DISSERTATION

New Cyclization Reactions Utilizing Alkenyl Copper Species and their Application

（アルケニル銅を用いた新規環化反応の開発とその応用）

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Contents

Abbreviation table

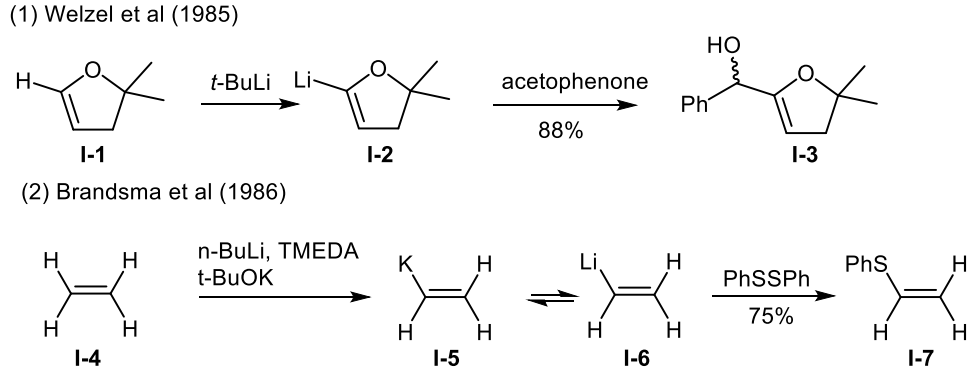
DMF	dimethylformamide
EA	ethyl acetate
LDA	lithium diisopropylamide
*m*CPBA	*m*-chloroperbenzoic acid
MT-sulfone	methylthio *p*-tolenesulfonyl methane
NMO	*N*-methylmorpholine *N*-oxide
NMP	*N*-methylpyrrolidinone
TBAF	tetra-*n*-butylammonium fluoride
TBS	tertiarybutyldimethylsilyl
TEMPO	2,2,6,6-tetramethylpiperidine 1-oxyl
TFA	trifluoroacetic acid
THF	tetrahydrofurane
TMP	tetramethylpyperridine
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate

Introduction

Alkenyl metal species had been widely used for introducing alkenyl groups into organic compounds through various kinds of reactions including addition reactions and coupling reactions.[1] The property of an alkenyl metal species is tunable by choosing an appropriate metal element such as Li, Mg, Al, Zn, Zr, and Cu *etc*[2]. In this section, the representative methods for generating, and the characteristic features of these alkenyl metal species are overviewed.

1.1 Lithium and other alkali metals[3]

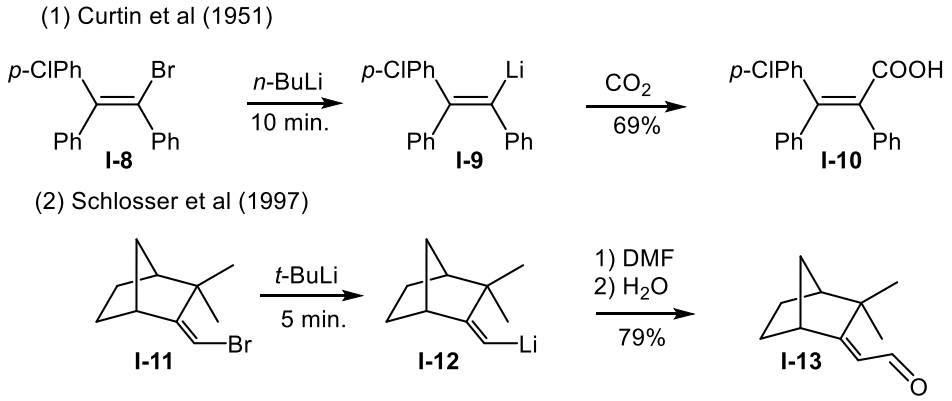
One of the most fundamental methods for the generation an alkenyllithium is the reaction of an alkene derivative with an alkyllithium reagent. Selected examples are shown in Scheme I-1. Welzel *et al.*[4] reported that the treatment of 2,2-dimethyl-2,3-dihydrofuran (**I-1**) with *t*-BuLi effected smooth deprotonation at the α-position of the vinyl ether. The resulting alkenyllithium was then subjected to an addition reaction with acetophenone, giving rise to alcohol **I-3** in good yield (Scheme I-1-(1)). While abstraction of a vinyl proton of simple alkenes is difficult, combined use of *n*-BuLi and *t*-BuOK (Schlosser-Lochmann base)[5] led to generation of vinyl anion species which was reacted with disulfide to afford sulfide **I-7** (Scheme I-1-(2))[6]. A serious drawback of this type of reaction is a poor tolerance of alkyllithium reagents to other functional groups such as aldehydes or ketones.



Scheme I-1.

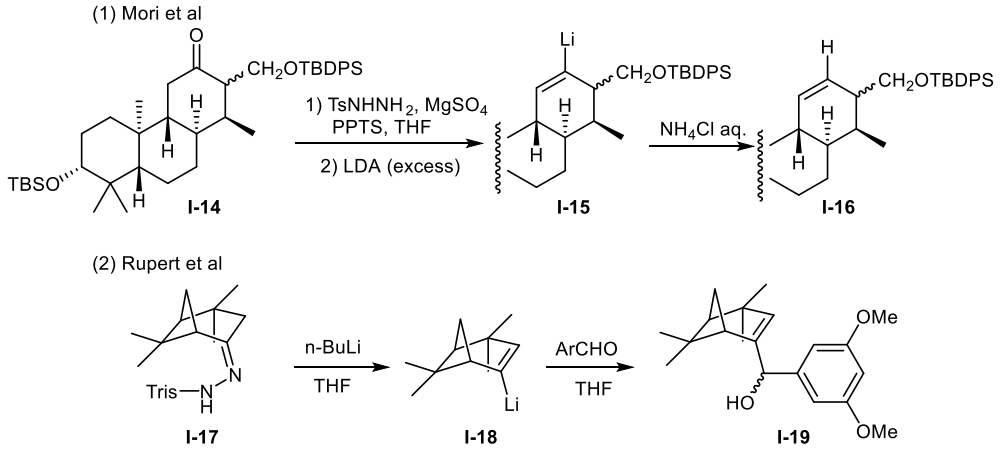
The halogen-lithium exchange reaction of a bromoalkene or an iodoalkene with an alkyllithium reagent has also found widespread use for generating an alkenyllithium species[7]. For example, Curtin *et al*[8]. reported that the bromine-lithium-exchange reaction of **I-8** afforded alkenyl lithium **I-9** which in turn was trapped by CO_2 to give carboxylic acid **I-10** (Scheme I-2-(1)). This type of reaction can be applied to sterically demanding bromides, and

bicyclo[2.2.1]heptane derivative **I-11** was converted to the corresponding aldehyde **I-13** by the successive treatment with *t*-BuLi and DMF[9]. It should be noted that the use of alkyllithium reagents causes problems similar with those in deprotonation reactions. In some cases, the difficulty in preparing haloalkene substrates in a regio- and stereoselective manner may reduce the utility of the halogen-lithium exchange strategy.



Scheme I-2.

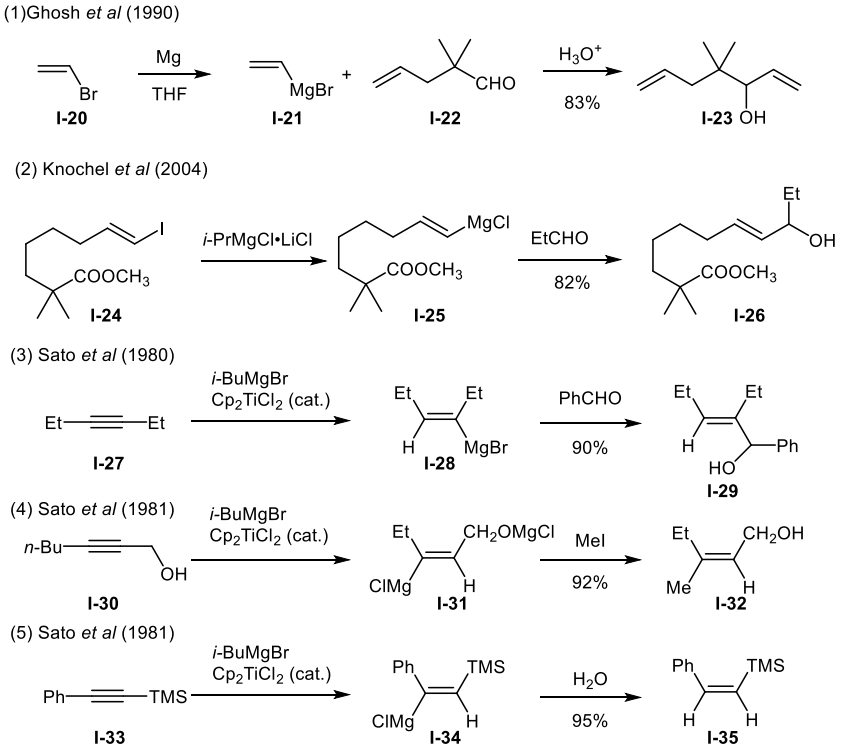
Shapiro olefination is one of the alternative methods for generating an alkenyl lithium species without using haloalkenes[10]. The sulfonyl hydrazone substrate, which is readily prepared from the corresponding ketone, reacts with a strong base to furnish an alkenyllithium species (Scheme I-3). For example, the reaction was applied for introducing an alkene moiety to cyclohexane ring in the total synthesis of phytocassane D (Scheme I-3-(1))[11]. The resulting anion species can be utilized to a reaction with electrophiles as shown in Scheme I-3-(2)[12]. Since the use of LDA as a base would cause protonation of the resulting alkenyllithium by diisopropylamine, the use of *n*-BuLi is required, which may result in poor tolerance to other functional groups.



Scheme I-3.

1.2 Magnesium (Grignard reagent)

Alkenyl Grignard reagents, which are generally more stable than the corresponding alkenyllithium, have been widely used for introducing alkenyl groups to carbonyl compounds[13]. While some alkenyl Grignard reagents are commercially available, generation of various kinds of Grignard reagents is easily conducted by treating the corresponding haloalkenes with magnesium metal (Scheme I-4-(1))[14]. A remarkable merit of alkenyl Grignard reagents is the tolerance to certain functional groups. For example, the treatment of a terminal iodoalkene with *i*-PrMgCl•LiCl (turbo Grignard reagent) resulted in formation of the corresponding alkenyl Grignard reagent without affecting the ester moiety (Scheme I-4-(2))[15]. It is noteworthy that an alkenyl Grignard reagent can be formed by the carbomagnesation reaction of an alkyne catalyzed by Cp_2TiCl_2 (Scheme I-4-(3))[16]. While the utility of carbomagnesation depends on the regioselectivity in the reactions with unsymmetrically substituted alkynes, propargyl alcohols (Scheme I-4-(4))[17] and silyl acetylenes (Scheme I-4-(5))[18] are found to be a good substrate for this purpose.

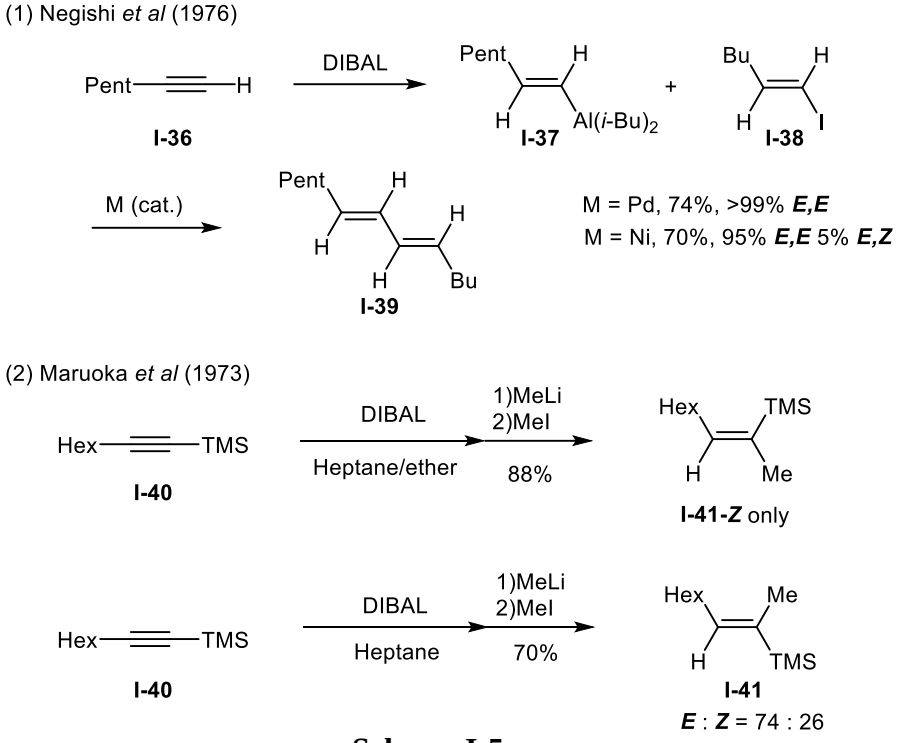


Scheme I-4.

1.3 Aluminum

Hydroalumination of alkynes with DIBAL provides alkenylaluminum species in a stereoselective manner. Terminal alkynes and 1-silylalkynes are usually employed as a substrate due to the high reactivity as well as the excellent regioselectivity[19]. While the resulting

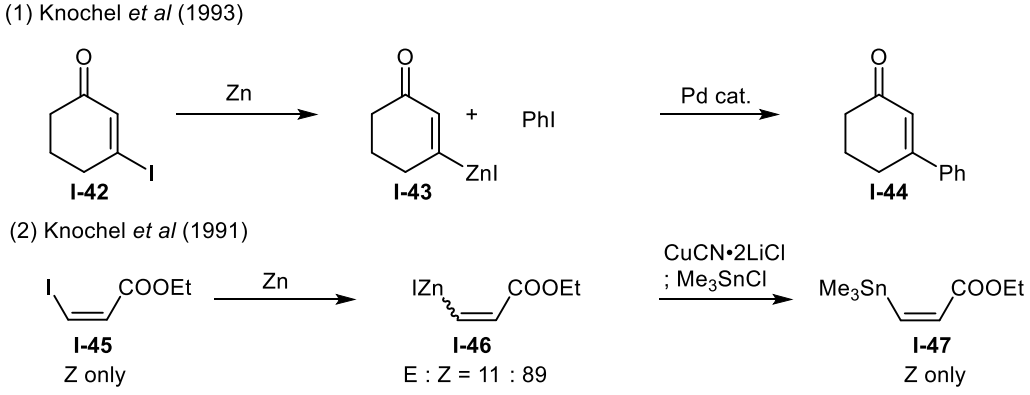
alkenylaluminum species exhibit lower reactivity than that of alkenyllithium or alkenyl Grignard reagents, palladium-catalyzed cross coupling reactions with aryl or alkenyl halides are often utilized for the synthesis of conjugated alkenes (Scheme I-5-(1))[20]. The nucleophilicity of alkenylaluminum species can be increased by adding MeLi, giving rise to an ate complex which undergoes methylation with MeI (Scheme I-5-(2))[21].



Scheme I-5.

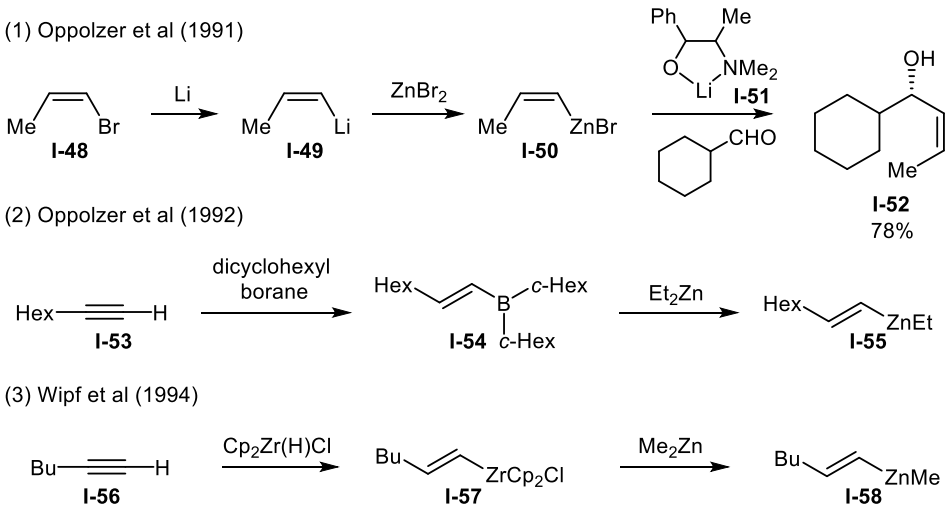
1.4 Zinc

Alkenylzinc species can be prepared by the reaction of an alkenyl iodide and activated zinc powder (Rieke zinc)[22, 23]. One of the most remarkable properties of organozinc reagents is their high functional group tolerance. As shown in Scheme I-6[24], conjugated enone or ester group can exist with the C-Zn bond. These alkenylzinc species are not nucleophilic enough to react with an aldehyde, but they act as a good cross coupling partner with organohalides.



Scheme I-6.

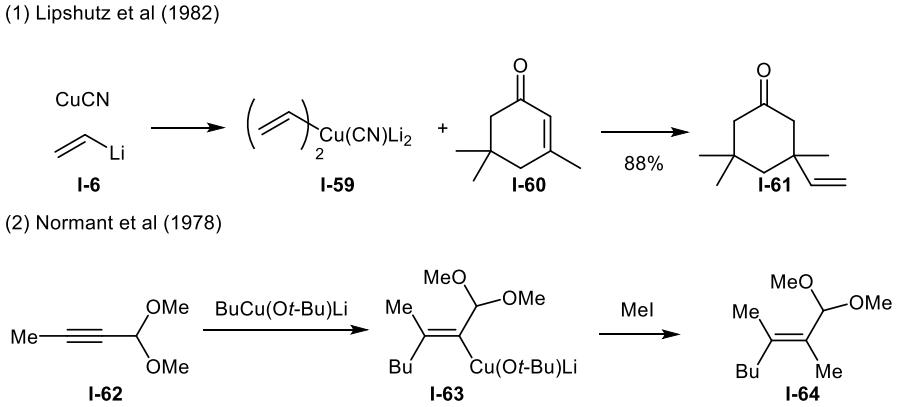
Indirect generation of alkenylzinc species from other organometallic species is widely utilized in organic synthesis (Scheme I-7). The use of an alkenyllithium[25] or an alkenyl Grignard reagent would reduce the functional group tolerance, but transmetalation from an organoborane[26] or an organozirconium[27] may solve the problem. The low reactivity of alkenylzinc species requires the use of an additive in the reaction with aldehydes, which showed promise for controlling the enantiofacial selectivity by the use of a chiral reagent such as an amino alcohol (Scheme I-7-(1)).



Scheme I-7.

