# Trimethylenemethane Diyl Mediated Tandem Cycloaddition Reactions: Mechanism Based Design of Synthetic Strategies

Published as part of the Accounts of Chemical Research special issue "Synthesis, Design, and Molecular Function".

Hee-Yoon Lee*

Molecular-Level Interface Research Center, Department of Chemistry, Korea Advanced Institute of Science and Technology, Daejeon, 305-701 Korea

CONSPECTUS: Several criteria for the measure of synthetic strategies toward "ideal synthesis" are available to guide the design and evaluation of the synthetic strategies toward the target molecules. One strategy toward "ideal synthesis" is developing a multistep reaction that involves dramatic change in complexity. Biogenesis of natural products and mechanistic investigation of complicated organic transformation provide good inspiration for design of new synthetic strategies. Trimethylenemethane diradical (TMM diyl), first introduced only as a theoretically interesting structure 60 years ago, gained interests of physical organic chemistry when it was first detected by Dowd. Study of characteristics and properties of TMM diyl was accelerated in a great deal when Koebrich observed dimeric hydrocarbon products from the reaction of 1,1-dibromo-2-methylhexa-1,5-diene with MeLi. Berson followed the mechanistic investigation of the reaction that involved 2-methylenecyclopentane-1,3-diyl, and thoroughly studied physical and chemical properties of the TMM diyl. This lead to the development of intramolecular [2 + 3] TMM diyl cycloaddition reaction for the construction of linearly fused triquinanes by Little.
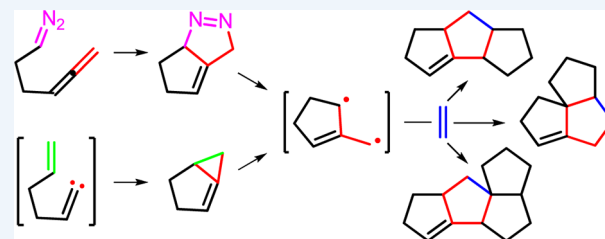
We envisioned that the generation of a TMM diyl through cycloaddition reaction discovered by Koebrich and [2 + 3] cycloaddition reaction of the TMM diyl could be combined together to form polyquinane structures. A cycloaddition reaction sequence of generating a TMM diyl from a alkylidene carbene of 2-methylhexa-1,5-diene structure in the presence of another olefin was designed and executed to produce linearly fused and angularly fused triquinanes depending on the connectivity of the second double bond. The successful transformation also inspired design of a tandem cycloaddition reaction strategy of using unprecedented tetrahydrocyclopentapyrazole to TMM diyl transformation. The new design involves two [2 + 3] cycloaddition reactions of 6-diazohexa-1,2-diene with an olefin attached at a proper position. When a diazo functionality is produced, the initial [2 + 3] cycloaddition reaction generates the TMM diyl, which undergoes the second [2 + 3] cycloaddition reaction to form triquinanes with high efficiency. The first tandem strategy involves a massive reorganization of molecular connectivity as one C=C double bond was cleaved and four C−C bonds were formed. The second tandem strategy connected two double bonds with one carbon center to form four C−C bonds without breaking any bond.

The developed tandem strategies were readily applied to the total synthesis of natural products, especially triquinanes. Thus, the total syntheses of hirsutene, ceratopicanol, pentalenene and panaginsene with structural revision were achieved and the strategy was extended to the total synthesis of crinipellins (tetraquinane natural products).

The newly designed tandem strategies not only demonstrated the efficiency and effectiveness of the process but also provided future opportunity of studying TMM diyl mediated reactions for designing variety of synthetic strategies.

1. INTRODUCTION

The ultimate goal and challenge of organic synthesis would arguably be the "ideal synthesis", the term first introduced by Hendrickson[1a] and further developed as *"the target molecule is assembled from readily available materials in one simple, safe, economical and efficient operation"* by Wender.[1b] The ideal synthesis offers a good guide to design and evaluation of synthetic strategies for target molecules or development of new molecular transformations. Criteria of ideality[2] such as step, atom, and redox-economy[3a] have been introduced for the measure of ideal synthesis. All of these criteria are measured for the efficiency of a reaction or a synthetic transformation and thus guide the design and evaluation of the synthetic strategies

used for the preparation of the target molecules.[3b] However, for a given target molecule, these criteria often provide contradicting efficiency guidance for the designed synthetic strategies. Thus, a holistic approach, finding a way to maximize the increase of molecular complexity closer to the target molecule, becomes more interesting.[4] To maximize the change of the molecular complexity toward the target molecule in each single operation, multicomponent reactions, tandem/cascade reactions and synthetic strategies with combination of these reactions have been developed.[5] Such transformations are
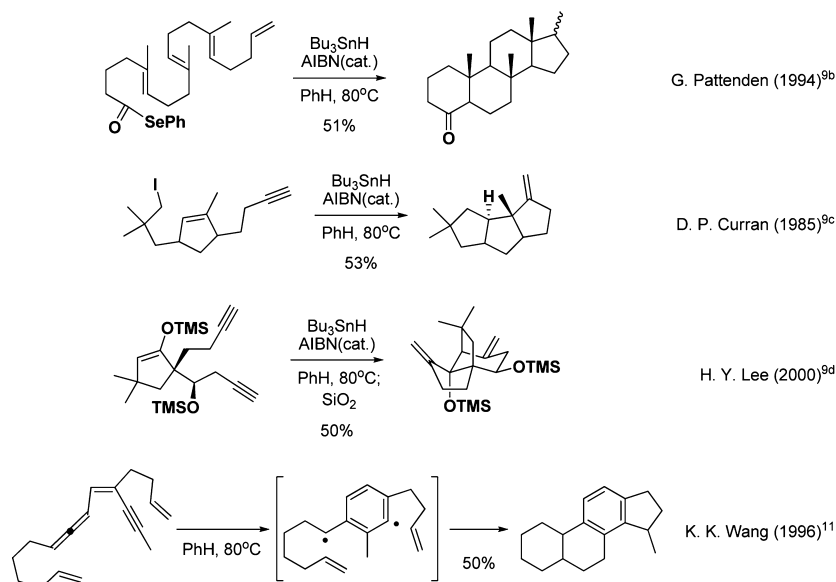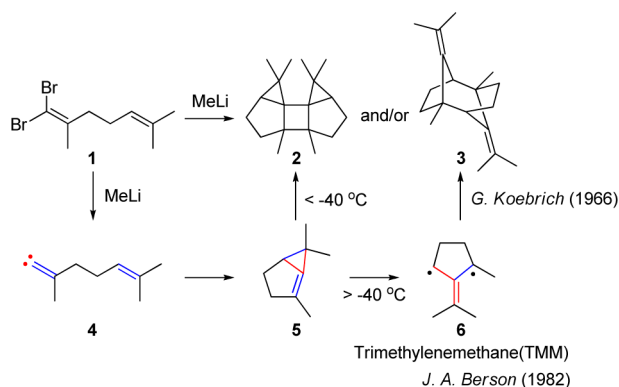
Figure 1. Free radical mediated cascade/tandem reactions.

Scheme 1. Dimerization Reactions of Trimethylenemethane Diyl

either inspired by Nature[6] or designed based on the reaction mechanism studies.[7] In all cases, reactive intermediates play important roles in such multiple transformations.

Cationic cascade reactions have been effectively used for construction of complex polycyclic compounds in Nature and these processes inspired synthetic organic chemistry to design synthetic methodologies for efficient total synthesis of complex natural and non-natural compounds.[8] Another related reactive intermediate, the free radical, has been used effectively in cascade reactions[9] to form various complex polycyclic structures such as steroids,[9b] polyquinanes,[9c] and quadranoids[9d] since the development of trialkyltin hydride as the source of hydrogen in the radical chain reaction by Stork that offered well-tailored control of radical reactions.[10] Extension of the radical cascade reaction into diradical reaction also provided quick entry into polycyclic structures in one operation (Figure 1).[11] Another reactive intermediate, carbene[12] could be used to increase the complexity of the system through design of a strategy that utilizes the interesting nature of carbene that is equivalent to zwitterionic species[7b] or diradical species. We became interested in utilizing carbene intermediate to generate diradical intermediate for tandem reaction strategy.

Trimethylenemethane (TMM)[13] was introduced as imaginary species studied in physical chemistry and organic reaction mechanisms to explain some organic transformations during the 50s. In the 60s, metal-coordinated TMM species that was too stable to show any reactivity was reported,[14] and eventually the actual TMM was observed at low temperature.[15] Due to the propensity of the TMM to form methylenecyclopropane, only limited information on TMM diyl was reported and synthetic viability of TMM diyl was unimaginable. For this reason surrogates of TMM diyl were developed. Trost developed [2-(acetoxymethyl)allyl]trimethylsilane as a TMM surrogate through Pd catalyzed [2 + 3] cycloaddition reaction[16a] and Nakamura introduced methylenecyclopropanone acetal as the precursor for dipolar trimethylenemethane that undergoes [2 + 3] cycloaddition reaction with polar 2π system.[16b] Transition metal catalyzed cycloaddition reactions of methylenecyclopropane were also developed as alternative to TMM mediated cycloaddition reaction.[16c] A breakthrough in the study of TMM diyl came about when Koebrich reported a new transformation of alkylidene carbenes (Scheme 1).[17] When an alkylidene carbene was generated from 1, unexpected dimeric products, 2 and 3 were formed in varying ratio depending on the reaction temperature. Formation of the dimeric product 3 could be explained by the formation of TMM diyl intermediates 6. The TMM diyl 6 possesses a unique structural feature of existing as a diradical rather than forming methylenecyclopropane ring. Even a slight alteration of the structural features prevented the formation of TMM diyls.[17a,26]

The special nature of the TMM diyl 6 enabled a study that probed the characteristics and reactivity of the TMM diyl.[18] Information obtained from Berson's thorough investigation led to the application of TMM diyl in organic synthesis. Intramolecular [2 + 3] cycloaddition reaction of TMM diyl generated from diazene 7 formed triquinane ring system[19] and cyclopropyl group-containing TMM diyl formed cyclooctanoid 15 through cyclopropylmethyl radical mediated rearrangement and recombination to form the cyclooctanoid[20] (Scheme 2).

