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Aziridinyl imines in organic synthesis: Development of tandem reaction strategies and application to total synthesis of natural products*

Hee-Yoon Lee‡, Seog-Beom Song, Taek Kang, Yoon Jung Kim, and Su Jeong Geum

Department of Chemistry, KAIST, Yuseong, Daejeon 305-701, Korea

Abstract: Aziridinyl imines are well-known carbene equivalents because they are precursors of diazo compounds from which reactive intermediates can be produced. These carbene equivalents can be utilized as zwitterionic species, diradicals, or 4π system for cycloaddition reactions. Thus, the intermediates derived from aziridinyl imines have been used in the sulfur-ylide-mediated epoxide formation, tandem free-radical reactions, or cyclopropanation reaction via carbene intermediates to form trimethylenemethane (TMM) diyls, which undergo [2 + 3] cycloaddition reactions to form cyclopentanoids. Diazo compounds generated from aziridinyl imines also react with allenes to form TMM diyls. This reaction was utilized in tandem cycloaddition reactions of linear substrates to form polyquinanes. These tandem reaction strategies were successfully applied to the total synthesis of various cyclopentanoid natural products.

Keywords: cycloadditions; domino reactions; hydrazones; polycyclic compounds; radical reactions; tandem reactions; total synthesis; trimethylenemethane.

INTRODUCTION

Though the "art" of organic synthesis was considered to have achieved the total synthesis of any given molecule, the goal of organic synthesis of the 20th century [1], organic synthesis in the 21st century faces new challenges as green chemistry has become the main subject of chemical processes [2]. As a result, the "ideal synthesis" has emerged as an important aim of organic synthesis [3], and various guidelines and criteria, including development of efficient synthetic strategies, were introduced toward achieving a significant aspect of the ideal synthesis [4]. Heteroatoms have played important roles in organic synthesis as synthetic intermediates as well as catalysts. Among many heteroatoms, nitrogen has played important roles in efficient total syntheses of various target compounds. As precursors to reactive intermediates, hydrazones are good candidates for development of efficient synthetic strategies. Hydrazones have shown various reactivity patterns by converting themselves into reactive intermediates such as carbenes. As depicted in Scheme 1, hydrazones can undergo cycloaddition reaction with dienophiles after being converted into the diazo functionality [5] in addition to conversion into carbenes [6]. Hydrazones can also generate ionic intermediates [7] and are implicated in radical reactions [8]. We

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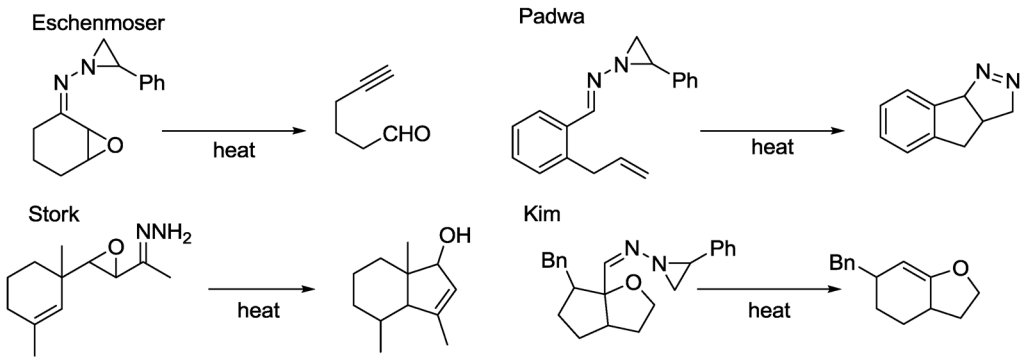
‡Corresponding author

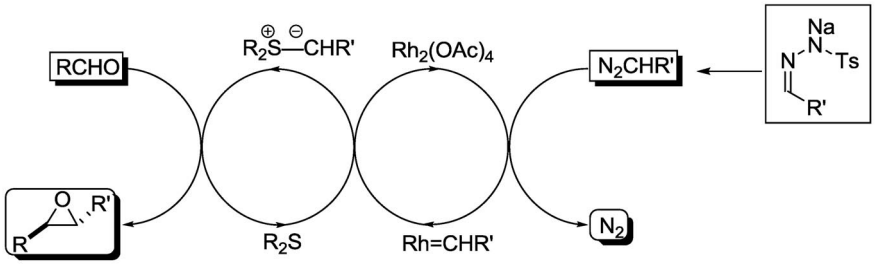


Scheme 1 Reactions of hydrazones.

have developed tandem reaction strategies using reactive intermediates generated from properly assembled hydrazone precursors.