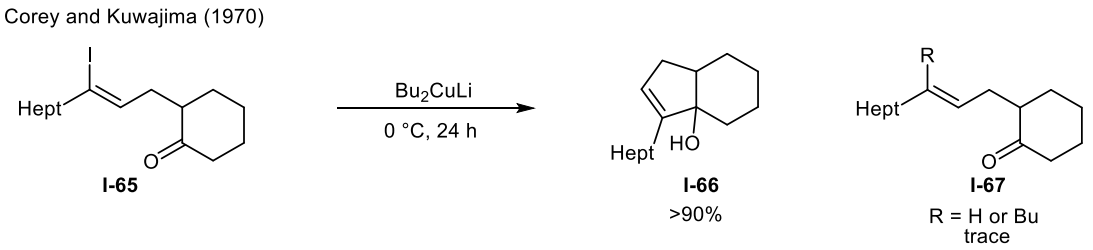
1.4 Copper

Alkenylcopper reagents are readily obtained from other alkenylmetal species and an appropriate copper salt[28]. From the view of enhanced reactivity, Gilman-type reagents are prepared by the use of two equivalent of an alkenyllithium or an alkenyl Grignard reagent (Scheme I-8-(1))[29]. Another method for generating alkenylcopper reagents is the carbocupration reaction of alkynes which proceeds with high regio- and stereoselectivity (Scheme I-8-(2))[19]. The resulting alkenylcopper reagents can be used in conjugate addition reaction with enones or alkylation reaction with haloalkanes.



Scheme I-8.

In some cases, the treatment of a haloalkene with a Gilman reagent leads to halogen-metal exchange reaction (Scheme I-9)[30]. In the reaction reported by Corey and Kuwajima, the high functional group tolerance of an organocopper reagent allowed the generation of alkenylcopper species possessing a ketone moiety which underwent an intramolecular addition reaction. This reaction gave an inspiration to the author to develop a new annulation reaction for obtaining cyclopentenol derivatives, which is described in Chapter 1.



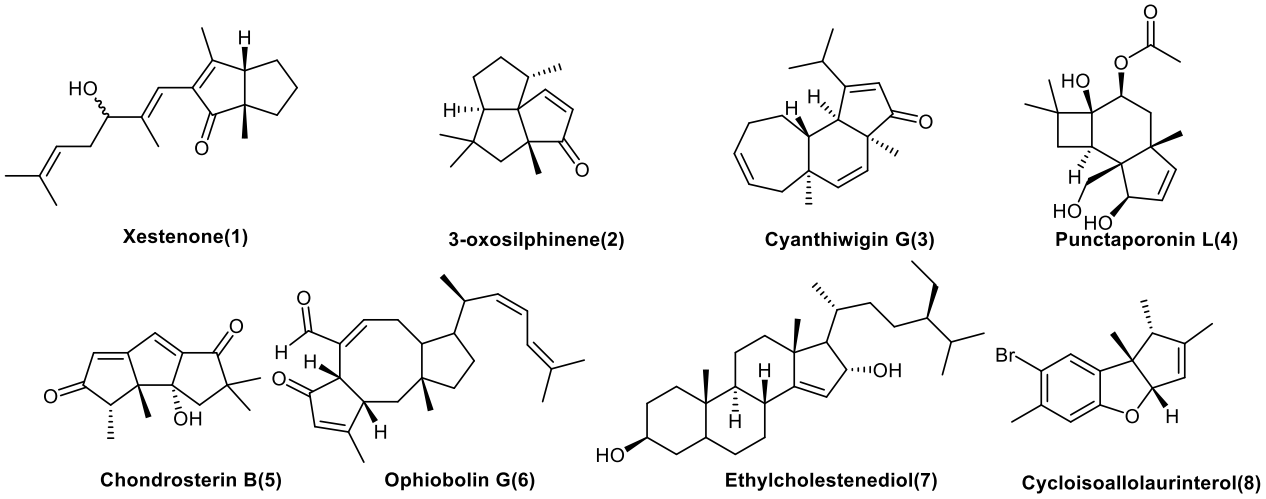
Scheme I-9.

Chapter 1

Synthesis of Substituted Cyclopentenol Derivatives via Intramolecular Addition Reaction of Alkenylcopper Species

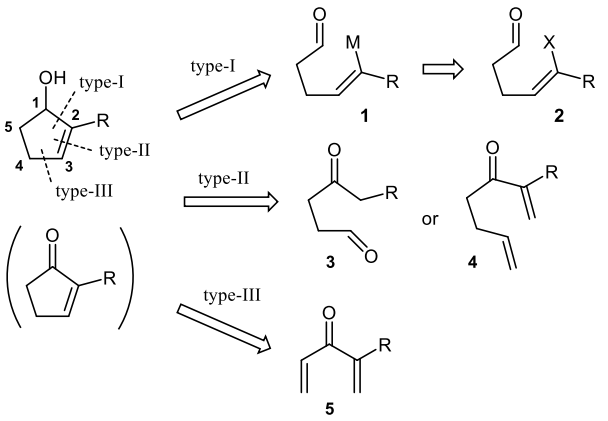
1.1 Introduction

There are a various kind of polycyclic natural products which have 2-cyclopenten-1-one or 2-cyclopenten-1-ol substructure (Scheme 1-1). The use of an efficient method for constructing the highly substituted cyclopentene moiety affects the total efficiency in the chemical synthesis of these natural products[31].



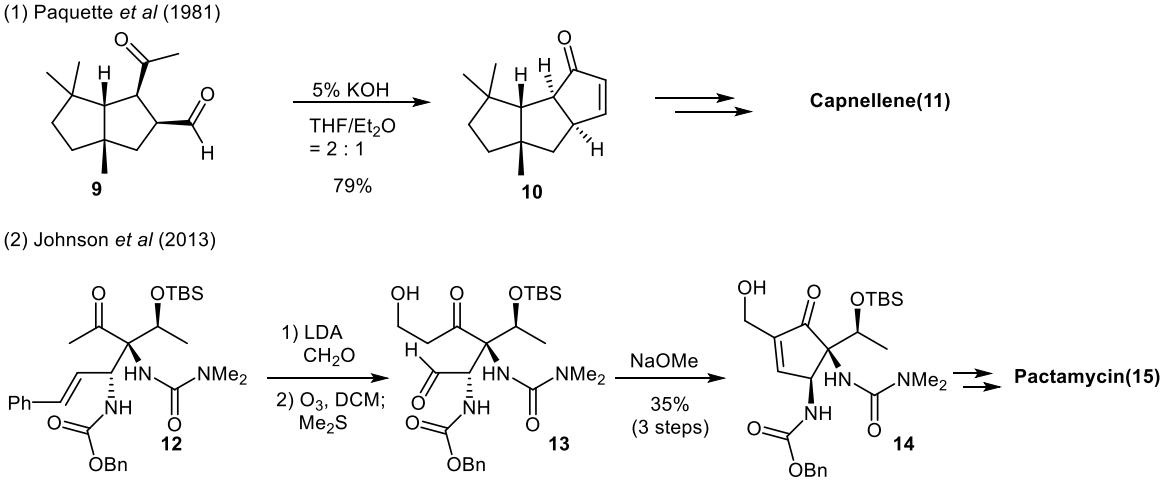
Scheme 1-1.

Therefore, a number of synthetic methods of 2-cyclopenten-1-one and 2-cyclopenten-1-ol had been reported, which can be categorized into three types of approaches (Scheme 1-2). In the type I and the type III approaches, the five membered ring is constructed by the formation of the C1-C2 bond and the C3-C4, respectively, while the type II approach requires the formation of the C2-C3 double bond.



Scheme 1-2.

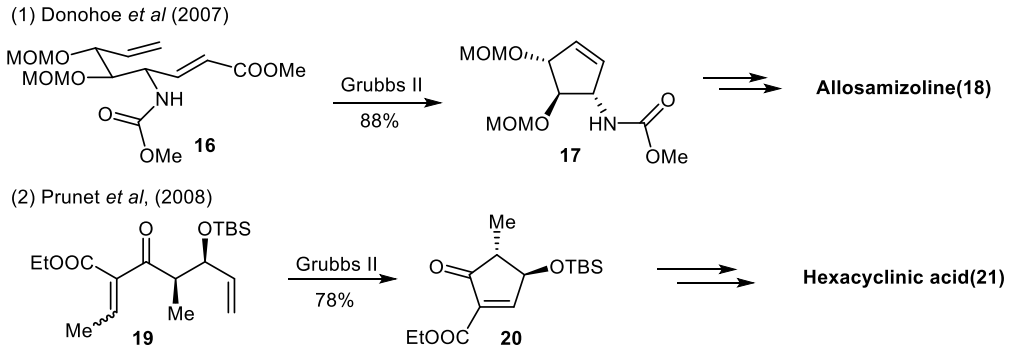
Two useful reactions have widely used as the type II approach, namely, an intramolecular aldol condensation of a 1,4-dicarbonyl compound[32] and the ring closing metathesis of a 1,6-diene compound[33]. The representative examples of the classical intramolecular aldol reactions are shown in Scheme 1-3. In the total synthesis of capnelene by Paquette *et al*. (Scheme 1-3-(1))[34], the C-ring enone moiety was constructed by the treatment of ketoaldehyde **9** with an aqueous solution of KOH. Johnson *et al*[35]. also used this type of reaction for the synthesis of multi-substituted cyclopentenone **14** which is the key intermediate of the total synthesis of pactamycin (Scheme 1-3-(2)).



Scheme 1-3.

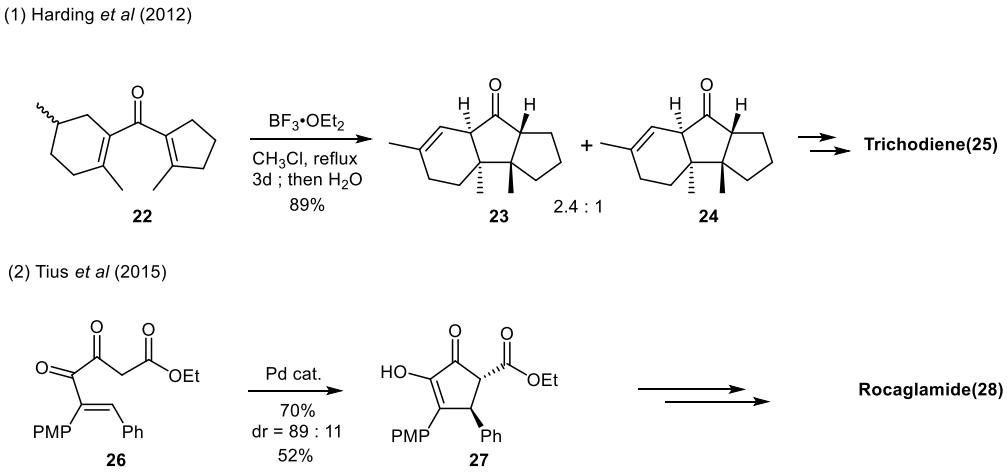
On the other hand, the ring closing metathesis reactions have widely been used for constructing cycloalkene derivatives. As shown in Scheme 1-4, this type of approach show promise for the synthesis of multi-functional cyclic compounds, because of the high functional

group tolerance. Thus, the use of highly functionalized substrate, which was prepared from a sugar, afforded the cyclopentene derivative under the influence of Grubbs II catalyst (Scheme 1-4-(1))[36]. The neutral conditions of the cyclization reaction in Scheme 1-4-(2) led to formation of the easily enolizable cyclopentenone derivative without any epimerization of the stereogenic centers[37].



Scheme 1-4.

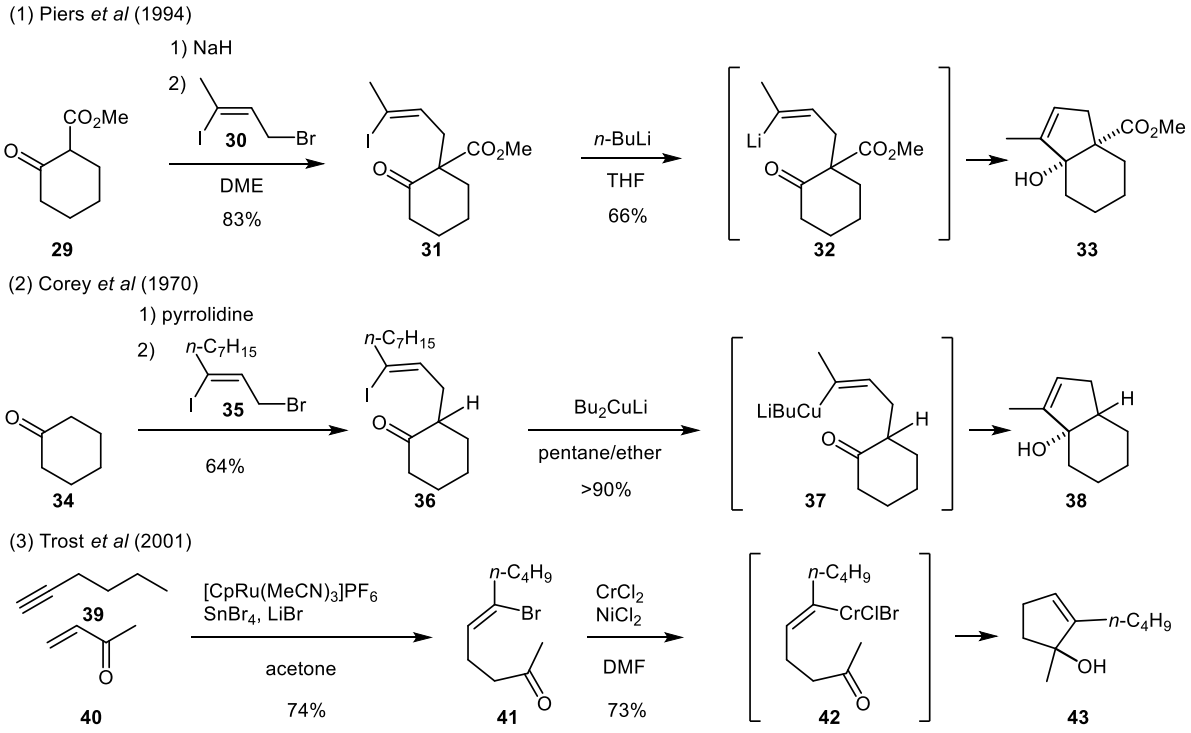
The representative method in the type III approach is the Nazarov cyclization reaction (Scheme 1-5)[38]. While the classical Nazarov cyclization reaction had been conducted by the treatment of a divinyl ketone substrate with a Lewis acid or a Brønsted acid (Scheme 1-5-(1))[39], the use of an appropriate transition metal catalyst can facilitate the cyclization reaction (Scheme 1-5-(2))[40].



Scheme 1-5.

The synthesis of 2-cyclopenten-1-ol derivatives by the type II approach can be achieved by generating an alkenyl anion at the δ-position of a γ,δ-unsaturated carbonyl compound (Scheme 1-6). It should be noted that stereoselective generation of a (Z)-alkenyl anion is necessary for inducing the intramolecular addition reaction with the carbonyl group. For example, Piers *et al.*

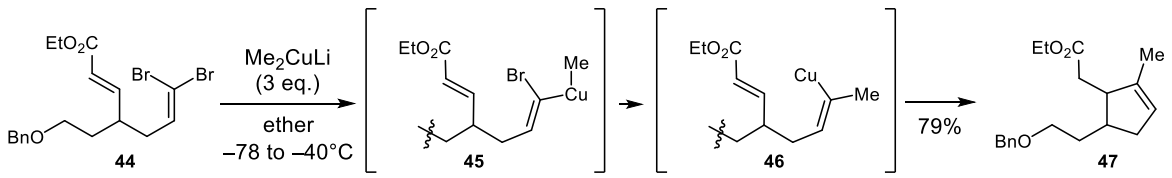
prepared the substrate by the use of (*Z*)-1-bromo-3-iodo-2-butene, and the cyclization reaction was performed by the treatment with *n*-BuLi (Scheme 1-6-(1))[41]. The halogen-metal exchange strategy for generating alkenylcopper or alkenylchromium species was also applied to the type II approach. Thus, Corey and Kuwajima reported that the treatment of an iodoketone with Bu_2CuLi resulted in formation of a five-membered ring through generation of a *Z*-alkenylcopper species (Scheme 1-6-(2))[30]. The intramolecular NHK coupling reaction was utilized by Trost *et al*[42]. (Scheme 1-6-(3)) the substrate of which was prepared by their original coupling reaction in a stereoselective manner.



Scheme 1-6.

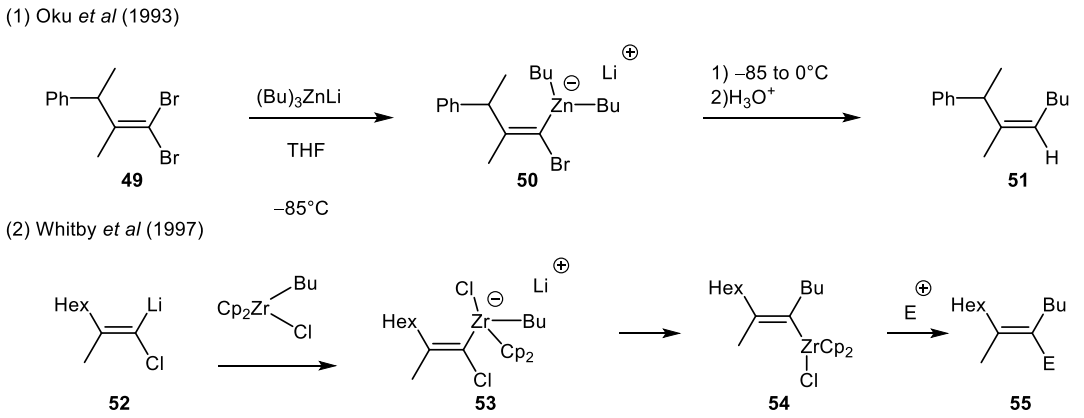
1.2 Generation of alkenyl metal species from a *gem*-dihaloalkene

In 2006, the author's laboratory reported the cyclization reaction of α,β-unsaturated esters possessing a *gem*-dibromoalkene moiety (Scheme 1-7)[43] Upon treatment with Me_2CuLi (3 equiv.) at -78°C, the substrate underwent an intramolecular conjugate addition reaction to furnish a cyclopentene derivative in good yield. The reaction was expected to proceed through the halogen-metal exchange reaction at the less hindered bromine atom, and the resulting copper carbenoid would be converted to a Z-alkenylcopper species by a 1,2-rearrangement of the methyl group. In this cyclization reaction, stereoselective preparation of the haloalkene moiety is not required[44].



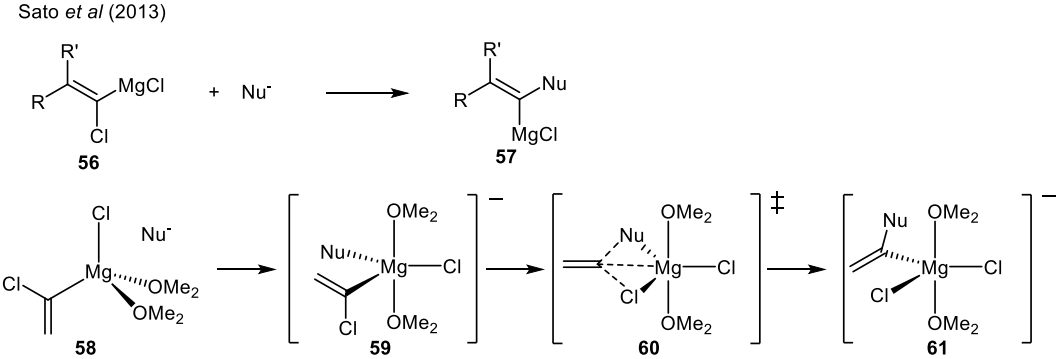
Scheme 1-7.