Information obtained for the generation, stability, and reactivity of the TMM diyl intermediate prompted us to design a bold strategy of combining all of these transformations around

Scheme 2. Intramolecular Reactions of TMM Diyls Generated from Diazene Precursor
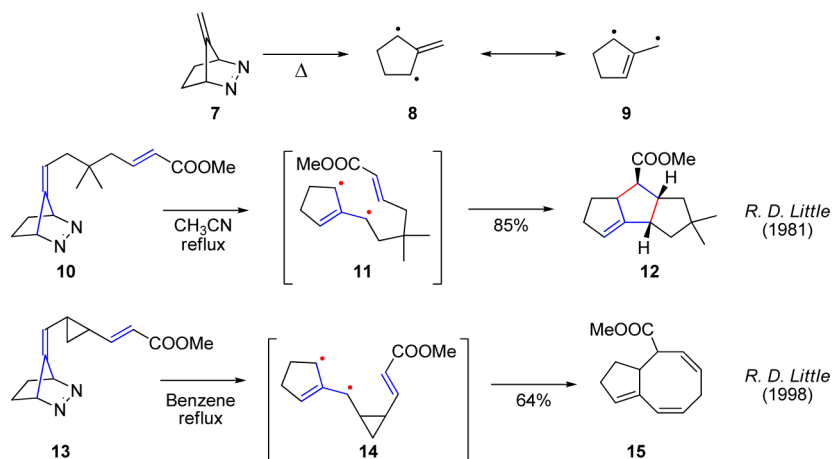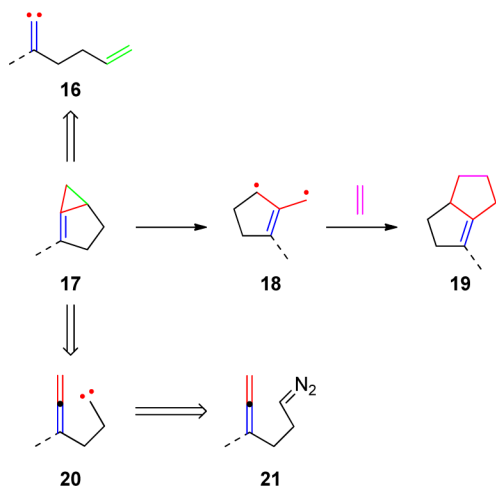

the TMM diyl in a single operation using relatively simple substrate that would increase the molecular complexity greatly.

2. DESIGNING TANDEM CYCLOADDITION STRATEGIES VIA TMM DIYL

Discoveries of Koebrich followed by Berson's thorough investigation and application by Little could be linked together to design tandem cycloaddition strategies to polyquinane structures from linear substrates; that is, if an alkylidene

Scheme 3. Designing Tandem Cycloaddition Reaction Starting from Carbenes via TMM Diyls

carbene **16** were generated from a substrate containing an olefin at a proper position, it could undergo cyclopropanation reaction to form a methylenecyclopropane ring **17** and then the opening of the cyclopropane ring would convert **17** into TMM diyl **18**. The TMM diyl **18**, in turn, could undergo a cycloaddition reaction with another olefin to form the diquinane structure **19**. Though it has not been reported, the methylenecyclopropane intermediate **17** could also be generated through intramolecular cyclopropanation of an alkyl carbene attached to an allene **20** that could be produced from the corresponding diazo compound **21** (Scheme 3).

### 2.1. Designing Intramolecular Tandem Cycloaddition Reactions via Alkylidene Carbenes

We designed intramolecular tandem cycloaddition routes starting from alkylidene carbenes that would produce different triquinane structures depending on the connectivity of the olefin for the final [2 + 3] cycloaddition reaction (Scheme 4). If a pentenyl tether were attached to the end of **16**, **22** could produce TMM diyl **24** that would undergo cycloaddition reaction to form the linearly fused triquinane **25**. If a pentenyl

Scheme 5. Generation of Alkylidene Carbene from Epoxyaziridinyl Imine
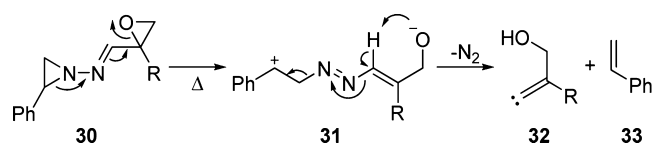
Scheme 4. Design of Tandem Cycloaddition Reactions from Alkylidene Carbene via TMM Diyl
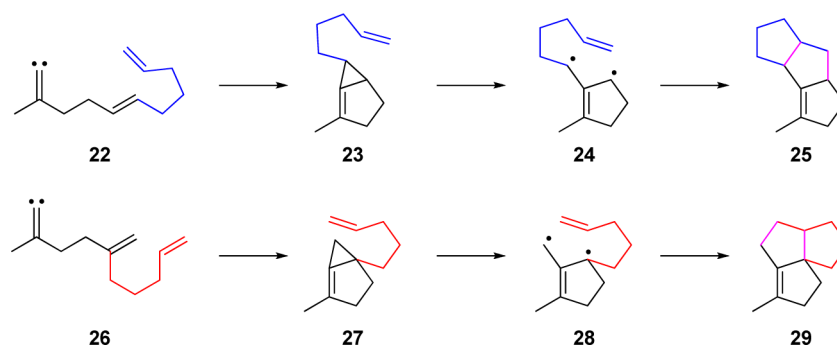
Scheme 6. Tandem Reaction Sequence Initiated by Alkylidene Carbene Generated from Epoxyaziridinyl Imine

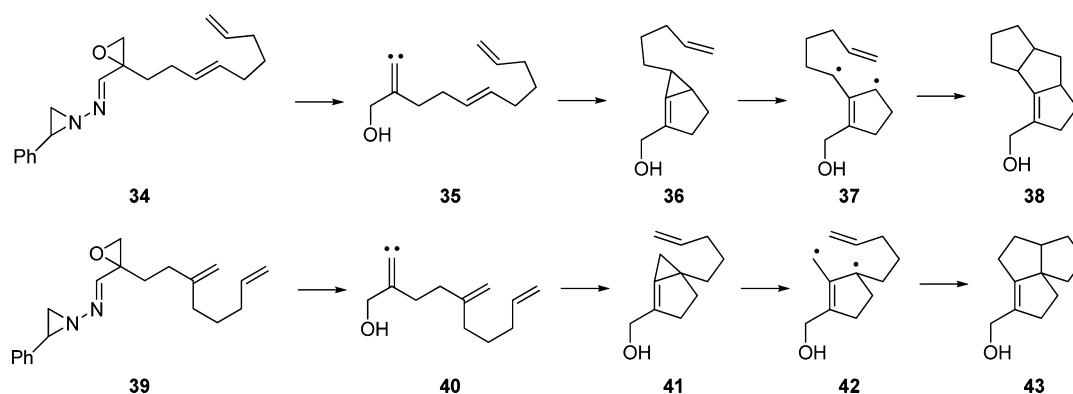**Table 1. Linearly Fused Triquinanes from Epoxyaziridinyl Imines**

34a–e : A=C(COOEt)$_2$　　　　　　**38a–e** : A=C(COOEt)$_2$

entry	product	R^1	R^2	R^3	yield (%)
1	38a	Ph	H	H	54
2	38b	CO$_2$Et	H	H	49
3	38c	H	H	H	52
4	38d	Me	H	H	50
5	38e	H	Me	Me	52

Table 2. Angularly Fused Triquinanes from Epoxyaziridinyl Imines

39a–d　　　　　**43a–d**　　　　　**44a–d**

entry	R^1	product	yield (%)	product	yield (%)
1	COOEt	43a	18	44a	
2	CH$_2$OMe	43b	8	44b	24

entry	R^1	product	yield (%)	product	yield (%)
3	CH$_3$	43c		44c	36
4	H	43d		44d	26

Table 3. Linearly Fused Triquinanes from Alkynyl Iodonium Salt Route

46a–f　　　**45'**　　　**49a–f**

entry	product	R	R^1	R^2	yield (%)
1	49a	H	COOEt	Meldrum's	31
2	49b	Ph	COOEt	Meldrum's	29
3	49c	H	Me	Meldrum's	46
4	49d	Ph	H	Meldrum's	17
5	49e	Ph	ether linkage	Meldrum's	43
6	49f	H	COOEt	Et	50

methods that generate alkylidene carbenes at the temperature higher than −40 °C.