Sulfur ylides from hydrazones

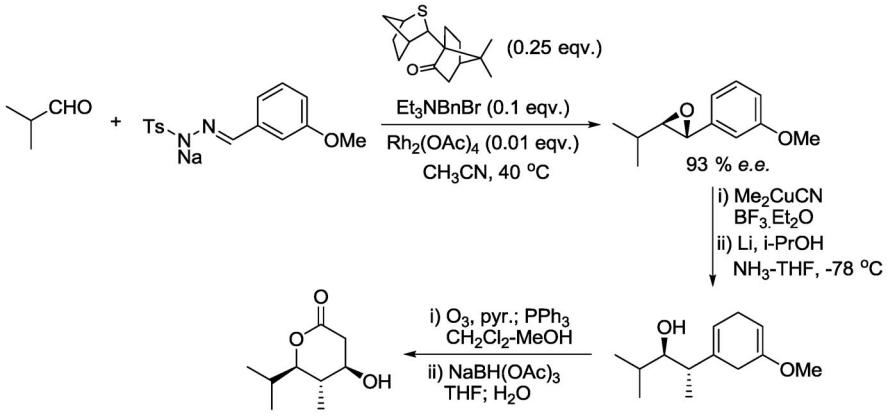
Sodium salts of tosylhydrazones can generate diazo compounds that, in the presence of Rh catalyst, react with sulfide to form sulfur ylides [9]. Sulfur ylides have been known to react with carbonyl compounds to produce epoxides along with regeneration of the sulfide that was used to form sulfur ylides [10]. We designed a catalytic process of sulfur-ylide-mediated epoxidation reaction (Scheme 2) [11], which marked one of the early examples of organocatalytic reactions.



Scheme 2 Organocatalytic process of sulfur-ylide-mediated epoxidation.

The turnover number for the sulfide catalyst is in the typical range of organocatalytic reactions, and chiral sulfides were designed for asymmetric synthesis of epoxides [12]. The structure of the chiral sulfide was optimized both for high enantioselectivity and reactivity along with the reaction conditions to minimize various side reactions. Versatility of the sulfide-mediated asymmetric epoxidation reaction was demonstrated in the total synthesis of natural products and medicinally important compounds as shown by the five-step synthesis of prelactone B starting from isobutyl aldehyde (Scheme 3) [13].

The rhodium catalyst that generates sulfur ylide from diazo compound was also found to accelerate the formation of the diazo compound from hydrazone precursor as the transformation proceeded smoothly at 40 °C, a temperature much lower than the usual 110 °C used for the same transformation without the rhodium catalyst [14]. Thus, isobutyl aldehyde reacted with the tosylhydrazone sodium salt of *m*-methoxybenzaldehyde in the presence of chiral sulfide to produce the desired epoxide with high

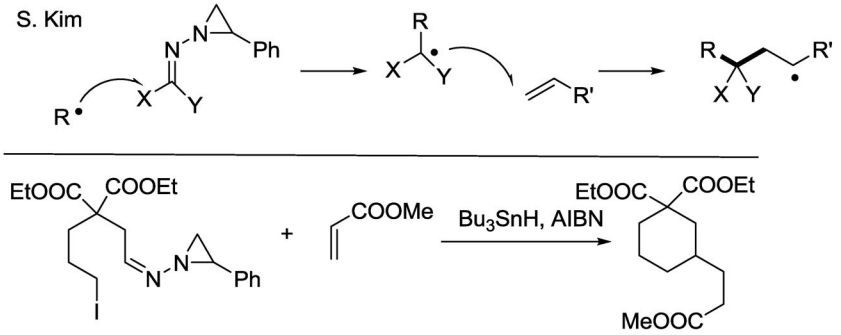


Scheme 3 Total synthesis of prelactone B.

enantiomeric excess. The benzene ring in the synthesis was the masked β-ketoester and readily converted into the lactone ring with well-controlled stereochemistry of all the ring substituents.