Similar examples for generating an alkenylmetal species by the alkylative rearrangement of a carbenoid intermediate is shown in Scheme 1-8. Oku *et al*[45]. reported that the reaction of a *gem*-dibromoalkene and a trialkyl zincate reagent afforded the coupling product (Scheme 1-8-(1)). It is noteworthy that the configuration of the coupling product indicated the stereoselective formation of an *E*-alkenylzinc species. On the other hand, Whitby *et al*[46]. utilized a zirconium carbenoid for generating a *Z*-alkenylzirconium species (Scheme 1-8-(2)).



Scheme 1-8.

Sato *et al.* reported the theoretical studies on a 1,2-rearrangement of magnesium carbenoid species by DFT calculations (Scheme 1-9)[47].

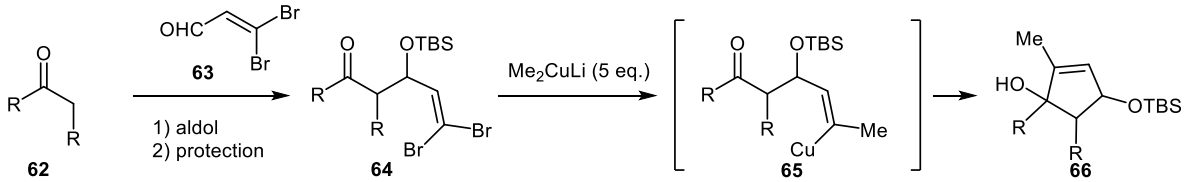


Scheme 1-9.

The ate complex which was generated by the reaction of a magnesium carbenoid and a nucleophile (Nu^-) undergoes rearrangement of the Nu group through the transition state with trigonal-bipyramidal geometry. The activation energy of 1,2-miglation of nucleophiles were estimated to be 21.3-23.2 kcal/mol.

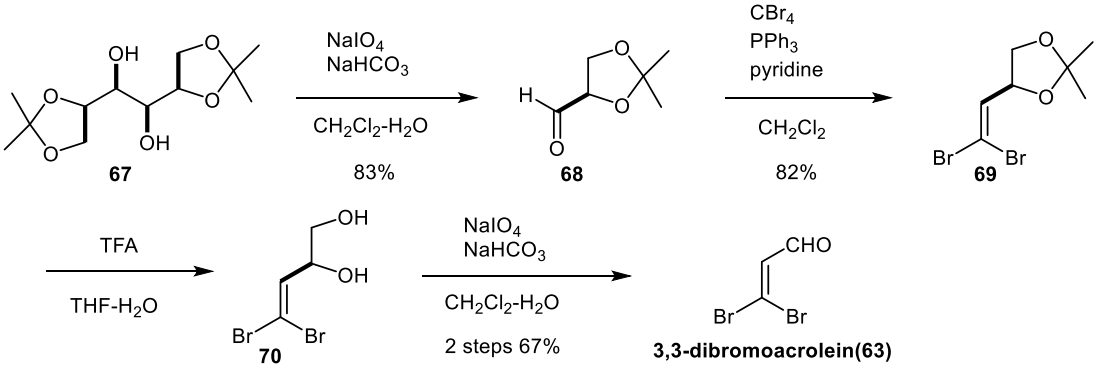
1.3 Cyclization reaction of ketones having a *gem*-dibromoalkene moiety

From those backgrounds, the author was motivated to explore the utility of the *Z*-alkenylcopper species generated from a *gem*-dibromoalkene and a Gilman reagent, and designed an intramolecular addition reaction with a ketone moiety (Scheme 1-10). The substrate would be prepared from a ketone through an aldol reaction with 3,3-dibromoacrolein[48] followed by protection of the aldol with a silyl group. Upon treatment with a Gilman reagent, the dibromoalkene would generate *Z*-alkenylcopper species which undergoes addition reaction with the carbonyl group.



Scheme 1-10.

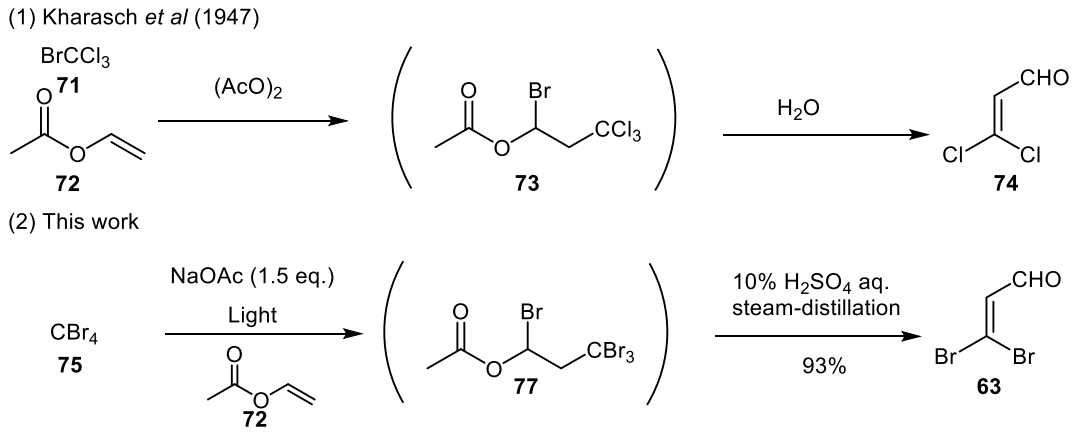
At first, 3,3-dibromoacrolein was prepared as shown in Scheme 1-11. The commercially available mannitol derivative **67** was oxidized by $NaIO_4$ to afford aldehyde **68** which was subjected to the Wittig reaction using CBr_4 and PPh_3[49]. After removal of the acetal group by TFA, the resulting diol **70** was oxidized with $NaIO_4$ on silica gel and $MgSO_4$, giving rise to the desired aldehyde **63**.



Scheme 1-11.

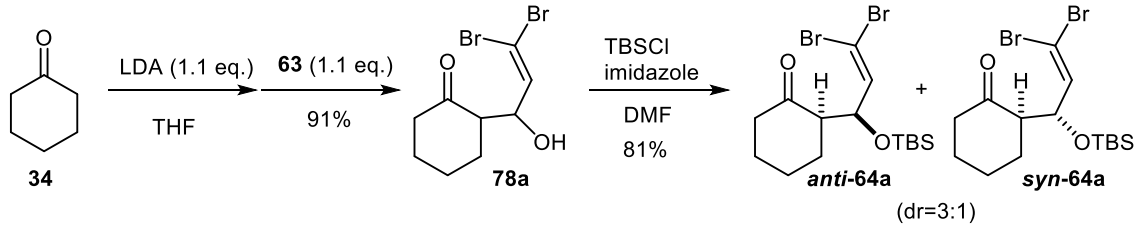
The “first generation synthesis” of the aldehyde was not suitable for a large-scale synthesis, mainly because the Wittig reaction requires the removal of triphenylphosphine oxide by silica gel chromatography. Therefore, the author decided to explore the much simpler “second generation synthesis” of the aldehyde.

In 1947, Kharasch *et al*[50]. reported the concise synthesis of 3,3-dichloroacrolein (**74**) starting from vinyl acetate (Scheme 1-12-(1)). Thus, the addition reaction with $BrCCl_3$ in the presence of diacetyl peroxide condition gave **73** which was hydrolyzed to yield aldehyde **74**. Inspired by this reaction, the author established new protocol for providing 3,3-dibromoacrolein (Scheme 1-12-(2)). The radical addition reaction between vinyl acetate and CBr_4 was performed in the presence of sodium acetate under the irradiation with a fluorescent lamp[51]. The adduct was then hydrolyzed by heating with diluted sulfuric acid during which the product was distilled off with steam. The improved synthesis enabled the author to obtain the desired aldehyde in excellent yield even at large scale (>100 mmol).



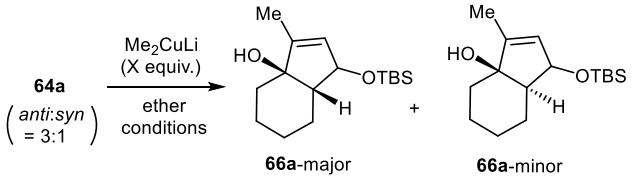
Scheme 1-12.

Cyclohexanone (**34**) was successively treated with LDA and aldehyde **78a**, giving rise to the aldol adduct **64a**. The isomeric mixture was then subjected to the protection of the hydroxy group with TBSCl, and the cyclization precursor was obtained as a 3:1 mixture of *anti*- and *syn*-**64a** (Scheme 1-13).



Scheme 1-13.

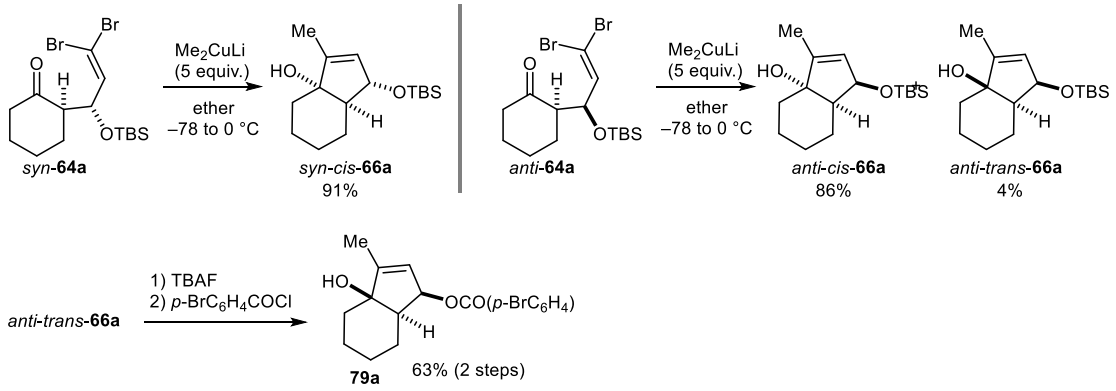
The cyclization reaction of ketone **64a** was initially conducted in THF at -78 °C with 3 equivalents of Me_2CuLi, according to the typical procedure in the intramolecular conjugate addition reaction previously reported (Table1-1, entry 1). Disappointedly, the desired cyclopentenol derivative **66a** was obtained in only 6% yield, and the use of 5 equivalents of Me_2CuLi led to slightly increased yield (Table1-1, entry 2). On the other hand, worming up of the reaction mixture to 0 °C dramatically increased the yield of **64a** (Table 1, entries 3 and 4), which is consistent with that an organocopper reagent exhibit lower reactivity in addition to a ketone than that in a conjugate addition to an α,β-unsaturated carbonyl compound. The reaction seemed to proceed in a stereoselective manner, but the main product was obtained as an inseparable mixture of isomers along with a small amount of another epimer **66a**-minor.



entry	X	conditions	NMR yield of **66a** (%) major	major
1	3	–78 °C, 20 min	6	-
2	5	–78 °C, 20 min	19	-
3	3	–78 °C then 0°C, 10 min	80	7
4	5	–78 °C then 0°C, 10 min	86	4

Table 1-1.

In order to clarify the relationship between the isomers of the substrates and the products, the mixture of ketones *anti*-**64a** and *syn*-**64a** was purified repeatedly. Each of the pure diastereomers was subjected to the cyclization reaction under the conditions in entry 4 of Table 1-1. The reaction of *anti*-**64a** afforded *anti-cis*-**66a** along with a small amount of *anti-trans*-**66a**, while *syn-cis*-**64a** was obtained as a single diastereomer in 91% yield from *syn*-**64a**.



Scheme 1-14.

The configuration of the minor isomer *anti-trans*-**66a** was confirmed by the X-ray crystallographic analysis after conversion into *p*-bromo-benzoate **79a**. Since determination the configuration of the major products *anti-cis*-**66a** and *syn-cis*-**66a** was difficult, further transformation was required to obtain crystalline derivatives (vide infra). The complete stereoselection in the reaction of *syn*-**64a** affording *syn-cis*-**66a** is consistent with the general tendency of *cis*-selective formation of a 6-5 bicyclic system. On the other hand, unusual formation of the trans-fused compound *anti-trans*-**66a**, albeit as a minor isomer, would come from the sterically demanding TBS group which affects the formation of the major isomer *anti-cis*-**66a** possessing the TBS group at the concave face.

The stage was set for the exploration of the scope of the cyclization reaction starting from various ketones. In general, separation of the diastereomers arising from the aldol reaction with 3,3-dibromoacrolein was difficult, and the mixture of diastereomers were silylated to give the substrates of the cyclization reactions. The results are shown in Table 1-2.

The desired products were obtained from five-, seven-, eight-, and twelve-membered ketones in the good yield (Table 2, entries 1-4). The substituted cyclohexanones were also converted to the bicyclic compounds without any problems (Table 1-2, entries 5-7). The transformation of acyclic ketones afforded the monocyclic products in a stereoselective manner (Table 1-2, entries 8 and 9). The trans relationship between the phenyl or the *tert*-butyl group and the TBS group in the products suggested the steric repulsion played an important role in stereocontrol. The intramolecular cyclization reaction of alkenylcopper species was applicable to the transformation of sterically demanding ketones, and epi-androsterone benzyl ether were converted to the corresponding cyclopentene derivative in the good yield (Table1-2, entry 10). The steroidal product **66k** was converted to a *p*-bromo benzoate the X-ray crystallographic analysis of which indicated the configuration of the cyclopentene moiety (Figure 1-1).

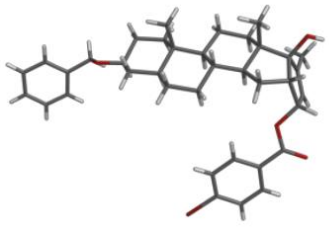
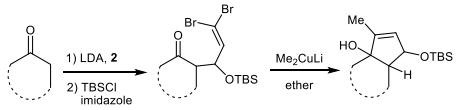


Figure 1-1.



Ketone **62b-k** Cyclization Precursor **64b-k** Cyclization Product **66b-k**

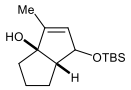
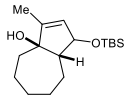
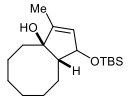
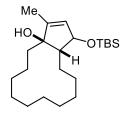
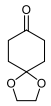
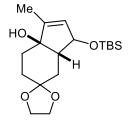
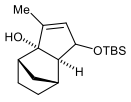
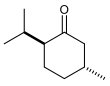
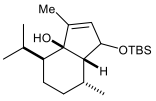
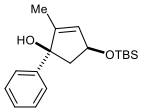
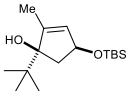
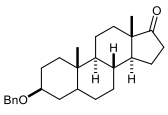
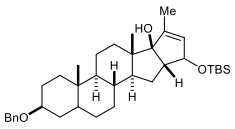
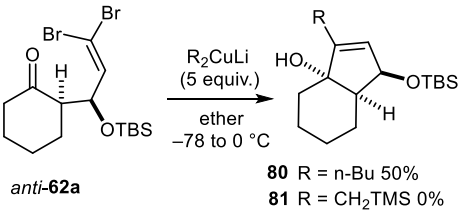
entry	ketone	Yield of **64** (%)	dr of **62**	cyclization product **66**	Yield of **66** (%)	dr of **66**
1		97	1.5:1		79	2:1
2		84	1:1		77	1.2:1
3		84	1.1:1		85	1:1
4		86	1:1		65	2.5:1
5		67	2:1		99	2:1
6		97	2:1		71	1.7:1
7		86	>10:1		93	>10:1
8		83	-		76	>100:1
9		57	-		75	3:1
10		86 (68% after recrystallization)	-		71	-

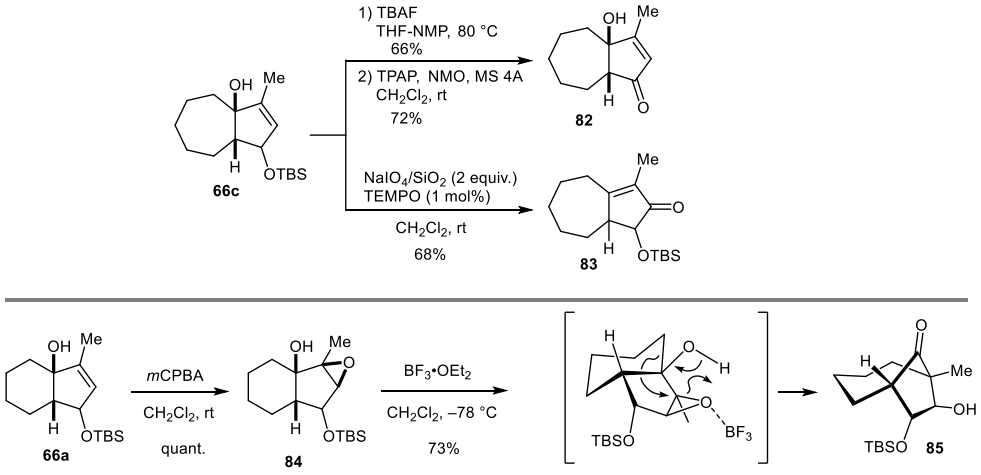
Table 1-2.

The use of other Gilman reagents was briefly examined. While the treatment of *anti*-@ with Bu_2CuLi gave the corresponding product in 50% yield, a similar reaction with $(TMSCH_2)_2CuLi$ gave a complex mixture (Scheme 1-15).



Scheme 1-15.

Finally, the utility of the resulting cyclopentenol derivatives was explored (Scheme 1-16). Removal of the TBS group of **66c** with TBAF followed by TPAP oxidation gave enone **82**. On the other hand, upon treatment with a catalytic amount of TEMPO and $NaIO_4$ on silica gel, alcohol **66c** was converted to **83** via transposition of the allylic system[52]. Therefore, two different types of enones could be synthesized from a common substrate **66c**. The allyl alcohol moiety can be utilized to induce rearrangement of the carbon skeleton. The substrate was prepared from **66a** by the treatment with *m*CPBA, which induced oxidation of the alkene from the convex face of the bicyclic skeleton. The resulting epoxy alcohol was subjected to the semi-pinacol rearrangement reaction mediated with $BF_3{\cdot}OEt_2$, giving rise to bicylo[4.2.1]nonane derivative. The bicyclic ketones were converted to bis *p*-bromobenzoate esters, respectively (Figure 1-2), and their configuration was determined by X-ray crystallographic analysis. These results indicated the relative configuration of the parent compounds **66** which could not be estimated before (vide supra).



Scheme 1-16.

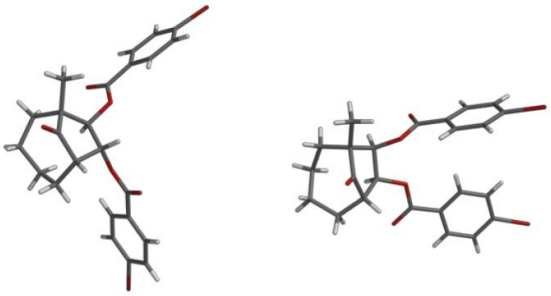


Figure 1-2.