2.1.1. Alkylidene Carbenes from Epoxyaziridinyl Imines. The generation of alkylidene carbenes from epoxyaziridinyl imines developed by Kim and Cho[21c] was selected as an appropriate candidate for the tandem reaction strategy since the alkylidene carbenes would be generated at 110 °C under neutral conditions and thus believed to minimize undesired reactions (Scheme 5).

Substrates for the tandem cycloaddition reaction (34, 39) were designed, synthesized, and subjected to the reaction conditions to generate alkylidene carbenes (35, 40). Intramolecular cycloaddition of the carbenes formed strained bicyclic intermediates (36, 41) that transformed themselves into TMM diyls (37, 42). Thus, formed TMM diyls underwent [2 + 3] cycloaddition reaction to form linearly fused triquinane (38) and angularly fused triquinane (43) according to the designed connectivity between two olefins and an epoxyaziridinyl imine (Scheme 6).

The tandem reaction sequence starting from 34 proceeded smoothly and stereoselectively to produce linearly fused triquinanes in moderate yield stereoselectively with retention of the olefin stereochemistry regardless of the substitution pattern (Table 1).[22]

Contrary to the linearly fused triquinane formation, 39 produced the desired angularly fused triquinanes only in a few cases with low yield (Table 2).[23]

Surprisingly, a seemingly unfavorable rearrangement of alkylidene carbene to the alkyne product 44 became the major reaction pathway. Only in the case of the electron deficient olefin (39a) (Table 3, entry 1), the desired triquinane

tether were attached to the inside of the olefin of 16, 16 could produce the angularly fused triquinane 29 via TMM diyl 28.

While there are many ways to generate alkylidene carbenes,[21] Koebrich's observation of the temperature dependency in the dimerization reaction guided the desirable reaction conditions for alkylidene carbene preparation. When the temperature was lower than −40 °C, the methylenecyclopropane intermediate 5 formed the dimer 2 and at the temperature higher than −40 °C TMM diyl 6 was generated and dimer 3 was obtained. This observation implied that at low temperature an undesired reaction might occur and it would be desirable to use the

Scheme 7. Alkylidene Carbene from Alkynyl Iodonium Salt for Tandem Cycloaddition Reaction toward Linearly Fused Triquinane
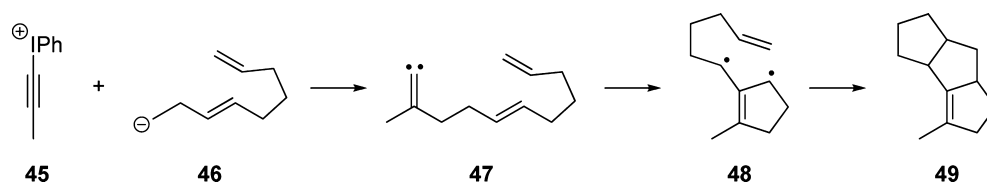

Table 4. Angularly Fused Triquinanes from Alkynyl Iodonium Salt Route

entry	product	X	R^1	R^2	R^3	yield (%)
1	51a	C(COOEt)$_2$	H	H	H	33
2	51b	C(COOEt)$_2$	CH$_3$	CH$_3$	H	38
3	51c	C(COOEt)$_2$	H	H	CH$_3$	34
4	51d	C(S(CH$_2$)$_3$S)	H	H	CH$_3$	34
5	51e	C(OMe)$_2$	H	H	CH$_3$	28
6	51f	CH$_2$	H	H	CH$_3$	0
7	51g	O	Ph	H	H	<10

product was the major product. Intramolecular cyclopropanation of alkylidene carbene with 1,1-disubstituted olefins appeared to be so slow that alkyl migration to form alkyne (44) prevailed though the alkyl migration was not expected to occur readily at the reaction temperature.

Nevertheless, the significance of this tandem transformation is that the first cycloaddition reaction of the alkylidene carbene generates new diradical intermediate that undergoes another cycloaddition reaction and thus effectively utilizes the carbene as the diradical source. A noteworthy point of the transformation is that the double bond in the substrate was cleaved and the connectivity of the substrate was lost in the product.

2.1.2. Alkylidene Carbenes from Alkynyl Iodonium Salts. Alkynyl iodonium salts generate alkylidene carbenes when reacted with appropriate nucleophiles such as malonate anion, alkoxides or sulfonamide anions.[21e,f] The tandem cycloaddition reaction strategy involving an alkynyl iodonium salt could be triggered by a C−C bond formation reaction to form an alkylidene carbene with properly located olefins. Therefore, the tandem reaction could become a convergent route to a complex structure from two simple linear substrates. The nucleophilic diene unit 46 can be added to an alkynyl

iodonium salt 45 to generate the alkylidene carbene intermediate 47, which undergoes a tandem reaction sequence (Scheme 7).[24]

As anticipated, linearly fused triquinanes were obtained with efficiency similar to the aziridinylimine route (Table 3). Formation of angularly fused triquinanes was much more effective than the aziridinylimine route since the reaction conditions for alkynyl iodonium salt route virtually eliminated the generation of the rearranged alkyne products (Table 4).[23] Results in entries 6 and 7 indicated that the efficiency of the cycloaddition reaction relied on the existence of substituents on the tether.

The tandem reaction could operate on a substrate possessing both alkynyl iodonium salt and diene substituent (52) with external nucleophile generating the alkylidene carbene (Scheme 8). The advantage of this transformation is that the product 55 could have substituents other than a methyl group at the vinyl position. This appeared to be a requirement in the previous cases. The stereoselectivity was explored on the alkynyl iodonium substrates possessing two olefins at the proper places and a substituent for the stereo selectivity. In this way, every possible substitution position was explored (Scheme 9).[25]
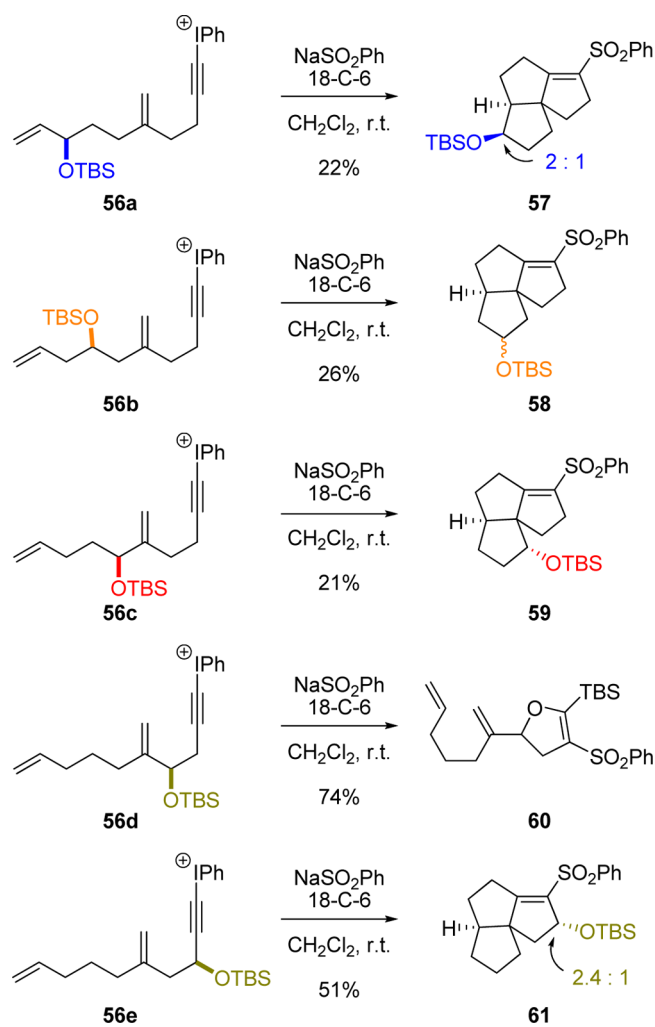
Alkylidene carbenes were generated by addition of heteroatom nucleophiles. Among the substrates, only 56c produced the product 59 with good stereoselectivity; all the other substrates showed low selectivity. It is also noteworthy that the substrate 56d underwent O−Si insertion reaction to form dihydrofuran 60 following the mechanism in the Scheme 10. The good stereoselectivity of 56c can easily be explained by the more stable pseudoequatorial position of the substituent at the transition state (Scheme 10). No such bias in the transition state can be clearly seen with the other substrates.