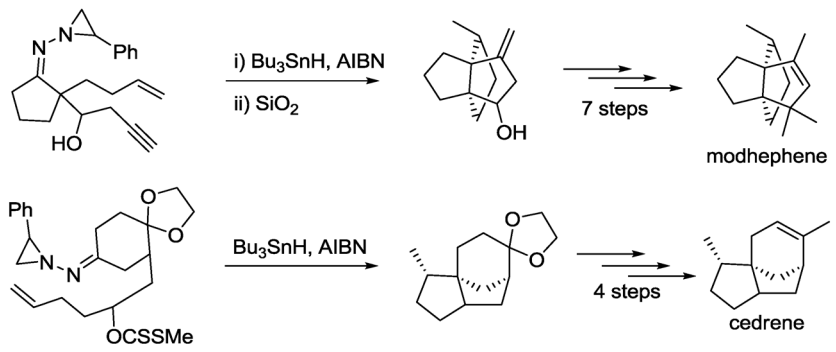
Tandem radical cyclization reaction of carbenes from aziridinyl imines

Aziridinyl imines can be considered as the precursors of diradicals as they are good radical acceptors and subsequently generate radicals. When they react with free radicals, new carbon radicals are produced. These newly generated carbon radicals can react with other radical acceptors (Scheme 4) [15].



Scheme 4 Tandem radical cyclization reaction of aziridinyl imine.

The tandem radical cyclization reaction of aziridinyl imines is not only an efficient way of constructing complex structures but also a great way of generating quaternary carbon centers with all C–C bonds. When aziridinyl imines of ketones are used for the tandem radical cyclization reaction, quaternary centers are formed readily. This tandem cyclization reaction is especially powerful for the synthesis of polyquinane structure and has been applied to the total synthesis of various natural products (Scheme 5). 2,2-Disubstituted cyclopentanone was readily transformed into the modhephane skeleton stereoselectively through tandem radical cyclization reaction. This tandem cyclization reaction was applied to the total synthesis of modhephene [16]. The tandem cyclization reaction also introduced the chiral centers stereoselectively with the desired stereoisomer for natural modhephene as the major



Scheme 5 Total synthesis of natural products through tandem radical cyclization reaction of aziridinyl imines.

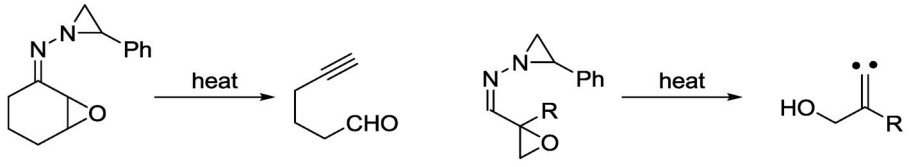
product. The tandem cyclization reaction was also applied to more challenging cyclization reactions. A properly substituted cyclohexanone was cyclized into tricyclic structure of cedrene stereoselectively and was readily transformed into cedrene in a four-step sequence [17]. These two examples clearly demonstrated the power of the tandem radical cyclization reaction of hydrazone derivatives.

We extended the versatility of hydrazine derivatives to cycloaddition reactions by converting the precursors into carbenes and diradical intermediates. These intermediates were applied to the tandem cycloaddition reactions and the total synthesis of related natural products.

RESULTS AND DISCUSSION

Tandem cycloaddition reactions of alkylidene carbenes from aziridinyl imines

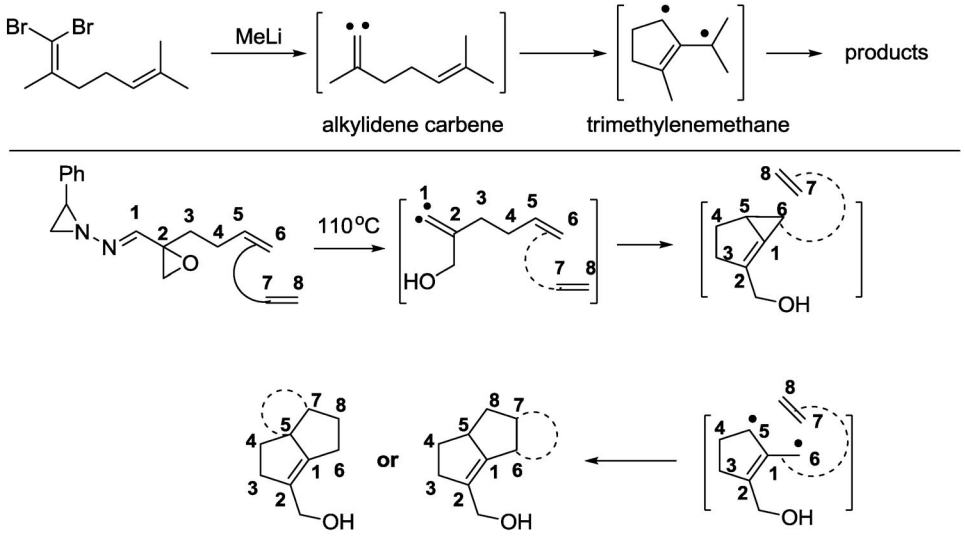
When the Eschenmoser fragmentation reaction [18] was applied to the aziridinyl imines of epoxyaldehydes, alkylidene carbenes were generated instead of fragmentation reaction of a C–C bond (Scheme 6) [19].