In conclusion, the author developed a new synthetic method of substituted cyclopentene derivatives by an intramolecular addition reaction of an alkenylcopper species. The substrates were prepared from a ketone through an aldol reaction with 3,3-dibromoacrolein followed by the protection of the hydroxy group by a TBS group. Upon treatment with an excess amount of Me_2CuLi, the gem-dibromoalkene moiety was converted to a Z-alkenylcopper species which underwent an intramolecular addition reaction with the ketone moiety. The new cyclization reaction can be applied to various alicyclic and cyclic ketones.

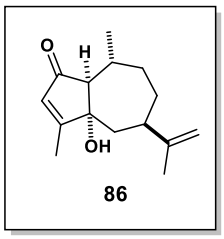
Chapter 2

Total Synthesis of Natural Product Based on the Intramolecular Addition Reaction of Alkenylcopper Species

2.1 Introduction

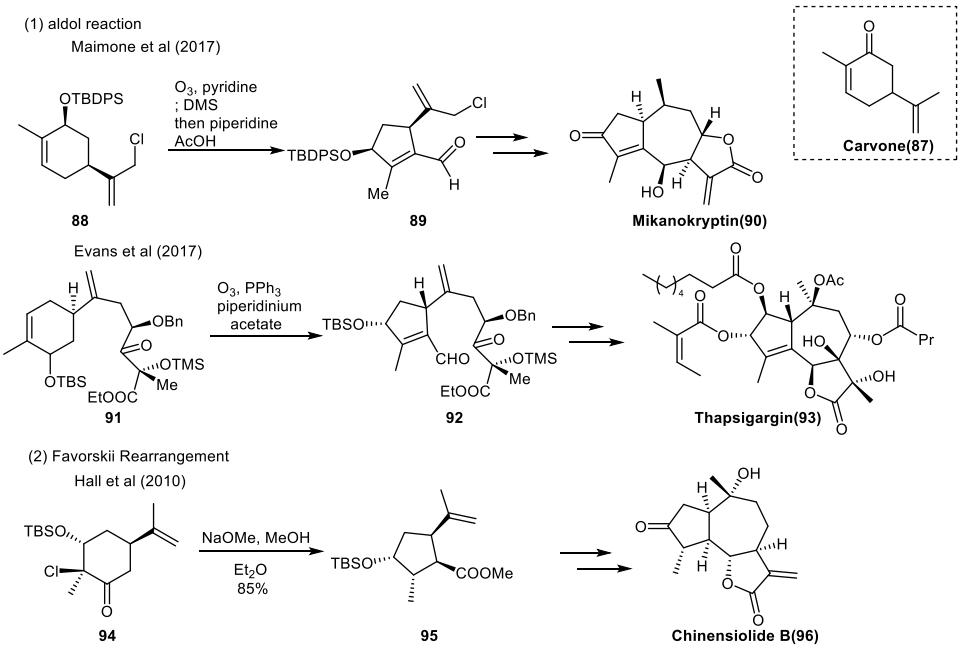
In chapter 1, the author established the synthetic method of substituted cyclopentene derivatives by an intramolecular addition reaction of an alkenylcopper species. One of the advantages of the new cyclization reaction is a wide applicability to various alicyclic and cyclic ketones from which the cyclization precursors were prepared in only two steps. The use of a Gilman reagent, which shows low basicity, is suitable for avoiding epimerization at the ketone moiety. The excellent properties of the present method led the author to explore the utility in the total synthesis of natural products.

In this chapter, the author describes the total synthesis of sesquiterpene **86** which possesses a hydroazulene skeleton involving four stereogenic centers[53]. Sesquiterpene **86** was isolated from the roots of *Jatropha integerrima* by Sutthivaiyakit *et al.* in 2009. The total synthesis of **86** has not been reported, a number of total synthesis of related sesquiterpenes have been achieved.



86

It is noteworthy that naturally occurring monoterpenes have been employed as a chiral starting material in many successful asymmetric total syntheses of terpenoids. Selected examples[54] of preparation of five-membered intermediates from carvone are shown in Scheme 2-1. The isopropenyl group of carvone can be functionalized via chlorination, and the six-membered ring is easily converted to a cyclopentene ring through oxidative cleavage followed by intramolecular aldol reaction. According to this strategy, Maimone and Evans obtained the optically active key intermediates of total synthesis, respectively (Scheme 2-1-(1)[55], (2)[56]). The Favorskii rearrangement reaction is also effective for the ring contraction of a six-membered ring, and Hall *et al*[57]. reported that treatment of chloro ketone **94** with NaOMe gave the highly substituted cyclopentane derivative in a highly stereoselective manner.

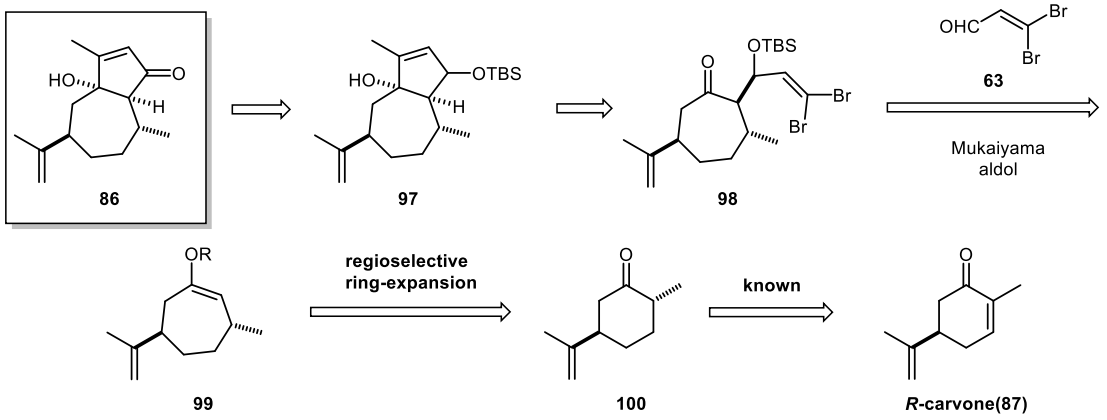


Scheme 2-1.

In these reports, stereoselective construction of the seven-membered ring required multi-step transformations before accomplishing the total synthesis of the target terpenoids. In contrast, the author planned to use carvone as a precursor of the seven-membered ring, and construction of the five-membered ring would be achieved by the intramolecular cyclization reaction of an alkenylcopper species.

2.2 Total synthesis of sesquiterpene 86

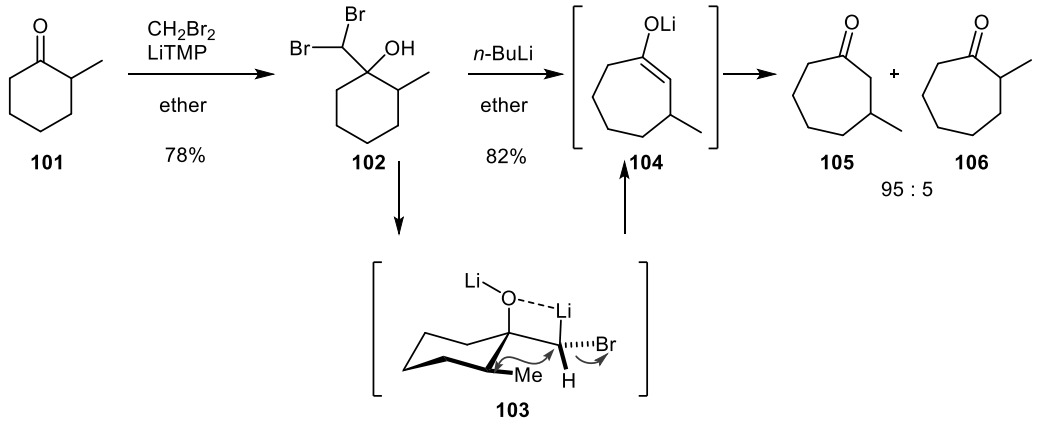
The retrosynthetic analysis is shown in Scheme 2-2. The target compound **86** would be derived from silyl ether **97**, which would be synthesized by the cyclization reaction, through desilylation followed by oxidation.



Scheme 2-2.

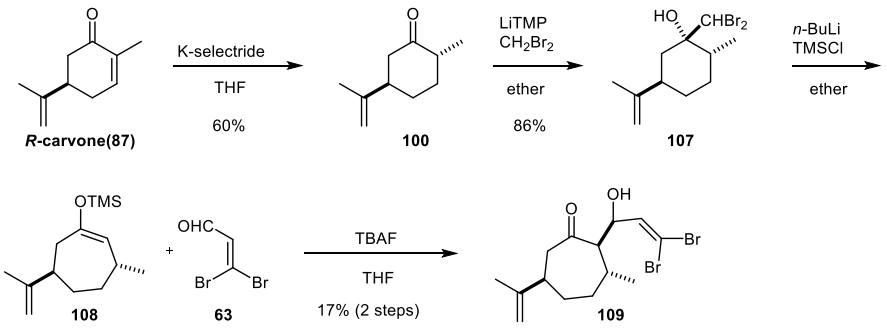
The key point in the preparation of the cyclization precursor **98** is the regio- and stereoselective introduction of a *gem*-dibromoalkene side chain to the unsymmetrically substituted cycloheptanone. The author planned to conduct a Mukaiyama-aldol reaction of the corresponding enol silyl ether **99**. The configuration of the isopropenyl group and the methyl group on the cycloheptane ring is consistent with that of dihydrocarvone **100**, preparation of which was reported by Yadav[58]. Therefore, it was supposed that regioselective ring expansion of cyclohexanone **100** would be suitable for obtaining cycloheptanone **99**.

Nozaki *et al*. reported a useful one-carbon ring expansion reaction of cyclohexanone derivatives (Scheme 2-3)[59]. The addition reaction of 2-methylcyclohexanone and dibromomethyllithium, which was generated from CH_2Br_2 and LiTMP, afforded alcohol **102** in good yield. The ring expansion reaction was performed by the treatment of **102** with 2 equivalents of *n*-BuLi, giving rise to a 95:5 mixture of cycloheptanones **105**, **106**. The reaction proceeds through formation of a carbenoid species which undergoes the regioselective insertion with the more substituted ring carbon.



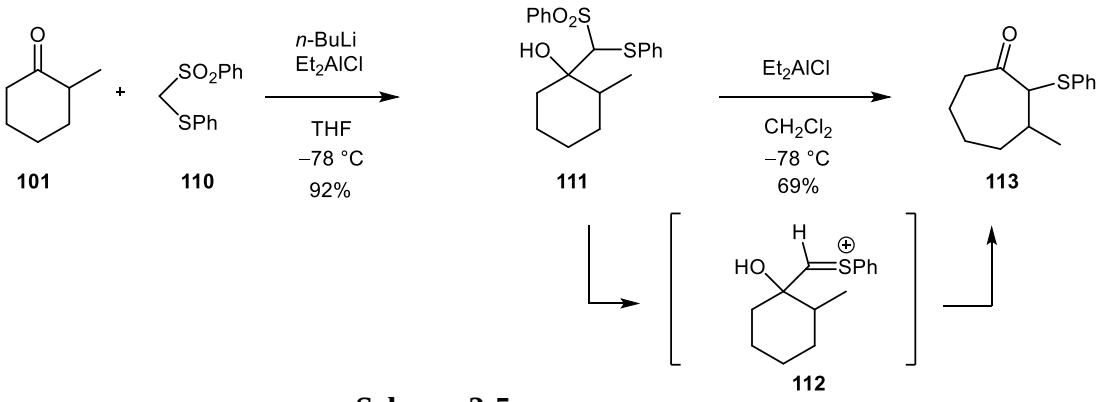
Scheme 2-3.

The author planned to apply the Nozaki's protocol to dihydrocarvone **100**, which was prepared by the conjugate reduction of carvone by K-selectride (Scheme 2-4). The addition reaction with dibromomethyllithium proceeded smoothly to afford alcohol **107** in high yield. The adduct was obtained as a single isomer, the configuration of which was assumed by postulating the selective attack from the opposite face of the methyl group. The ring expansion reaction was performed according to the Nozaki's protocol, and the anionic species was captured by adding TMSCl. The crude product was, however, found to be a complex mixture containing an epoxide, dibromoalkene, and many unidentified compounds. While isolation of the desired enol silyl ether from the mixture was difficult, aldol product **109** was obtained in 17% yield through treatment of the mixture and 3,3-dibromoacrolein with TBAF.



Scheme 2-4.

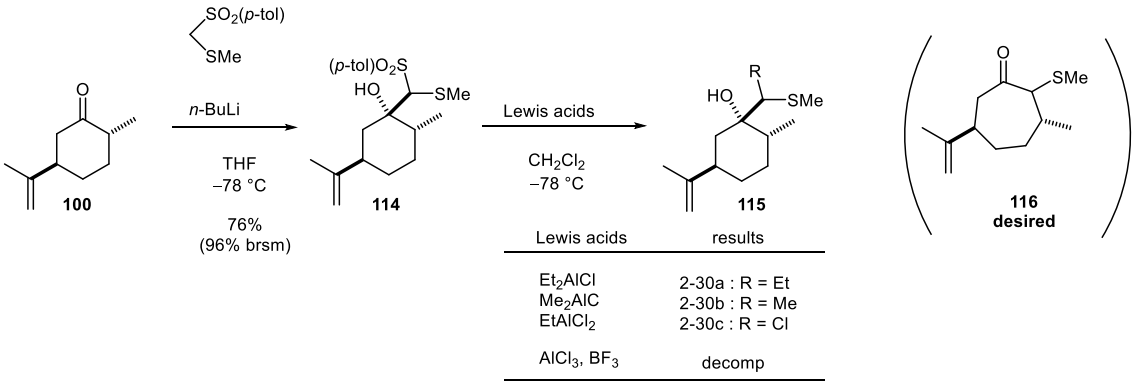
These results led the author to explore another ring expansion method. Trost *et al*[60]. reported a one-carbon ring expansion reaction cyclic ketones utilizing a sulfur reagent (Scheme 2-5). Thus, 2-methylcyclohexanone was reacted with an anionic species generated from phenylthio phenyl sulfone, giving rise to alcohol **111** in excellent yield. Upon treatment with Et_2AlCl in CH_2Cl_2, the sulfonyl group was abstracted to generate an α-phenylthio carbocation which underwent a semi-pinacol rearrangement to afford cycloheptanone **113**. The reaction also proceeded in a regioselective manner, and the preferential shift of the more substituted ring carbon was observed. It is noteworthy that the phenylthio group at the α-position of the product would be utilized for the regiospecific generation of the corresponding enolate by an appropriate reductant.



Scheme 2-5.

Since phenylthio phenyl sulfone was not commercially available, the author employed an analogous reagent, methylthio *p*-tolyl sulfone (MT-sulfone), as an alternative (Scheme 2-6). Upon treatment with the anion species generated from MT-sulfone and *n*-BuLi, dihydrocarvone **100** underwent an addition reaction to give alcohol **114** along with a small amount of recovery of ketone **100**. The adduct was obtained as a single isomer, the configuration of which was assumed by postulating the selective attack from the opposite face of the methyl group. Unfortunately, the attempted ring expansion reactions of sulfone **114** by adopting the Trost's conditions failed to give

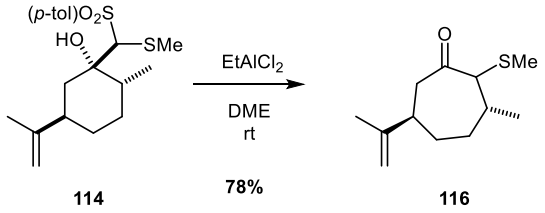
the desired product. Thus, the reaction in CH_2Cl_2 under the influence of Et_2AlCl or Me_2AlCl resulted in introduction of an ethyl or a methyl group at α-position of the methylthio group, respectively. The use of $EtAlCl_2$ induced introduction of a chlorin atom at the same position, while $AlCl_3$ and BF_3•OEt_2 merely gave a complex mixture.



Scheme 2-6.

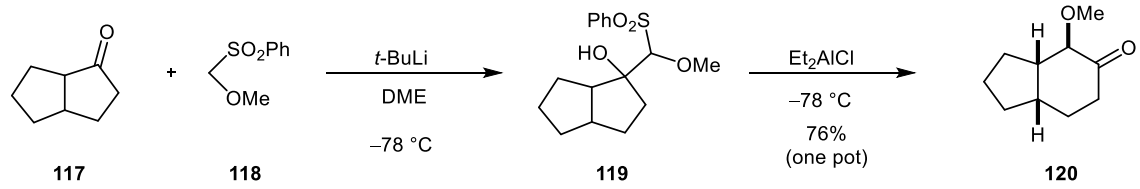
These results indicated that the *p*-toluenesulfonyl group is abstracted by these Lewis acids, but the resulting an α-methylthio carbocation is readily captured by the ligand of the aluminum reagents. In the Trost's ring expansion method, an α-phenylthio carbocation was the intermediate of the rearrangement reaction. The different behavior of the present unsuccessful reaction may come from the higher stability of the α-methylthio carbocation which would affect the rearrangement of the ring carbon.

After further investigations, it was found that the use of $EtAlCl_2$ in DME, which may reduce the Lewis acidity of the aluminum reagent, at higher temperature works nicely to afford the desired ketone **116** in good yield. Interestingly, the reactions in THF or diethyl ether failed to promote the desired transformation[61].



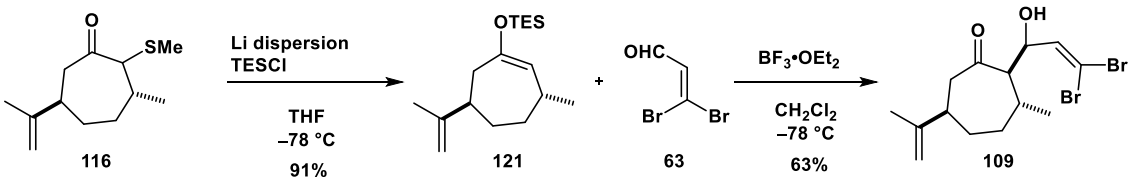
Scheme 2-7.

The origin of the remarkable result in DME is not clear, but Trost reported that the use of DME as a solvent of the one-pot transformation of ketone **117** worked very well to give the desired ring expansion product **120** (Scheme **2-8**)[60].



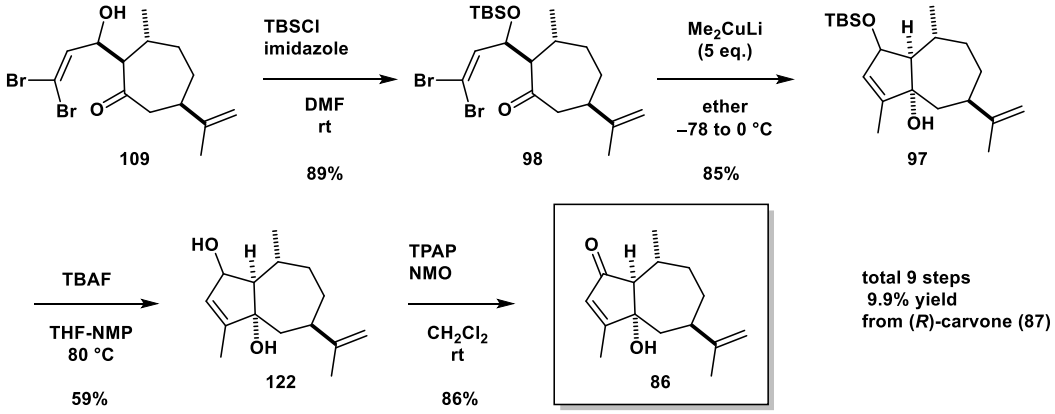
Scheme 2-8.