Another possible variation for the alkylidene carbene generation from alkynyl iodonium salt was the addition of the heteroatom nucleophile containing a diene, which could form a heterocyclic product. When nitrogen nucleophile 66 was used as the nucleophile, the tandem cycloaddition reaction sequence was interrupted at the methylenecyclopropane stage. Instead of generating the TMM diyl intermediate by breaking the cyclopropane ring, the olefin of the methylenecyclopropane

Scheme 8. Heteroatom Nucleophilic Addition to an Alkynyl Iodonium Salt for Angularly Fused Triquinane Synthesis

Nu = Ph SO$_2^-$	40%
Nu = Ph S$^-$	25%
Nu = CN$^-$	33%
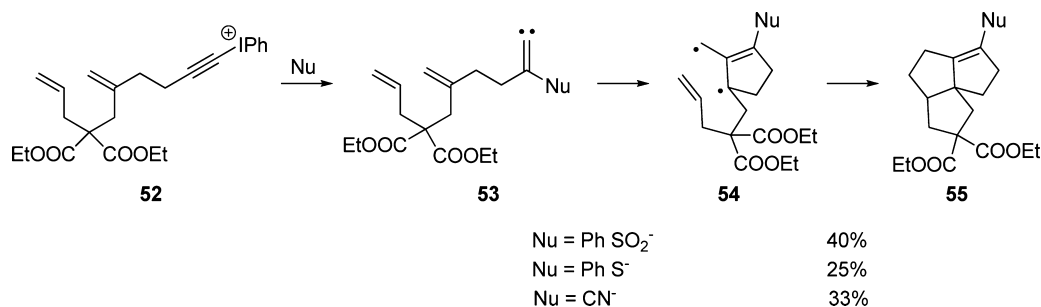
Scheme 9. Stereoselectivity of the Tandem Cycloaddition Reaction in Angularly Fused Triquinane Formation

Scheme 11. Interrupted Tandem Cycloaddition Reaction to Form Cyclopropanes Stereoselectively
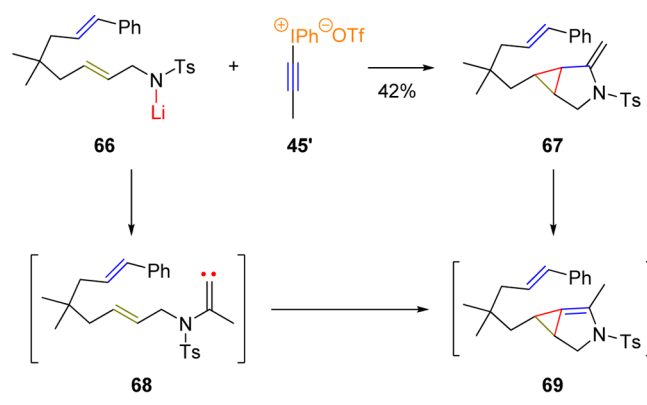
Table 5. Synthesis of Cyclopropylaminoketone via Alkylidene Cycloaddition Reaction


entry	product	R^1	R^2	R^3	yield (%)
1	71a	H	H	H	76
2	71b	H	Me	H	54
3	71c	H	Et	H	51
4	71d	Et	H	H	61
5	71e	H	H	Me	70
6	71f	Me	Me	H	52

intermediate **69** rearranged into the enamine compound **67** to release strain (Scheme 11).[26]

The rearrangement resulted in the formation of stereochemically intact, substituted cyclopropanes after hydrolysis of enamine to the ketosulfonamide **71** in good yield (Table 5). This result confirmed that formation of TMM diyls from methylenecyclopropanes is sensitive to the strain associated with the structural features of **69**.[17a]

2.1.3. Alkylidene Carbene from a Ketone and the TMS-Diazomethane anion. The method to generate alkylidene carbenes from ketones, Shioiri's TMS-diazomethane anion route was also explored (Scheme 12).[27] The reaction started with addition of TMS-diazomethane anion to the ketone **72**. 1,3-Brook rearrangement followed by the alkoxide elimination produces alkylidene carbene **74** after extrusion of nitrogen molecule. From this point on, the reaction followed the same sequence to produce the linearly fused triquinane **73**.

Though the synthetic strategy was synthetically simpler than the previous ones, the low overall efficiency of the outcome limited the substrate scope and the synthetic utility probably

Scheme 10. Stable Transition State Conformation (63) toward the Triquinane 59 and the Mechanism of the Formation of Dihydrofuran 60
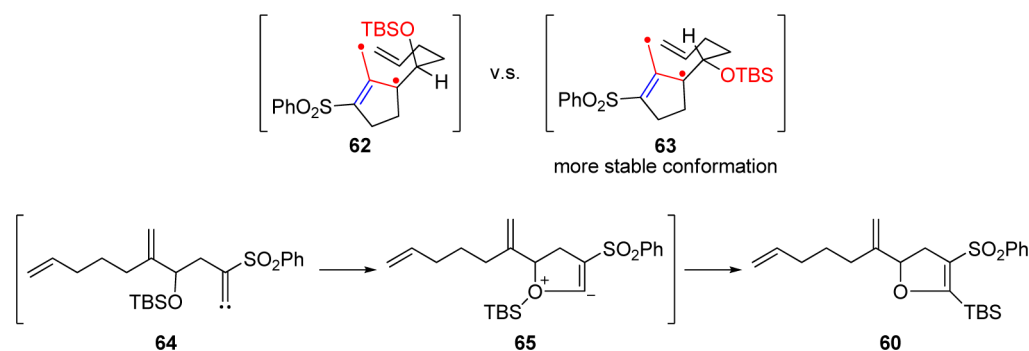
Scheme 12. Generation of Alkylidene Carbenes from Ketones
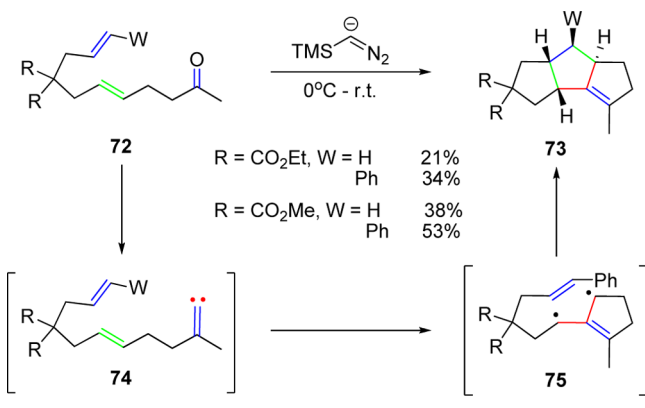
due to the use of strong bases to generate TMS-diazomethane anion.

2.2. Tandem Cycloaddition Reaction of Allenyl Diazo-Dipoles

As shown in the Scheme 3, there was another possible way of generating TMM diyls via bicycle[3.1.0]hex-1-ene by the intramolecular cyclopropanation reaction of an alkyl carbene with an allene moiety. While we contemplated this new route to TMM diyls, a new tandem cycloaddition reaction sequence evolved into a completely different way of performing a tandem cycloaddition reaction (Scheme 13).

While the alkyl carbene can be generated from the corresponding diazo group, this diazo group, before generation of the alkyl carbene, could undergo cycloaddition reaction with the allene[28] to form tetrahydrocyclopentapyrazole 78. Since 78

was reported to be interconvertible with 79, which was known to generate TMM diyl,[29] we envisioned another tandem cycloaddition strategy using two different [2 + 3] cycloaddition reactions to form triquinanes from linear substrates. Again, depending on the substitution pattern at the allene moiety, the tandem cycloaddition reaction would produce either linearly fused or angularly fused triquinanes. When the substrate 82 is generated, in which the allene moiety was substituted with a diazo-functionality on one side and an olefin on the other side, linearly fused triquinane 85 would be produced through the tandem cycloaddition reaction. A [2 + 3] cycloaddition reaction between diazo-dipole and the allene followed by extrusion of nitrogen molecule produces TMM diyl 84, which would undergo another [2 + 3] cycloaddition reaction to form 85. When the allene moiety was substituted at one end both with a diazo group and a tethered olefin (e.g., 86), angularly fused triquinane 90 would be produced through the same reaction mechanism.[30]

First, substrates for linearly fused triquinanes were prepared with aziridinyl imines as the precursor of diazo functionality since the aziridinyl imine was well-known to decompose to the diazo-dipole around 110 °C.[31] At that temperature, the diazoalkane underwent a dipolar cycloaddition reaction with allene moiety and the tandem sequence ensued to form linearly fused triquinanes (Table 6).

To our pleasant surprise, the tandem reaction produced the triquinanes stereoselectively in excellent efficacy. This result was a remarkable improvement in efficiency compared to the results from the alkylidene carbene route. This difference in overall efficiency implied that the cyclopropanation reaction step of the alkylidene carbene route could suffer from the high reactivity of the alkylidene carbene intermediate that could