Scheme 6 Eschenmoser fragmentation reaction of epoxyaziridines.

Based on the report by Koebrich [20] and further studies by Berson, it was known that the alkylidene carbenes undergo an intramolecular cyclopropanation reaction with alkenes to produce trimethylenemethane (TMM) [21]. We designed a TMM diyl-mediated [2 + 3] cycloaddition reaction route to triquinanes from alkylidene carbenes generated from aziridinyl imines of epoxyaldehydes (Scheme 7) [22].

When an appropriately tethered alkenyl epoxyaziridinyl imine is heated, the corresponding alkylidene carbene is generated. The alkylidene carbene undergoes intramolecular cyclopropanation reaction to form bicyclo[3.2.1]hex-1-ene structure that immediately breaks the cyclopropane ring to generate a TMM diyl. The TMM diyl undergoes [2 + 3] cycloaddition reaction with the tethered alkenes to form a triquinane structure. Depending on the connectivity of the alkenes, either a linearly fused triquinane or an angularly fused triquinane is formed. During this tandem process, four C–C bonds are

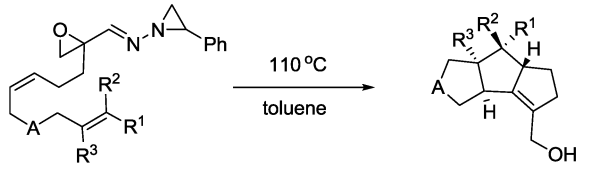


Scheme 7 Design of a tandem cycloaddition reaction from alkylidene carbene.

formed and one double bond is cleaved resulting in the complete reorganization of the connectivity of the linear starting material into the tricyclic structure.

When the two olefins were connected between C6 and C7, the tandem reaction sequence produced linearly fused triquinanes with good efficiency (Table 1).

Table 1 Tandem reaction sequence to linearly fused triquinanes.



1a,b: A=O
1c-g : A=C(COOEt)$_2$

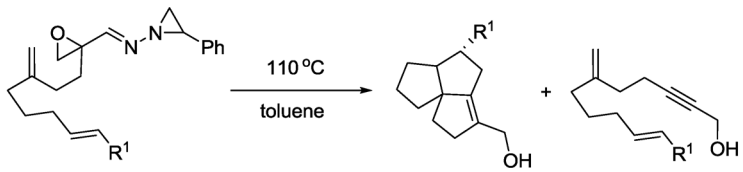
2a, b: A=O
2c-g : A=C(COOEt)$_2$

Entry	Product	R^1	R^2	R^3	Yield (%)
1	**2a**	Ph	H	H	68
2	**2b**	H	H	H	35
3	**2c**	Ph	H	H	54
4	**2d**	CO_2Et	H	H	49
5	**2e**	H	H	H	52
6	**2f**	Me	H	H	50
7	**2g**	H	Me	Me	52

With various substitution patterns on the alkene, the [2 + 3] cycloaddition reaction proceeds smoothly to produce triquinanes stereoselectively with retention of the stereochemistry of the olefins.

When the two olefins were connected between C5 and C7, the tandem reaction sequence produced angularly fused triquinanes along with the carbene rearranged alkyne products (Table 2) [23].

Table 2 Tandem reaction sequence to angularly fused triquinanes.



3 a-d **4 a-d** **5 a-d**

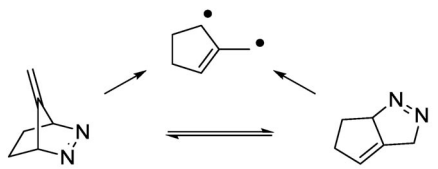
Entry	R^1	Product	Yield (%)	Product	Yield (%)
1	COOEt	**4a**	18	**5a**	–
2	CH_2OMe	**4b**	8	**5b**	24
3	CH_3	**4c**	–	**5c**	36
4	H	**4d**	–	**5d**	26

[a]Isolated yields.
[b]Obtained as 7:1 mixture with *syn–cis*-isomer.