Next, α-methylthio ketone **116** was subjected to the reductive silylation reaction by the treatment with lithium dispersion and TESCl in THF, giving rise to enol silyl ether **121** (Scheme 2-9). Under the influence of BF_3•OEt_2, the Mukaiyama aldol reaction of **121** and 3,3-dibromoacrolein (**63**) proceeded smoothly to give the desired adduct **109** as a 2:1 mixture of isomers. It was supposed that these products are the epimer at the hydroxy group to each other, because the reaction would occur from the opposite face of the methyl group.



Scheme 2-9.

After the protection of the hydroxy group with a TBS group, the resulting ketone **98** was treated with 5 equivalents of Me_2CuLi in ether (Scheme 2-10). The cyclization reaction through generation of an alkenylcopper species occurred smoothly, and the desired bicyclic product **97** was obtained in 85% yield. Removal of the TBS group by TBAF afforded alcohol **122** which was converted to the corresponding ketone **86** by TPAP oxidation.



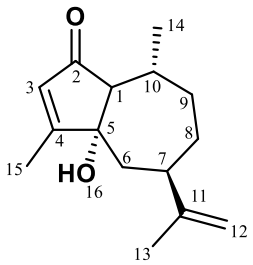
Scheme 2-10.

The spectral data of the product was identical with that of the reported natural product (Table 2-1). Therefore, the asymmetric total synthesis of **86** was accomplished through nine-step transformation in 9.9% overall yield.

Atom No.	^{1}H NMR Chemical shifts in ppm [multiplicity, *J* (Hz)]		^{13}C NMR chemicalshifts in ppm	
	Sutthivaiyakit	This synthesis	Sutthivaiyakit	This synthesis
1	2.16 (d, 10.1)	2.18 (d, 10.3)	67.2	67.34
2	-	-	205.8	205.63
3	5.80 (s)	5.83 (d, 1.1)	109.1	109.1
4	-	-	177.6	177.3
5	-	-	82.5	82.48
6	1.92 (brd 14.1)	1.56-1.96 (m)	40.7	40.6
7	2.53 (dt, 11.9, 2.7)	2.58 (m)	41.1	41.3
8	1.86 (m)	1.56-1.96 (m)	36.3	36.3
9	1.63 (tt, 12.1, 2.0) 1.56 (obs ddt 12.5, 5.8, 1.7)	1.56-1.96 (m)	35.2	35.2
10	1.76 (obs ddq, 10.3 6.4 1.7)	1.56-1.96 (m)	34.3	34.2
11	-	-	128.7	128.9
12	4.65 (brs) 4.67 (brs)	4.69 (m)	150.8	150.7
13	1.68 (s)	1.56-1.96 (m)	20.6	20.5
14	1.04 (s)	1.03 (s)	23.8	23.8
15	2.01 (s)	2.06 (s)	12.8	12.8

S. Sutthivaiyakit, W. Mongkolvisut, S. Prabpai, P. Kongsaeree, *J. Nat. Prod.* **2009**, *72*, 2024–2027.[53]

Table 2-1.



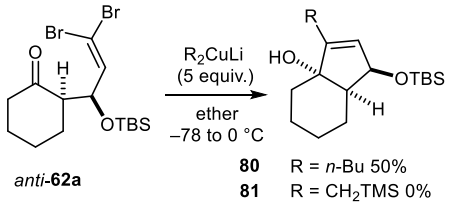
86

Chapter 3

Synthesis of Bromocyclopentenol Derivatives via Intramolecular Addition Reaction of Lithium carbenoid Species

3.1 Introduction

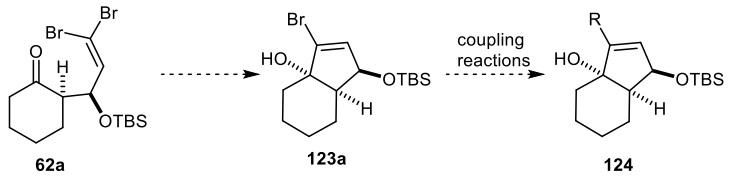
In Chapter 1, the author described the cyclization reaction of ketones possessing a *gem*-dibromoalkene moiety. The reaction is conducted by the treatment of the substrate with Me_2CuLi, and the resulting Z-alkenylcopper species undergoes an intramolecular addition with the ketone moiety. The synthetic utility was demonstrated through the concise total synthesis of a terpenoid which was described in Chapter 2. There are, however, some drawbacks in the cyclization reaction as follows: (1) The use of Me_2CuLi afforded the desired products in good yield, but other Gilman reagents such as Bu_2CuLi, Ph_2CuLi, and $(TMSCH_2)_2CuLi$ led to poor results (Scheme 3-1). The excellent reactivity of Me_2CuLi may come from the sterically less demanding nature of a methyl group. (2) The cyclization reaction with Me_2CuLi requires the use of 3-5 equivalents of the Gilman reagent for completion.



Scheme 3-1.

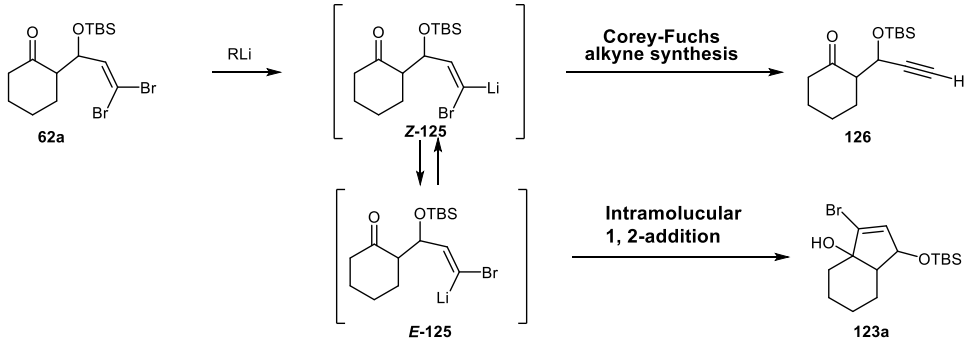
During the exploration of the cyclization reaction, the author found that a small amount of an unidentified product is formed in some cases. The proton NMR spectra indicated that the side product possessed a structure similar with that of the main product, although no alkyl or aryl group originated from the Gilman reagent was found. The mass spectra of the compound showed existence of a bromine atom, and it was identified as the corresponding bromoalkene derivative. The result suggested that the cyclization reaction may occur from an α-bromoalkenyl anion species. The product possessing a bromoalkene moiety instead of a methyl group showed promise

for the synthesis of various cyclopentenol derivatives, which are hardly obtained by the use of R_2CuLi, through cross-coupling reactions with organometallic compounds (Scheme 3-2).



Scheme 3-2.

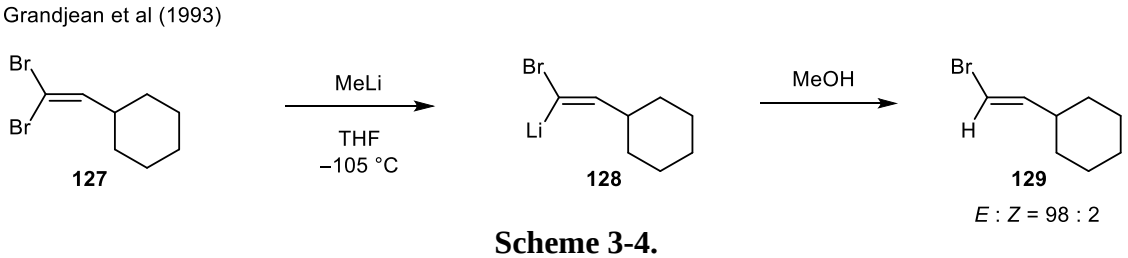
The author postulated that the bromocyclopentenol would be formed by a lithium carbenoid, which may be generated by the halogen-metal exchange reaction with an RLi, a small amount of which was remained after the preparation of the corresponding R_2CuLi (Scheme 3-3)[62].



Scheme 3-3.

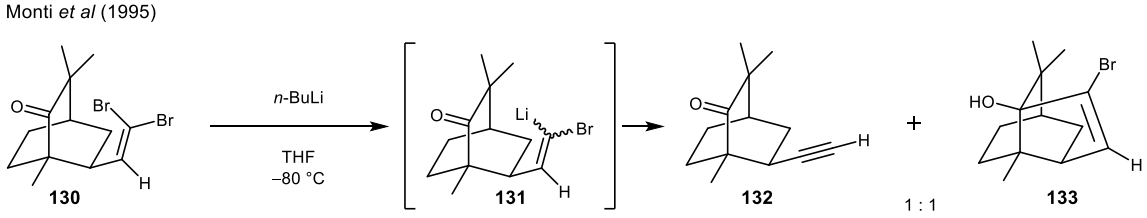
The halogen-metal exchange reaction is expected to occur at the less hindered bromine atom, giving rise to a Z-isomer of lithium carbenoid. In order to induce the intramolecular addition reaction, however, the geometry of the lithium carbenoid should be isomerized from Z to E form. In addition, this type of reaction may be accompanied with a rearrangement to give an alkyne, which is well known as Corey-Fuchs method.

Grandjean *et al*[63]. reported that a halogen-metal exchange reaction of a *gem*-dibromoalkene **127** with methyllithium at low temperature followed by quenching with methanol afforded the *E*-isomer of bromoalkene **129** predominantly (Scheme 3-4). The result indicated that the geometry of the lithium carbenoid can readily isomerize to E form.



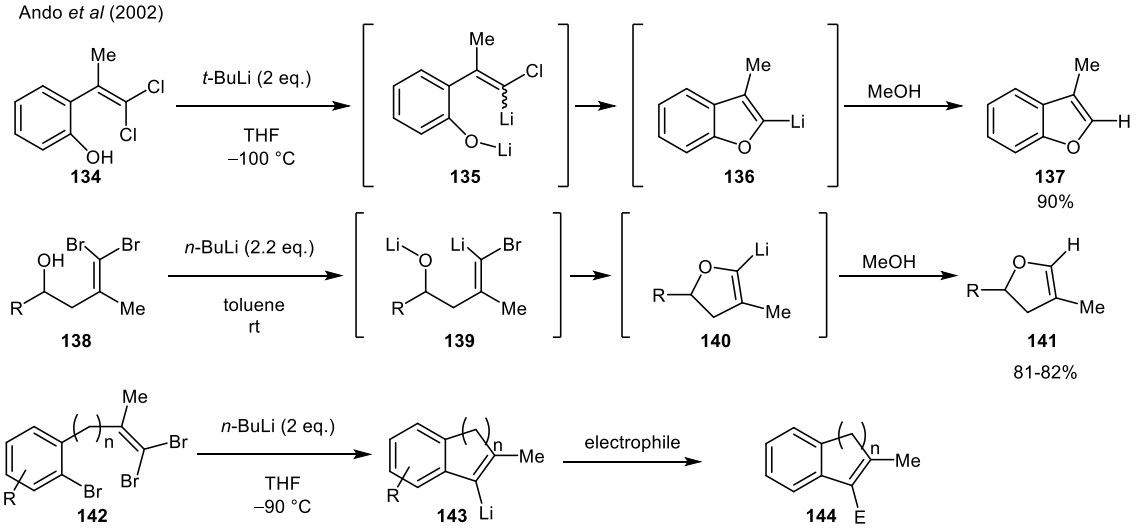
Scheme 3-4.

There is only one example of a similar intramolecular addition reaction of a lithium carbenoid possessing a carbonyl group which was reported by Monti *et al*. (Scheme 3-5)[64]. They expected to obtain the corresponding alkyne through Corey-Fuchs method, but the product was found to be a 1:1 mixture of the desired alkyne **132** and an unexpected alcohol **133** arising from the intramolecular addition reaction.



Scheme 3-5.

On the other hand, Ando *et al.* reported the cyclization reaction of *gem*-dihaloalkene derivatives under the influence of an alkyllithium (Scheme 3-6)[62g, 62h]. From the viewpoint of a reaction mechanism, these examples are to be categorized to the insertion reaction of carbenoids with anionic species.

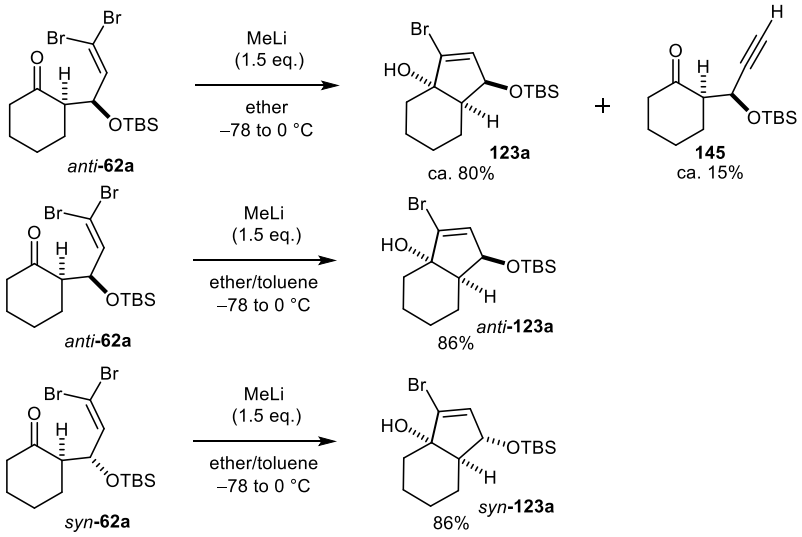


Scheme 3-6.

The information led the author to explore the cyclization reactions of the ketones possessing a *gem*-dibromoalkene moiety, the preparation of which was described in Chapter 1

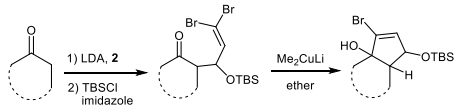
3.2 Synthesis of bromocyclopentenol derivatives by cyclization reactions of ketones possessing a *gem*-dibromoalkene moiety

At first, ketone *anti*-**62a** was treated with MeLi at -78 °C, and the reaction mixture was allowed to warm up to 0 °C. The product was obtained as a mixture of the desired bromocyclopentenol **123a** (80%) and alkyne **145** (15%). After several explorations, toluene was found to be a solvent of choice for reducing the formation of alkyne. While the reaction was conducted in a mixture of toluene and ether, which came from the ethereal solution of methyllithium, the desired product was obtained in 86% isolated yield. The corresponding diastereomeric substrate *syn*-**62a** also underwent a smooth cyclization reaction, giving rise to *syn*-**123a** in the same yield.



Scheme 3-7.

Then, the scope of the new cyclization reaction was investigated (Table 3-1). The substrates were reacted with MeLi (1.5 equivalent) at -78 °C under vigorous stirring for 10 minutes. After gradual warming to 0 °C, the mixture was stirred for additional 30 minutes. All ketone substrates, which were prepared in Chapter 1, were converted to the corresponding bromocyclopentenol derivatives in good yield (Table 3-1, entries 1-10). Acetophenone (**62i**) gave the monocyclic product with lower stereoselectivity than that in the reaction with a Gilman reagent (Table 3-1, entry 8). The advantage of the present cyclization reaction is the applicability to conjugated enones which could not be used in the reactions with a Gilman reagent. Thus, cyclohexenone (**62l**), 3-methylcyclohexanone (**62m**), ionone, and methyl styryl ketone were transformed into the corresponding bromocyclopentenol derivatives, respectively.



Ketone **62b-o** Cyclization Precursor **64b-o** Cyclization Product **123b-o**

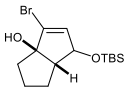
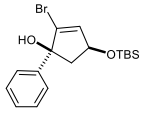
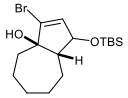
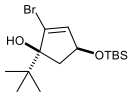
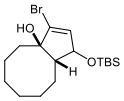
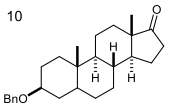
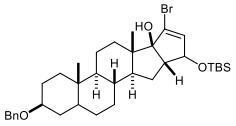
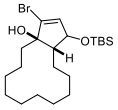
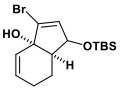
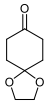
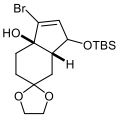
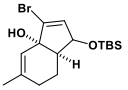
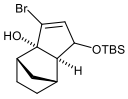
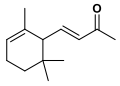
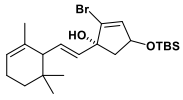
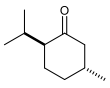
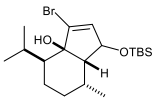
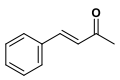
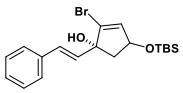
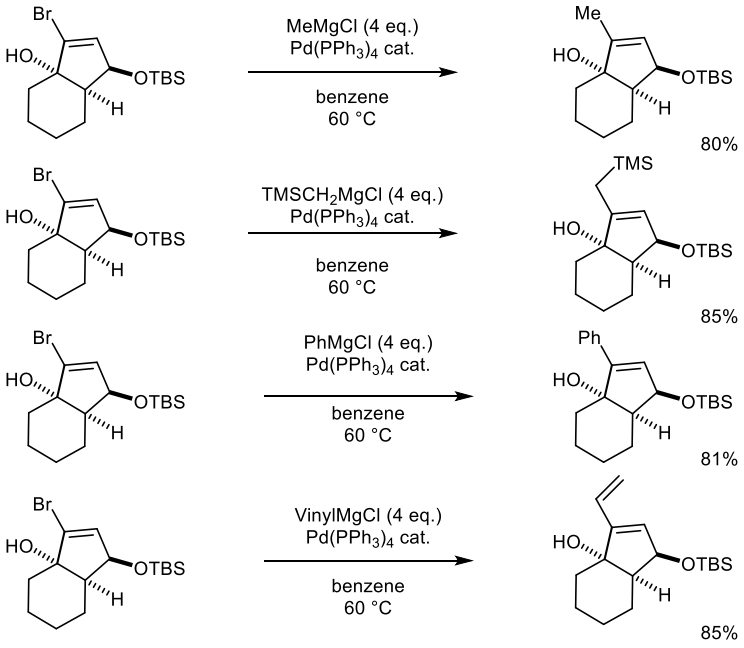
entry	ketone	cyclization product	Yield of **123** (%)	dr of **123**	entry	ketone	cyclization product	Yield of **123** (%)	dr of **123**
1			96	2:1	8			95	3:1
2			86	3:1	9			86	3:1
3			92	2:1	10			71	-
4			65	2.5:1	11			83	5:1
5			99	2:1	12			69	5:1
6			87	2:1	13			96	4:1
7			85	>10:1	14			88	5:4

Table 3-1.

Therefore, the utilities of the new cyclization reaction are summarized as follows: (1) The use of only 1.5 equivalents of MeLi led to completion of the reaction. (2) Conjugated enones can be used as a starting material. (3) The bromoalkene moiety of the cyclization product show promise for the installation of various substituents.

Indeed, the coupling reactions of bromocyclopentenol **123a** indicated the utility of the products (Scheme 3-8). Thus, methyl, (trimethylsilyl)methyl, phenyl, and vinyl groups were successfully introduce to the cyclopentene ring by the Kumada coupling using the corresponding Grignard reagents.