Scheme 13. New Cycloaddition Route to TMM Diyls for Tandem Cycloaddition Reaction
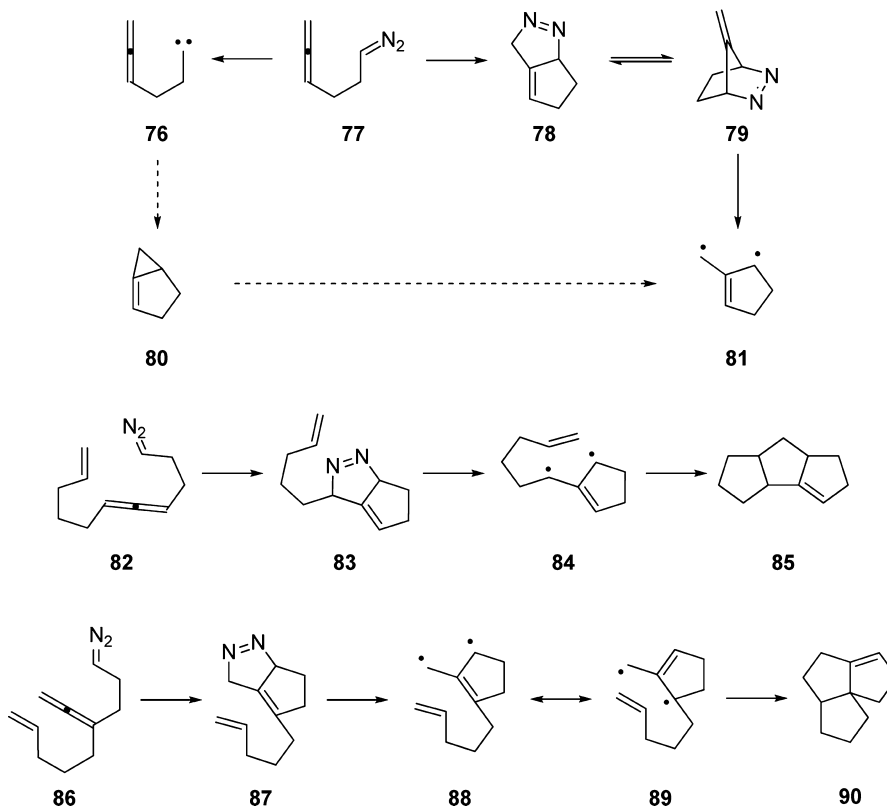
Table 6. Tandem [2 + 3] Cycloaddition Reaction to Form Linearly Fused Triquinanes
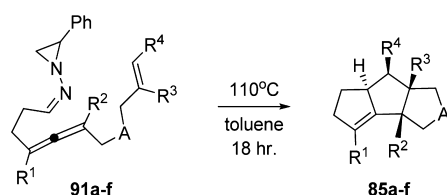
entry	product	A	R^1	R^2	R^3	R^4	yield (%)^a
1	85a	C(COOEt)$_2$	H	H	H	H	83 (7:1)^b
2	85b	C(COOEt)$_2$	H	H	H	Ph	86
3	85c	C(COOEt)$_2$	Me	H	H	H	84
4	85d	C(COOEt)$_2$	H	Me	H	H	76
5	85e	C(COOEt)$_2$	H	Me	Me	H	70
6	85f	NTs	H	H	H	H	82^b

^{a}Isolated yields. ^{b}Syn-cis isomer was the minor product.

undergo various side reactions such as rearrangement and insertion reaction. The new tandem reaction route also allowed easy incorporation of a heterocyclic ring in the product (Table 6, entry 6).
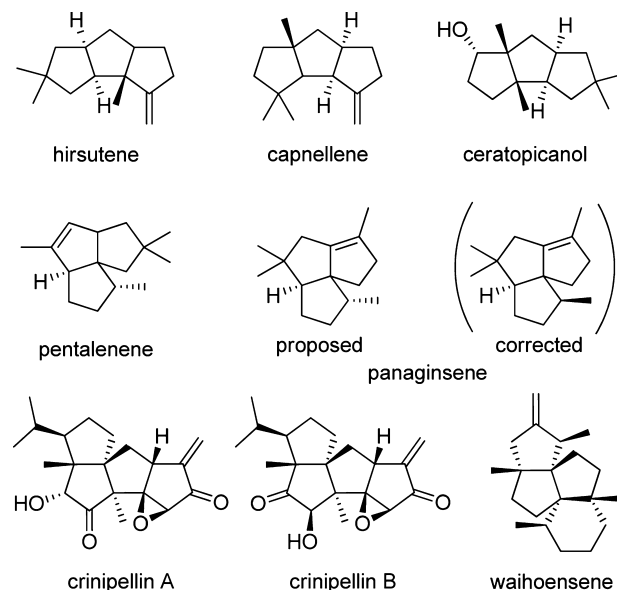
Avoiding the carbene intermediate during the tandem cycloaddition reaction eliminated other reaction pathways and effectively formed angularly fused triquinanes (Table 7).

The results in Table 7 demonstrated the high reactivity of TMM diyl cycloaddition even under large steric interaction or ring strain. A diazo-species derived from a ketone also undergo the tandem reaction (Table 7, entry 3) and good selectivity was reconfirmed with good yield (Table 7, entries 4−6). When the large steric congestion hindered the cycloaddition reaction, a side product is produced (Table 7, entry 5). The intermolecular cycloaddition reaction with styrene of the TMM diyl that was the byproduct during the formation of the diazo intermediate from an aziridinyl imine, competed during the cycloaddition reaction by forming the styrene adduct with TMM diyl. This unanticipated side reaction could be circumvented by using another source of the diazo-group. Replacing aziridinyl imine with sodium salt of tosylhydrazone that also generates the diazo-functionality at the same reaction temperature eliminated the competing intermolecular reaction (Table 7, entry 6). The reaction also worked with a ketone derived diazo intermediate (Table 7, entry 3) though the

reaction required longer reaction time or higher reaction temperature.

## 3. TOTAL SYNTHESIS OF NATURAL PRODUCTS

The tandem cycloaddition reaction via TMM diyl produces triquinanes from linear substrates with a great increase in molecular complexity and thus appears suitable for total synthesis of polyquinane natural products. Chart 1 shows selected

Chart 1. Polyquinane Natural Product Targets

hirsutene capnellene ceratopicanol

pentalenene proposed / corrected — panaginsene

crinipellin A crinipellin B waihoensene

polycyclic natural products that could be synthesized readily through the TMM diyl-mediated tandem cycloaddition reaction.

3.1. Hirsutene[32]

Hirsutene has been a signature natural product target for new synthetic methods or strategies to test the synthetic economy and applicability of newly developed synthetic methods. Therefore, it became the target to prove the practicality of the tandem cycloaddition reaction. The total synthesis of hirsutene was achieved from an epoxyaziridinyl imine precursor **93**, which demonstrated the practicality of the synthetic methodology (Scheme 14). The tandem cycloaddition reaction

Table 7. Angularly Fused Triquinanes from Diazoallenes
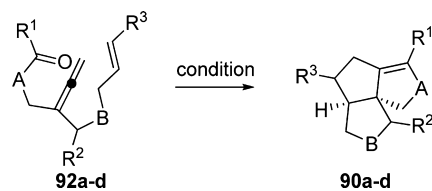
entry	product	A	B	R^1	R^2	R^3	condition^a	yield (%)^b
1	90a	CH$_2$	C(COOEt)$_2$	H	CH$_2$	H	A	93
2	90a	CH$_2$	C(COOEt)$_2$	H	CH$_2$	H	B	98
3	90b	CH$_2$	C(COOEt)$_2$	Me	CH$_2$	H	A^c	84
4	90c	CH$_2$	CH$_2$	H	OTBDPS	H	A	78
5	90d	C(CH$_3$)$_2$	CH$_2$	H	OTBDPS	Me	A	45
6	90d	C(CH$_3$)$_2$	CH$_2$	H	OTBDPS	Me	B	61

^{a}Condition A: 2-phenylaziridin-1-amine, CH$_2$Cl$_2$; toluene, 110 °C, 12 h. Condition B: NH$_2$NHTs/MeOH; NaH/toluene, 110 °C, 4 h. ^{b}Isolated yields. ^{c}Xylene, 160 °C, 12 h.

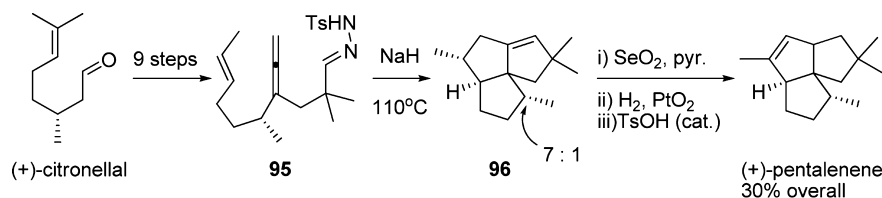**Scheme 14. Total Synthesis of Linearly Fused Triquinane, Hirsutene**
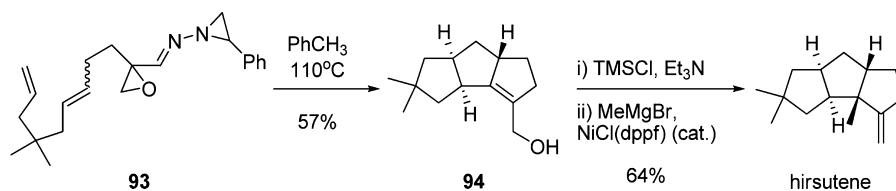
Scheme 15. Total Synthesis of Angularly Fused Triquinane, Pentalenene

of the substrate **93** afforded the hirsutane skeleton **94** without formation of the significant amount of other isomeric products. Hirsutene was obtained directly from **94** through Ni catalyzed regioselective methylation.[22]

3.2. (+)-Pentalenene[33]

While hirsutene is the test bed for newly developed synthetic methodology/strategy for linearly fused triquinanes, pentalenene serves the same purpose for the angularly fused triquinanes. The tertiary methyl-substituted stereocenter of pentalenene could be the guiding handle of the stereoselective construction of the pentalenene skeleton and thus citronellal was selected as the starting material of the synthesis (Scheme 15). After replacing the dimethyl substituents of the olefin part in citronellal with monomethyl substitution, the substrate **95** was obtained in 6 steps from the desmethylcitronellal. The tandem cycloaddition reaction proceeded stereoselectively to form the angularly fused triquinane **96** with 7:1 ratio and the major isomer produced (+)-pentalenene after three-step sequence of allylic oxidation, hydrogenation and dehydration.[34]