To our surprise, the initially generated alkylidene carbene underwent an unanticipated rearrangement reaction to the alkyne products depending on the substitution patterns of the tethered olefin. When an electron-deficient olefin was used, the triquinane was obtained without the rearranged alkyne in low yield (entry 1). The low efficiency of the tandem reaction sequence was due to the low reactivity of the exo-olefins toward alkylidene carbenes and relatively high reaction temperature for carbene generation. This shortcoming of the reaction sequence was partially circumvented by using different alkylidene carbene sources with lower reaction temperature to suppress the carbene rearrangement [24].

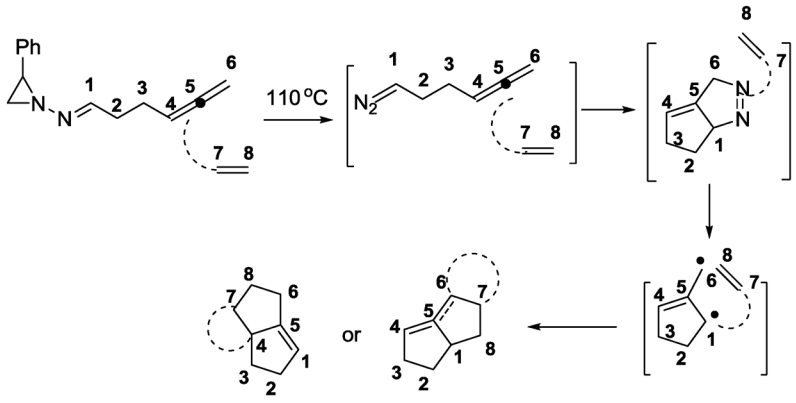
Tandem cycloaddition reaction of diazo-dipoles from aziridinyl imines

Methylene-2,3-diazabicyclo[2.2.1]hept-2-ene has been used as the stable precursor of the TMM diyl for physical organic chemistry studies. In those studies it was indicated that tetrahydrocyclopentapyrazole also was a precursor for the TMM diyl as those two precursors could be in equilibrium and have the similar activation barrier to form the TMM diyl intermediate (Scheme 8) [25].



Scheme 8 Routes to methylcyclopentene TMM diyl.

Since tetrahydrocyclopentapyrazole can be obtained from the [2 + 3] cycloaddition reaction of allenes with diazo compound that can readily be generated from aziridinyl imines, a new tandem sequence for the TMM diyl [2 + 3] cycloaddition reaction was designed and executed from a precursor containing an aziridinyl imine, an allene, and an olefin (Scheme 9) [26].



Scheme 9 A new tandem [2 + 3] cycloaddition reaction route via TMM diyls.

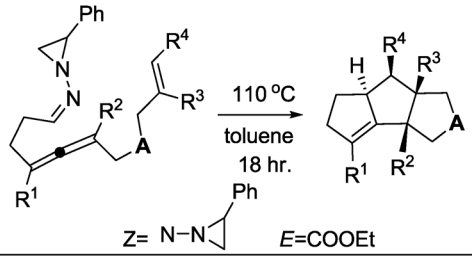
Intramolecular [2 + 3] cycloaddition reaction of a diazo compound with an allene would produce a methylenepyrazole structure, and the initial cycloaddition product would lose a nitrogen molecule immediately to generate the TMM diyl. A subsequent [2 + 3] cycloaddition reaction would produce a linear triquinane or an angular triquinane depending on the connectivity of the alkene in the substrate.