Br
HO
OTBS
H
MeMgCl (4 eq.)
Pd(PPh3)4 cat.
benzene
60 °C
Me
80%
TMSCH2MgCl (4 eq.)
TMS
85%
PhMgCl (4 eq.)
Ph
81%
VinylMgCl (4 eq.)
85%

Scheme 3-8.

Conclusion

In the present thesis, the author described the development of a new cyclization reaction via alkenylcopper species and its application for the total synthesis of a natural product. Furthermore, the corresponding lithium carbenoid was also found to undergo an intramolecular cyclization reaction, which can overcome some drawbacks of the cyclization reaction of alkenylcopper species.

In Chapter 1, the author applied the method for generating a Z-alkenylcopper species, which had been reported by the author's laboratory, to the synthesis of cyclopentenol derivatives. At first, the large-scale synthesis of 3,3-dibromoacrolein was achieved in two steps from CBr_4 and vinyl acetate. The cyclization precursors were prepared from ketones through an aldol reaction with 3,3-dibromoacrolein followed by silylation of the hydroxy group. Upon treatment with a Gilman reagent, the *gem*-dibromoalkene moiety of the substrate was converted to a Z-alkenylcopper species which underwent an addition reaction with the ketone moiety, giving rise to a cyclopentenol derivative. The transformation was applicable to a wide range of alicyclic and cyclic ketones.

In Chapter 2, the author described the total synthesis of a sesquiterpene which has a hydroazulene skeleton, with a view to demonstrating the utility of the cyclization reaction described in Chapter 1. The total synthesis started with the regioselective one-carbon ring expansion of dihydrocarvone for preparing a cycloheptanone derivative. The transformation was achieved based on the Trost's protocol, that is, an addition reaction with MT-sulfone followed by the rearrangement reaction mediated by $EtAlCl_2$. The resulting α-methylthio ketone was converted to an enol silyl ether which was subjected to the Mukaiyama aldol reaction with 3,3-dibromoacrolein. After silylation of the hydroxy group, the cyclization reaction was conducted by the treatment with a Gilman reagent, giving rise to the desired bicyclic compound which was converted to the desired natural product in two steps. The nine-step total synthesis in 9.9% overall yield showed the utility of the new cyclization reaction of alkenylcopper species.

In Chapter 3, an alternative cyclization reaction of the common substrates in Chapter 1 was developed based on a lithium carbenoid chemistry. Upon treatment with 1.5 equivalents of methyllithium, the *gem*-dibromoalkene moiety of the substrate was converted to a lithium carbenoid which underwent an addition reaction with the ketone moiety. The wide range of

applicability to various ketones involving conjugated enones makes the new cyclization reaction more useful than the cyclization reaction in Chapter 1. Furthermore, the resulting bromocyclopentenol derivative was found to be a good substrate of Kumada coupling reactions with Grignard reagents.

These findings by the author would certainly contribute to the improvement of synthetic organic chemistry, organometallic chemistry, and natural product chemistry.

Experimental and Characterization Details

General experimental techniques

All reactions involving air or moisture sensitive compounds were performed using flame-dried glassware, a round bottom flask with appropriate number of necks and side arms connected, under a positive pressure of argon.

Physical data

^{1}H-NMR spectra were measured at 500 MHz using a JOEL ECA-500 instrument in $CDCl_3$ (δH 7.26). Chemical shifts are reported in parts per million (ppm), and signal are expressed as singlet (s), doublet (d), triplet (t), quartet (q), septet (sept), and multiplet (m). Coupling constants are reported in Hz. ^{13}C-NMR spectra were measured at 125 MHz using the same instrument in $CDCl_3$ (δC 77.00).

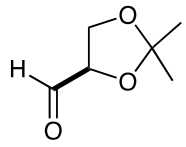
Chromatography

All reactions were monitored by thin layer chromatography with recoated silica gel plates (E. Merk, Silica gel 60F-254). Reaction components were visualized illumination with ultraviolet light (254 nm) and by staining with 6% ethanolic *p*-anisaldehyde (includes 6% conc. Sulfuric acid and 1% acetic acid), 8% ethanolic phosphor molybdic acid, or ceric ammonium molybdate in 10% sulfuric acid. Preparative TLC was carried out using Kanto Chemicals Co. Silica gel 60N (particle size 0.040-0.050 μm). Silica Gel 60N (Kanto Chemical Co., particle size 40–50 μm) was used for flash column chromatography.

Solvents and reagents

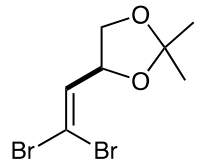
THF and diethyl ether were distilled from benzophenone ketyl immediately before use. Anhydrous CH_2Cl_2, NMP, toluene, and methanol were purchased from Kanto Chemicals Co. and Wako Pure Chemicals Co. Diisopropylethylamine and triethylamine were distilled from CaH_2 and stored over NaOH (s). All other reagents were used as obtained from commercial sources or were purified according to standard procedures.

(R)-2,2-Dimethyl-1,3-dioxolane-4-carbaldehyde (8)



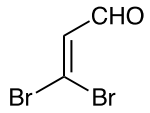
Aldehyde **8** was prepared from 1,2:5,6-di-O-isopropylidene- D-mannitol (6.60 g, 25.2 mmol) in 83% yield (5.74 g, 40.8 mmol) according to the known procedure.[1)] The spectral data was identical with that in the literature. Colorless oil; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 9.72 (1H, d, J = 1.1 Hz), 4.38 (1H, q, J = 2.1 Hz), 4.17 (1H, m), 4.10 (1H, m), 1.49-1.36 (6H, m).

(S)-4-(2,2-Dibromovinyl)-2,2-dimethyl-1,3-dioxolane (9)



To a solution of CBr_4 (20.3 g, 61.2 mmol) and PPh_3 (32.1 g, 122 mmol) in CH_2Cl_2 (150 mL) was added dropwise pyridine (13.2 mL, 163 mmol) at 0 °C. The mixture was stirred for 5 min at 0 °C, and to this was added aldehyde **8** (5.74 g, 40.8 mmol) in CH_2Cl_2 (50 mL). The resulting dark violet solution was stirred for 1 h at room temperature and concentrated in vacuo. Purification by the column chromatography gave compound **9** (9.58 g, 33.5 mmol) in 82% yield. The spectral data was identical to that in the literature.[2)] Colorless oil; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 6.53 (1H, d, J = 7.4 Hz), 4.73 (1H, d, J = 6.3 Hz), 4.18 (1H, d, J = 6.3 Hz), 3.69 (1H, m), 1.42-1.38 (6H, m).

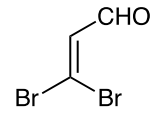
3,3-Dibromoacrolein (11)



To a mixture of compound **9** (9.58 g, 33.5 mmol), water (50 mL), and THF (100mL) was added trifluoroacetic acid (40 mL) at 0 °C. The solution was stirred at room temperature for 16 h and was quenched with triethylamine (50 mL) at 0 °C. The aqueous layer was saturated with an excess amount of NaCl and extracted with ethyl acetate (150 mL). The solution was dried over $MgSO_4$ and concentrated in vacuo. The crude diol **10** was used in the next step without further purification.

To a cooled (0 °C) mixture of the diol, a saturated aqueous solution of $NaHCO_3$ (5 mL), and CH_2Cl_2 (70 mL) was added $NaIO_4$（15 g, 70 mmol）in portions. After being stirred for 1 h at room temperature, the reaction mixture was passed through a short pad of silica gel which was eluted with hexane-ether (3:1, 200 mL). Concentration in vacuo gave aldehyde **11** (4.79 g, 22.4 mmol) in 67% yield (2 steps). The spectral data was identical to that in the literature.[3)] Yellow oil; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 9.69 (1H, d, J = 6.3 Hz), 6.98 (1H, d, J = 6.3 Hz).

Refines synthesis route of 11



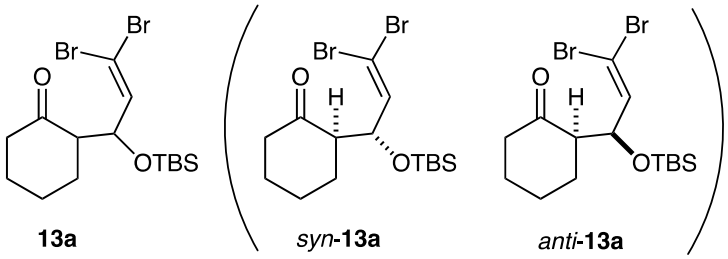
To the CBr_4 () was added NaOAc() and vinyl acetate as a solvent (). The suspension was stirred vigorously and irradiated by the fluorescent light (30W). The reaction mixture gradually showed exotherm to 30-40 °C in 30 minutes and stirred further 2 hours until the mixture got cool down. The suspension was filtered and evaporated in vacuo to remove vinyl acetate. Then, the solution was added ethyl acetate (50 mL×2) and evaporated to remove vinyl acetate azeotropicly. To the resulted solution was added 5% H2SO4 aq. (300 mL) and warmed up to 115 °C Following steam-distillation gave desired aldehyde in water. Sat. $NaHCO_3$ aq. was added and resulted suspension was extracted with ether twice. Evaporation of organic phase gave @ in 91% yield.

General procedure for the synthesis of ketones 13a-k (Table 2)

Ketone (1.0 eq.) was added to a cooled (-78 °C) solution of LDA (1.1 eq.) in THF (0.1 M), which was prepared from diisopropylamine (1.1 eq.) and a hexane solution of *n*-BuLi (1.1 eq.) at 0 °C. After 1 h, dibromoacrolein (**11**) was added, and the mixture was stirred for 5 min. The reaction was quenched with 10% AcOH in THF, and the mixture was wormed up to room temperature. A saturated aqueous NH_4Cl solution was added, and the aqueous layer was extracted with ether and dried over $MgSO_4$. Concentration in vacuo gave a crude aldol adduct which was used in the next step without father purification.

A solution of the adduct and imidazole (6 eq.) in DMF (0.1 M) was cooled to 0 °C, and TBSCl (5 eq.) was added in portions. After being stirred for 16 h at room temperature, the mixture was treated with methanol (>3 eq.) for 5 min. A saturated aqueous NH_4Cl solution was added slowly, and the aqueous layer was extracted with hexane-ethyl acetate (1:1). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. Purification through silica gel column chromatography gave the cyclization precursor **13**.

2-(3,3-Dibromo-1-((tert-butyldimethylsilyl)oxy)allyl)cyclohexanone (13a)

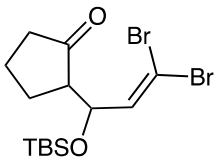


Ketone **13a** (715 mg, 1.68 mmol, 86%) was obtained as a 3:1 mixture of diastereomers from cyclohexanone (0.21 mL, 2.00 mmol), diisopropylamine (0.31 mL, 2.2 mmol), *n*-BuLi 2.65 M in hexane (0.83 mL, 2.2 mmol), TBSCl (1.59 g, 10.5 mmol), and imidazole (816 mg, 12.0 mmol) according to the general procedure described above. Further purification of the diastereomeric mixture by silica gel column chromatography provided each diastereomer *syn*-**13a** and *anti*-**13a** in small quantity which was used for the NMR analysis and the cyclization reactions.

syn-**13a**: White solid; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 6.37 (1H, d, *J* = 8.0 Hz), 4.77 (1H, dd, *J* = 4.0, 8.0 Hz), 2.30 (2H, m), 2.18 (1H, m), 1.97-1.91 (2H, m), 1.83 (1H, m), 1.73 (1H, q, *J* = 12.0 Hz), 1.60-1.53 (2H, m), 0.76 (9H, s), 0.01 (6H, m); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 209.29, 140.35, 88.92, 70.90, 55.25, 42.00, 26.80, 26.62, 25.71, 24.21, 17.97, -4.55, -5.16.

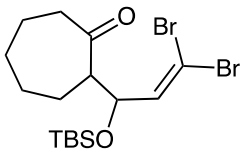
anti-**13a**: Yellow oil; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 6.33 (1H, d, *J* = 9.2 Hz), 4.54 (1H, d, *J* = 8.0, 9.2 Hz), 2.43-2.38 (1H, m), 2.31-2.18 (2H, m), 1.89-1.78 (3H, m), 1.67-1.46 (3H, m), 0.74 (9H, s), 0.00 (6H, s); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 209.78, 139.86, 90.10, 72.52, 56.43, 42.11, 29.67, 27.93, 25.67, 24.34, 17.95, -4.49, -5.09.

2-(3,3-Dibromo-1-((tert-butyldimethylsilyl)oxy)allyl)cyclopentanone (13b)



Ketone **13b** (804 mg, 1.95 mmol, 97%) was obtained as a 1.5:1 mixture of diastereomers from cyclopentanone (0.18 mL 2.00 mmol), diisopropylamine (0.31 mL, 2.2 mmol), *n*-BuLi 2.65 M in hexane (0.83 mL, 2.2 mmol), TBSCl (1.59 g, 10.5 mmol), and imidazole (0.82 g, 12 mmol) according to the general procedure described above. Yellow oil; ^{1}H-NMR ($CDCl_3$) δ: 6.88 (1.5H, d, *J* = 8.0 Hz), 6.41 (1H, d, *J* = 8.0 Hz), 4.82 (1H, dd, *J* = 8.0, 2.3 Hz), 4.43 (1.5H, dd, *J* = 8.0, 3.8 Hz), 2.32-1.92 (14H, m), 1.78-1.72 (3.5H, m), 0.88-0.80 (22.5H, m), 0.04 (15H, m); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 217.79, 217.73, 140.00, 139.91, 88.56, 73.42, 71.78, 53.21, 53.14, 39.51, 38.98, 31.54, 26.54, 25.66, 25.60, 22.61, 22.51, 21.00, 20.91, 17.93, 17.89, 14.09, -4.49, -4.67, -5.16, -5.45.

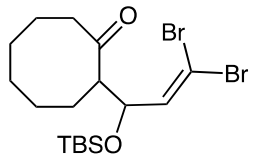
2-(3,3-Dibromo-1-((tert-butyldimethylsilyl)oxy)allyl)cycloheptanone (13c)



Ketone **13c** (746 mg, 1.70 mmol, 84%) was obtained as a 1:1 mixture of diastereomers from cycloheptanone (0.236 mL, 2.00 mmol), diisopropyl- amine (0.31 mL, 2.2 mmol), *n*-BuLi 2.65 M in hexane (0.83 mL, 2.2 mmol), TBSCl (1.59 g, 10.5 mmol), and imidazole (0.82 g, 12 mmol) according to the general procedure described above. Yellow oil; ^{1}H-NMR ($CDCl_3$) δ: 6.46 (1H, d, *J* = 8.0 Hz), 6.37 (1H, d, *J* = 9.2 Hz), 4.67 (1H, dd, *J* = 9.2, 4.2 Hz), 4.56 (1H, dd, *J* = 8.0, 7.4 Hz), 2.67-2.63 (1H, m), 2.57-2.40 (3H, m), 2.01-1.97 (1H, m), 1.89 (7H, dt, *J* = 14.7, 4.7 Hz), 1.76-1.20 (10H,

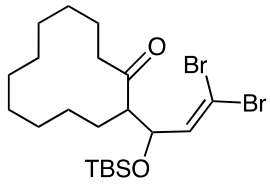
m), 0.84 (18H, m), 0.05 (12H, m); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 214.11, 213.17, 140.04, 139.74, 90.29, 89.12, 75.11, 74.56, 57.94, 57.85, 44.40, 44.02, 30.22, 28.79, 28.46, 28.42, 27.32, 26.68, 25.65, 25.03, 24.75, 24.25, 17.92, -4.54, -4.66, -5.27.

2-(3,3-Dibromo-1-((tert-butyldimethylsilyl)oxy)allyl)cyclooctanone (13d)



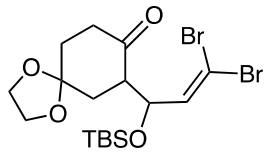
Ketone **13d** (771 mg, 1.69 mmol, 84%) was obtained as a 1.1:1 mixture of diastereomers from cyclooctanone (252 mg, 2.00 mmol), diisopropyl- amine (0.31 mL, 2.2 mmol), *n*-BuLi 2.65 M in hexane (0.83 mL, 2.2 mmol), TBSCl (1.59 g, 10.5 mmol), and imidazole (0.82 g, 12 mmol) according to the general procedure described above. Yellow oil; ^{1}H-NMR ($CDCl_3$) δ: 6.52 (1H, d, *J* = 8.6 Hz), 6.31 (0.8H, d, *J* = 8.6 Hz), 4.55 (0.8H, t, *J* = 8.6 Hz), 4.43 (1H, dd, *J* = 8.6, 6.9 Hz), 2.91-2.87 (2H, m), 2.40-2.27 (3.6H, m), 2.01-1.90 (3H, m), 1.81-1.24 (16.8H, m), 0.87 (9H, d, *J* = 13.2 Hz), 0.81 (7.2H, d, *J* = 9.2 Hz), 0.05 (10.8H,m); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 217.35, 217.05, 139.89, 139.50, 90.99, 90.34, 75.61, 74.82, 55.74, 54.95, 45.31, 44.35, 30.17, 29.32, 28.30, 27.88, 25.72, 25.63, 25.54, 24.83, 24.78, 24.72, 24.31, 22.73, 17.98, 17.88, -4.45, -4.59, -5.06, -5.45.

2-(3,3-Dibromo-1-((tert-butyldimethylsilyl)oxy)allyl)cyclododecanone (13e)



Ketone **13e** (880 mg, 1.72 mmol, 86%) was obtained as a 1:1 mixture of diastereomers from cyclododecanone (364 mg, 2.00 mmol), diisopropyl- amine (0.31 mL, 2.2 mmol), *n*-BuLi 2.67 M in hexane (0.82 mL, 2.2 mmol), TBSCl (1.59 g, 10.5 mmol), and imidazole (0.82 g, 12 mmol) according to the general procedure described above. Yellow oil; ^{1}H-NMR ($CDCl_3$) δ: 6.33 (1H, d, *J* = 8.6 Hz), 6.29 (1H, d, *J* = 8.6 Hz), 4.44 (2H,m), 3.06-3.02 (1H, m), 2.76 (2H, dt, *J* = 11.5, 4.7 Hz), 2.63 (1H, td, *J* = 11.3, 5.3 Hz), 2.49 (1H, dt, *J* = 16.4, 6.3 Hz), 2.32 (1H, ddd, *J* = 15.6, 9.3, 3.3 Hz), 1.77 (6H, m), 1.27 (30H, m), 0.86 (18H,m), 0.14-0.05 (12H, m);^{13}C-NMR (125 MHz, $CDCl_3$) δ: 212.52, 212.32, 139.70, 139.06, 91.25, 90.68, 75.09, 74.00, 57.21, 55.86, 42.69, 41.38, 26.46, 26.31, 26.11, 25.76, 25.69, 25.64, 25.59, 25.52, 25.20, 25.11, 24.81, 24.47, 24.45, 24.29, 23.78, 23.40, 22.38, 22.31, 21.65, 17.98, 17.89, -4.41, -5.12, -5.31.