3.3. Panaginsene[35]

Panaginsene is a very interesting natural product, since it is the only natural product that belongs to the senoxydane family of natural products. Ironically, the first natural product claimed to possess senoxydane structure was senoxydene,[36] the structure of which turned out to be incorrect as the synthetic senoxydene showed spectroscopic data remote from the reported one for the natural product.[36] Though the senoxydane structure was biogenetically viable, structural feature of panaginsene should be confirmed unequivocally. The reported structure of panaginsene could readily be synthesized from citronellal (Scheme 16).[37] When the substrate (**97**) for the tandem cycloaddition reaction sequence was subjected to the general reaction conditions, the desired product **98** was obtained along with a mixture of few other isomers. Due to the volatility and the nonpolar nature of the products, column chromatography using silver nitrate impregnated silica was required to isolate **98**. It turned out that the reported structure of panaginsene did not match the one produced synthetically. A plausible biogenetic pathway hinted that panaginsene might possess the opposite stereochemistry at the tertiary carbon center with a methyl group. To obtain the epimeric structure of the reported structure for panaginsene, a functional group that could change the stereochemistry of the methyl group at the

**Scheme 16. Total Synthesis of Panaginsene and Its Methyl Epimer**
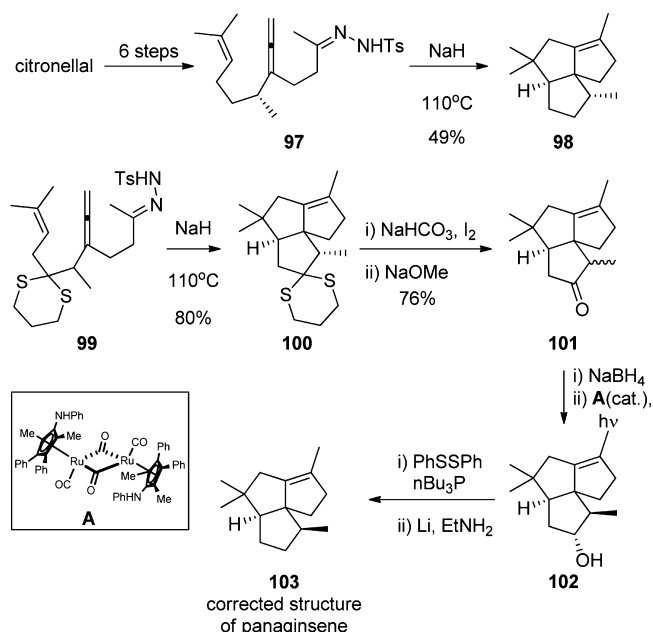
tertiary center was required in the product of the tandem cycloaddition reaction. Thus, we prepared the dithiane functionalized substrate **99** and subjected to the standard reaction conditions. The tandem reaction proceeded much more efficiently than the one without the dithiane substituent to produce **100** with almost complete stereoselectivity. The presence of dithiane functionality appeared to provide the higher efficiency and stereoselectivity during the cycloaddition reaction. After generation of a ketone from the dithiane, and subsequent epimerization, the resulting mixture of the methyl epimers **101** was produced in a 1:1 ratio. To separate two epimers, the ketone was reduced to generate the β-alcohol and the β-hydroxy-β-methyl isomer was isolated. To remove the alcohol, the stereochemistry of the alcohol had to be inverted to the α-configuration for further functionalization. Ru-catalyzed epimerization of the β-alcohol produced **102**. Reduction of the alcohol **102** using Mitsunobu type sulfide formation followed by dissolving metal reduction produced **103**. The spectroscopic date of **103** suggested that the epimer of the reported structure of panaginsene **103** was the real structure of panaginsene and

this stereochemical outcome was also supported by biogenetic consideration of panaginsene's likely biosynthesis.[38]

3.4. Ceratopicanol[39]

Ceratopicanol, a linearly fused triquinane natural product with consecutive quaternary centers at the ring junction posed another challenge to the tandem cycloaddition strategy (Scheme 17). The substrate (104) for tandem cycloaddition

Scheme 17. Total Synthesis of Ceratopicanol
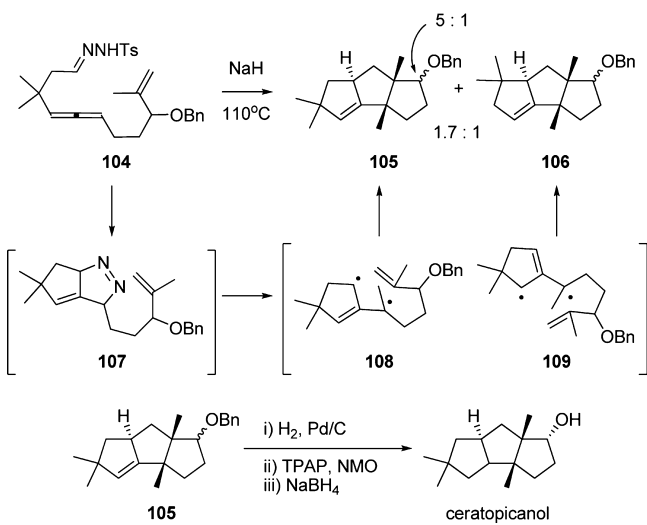
reaction was obtained from pentynol and succinic acid. Contrary to the other previous synthesis, the TMM diyl

intermediate generated from 104 was not symmetrical and thus the tandem cycloaddition reaction could produce two regioisomeric products. The tandem cycloaddition showed little regioselectivity producing regioisomers 105 and 106 in 1.7:1 ratio. Further, each regioisomer was an inseparable mixture of alcohol epimers with 5:1 ratio. Dehydroceratopicanol was the major product among the isomeric products. The major regioisomer (105) was hydrogenated to a mixture of ceratopicanol and its epimer. Without separating the epimeric alcohols, oxidation and stereoselective reduction of the mixture produced ceratopicanol.[40]

3.5. Crinipellins[41]

Crinipellins are the only tetraquinane natural products known and pose a great challenge to synthetic organic chemistry as the basic structure of crinipellins contains four quaternary centers with eight consecutive stereocenters. For the synthesis of tetraquinanes, the synthesis requires a five membered ring in the substrate. Extension of the scope of the synthetic strategy into the substrates with existing rings would be another challenge of the current tandem cycloaddition reaction. A 12 step-sequence from 2-methylpentenone produced the substrate (111) for the tetraquinane synthesis in a single enantiomeric form (Scheme 18). The substrate 111 was designed to minimize unnecessary steric interactions in the transition state 112 by setting the relative stereochemistry of −OTBDPS to occupy a pseudoequatorial orientation during the cyclo-addition reaction of the TMM diyl intermediate. The tandem cycloaddition reaction proceeded uneventfully to produce tetraquinane product 113 with efficiency similar to the case of triquinane forming reaction. The structural integrity of 113 was firmly confirmed as three-step conversion of 113 to a

Scheme 18. Total Synthesis of Crinipellins
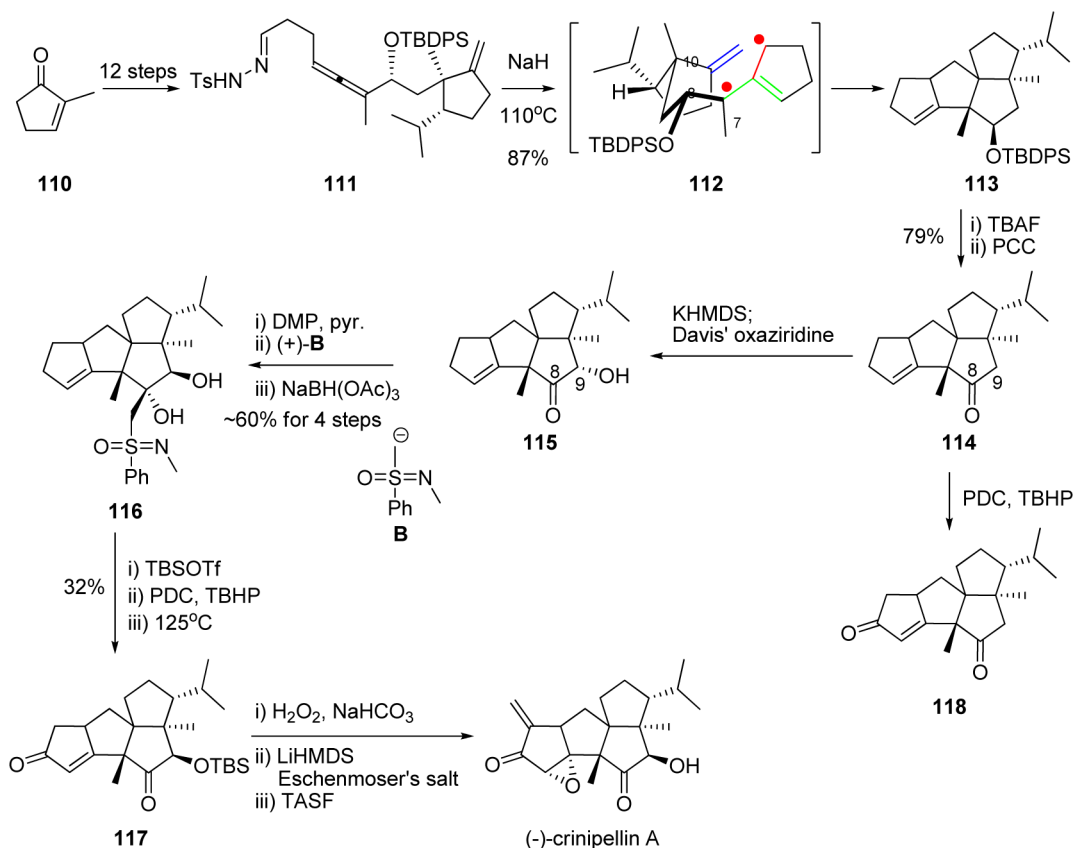
known synthetic intermediate (**118**) that furnished a formal total synthesis of crinipellin B.[42,43a] Thus, the synthetic intermediate **114** was advanced toward the total synthesis of crinipellin A. Introduction of a hydroxyl group at the C-9 position produced the alcohol **115** corresponding to the opposite stereochemistry of crinipellin A at the C-9 position. To invert the stereochemistry of the alcohol, a three-step sequence of alcohol oxidation to the corresponding diketone, selective addition of sulfoximine anion to the C-8 ketone from the top face, and the hydroxyl group-directed ketone reduction was applied to produce **116** with the correct stereochemistry at the C-9 alcohol. Allylic oxidation of the cyclopentene into the cyclopentenone and regeneration of the C-8 ketone produced dione **117**. The fragile dione **117** was oxidized to the epoxiketone and the exomethylene group was introduced. A careful deprotection furnished the total synthesis of (−)-crinipellin A.[43]