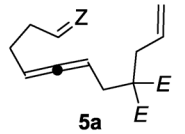
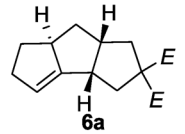
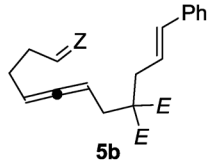
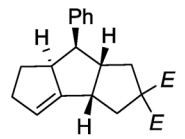
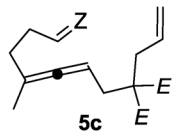
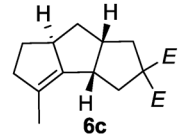
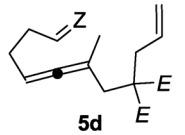
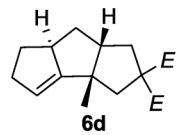
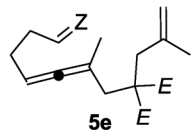
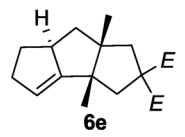
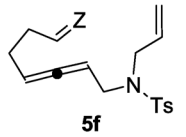
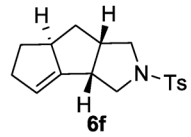
As anticipated, linearly fused triquinanes were obtained from substrates with various substitution patterns on the alkene and the allene with high efficiency (Table 3). In all cases, including highly congested substrates, the tandem reaction produced the products in good yields. When compared to the alkylidene carbene-mediated tandem cycloaddition reaction, the current tandem process showed much higher efficiency and broader substrate scope.

The efficiency of this tandem cycloaddition reaction turned out to be more dramatic for the formation of angularly fused triquinanes (Table 4). Unlike the alkylidene carbene route to the angularly fused triquinanes, which showed very low efficiency and narrow substrate scope, the new tandem cycloaddition route produced the angularly fused triquinanes in higher efficiency than the linearly fused triquinanes. This result confirmed the power of TMM diyl cycloaddition reaction as the reaction tolerated steric congestion as well as high ring strain.

Results in Table 4 also reveal the versatility of the tandem reaction. A diazo compound from a ketone also underwent the tandem reaction (entry 3). Excellent diastereoselectivities were observed in cases where substrates have stereocenters (entries 4, 5, and 6). When there was extra steric congestion (entry 5), intermolecular cycloaddition reaction product from the TMM diyl with styrene that was generated from the aziridinyl imine during the formation of the diazo compound became the dominant byproduct. Substituting the aziridinyl imine with the sodium salt of tosylhydrazone eliminated the styrene byproduct and the competing intermolecular reaction.

Table 3 Tandem cycloaddition reaction of linear substrates to linearly fused triquinanes.

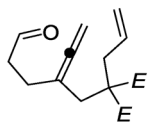
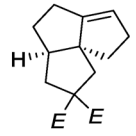
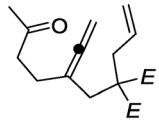
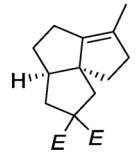
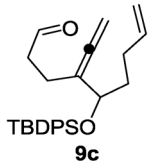
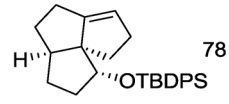
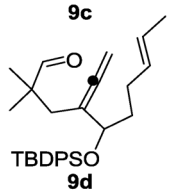
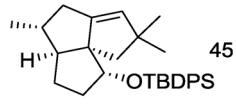


entry	substrate	product	yield[a]
1	 **5a**	 **6a**	83%[b]
2	 **5b**	 **6b**	86%
3	 **5c**	 **6c**	84%
4	 **5d**	 **6d**	76%
5	 **5e**	 **6e**	70%
6	 **5f**	 **6f**	82%[b]

[a] Isolated yields. [b] Obtained as 7:1 mixture with *syn-cis* isomer.

Table 4 Tandem cycloaddition reaction of linear substrates to angularly fused triquinanes.

E=COOEt

entry	substrate	condition	product	yield[a]
1	 **9a**	**A**	 **10a**	93 %
2		**B**		98 %
3	 **9b**	**A**[b]	 **10b**	84 %
4	 **9c**	**A**	 **10c**	78 %
5	 **9d**	**A**	 **10d**	45 %
6		**B**		61 %

condition A:  , CH_2Cl_2; toluene 110 °C, 12 hr.

condition B: NH_2NHTs/MeOH; NaH/Toluene 110 °C, 4 hr.

Total synthesis of natural products using tandem cycloaddition reaction routes from aziridinyl imines

The tandem cycloaddition reactions were readily applied to the total synthesis of various polyquinane natural products (Fig. 1). The natural products in Fig. 1 were selected as the signature targets to demonstrate the efficiency of the synthetic strategies (hirsutene [27], pentalenene [28], and panaginsene [29]), verification of the steric tolerance of the methodology (ceratopicanol) [30], and extension of the methodology to the tetraquinane structure (crinipellins [31]).