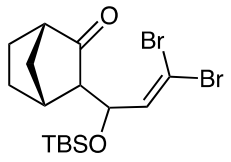
7-(3,3-Dibromo-1-((tert-butyldimethylsilyl)oxy)allyl)-1,4-dioxaspiro[4.5]decan-8-one (13f)



Ketone **13f** (646 mg, 1.33 mmol, 67%) was obtained as a 2:1 mixture of diastereomers from 1,4-cyclohexanedione monoacetal (312 mg, 2.00 mmol), diisopropylamine (0.31 mL, 2.2 mmol), *n*-BuLi 2.67 M in hexane (0.82 mL, 2.2 mmol), TBSCl (1.59 g, 10.5 mmol), and imidazole (0.82 g, 12 mmol) according to the general procedure described above. Colorless oil; ^{1}H-NMR ($CDCl_3$) δ: 6.53 (2H, d, *J* = 8.6 Hz), 6.40 (1H, d, *J* = 8.0 Hz), 4.99 (1H, dd, *J* = 8.0, 2.9 Hz), 4.60 (2H, dd, *J* = 8.6, 6.3 Hz), 4.08-4.01 (12H, m), 2.89-2.84 (2H, m), 2.65-2.57 (4H, m), 2.39 (4H,m), 2.23 (1H, m), 2.05-1.86 (10H, m), 0.86 (27H, m), 0.13-0.06 (18H, m); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 207.76, 207.15, 139.63, 139.32, 107.60, 107.23, 90.08, 89.08, 72.05, 70.42, 64.73, 64.62, 64.47, 52.04, 51.30, 38.40, 38.04, 36.65, 34.52, 33.44, 33.28, 25.61, 17.85, -4.59, -4.67, -5.16, -5.25.

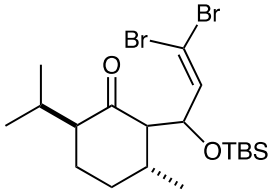
3-(3,3-Dibromo-1-((tert-butyldimethylsilyl)oxy)allyl)bicyclo[2.2.1]heptan-2-one

(13g)



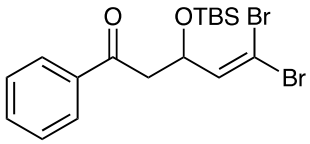
Ketone **13g** (846 mg, 1.94 mmol, 97%) was obtained as a 2:1 mixture of diastereomers from 2-norbornanone (220 mg, 2.00 mmol), diisopropylamine (0.31 mL, 2.2 mmol), *n*-BuLi 2.67 M in hexane (0.82 mL, 2.2 mmol), TBSCl (1.59 g, 10.5 mmol), and imidazole (0.82 g, 12 mmol) according to the general procedure described above. Colorless oil; ^{1}H-NMR ($CDCl_3$) δ: 6.70 (2H, d, *J* = 8.6 Hz), 6.51 (1H, d, *J* = 8.0 Hz), 4.67 (1H, dd, *J* = 8.0, 4.2 Hz), 4.51 (2H, dd, *J* = 8.6, 4.4 Hz), 2.53 (6H,m), 2.25 (1H, d, *J* = 10.3 Hz), 2.18 (2H,m), 1.90 (2H, m), 1.80 (8H,m), 1.47 (8H, m, 10.8 Hz), 0.89 (27H, m), 0.09 (18H, m); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 215.35, 140, 139.89, 88.88, 88.64, 73.72, 72.29, 57.70, 57.44, 49.25, 48.68, 39.20, 36.54, 35.59, 35.55, 31.51, 28.70, 28.68, 25.69, 25.64, 25.48, 23.97, 23.92, 22.57, 17.93, 17.86, 14.07, -4.63, -4.74, -4.98, -5.33.

2-(3,3-Dibromo-1-((*tert*-butyldimethylsilyl)oxy)allyl)-6-isopropyl-3-methylcyclohexanone (13h)



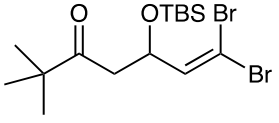
Ketone **13h** (829 mg, 1.72 mmol, 86%) was obtained as a >10:1 mixture of diastereomers from L-menthone (0.345 mL, 2.00 mmol), diisopropylamine (0.31 mL, 2.2 mmol), *n*-BuLi 2.67 M in hexane (0.82 mL, 2.2 mmol), TBSCl (1.59 g, 10.5 mmol), and imidazole (0.82 g, 12 mmol) according to the general procedure described above. Colorless oil; ^{1}H-NMR ($CDCl_3$) δ: 7.09 (1H, d, *J* = 8.0 Hz), 4.50 (1H, dd, *J* = 8.0, 2.0 Hz), 2.24-2.15 (1H, m), 2.09 (1H, d, *J* = 11.5 Hz), 1.99-1.89 (4H, m), 1.47-1.29 (2H, m), 1.10 (3H, d, J = 6.3 Hz), 0.87 (4H, t, *J* = 4.9 Hz), 0.83 (9H, m), 0.79 (3H, d, *J* = 6.3 Hz), 0.05 (6H, m); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 209.00, 141.98, 86.99, 71.33, 62.05, 56.63, 35.78, 34.19, 31.55, 26.17, 25.90, 25.83, 25.66, 22.61, 21.09, 20.46, 18.29, 17.89, 14.09, -4.23, -5.25, -5.83.

5,5-Dibromo-3-((tert-butyldimethylsilyl)oxy)-1-phenylpent-4-en-1-one (13i)



Ketone **13i** (740 mg, 1.65 mmol, 83%) was obtained from acetophenone (0.232 mL, 2.00 mmol), diisopropylamine (0.31 mL, 2.2 mmol), *n*-BuLi 2.67 M in hexane (0.82 mL, 2.2 mmol), TBSCl (1.59 g, 10.5 mmol), and imidazole (0.82 g, 12 mmol) according to the general procedure described above. Colorless oil; ^{1}H-NMR ($CDCl_3$) δ: ^{1}H -NMR ($CDCl_3$) δ: 7.95 (2H, t, *J* = 4.3 Hz), 7.56 (1H, t, *J* = 7.4 Hz), 7.46 (2H, t, *J* = 7.4, 4.3 Hz), 6.53 (1H, d, *J* = 8.0 Hz), 4.98 (1H, ddd, *J* =8.4, 8.0, 3.8 Hz), 3.35 (1H, dd, *J* = 15.2, 8.4 Hz), 2.93 (1H, dd, *J* = 15.2, 3.8 Hz), 0.77 (9H, s), 0.06 (3H, s), -0.03 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 197.08, 140.92, 137.27, 133.13, 128.53, 128.36, 89.31, 70.81, 44.89, 25.57, 17.88, -4.72, -5.26.

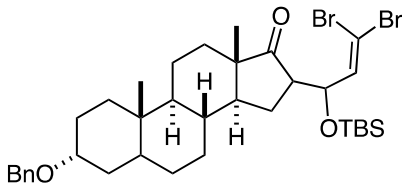
7,7-Dibromo-5-((tert-butyldimethylsilyl)oxy)-2,2-dimethylhept-6-en-3-one (13j)



Ketone **13j** (482 mg, 1.14 mmol, 57%) was obtained from pinacolin (0.247 mL, 2.00 mmol), diisopropylamine (0.308 mL, 2.2 mmol), *n*-BuLi 2.67 M in hexane (0.82 mL, 2.2 mmol), TBSCl (1.59 g, 10.5 mmol), and imidazole (0.82 g, 12 mmol) according to the general procedure described above. Yellow oil; ^{1}H-NMR ($CDCl_3$) δ: 6.46 (1H, d, *J* = 8.0 Hz), 4.90-4.87 (1H, ddd, *J* = 8.4, 8.0, 3.2 Hz), 2.94 (1H, dd, *J* = 15.0, 8.4 Hz), 2.35 (1H, dd, *J* = 15.0, 3.2 Hz), 1.12 (9H, s), 0.83 (9H, t, *J* = 2.9 Hz), 0.07 (6H, dt, *J* = 10.9, 4.6 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 211.39, 141.16, 88.62, 69.98, 44.16,

42.79, 25.93, 25.81, 25.66, 17.86, -4.77, -5.12.

Androsteron derivative 13k



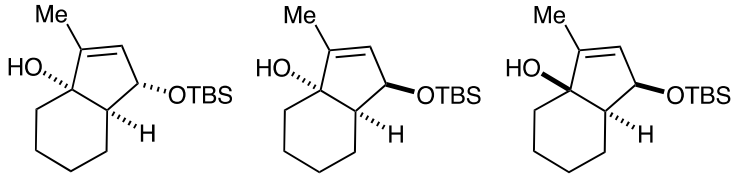
Ketone **13k** (215 mg, 0.30 mmol, 86% (68% after recrystallization)) was obtained from 3-benzyloxyepiandro- sterone (224 mg, 0.590 mmol), diisopropylamine (91 µL, 0.65 mmol), *n*-BuLi 2.67 M in hexane (0.243 mL, 0.65 mmol), TBSCl (0.42 g, 2.8 mmol), and imidazole (0.21 g, 3.1 mmol) according to the general procedure described above. The obtained solid was recrystallized from hexane.

White solid; ^{1}H-NMR ($CDCl_3$) δ: 7.22 (5H, m), 6.90 (1H, d, *J* = 8.6 Hz), 4.47 (2H, s), 4.38 (1H, dd, *J* = 8.6, 2.9 Hz), 3.28-3.24 (1H, m), 2.56 (1H, t, *J* = 4.6 Hz), 1.85 (1H, d, *J* = 12.6 Hz), 1.76-1.09 (17H, m), 0.98 (1H, t, *J* = 11.7 Hz), 0.79 (9H, s), 0.77 (3H, d, *J* = 5.2 Hz), 0.76 (3H, d, J = 4.6 Hz), 0.53 (1H, q, J = 7.4 Hz), 0.00 (3H, s), -0.03 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 218.60, 140.76, 139.12, 128.31, 127.50, 127.34, 87.85, 76.76, 75.67, 69.75, 54.63, 50.00, 49.43, 48.86, 44.92, 36.90, 35.95, 35.13, 34.77, 30.88, 28.54, 28.17, 27.49, 25.81, 22.64, 20.35, 17.89, 14.58, 12.29, -4.51, -4.95.

General procedure for the vinyl-copper cyclization reaction

To a cooled (-78 °C) suspension of CuI (5 eq.) in ether (0.1 M) was dropwise added an ethereal solution of MeLi (10 eq.). The mixture was warmed up to 0 °C and stirred for 10 min. The resulting clear solution was cooled to appropriate temperature, and a ketone substrate in ether (0.1 M) was added. The mixture was warmed up to 0 °C immediately and stirred for 10 min at the temperature. The reaction was quenched with a saturated aqueous NH_4Cl solution. The mixture was filtered through a short pad of Celite, and the aqueous layer was extracted with ether. Concentration in vacuo and purification by silica gel column chromatography gave the desired cyclopentenol derivative.

7-((*tert*-Butyldimethylsilyl)oxy)-9-methylbicyclo[4.3.0]non-8-en-1-ol (14a)



syn-cis-**14a** *anti-cis*-**14a** *anti-trans*-**14a**

The reaction of a 3:1 diastereomeric mixture of **13a** (426 mg, 1.00 mmol) by using CuI (952 mg, 5.00 mmol) and a 1.17 M ethereal solution of MeLi (8.55 mL, 10.0 mmol) according to the general procedure described above afforded a 2.5:1 mixture of *anti-cis*-**14a** and *syn-cis*-**14a** (232 mg, 0.820 mmol, 86%) along with *anti-trans*-**14a** (8 mg, 0.028 mmol, 3%).

On the other hand, *syn-cis*-**14a** (51 mg, 0.18 mmol, 91%) was obtained as a single product starting from *syn*-**13a** (85 mg, 0.20 mmol), CuI (190 mg, 1.00 mmol), and a 1.11 M ethereal solution of MeLi (1.8 mL, 2.0 mmol).

syn-cis-**14a** Yellow oil; ^{1}H-NMR ($CDCl_3$) δ: 5.37 (1H, s), 4.11 (1H, s), 1.98 (1H, s), 1.77 (1H, m), 1.62 (6H, m), 1.52-1.43 (2H, m), 1.35-1.30 (2H, m), 1.19-1.05 (2H, m),

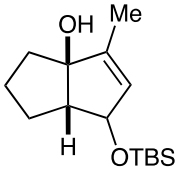
0.81 (9H, s), 0.00 (6H, m); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 149.16, 128.54, 81.24, 76.74, 55.15, 32.75, 25.87, 25.45, 23.26, 21.76, 18.08, 11.68, -4.61, -4.77.

The reaction of *anti*-**13a** (85 mg, 0.20 mmol) with CuI (190 mg, 1.00 mmol) and MeLi 1.11M in ether (1.8 mL, 2.0 mmol) afforded *anti-cis*-**14a** (49 mg, 0.17 mmol, 86%) and *anti-trans*-**14a** (1.7 mg, 0.0060 mmol, 3%).

anti-cis-**14a** Yellow oil; ^{1}H-NMR ($CDCl_3$) δ: 5.47 (1H, s), 4.86 (1H, s), 2.04 (1H, m), 1.80-1.59 (8H, m), 1.41-1.22 (4H, m), 0.90 (9H, s), 0.08 (6H, m); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 146.95, 130.96, 82.70, 76.28, 51.19, 34.53, 25.90, 24.15, 23.87, 22.13, 18.18, 11.59, -4.61, -4.79.

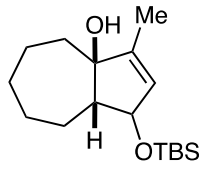
anti-trans-**14a** Yellow oil; ^{1}H-NMR ($CDCl_3$) δ: 5.57 (1H, s), 4.39 (1H, s), 2.25 (1H, d, *J* = 2.9 Hz), 1.90-1.70 (6H, m), 1.66 (1H, m), 1.50 (3H, m), 1.30-1.16 (3H, m), 0.87 (9H, m), 0.04 (6H, m); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 152.70, 128.90, 80.43, 75.96, 52.94, 31.49, 25.82, 25.66, 21.73, 21.22, 18.02, 12.02, -4.48, -4.91.

4-((*tert*-Butyldimethylsilyl)oxy)-2-methylbicyclo[3.3.0]oct-2-en-1-ol (14b)



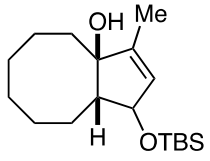
The reaction of a 1.5:1 diastereomeric mixture of **13b** (264 mg, 0.640 mmol) by using CuI (609 mg, 3.20 mmol) and a 1.17 M ethereal solution of MeLi (5.47 mL, 6.40 mmol) according to the general procedure described above afforded a 2:1 diastereomeric mixture of **14b** (136 mg, 0.50 mmol, 79%). Yellow oil; ^{1}H-NMR ($CDCl_3$) δ: 5.36 (0.5H, s), 5.33 (1H, s), 4.86 (1H, dt, *J* = 7.4, 1.7 Hz), 4.14 (0.5H, d, *J* = 1.1 Hz), 2.41 (1H, td, *J* = 8.3, 4.6 Hz), 2.16 (0.5H, t, *J* = 4.6 Hz), 2.03 (1H, dt, *J* = 10.7, 3.6 Hz), 1.90-1.80 (3H, m), 1.74 (1H, t, *J* = 1.4 Hz), 1.72 (3H, dd, *J* = 4.9, 3.7 Hz), 1.70-1.47 (3H, m), 0.88 (13.5H, m), 0.07 (3H, t, *J* = 3.2 Hz), 0.05 (6H, s); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 146.23, 144.46, 131.3, 129.61, 95.6, 93.69, 81.98, 74.89, 61.04, 54.82, 38.28, 36.55, 31.63, 26.52, 26.40, 25.98, 25.93, 25.63, 25.46, 18.33, 11.95, 11.54, -4.50, -4.58, -4.74, -4.91.

8-((*tert*-Butyldimethylsilyl)oxy)-10-methylbicyclo[5.3.0]dec-9-en-1-ol (14c)



The reaction of a 1:1 diastereomeric mixture of **13c** (251 mg, 0.570 mmol) by using CuI (542 mg, 2.85 mmol) and a 1.17 M ethereal solution of MeLi (4.87 mL, 5.70 mmol) according to the general procedure described above afforded a 1.2:1 diastereomeric mixture of **14c** (130 mg, 0.44 mmol, 77%). Colorless oil; ^{1}H-NMR ($CDCl_3$) δ: 5.44 (2.2H, s), 4.67 (1H, d, *J* = 6.3 Hz), 4.24 (1.2H, d, *J* = 1.7 Hz), 2.17-2.14 (1.2H, m), 1.99 (1.2H, m), 1.91-1.27 (30.6H, m), 0.88 (19.8H, m), 0.09-0.03 (13.2H, m); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 147.57, 147.52, 129.76, 129.22, 87.30, 86.34, 79.89, 75.27, 62.22, 57.03, 35.38, 34.57, 31.98, 31.38, 29.49, 27.53, 27.4, 26.63, 25.93, 25.91, 23.18, 22.77, 22.63, 18.25, 18.13, 14.10, 11.60, 11.57, -4.46, -4.48, -4.57, -4.90.

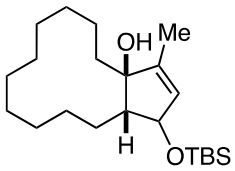
9-((*tert*-Butyldimethylsilyl)oxy)-11-methylbicyclo[6.3.0]undec-10-en-1-ol (14d)



The reaction of a 1.1:1 diastereomeric mixture of **13d** (227mg, 0.50mmol) by using CuI (476mg, 2.50 mmol) and a 1.17 M ethereal solution of MeLi (4.27 mL, 5.00 mmol) according to the general procedure described above afforded a 1:1 diastereomeric mixture of **14d** (132 mg, 0.425 mmol, 85%). Yellow oil; ^{1}H-NMR ($CDCl_3$) δ: 5.61 (1H, s), 5.46 (1H, s), 4.30 (1H, q, *J* = 2.3 Hz), 4.15 (1H, s), 2.15 (1H, s), 1.95 (1H, m), 1.91-1.35 (24H, m), 0.88 (18H, t, *J* = 9.5 Hz), 0.08-0.04 (12H, m); ^{13}C-NMR (125 MHz, CDCl3) δ: 152.43, 149.65, 129.37, 128.48, 84.77, 82.68, 82.18, 77.52, 59.95, 49.31, 35.01,

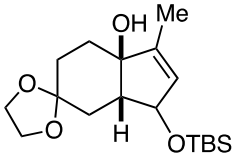
31.57, 29.44, 29.22, 28.89, 28.51, 25.89, 25.83, 25.38, 23.60, 23.40, 22.63, 21.58, 18.06, 17.98, 14.09, 12.72, 12.26, -4.23, -4.48, -4.67, -4.92.