4. SUMMARY AND OUTLOOK

Based on the mechanistic work around TMM diyls, tandem cycloaddition reactions were designed and successfully executed that involve two cycloaddition reaction steps to form three rings from linear substrate in one step. Application of these methodologies to the preparation of natural products with various structural features demonstrated the efficiency of the tandem cycloaddition strategy in the total synthesis of polycyclic natural products through a big complexity increase. There are still many natural products with complex structural features that could be assembled readily through these tandem cycloaddition reactions. The versatility of the tandem cyclo-addition reaction strategy that generates a TMM diyl as the key intermediate does not have to be limited to the intramolecular reactions as the intermolecular cycloaddition of a TMM diyl could shorten the total number of steps to construct polycyclic systems. TMM diyls that could be generated through current methodology has been only used in the cycloaddition reaction and there are many possibilities of designing other types of tandem reactions that exploit the radical nature of the TMM diyl. After all, mechanism based design and development of new reactions or synthetic methodologies would allow us to drive organic synthesis toward the "ideal synthesis" and continue to expand the research area of organic synthesis into material sciences and the life sciences.

■ AUTHOR INFORMATION

Corresponding Author

*Phone: +8242-350-2835. Fax: +8242-350-2810. E-mail: leehy@kaist.ac.kr.

Notes

The authors declare no competing financial interest.

Biography

Hee-Yoon Lee was born in Seoul, Korea and received his B.S. (1980) and M.S. (1982) in Chemistry from the Seoul National University under the direction of Professor Eun Lee, and his Ph.D. in 1988 from Stanford University under the supervision of Professor Paul A. Wender. After postdoctoral experience with Professor Gilbert Stork at Columbia University, he joined Merck Research Laboratories at Westpoint, PA. in 1990. In 1994, he left Merck to join the department of chemistry at KAIST as an assistant professor. Currently, he is a professor in chemistry and vice president of research at KAIST.

■ ACKNOWLEDGMENTS

■ REFERENCES

(1) (a) Hendrickson, J. B. Systematic synthesis design. IV. Numerical codification of construction reactions. *J. Am. Chem. Soc.* **1975**, *97*, 5784−5800. (b) Wender, P. A. Toward the ideal synthesis and molecular function through synthesis-informed design. *Nat. Prod. Rep.* **2014**, *31*, 433−440.

(2) Crow, J. M. Stepping toward ideality. *Chem. World* **2012**, *9*, 48−52.

(3) (a) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. The economies of synthesis. *Chem. Soc. Rev.* **2009**, *38*, 3010−3021. (b) Qiu, F. Strategic efficiency - The new thrust for synthetic organic chemists. *Can. J. Chem.* **2008**, *86*, 903−906.

(4) Green, N. J.; Sherburn, M. S. Multi-bond forming processes in efficient synthesis. *Aust. J. Chem.* **2013**, *66*, 267−283.

(5) (a) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2006. (b) Ruijter, E.; Scheffelaar, R.; Orru, R. V. A. Multicomponent Reaction Design in the Quest for Molecular Complexity and Diversity. *Angew. Chem., Int. Ed.* **2011**, *50*, 6234−6246.

(6) (a) Poupon, E., Nay, B., Eds. *Biomimetic Organic Synthesis*; Wiley-VCH: Weinheim, 2011. (b) Li, X.-W.; Nay, B. Transition metal-promoted biomimetic steps in total syntheses. *Nat. Prod. Rep.* **2014**, *31*, 533−549.

(7) (a) Streit, U.; Bochet, C. G. The arene−alkene photo-cycloaddition. *Beilstein J. Org. Chem.* **2011**, *7*, 525−542. (b) Aggarwal, V. K.; Winn, C. L. Catalytic, asymmetric sulfur ylide-mediated epoxidation of carbonyl compounds: scope, selectivity, and applications in synthesis. *Acc. Chem. Res.* **2004**, *37*, 611−620.

(8) (a) Heathcock, C. H. Nature knows best: an amazing reaction cascade in uncovered by design and discovery. *Proc. Natl. Acad. Sci. U. S. A.* **1996**, *93*, 14323−14327. (b) Kim, J.; Movassaghi, M. Biogenetically inspired synthesis of alkaloid natural products. *Chem. Soc. Rev.* **2009**, *38*, 3035−3050. (c) Johnson, W. S. Biomimetic polyene cyclizations. A review. *Bioorg. Chem.* **1976**, *5*, 51−98. (d) Tantillo, D. J. The carbocation continuum in terpene biosynthesis − where are the secondary cations? *Chem. Soc. Rev.* **2010**, *39*, 2847−2854.

(9) (a) McCarroll, A. J.; Walton, J. C. Programming organic molecules: Design and management of organic synthesis through free-radical cascade process. *Angew. Chem., Int. Ed.* **2001**, *40*, 2224−2248. (b) Chen, L.; Gill, G. B.; Pattenden, G. New radical mediated polyolefin cyclisations directed towards steroid ring system. *Tetrahedron Lett.* **1994**, *35*, 2593−2596. (c) Curran, D. P.; Rakiewicz, D. M. Tandem radical approach to linear condensed cyclopentanoids. Total synthesis of (±)-hirsutene. *J. Am. Chem. Soc.* **1985**, *107*, 1448−1449. (d) Lee, H.-Y.; Kim, B. G. A facile construction of the quadranoid skeleton: Application to the total synthesis of (±)-suberosenone. *Org. Lett.* **2000**, *2*, 1951−1953.

(10) (a) Stork, G.; Mook, R., Jr.; Biller, S. A.; Rychnovsky, S. D. Free radical cyclization of bromoacetals. Used in the construction of bicyclic acetals and lactones. *J. Am. Chem. Soc.* **1983**, *105*, 3741−3742. (b) Wille, U. Radical cascades initiated by intermolecular radical addition to alkynes and related triple bond systems. *Chem. Rev.* **2013**, *113*, 813−853.

(11) Wang, K. K.; Wang, Z.; Tarli, A.; Gannett, P. Cascade radical cyclization via biradicals generated from (Z)-1,2,4-heptatriene-6-ynes. *J. Am. Chem. Soc.* **1996**, *118*, 10783−10791.

(12) Bertrand, G., Ed. *Carbene chemistry: From fleeting intermediates to powerful reagents*; Marcel Dekker: Lausanne, Switzerland, 2002.

(13) Yamago, S.; Nakamura, E. [3 + 2] Cycloaddition of Trimethylenemethane and its Synthetic Equivalents. *Org. React.* **2002**, *61*, 1−217.

(14) Emerson, G. F.; Ehrlich, K.; Giering, W. P.; Lauterbur, P. C. Trimethylenemethaneiron Tricarbonyl. *J. Am. Chem. Soc.* **1966**, *88*, 3172−3173.

(15) (a) Dowd, P. Trimethylenemethane. *Acc. Chem. Res.* **1972**, *5*, 242−248. (b) Slipchenko, L. V.; Krylov, A. I. Electronic structure of the trimethylenemethane diradical in its ground and electronically excited states: Bonding, equilibrium geometries, and vibrational frequencies. *J. Chem. Phys.* **2003**, *118*, 6874−6883. (c) Borden, W. T.; Iwamura, H.; Berson, J. A. Violations of Hund's rule in Non-Kekule hydrocarbons: Theoretical prediction and experimental verification. *Acc. Chem. Res.* **1994**, *27*, 109−116.

(16) (a) Trost, B. M. [3 + 2] cycloaddition approaches to five-membered rings via trimethylenemethane and its equivalents. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1−20. (b) Nakamura, E.; Yamago, S. Thermal reactions of dipolar trimethylenemethane species. *Acc. Chem. Res.* **2002**, *35*, 867−877. (c) Yamago, S.; Nakamura, E. Synthesis of propellanes by exocyclic transannular cycloaddition of olefinic methylenecyclopropnae. *Tetrahedron* **1989**, *45*, 3081−3088.