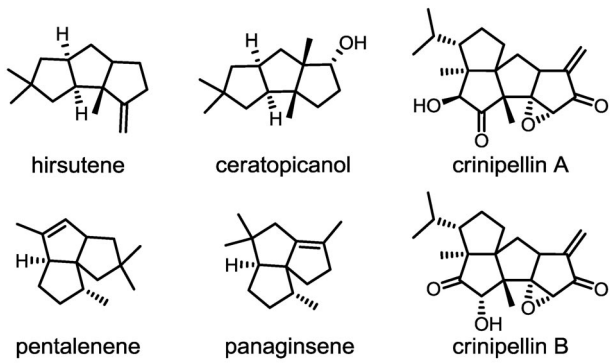
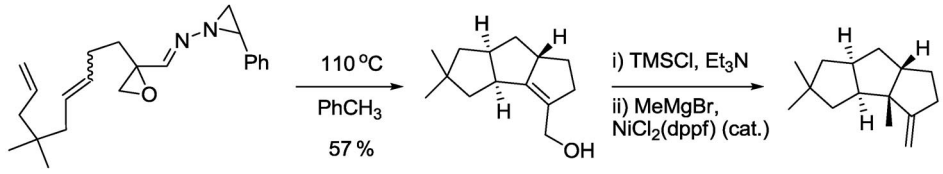


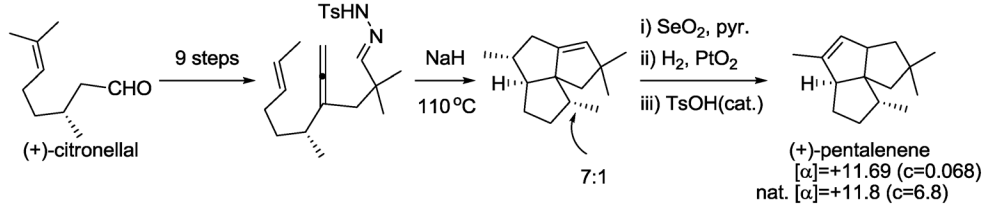
Fig. 1 Polyquinane natural products.

The total synthesis of hirsutene was accomplished via the tandem cycloaddition reaction of an epoxyaziridinyl imine precursor, which marked the first practical application of the synthetic methodology (Scheme 10) [22]. The tandem cycloaddition reaction of the linear substrate produced the hirsutene skeleton with complete stereoselectivity. Hirsutene was obtained directly from the cycloaddition reaction product using Ni-catalyzed regioselective methylation of the allylic alcohol.



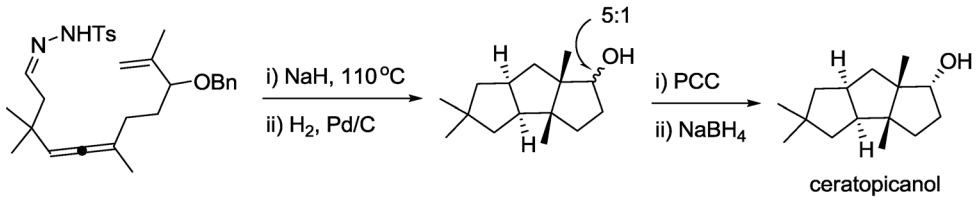
Scheme 10 Total synthesis of hirsutene.

The total synthesis of pentalenene was achieved through the tandem cycloaddition reaction of an allenyl hydrazone precursor prepared from (+)-citronellal in a 9-step sequence to produce the angularly fused triquinane intermediate stereoselectively with the 7:1 diastereomeric ratio (Scheme 11) [32]. The total synthesis was completed through the stereoselective allylic oxidation of the alkene using SeO_2 to the allylic alcohol followed by hydrogenation and a subsequent dehydration reaction.



Scheme 11 Total synthesis of (+)-pentalenene.

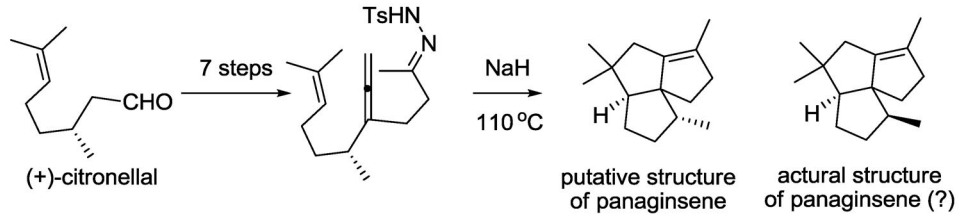
With the total synthesis of hirsutene and pentalenene, the efficiency and the practicality of the tandem cycloaddition reaction were well demonstrated. Next, we applied the tandem cycloaddition strategy to the sterically challenging target natural product, ceratopicanol, which possesses consecutive quaternary centers. The total synthesis of ceratopicanol was accomplished through the tandem



Scheme 12 Total synthesis of ceratopicanol.

