme 92). The same strategy was applied for the construction of indole-based propellanes, which, on further oxidation with SeO_2, gave the corresponding keto propellanes in good yields.[89]

To expand the library of polyquinane containing bis-indoles via FI and RCM as key steps, we used the tetracyclic dione **190** as a starting material. In this regard, the compound **190** was subjected to the FI with *N*-methylphenylhy-



Scheme 90 Synthesis of indole-based polyquinanes

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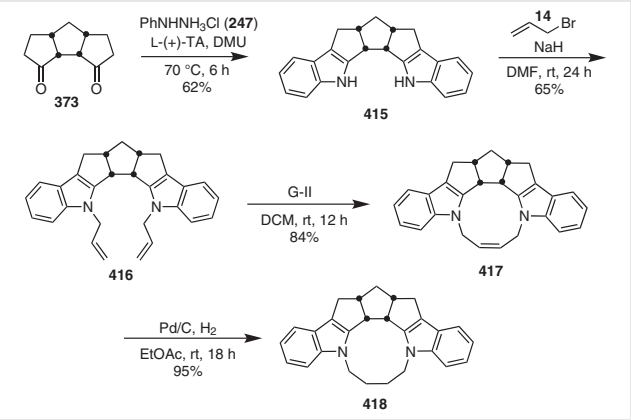
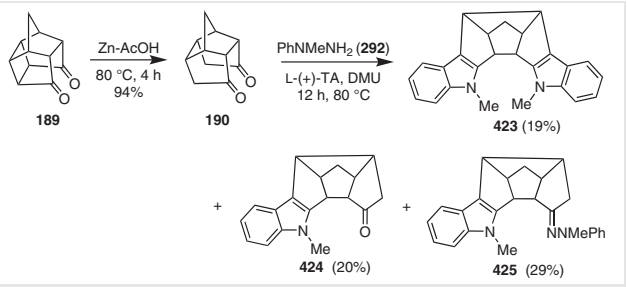


Scheme 91 Synthesis of aza-polyquinane containing bis-indole

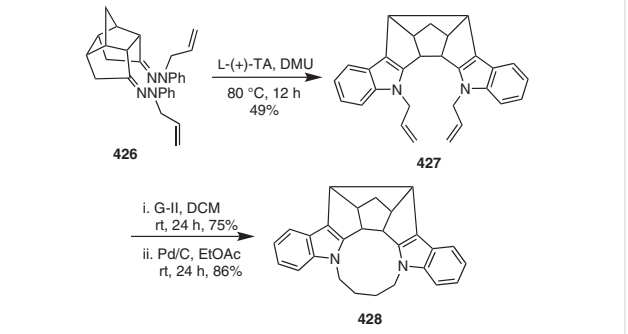
drazine (**292**) to give a mixture of polyquinane bearing indole derivatives **423**, **424** and **425** (Scheme 93). Afterwards, the key precursor **426** was prepared from dione **190** and subsequent base mediated allylation. Next, the diallyl compound **426** was treated with a low-melting mixture of TA and DMU to generate the aza-polyquinane **427** composed of a bis-indole unit. The RCM of bis-indole **427** with G-II catalyst and subsequent hydrogenation with Pd/C furnished the macrocycle fused bis-indole derivative **428** in good yield (Scheme 94).[90]

18 Conclusions

In conclusion, cyclopentanoids are privileged structures that are present in a numerous bioactive molecules. This review demonstrates a collection of our unique strategies for the construction of cyclopentanoids and their hetero derivatives by using various types of named or unnamed reactions. Based on these examples, it is evident that along with previous methods we added some new protocols for the synthesis of these intricate cyclopentanoids. Herein, we have summarized the use of various types of metathesis and cycloaddition protocols as key steps to construct the stereochemically well-defined cyclopentanoids from readily available starting materials. These new strategies may



Scheme 93 Synthesis of polyquinane-containing indole moiety

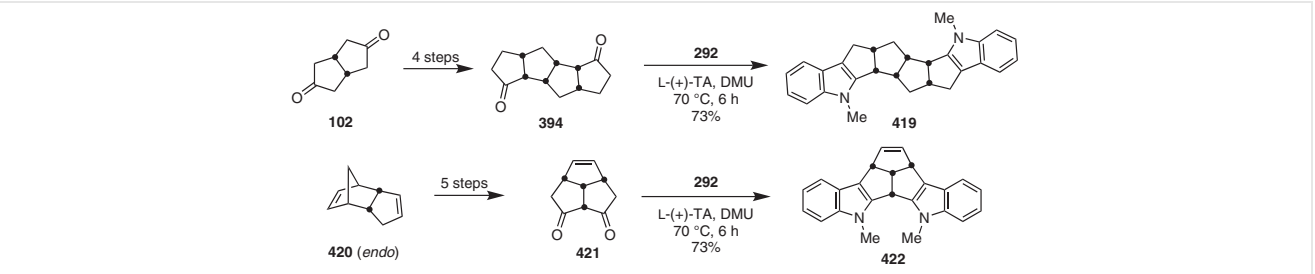


Scheme 94 Synthesis of macrocycle-containing cyclopentane rings

find a broad range of synthetic applications in natural product synthesis, bioorganic chemistry and material science, which, in turn, should catalyze further developments in this area.

19 Acronyms

BTEAB: benzyltriethylammonium bromide
BTEAC: benzyltriethylammonium chloride
$CpCo(CO)_2$: cyclopentadienylcobalt dicarbonyl
CR: Claisen rearrangement
DEAM: diethyl acetamidomalonate
DMU: dimethylurea
EICA: ethyl isocyanoacetate
EM: enyne metathesis
ERRM: enyne ring-rearrangement metathesis



Scheme 92 Synthesis of indole-based polyquinanes

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FI: Fischer indolization
LiHMDS: lithium bis(trimethylsilyl)amide
RCEM: ring-closing enyne metathesis
ROCM: ring-opening cross-metathesis
ROM: ring-opening metathesis
RRM: ring-rearrangement metathesis
TA: tartaric acid
TBAB: tetrabutylammonium bromide
TBAHS: tetrabutyl ammonium hydrogen sulfate

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