(17) (a) Koebrich, G.; Baumann, M. Bridged Methylenecyclopropanes as Test Cases for Bredt's Rule: 2,5,5,7,7-Pentamethylbicyclo[4.1.0]-hept-1-ene. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 52−53. (b) Koebrich, G.; Heinemann, H. Evidence for a bicycle[3.1.0]hex-1-ene intermediate in a carbenoid route to the 9,10-diisopropylidenetricyclo[4.2.1.1.2,5]decane system. *J. Chem. Soc. D* **1969**, 493−494. (c) Koebrich, G. Bredt compounds and the Bredt rule. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 464−473.

(18) (a) Berson, J. A. The chemistry of trimethylenemethanes, a new class of biradical reactive intermediates. *Acc. Chem. Res.* **1978**, *11*, 446−453. (b) Berson, J. A. Capturable diradicals of the trimethylenemethane series. In *Diradicals*; Borden, W. T., Ed.; Wiley: New York, 1982, 151−194. (c) Lazzara, M. G.; Harrison, J. J.; Rule, M.; Hilinski, E. F.; Berson, J. A. Observation of two characteristic methylenecyclopropane stereomutations in a system that also forms trimethylenemethane dimers. An experimental connection between putative and directly observed biradicals. *J. Am. Chem. Soc.* **1982**, *104*, 2233−2243.

(19) (a) Little, R. D. Diyl Trapping and Electro reductive Cyclization Reactions. *Chem. Rev.* **1996**, *96*, 93−114. (b) Little, R. D.; Ott, M. M. In *Studies in Natural Product Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 2000, Vol. 22, pp195−243.

(20) Carroll, G. L.; Little, R. D. TMM diyl-induced vinyl-cyclopropane fragmentation and recombination. *Tetrahedron Lett.* **1998**, *39*, 1893−1896.

(21) (a) Shioiri, T.; Aoyama, T. Trimethylsilyldiazomethane: A Useful Reagent for Generating Alkylidene Carbenes and Its Application to Organic Synthesis. *Yuki Gosei Kagaku Kyokaishi* **1996**, *54*, 918−928. (b) Wolinsky, J.; Clark, G. W.; Thorstenson, P. C. Alkylidenecarbenes from acyclic vinyl bromides and potassium tert-butoxide. *J. Org. Chem.* **1976**, *41*, 745−750. (c) Kim, S.; Cho, C. M. Generation of alkylidene carbenes from α,β-epoxy-N-aziridinyl imines. A new route to cyclopentenols. *Tetrahedron Lett.* **1994**, *35*, 8405−8408. (d) Corey, E. J.; Letavic, M. A.; Noe, M. C.; Sarshar, S. Correlation of the structure of chiral o,o′-bisphenol-Ti(IV) complexes with ligand electronic effects. A relationship between Lewis acidity and angle strain. *Tetrahedron Lett.* **1994**, *35*, 7553−7556. (e) Ochiai, M.; Kunishima, M.; Nagao, Y.; Fuji, K.; Shiro, M.; Fujita, E. Tandem Michael-carbene insertion reactions of alkynyliodonium salts. Extremely efficient cyclopentene annulations. *J. Am. Chem. Soc.* **1986**, *108*, 8281−8283. (f) Zhdankin, V. V.; Stang, P. J. Alkynyliodonium salts in organic synthesis. *Tetrahedron* **1998**, *54*, 10927−10966. (g) Gilbert, J. C.; Giamalva, D. H.; Weerasooriya, U. Intramolecular carbon-hydrogen insertions of alkylidenecarbenes. I. Selectivity. *J. Org. Chem.* **1983**, *48*, 5251−5256.

(22) Lee, H.-Y.; Kim, Y. Triquinanes from Linear Alkylidene Carbenes via Trimethylenemethane Diyls. *J. Am. Chem. Soc.* **2003**, *125*, 10156−10157.

(23) Lee, H.-Y.; Jung, Y.; Yoon, Y.; Kim, B. G.; Kim, Y. Angularly Fused Triquinanes from Linear Substrates through Trimethylenemethane Diyl [2 + 3] Cycloaddition Reaction. *Org. Lett.* **2010**, *12*, 2672−2674.

(24) Lee, H.-Y.; Yoon, Y.; Lim, Y.-H.; Lee, Y. Cycloaddition reactions of trimethylenemethane diyls generated from alkynyl iodonium salts. *Tetrahedron Lett.* **2008**, *49*, 5693−5696.

(25) Yoon, Y.; Kang, T.; Lee, H.-Y. Stereoselectivity in Trimethylenemethane (TMM) Diyl Mediated Cycloaddition Reaction to Angularly Fused Triquinanes. *Chem. - Asian J.* **2011**, *6*, 646−651.

(26) Lee, H.-Y.; Lee, Y.-H. A Stereo selective Synthesis of 1-Acetyl-2-aminomethylcyclopropanes from Allylsulfonamides and Phenyl-(alkynyl)iodonium Salts. *Synlett* **2001**, *2001*, 1656−1658.

(27) Lee, H.-Y.; Kim, W.-Y.; Lee, S. Triquinanes from linear ketones via trimethylenemethane diyls. *Tetrahedron Lett.* **2007**, *48*, 1407−1410.

(28) Crawford, R. J.; Cameron, D. M. Evidence for Trimethylenemethane as an Intermediate in a Pyrolysis Reaction. *J. Am. Chem. Soc.* **1966**, *88*, 2589−2590.

(29) Cichra, D. A.; Duncan, C. D.; Berson, J. A. Mechanistic characterization of the intermediates in the thermal and photochemical deazetation of two isomeric methylenepyrazolines, 7-isopropylidene-2,3-diazabicyclo[2.2.1]hept-2-ene and 2,2-dimethyl-3,4-diazabicyclo[3.3.0]octa-3,8-diene. An approach to the generation and capture of protoplanar and protobisected trimethylene methanes. *J. Am. Chem. Soc.* **1980**, *102*, 6527−6533.

(30) Kang, T.; Kim, W.-Y.; Yoon, Y.; Kim, B. G.; Lee, H.-Y. Tandem Cycloaddition Reactions of Allenyl Diazo Compounds Forming Triquinanes via Trimethylenemethane Diyls. *J. Am. Chem. Soc.* **2011**, *133*, 18050−18053.

(31) Kim, S.; Yoon, J.-Y.; Cho, C. M. Generation and reaction of carbenes from a-ozacyclo-N-aziridinyl imines − a new method for ring expansion of cyclic ether. *Chem. Commun.* **1996**, 909−910.

(32) Nozoe, S.; Furukawa, J.; Sankawa, U.; Shibata, S. Isolation, structure and synthesis of hirsutene, a precursor hydrocarbon of coriolin biosynthesis. *Tetrahedron Lett.* **1976**, *17*, 195−198.

(33) Seto, H.; Yonehara, H. Studies on the biosynthesis of pentalenolactone. III. Isolation of a biosynthetic intermediate hydrocarbon, pentalenene. *J. Antibiot.* **1980**, *33*, 92−93.

(34) Kim, Y.-J.; Yoon, Y.; Lee, H.-Y. An asymmetric total synthesis of (+)-pentalenene. *Tetrahedron* **2013**, *69*, 7810−7816.

(35) Richter, R.; Basar, S.; Koch, A.; Koenig, W. A. Three sesquiterpene hydrocarbons from the roots of Panax ginseng C.A. Meyer (Araliaceae). *Phytochemistry* **2005**, *66*, 2708−2713.

(36) Bohlmann, F.; Zdero, C. Senoxyden, ein neuer sesquiterpenkohlenwasserstoff aus Senecio oxyodontus. *Phytochemistry* **1979**, *18*, 1747−1748.

(37) Paquette, L. A.; Galemmo, R. A.; Caille, J. C.; Valpey, R. S. Synthetic studies relating to the structure of senoxydene. A sequential annulation approach to angular triquinane construction capable of varied tetramethyl substitution patterns. *J. Org. Chem.* **1986**, *51*, 686−695.

(38) Geum, S.; Lee, H.-Y. Total Synthesis of Panaginsene with Structural Revision. *Org. Lett.* **2014**, *16*, 2466−2469.

(39) Hanssena, H. P.; Abrahamb, W. R. Sesquiterpene alcohols with novel skeletons from the fungus Ceratocystis piceae (ascomycotina). *Tetrahedron* **1988**, *44*, 2175−2180.

(40) Lee, S.-S.; Kim, W.-Y.; Lee, H.-Y. Total synthesis of ceratopicanol through tandem cycloaddition reaction of a linear substrate. *Chem. - Asian J.* **2012**, *7*, 2450−2456.

(41) Anke, T.; Heim, J.; Knoch, F.; Mocek, U.; Steffan, B.; Steglich, W. Crinipellins, the First Natural Products with a Tetraquinane Skeleton. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 709−711.

(42) Piers, E.; Renaud, J. Total synthesis of the tetraquinane diterpenoid (±)-crinipellin B. *J. Org. Chem.* **1993**, *58*, 11−13.

(43) (a) Kang, T.; Lee, H.-Y. Total synthesis of the crinipellins. In *Strategies and tactics in organic synthesis*; Harmata, M., Ed.; Academic Press: Amsterdam, 2014; Vol. 10, pp 271−291. (b) Kang, T.; Song, S. B.; Kim, W.-Y.; Kim, B. G.; Lee, H.-Y. Total Synthesis of (−)-Crinipellin A. *J. Am. Chem. Soc.* **2014**, *136*, 10274−10276.