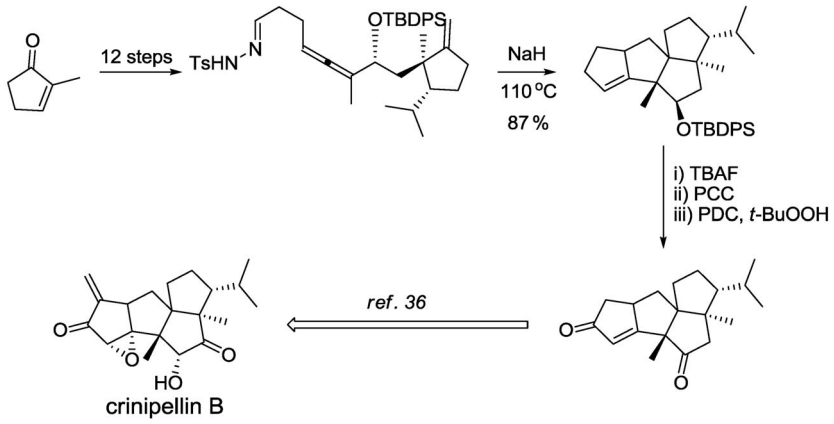
cycloaddition reaction of the substrate with a trisubstituted allene and a 1,1-disubstituted olefin (Scheme 12) [33]. The cycloaddition proceeded stereoselectively to form ceratopicanol along with its epimeric alcohol as the minor product directly from the tandem cycloaddition reaction after the hydrogenation/hydrogenolysis reaction of the cycloaddition reaction product. Instead of separating the two isomers, oxidation of the mixture of the alcohols followed by $NaBH_4$ reduction converted the mixture into ceratopicanol as the sole product.

Next, we selected panaginsene as another challenging target for the tandem cycloaddition reaction, since the synthesis required a trisubstituted olefin and a disubstituted diazo functionality that set up a sterically crowded environment during the TMM diyl cycloaddition reaction. This would be the only synthetic route that produces the natural product in one step with the desired position of the olefin. Panaginsene was an interesting natural product as the only reported natural product with the same skeleton was senoxydene. Since the structure of senoxydene was later disproved through total synthesis of the reported structure, the structural integrity of panaginsene also had to be confirmed through total synthesis. The allenyl hydrazone precursor for the tandem cycloaddition reaction was prepared from (+)-citronellal and was subjected to the tandem cycloaddition reaction conditions to produce the compound reported as the structure for panaginsene (Scheme 13) [34]. As suspected, the spectroscopic data of the synthetic panaginsene did not match that of the natural product. From a comparison of ^{1}H NMR data of synthetic and natural panaginsene, and consideration of the plausible biosynthetic route, the actual structure of panaginsene might quite likely be the diastereomer of the reported structure.



Scheme 13 Total synthesis of the putative structure of panaginsene.

Finally, the tandem cycloaddition reaction was applied to the synthesis of the tetraquinane structure, which extended the scope of the tandem cycloaddition reaction via TMM diyl to more complex and more challenging structures. As shown in Scheme 14, the tandem cycloaddition reaction of a cyclopentane-ring-containing substrate produced a tetraquinane structure that was used for the synthesis of crinipellins [35]. The substrate for the cycloaddition reaction was prepared from 2-methylcyclopentene in 12 steps. The tandem cycloaddition reaction produced tetraquinane product in surprisingly good yield. This tetraquinane product was converted into a known synthetic intermediate for the total synthesis of crinipellin B [36]. The same synthetic intermediate was also used for the total synthesis of crinipellin A.



Scheme 14 Formal total synthesis of crinipellin B.

SUMMARY

In summary, it was demonstrated that the hydrazones could not only be converted into free radical acceptor-free radical pairs on the same carbon atom for the tandem radical cyclization reaction but also into alkylidene carbenes for further transformation into diradial species for a TMM diyl-mediated cycloaddition reaction, and into a diazo functionality that undergoes tandem cycloaddition reaction to polyquinanes. The efficiency and practicality of the new synthetic strategies were exhibited through application to the total synthesis of natural products.

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