13-((*tert*-Butyldimethylsilyl)oxy)-15-methylbicyclo[10.3.0]pentadec-14-en-1-ol (14e)



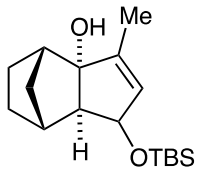
The reaction of a 1.1:1 diastereomeric mixture of **13e** (102 mg, 0.200 mmol) by using CuI (190 mg, 1.00 mmol) and a 1.11 M ethereal solution of MeLi (1.80 mL, 2.00 mmol) according to the general procedure described above afforded a 2.5:1 diastereomeric mixture of **14e** (132 mg, 0.425 mmol, 65%). Yellow oil; ^{1}H-NMR ($CDCl_3$) δ: 5.66 (2.5H, s), 5.47 (1H, s), 4.41 (2.5H, s), 4.19 (1H, s), 2.46 (1H, dd, *J* = 12.6, 4.0 Hz), 1.97 (2.5H, q, *J* = 5.0 Hz), 1.84 (1H, d, *J* = 8.6 Hz), 1.77-1.66 (20.5H, m), 1.55-1.26 (60H, m), 1.07-0.98 (2.5H, m), 0.97-0.80 (31.5H, m), 0.78-0.72 (1H, m), 0.12--0.01 (21H, m); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 150.09, 130.8, 128.23, 86.92, 85.01, 79.52, 73.73, 56.65, 44.33, 31.57, 30.33, 29.28, 27.24, 26.75, 26.72, 26.40, 26.20, 25.87, 25.78, 25.67, 24.47, 24.40, 24.02, 23.99, 22.63, 22.47, 22.23, 21.79, 21.58, 20.55, 19.48, 17.97, 17.92, 17.84, 14.09, 12.57, 12.33, -4.10, -4.53, -4.65, -5.02.

3-((tert-Butyldimethylsilyl)oxy)-1-methyl-3a,4,6,7-tetrahydrospiro[indene-5,2'-[1,3]dioxolan]-7a(3H)-ol (14f)



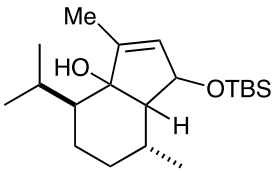
The reaction of a 2:1 diastereomeric mixture of **13f** (96.8 mg, 0.200 mmol) by using CuI (190 mg, 1.00 mmol) and a 1.11 M ethereal solution of MeLi (1.80 mL, 2.00 mmol) according to the general procedure described above afforded a 2:1 diastereomeric mixture of **14f** (68 mg, 0.20 mmol, 99%). Yellow oil; ^{1}H-NMR ($CDCl_3$) δ: 5.49 (2H, s), 5.43 (1H, s), 4.95 (2H, d, *J* = 6.3 Hz), 4.41 (1H, s), 3.96 (12H, m), 2.42-2.37 (2H, m), 2.08-1.49 (29H, m), 1.25 (1H, m), 0.86 (27H, m), 0.05 (18H,m); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 147.73, 143.81. 132.42, 128.79, 109.56, 108.94, 82.44, 80.22, 76.74, 75.46, 64.37, 64.18, 64.13, 55.63, 50.68, 32.97, 32.08, 30.98, 30.92, 30.47, 30.31, 25.89, 25.85, 18.19, 18.04, 11.65, 11.61, -4.56, -4.66, -4.73, -4.84.

1-((tert-Butyldimethylsilyl)oxy)-3-methyl-1,4,5,6,7,7a-hexahydro-3aH-4,7-methanoinden-3a-ol (14g)



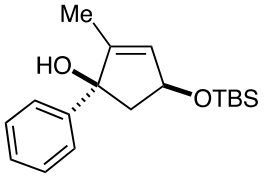
The reaction of a 2:1 diastereomeric mixture of **13g** (88 mg, 0.20 mmol) by using CuI (190 mg, 1.00 mmol) and a 1.11 M ethereal solution of MeLi (1.80 mL, 2.00 mmol) according to the general procedure described above afforded a 1.7:1 diastereomeric mixture of **14g** (42 mg, 0.1420 mmol, 71%). Yellow oil; ^{1}H-NMR (CDCl3) δ: 5.46 (1H, s), 5.40 (2H, s), 4.96 (2H, d, *J* = 8.0 Hz), 4.04 (1H, s), 2.34 (2H, d, *J* = 4.6 Hz), 2.17-2.10 (5H, m), 2.00 (2H, m), 1.88 (2H, m), 1.80 (2H, s), 1.72-1.25 (19H, m), 1.05 (5H, m), 0.90 (27H, m), 0.06 (18H, m); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 145.02, 143.42, 132.52, 131.04, 93.78, 91.85, 80.46, 76.38, 63.33, 57.05, 41.61, 41.20, 41.10, 37.60, 36.36, 35.06, 30.91, 28.36, 28.32, 26.00, 25.95, 25.84, 21.85, 21.48, 18.30, 11.83, 11.40, -4.46, -4.54, -4.62, -4.90.

7-((*tert*-Butyldimethylsilyl)oxy)-2-isopropyl-5,9-dimethylbicyclo[4.3.0]non-8-en-1-ol (14h)



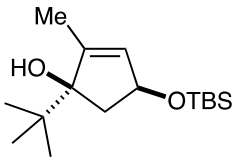
The reaction of **13h** (96 mg, 0.20 mmol) by using CuI (190 mg, 1.00 mmol) and a 1.11 M ethereal solution of MeLi (1.80 mL, 2.00 mmol) according to the general procedure described above afforded **14h** (65 mg, 0.186 mmol, 93%) as an almost single isomer the configuration of which was not determined. Yellow oil; ^{1}H-NMR ($CDCl_3$) δ: 5.61 (1H, s), 4.40 (1H, t, *J* = 3.2 Hz), 2.48-2.43 (1H, m), 2.25 (1H, s), 1.99-1.63 (5H, m), 1.50-1.47 (1H, m), 1.36 (1H, t, *J* = 6.9 Hz), 1.12 (2H, ddd, *J* = 27.5, 16.0, 5.4 Hz), 0.98 (3H, d, *J* = 6.9 Hz), 0.90 (6H, t, *J* = 6.3 Hz), 0.85 (9H, m), 0.03 (6H, m); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 154.17, 131.07, 83.94, 73.50, 61.85, 48.54, 35.48, 26.90, 26.59, 25.88, 25.77, 23.48, 20.84, 18.85, 18.16, 17.8, 16.69, -3.80, -5.24.

4-((tert-Butyldimethylsilyl)oxy)-2-methyl-1-phenylcyclopent-2-en-1-ol (14i)



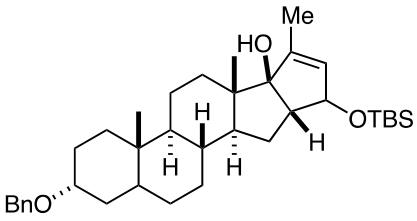
The reaction of **13i** (387 mg, 0.860 mmol) by using CuI (822 mg, 4.32 mmol) and a 1.11 M ethereal solution of MeLi (7.74 mL, 8.60mmol) according to the general procedure described above afforded **14i** (200 mg, 0.65 mmol, 76%) as a single isomer. Yellow oil; ^{1}H-NMR ($CDCl_3$) δ: 7.29-7.15 (5H, m), 5.62 (1H, d, *J* = 1.7 Hz), 4.75-4.73 (1H, m), 2.62 (1H, m), 2.30 (1H, s), 2.05-1.98 (1H, m), 1.52 (3H, d, *J* = 1.7 Hz), 1.28-1.17 (1H, m), 0.83 (9H, m), 0.03 (6H, m).^{13}C-NMR (125 MHz, $CDCl_3$) δ: 147.81, 144.63, 131.26, 128.20, 126.62, 124.82, 85.84, 74.04, 54.18, 25.91, 18.19, 11.93, -4.63, -4.65.

1-(tert-Butyl)-4-((tert-butyldimethylsilyl)oxy)-2-methylcyclopent-2-en-1-ol (14j)



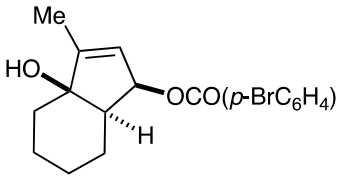
The reaction of **13j** (214 mg, 0.500 mmol) by using CuI (476 mg, 2.50 mmol) and a 1.17 M ethereal solution of MeLi (4.23 mL, 5.00 mmol) according to the general procedure described above afforded a 3:1 diastereomeric mixture of **14j** (107 mg, 0.373 mmol, 75%). Yellow oil; ^{1}H-NMR ($CDCl_3$) δ: 5.53 (1.3H, m), 4.81 (0.3H, m), 4.53-4.51 (1H, m), 2.88 (0.3H, q, *J* = 8.0 Hz), 2.62 (1H, q, *J* = 6.7 Hz), 1.82 (4.2H, m), 1.73 (2H, m), 1.65 (1.3H, m), 1.59-1.56 (5H, m), 1.13-1.08 (2H, m), 1.00 (3H, t, *J* = 10.3 Hz), 0.95 (11.7H, m), 0.89 (11.7H, dd, m), 0.05 (7.8H, m); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 146.94, 145.83, 134.75, 133.19, 89.30, 88.72, 73.26, 73.03, 48.48, 47.27, 37.17, 36.96, 26.07, 25.95, 25.93, 18.19, 15.68, 15.33, -4.54, -4.60, -4.64.

3-benzyloxy 16, 17-cycloepiandrostane (14k)



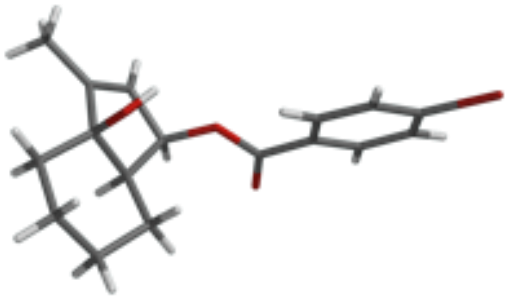
The reaction of **13k** (166 mg, 0.150 mmol) by using CuI (142 mg, 0.750 mmol) and a 1.17 M ethereal solution of MeLi (1.28 mL, 1.50 mmol) according to the general procedure described above afforded **14k** (60 mg, 0.11 mmol 71%) as a single isomer. Yellow oil; ^{1}H-NMR ($CDCl_3$) δ: 7.26-7.17 (5H, m), 5.47 (1H, s), 4.78 (1H, d, *J* = 8.0 Hz), 4.47 (2H, dd, *J* = 14.9, 12.0 Hz), 3.27-3.22 (1H, m), 2.32 (1H, t, *J* = 8.9 Hz), 1.93 (1H, q, *J* = 5.9 Hz), 1.79 (1H, t, *J* = 22.9 Hz), 1.71 (3H, s), 1.65-1.59 (5H, m), 1.51-0.95 (14H, m), 0.78 (14H, m), 0.54-0.50 (1H, m), -0.02 (6H, t, *J* = 4.6 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 135.70, 128.31, 127.52, 127.31, 98.02, 78.00, 74.91, 69.78, 53.86, 52.48, 50.81, 47.80, 44.84, 37.02, 36.05, 35.82, 34.80, 34.59, 31.68, 28.84, 28.28, 26.04, 24.73, 21.01, 18.38, 14.69, 14.16, 12.24, -4.71, -4.80.

***p*-Bromobenzoate 15** (Determination of the configuration of *anti-trans*-**14a**)



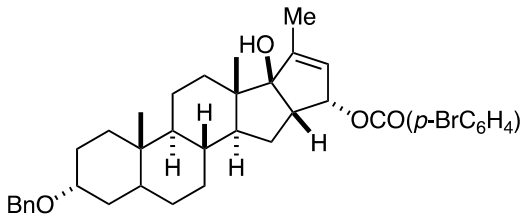
A mixture of *anti-trans*-**14a** (7 mg 0.04 mmol) and a 1 M THF solution of TBAF (0.126 mL, 0.126 mmol) was concentrated in vacuo. The residue was dissolved in *N*-methylpyrrolidone (0.4 mL), and the mixture was stirred at 80 °C for 2 h. A saturated aqueous NH_4Cl solution was added, and the aqueous layer was extracted with ethyl acetate and dried over $MgSO_4$. Concentration in vacuo afforded the crude diol which was used in the next step without father purification.

A mixture of the crude product, DMAP (10 mg, 0.084 mmol), and *p*-BrC_6H_4COCl (13 mg, 0.063 mmol) in CH_2Cl_2 (0.4 mL) was stirred at room temperature. After monitoring the full conversion of the starting material by TLC analysis, a saturated aqueous NH_4Cl solution was added, and the aqueous layer was extracted with ethyl acetate. The solution was dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude product through silica gel column chromatography gave *p*-bromobenzoyl ester **15** (9 mg, 0.03 mmol, 63%). White solid; ^{1}H-NMR ($CDCl_3$) δ: 7.83 (2H, d, *J* = 8.0 Hz), 7.57 (2H, d, *J* = 8.0 Hz), 5.81 (1H, s), 5.61 (1H, s), 1.96-1.80 (9H, m), 1.67 (2H, m), 1.30 (2H, m); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 165.57, 156.17, 131.82, 131.04, 129.19, 128.22, 125.77, 80.72, 78.88, 51.91, 31.89, 25.66, 21.39, 21.02, 12.11.

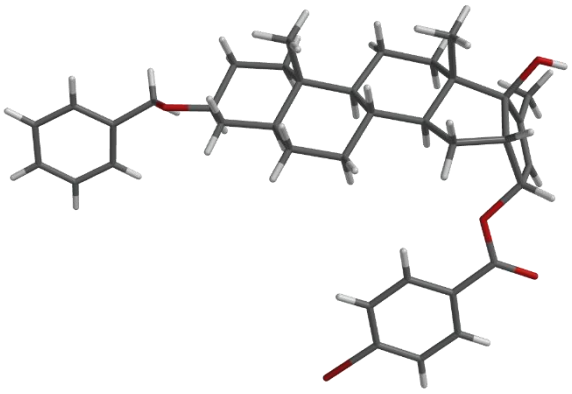


The structure of 15 determined by X-ray crystallographic analysis.

***p*-bromobenzoate 22** (Determination of the configuration of **14k**)

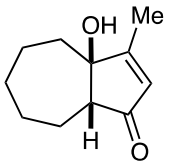


According to a similar procedure described above, cyclized product **14k** (210 mg 0.370 mmol) was transformed into *p*-bromobenzoate **22** (158 mg, 0.250 mmol, 68%) by using a 1 M THF solution of TBAF (3.7 mL, 3.7 mmol), *N*-methylpyrrolidone (3.7 mL), DMAP (231 mg, 1.89 mmol), *p*-BrC_6H_4COCl (138 mg, 0.630 mmol), and CH_2Cl_2 (3.2 mL). White solid; ^{1}H-NMR ($CDCl_3$) δ: 7.82 (2H, d, *J* = 8.6 Hz), 7.50 (2H, d, *J* = 8.0 Hz), 7.22 (5H, m), 5.86 (1H, d, *J* = 8.6 Hz), 5.64 (1H, s), 4.47 (2H,m), 3.27-3.23 (1H, m), 2.63 (1H, t, *J* = 9.2 Hz), 1.85-0.52 (30H, m). ;^{13}C-NMR (125 MHz, $CDCl_3$) δ: 165.53, 147.91, 139.15, 131.68, 131.04, 130.43, 129.28, 128.30, 128.02, 127.50, 127.32, 97.84, 78.60, 77.92, 69.77, 53.88, 51.27, 51.07, 47.47, 44.86, 36.99, 35.83, 35.70, 34.95, 34.69, 31.92, 28.68, 28.23, 25.64, 20.97, 14.52, 14.27, 12.23.



The structure of 22 determined by X-ray crystallographic analysis.

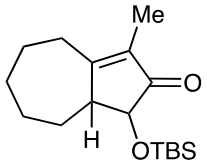
1-Hydroxy-10-methylbicyclo[5.3.0]dec-9-en-8-one (18)



A mixture of cyclized product **14c** (76 mg, 0.25 mmol) and a 1 M THF solution of TBAF (1.5 mL, 1.5 mmol) was concentrated in vacuo. The residue was dissolved in *N*-methylpyrrolidone (1.5 mL), and the mixture was stirred at 80 °C for 1 h. A saturated aqueous NH_4Cl solution was added, and the aqueous layer was extracted with ether (20 mL) and dried over $MgSO_4$. Concentration in vacuo afforded the crude product which was passed through a short pad of silica gel, giving rise to almost pure diol (30.0 mg, 0.165 mmol, 66%) as a diastereomeric mixture.

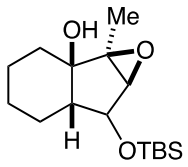
A mixture of the diol (30.0 mg, 0.165 mmol), 4A MS (1 tip), NMO (29.0 mg, 0.250 mmol), and tetrapropylammonium perruthenate (1 tip) in CH_2Cl_2 (1.65 mL) was stirred at 0 °C for 2.5 h. Silica gel (2.5 g) was added, and the resulting slurry was passed through a short pad of silica gel and eluted with ethyl acetate. The solution was concentrated in vacuo, and purification by silica gel column chromatography gave enone **18** (21 mg, 0.12 mmol, 72%). Colorless oil; ^{1}H-NMR ($CDCl_3$) δ: 5.96 (1H, d, *J* = 1.1 Hz), 2.48 (1H, q, *J* = 4.2 Hz), 2.07 (3H, s), 1.98-1.93 (2H, m), 1.84-1.69 (4H, m), 1.57-1.51 (3H, m), 1.25 (2H, m); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 208.00, 178.20, 130.72, 83.95, 59.90, 35.56, 31.02, 27.06, 26.77, 23.06, 13.32.

10-((*tert*-Butyldimethylsilyl)oxy)-8-methylbicyclo[5.3.0]dec-7-en-9-one (19)



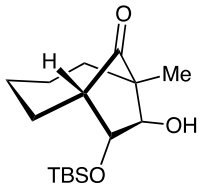
According to the protocol reported by Iwabuchi's group,[4] **14c** (59 mg, 0.2 mmol) was oxidized by using SiO_2-$NaIO_4$ (ca. 0.68 mol/g, 588 mg, 0.40 mmol) and TEMPO (1 tip). The desired enone **19** was obtained as a 1:1 diastereomeric mixture (41 mg, 0.14 mmol, 68%). Colorless oil; ^{1}H-NMR ($CDCl_3$) δ: 4.20 (1H, d, *J* = 6.3 Hz), 3.79 (1H, d, *J* = 3.4 Hz), 2.87 (1H, s), 2.67-2.47 (5H, m), 2.21 (1H, d, *J* = 9.7 Hz), 2.04-1.99 (1H, m), 1.92-1.75 (5H, m), 1.42 (20H, m), 0.93-0.86 (20H, m), 0.19 (6H, m), 0.12 (6H, m); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 206.71, 206.25, 175.59, 173.19, 132.65, 132.63, 79.69, 74.72, 51.83, 47.42, 31.27, 30.90, 30.86, 30.66, 30.57, 29.49, 29.27, 27.84, 26.58, 25.72, 25.66, 25.18, 18.35, 18.19, 7.68, 7.65, -4.25, -4.50, -5.27, -5.35.

7-((*tert*-Butyldimethylsilyl)oxy)-8,9-epoxy-9-methylbicyclo[4.3.0]nonan-1-ol (20)



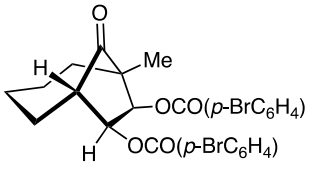
To a solution of a 2.5:1 diastereomeric mixture of **14a** (582 mg, 2.00 mmol) in CH_2Cl_2 (20 mL) was added *m*CPBA (70% purity, 739 mg, 3.00 mmol) portion wise at 0 °C. The mixture was stirred at 0 °C for 2 h and then at room temperature for 15 min. The reaction was quenched by treating with 2-methyl-2-butene (2 mL) for 1 h followed by a saturated aqueous $NaHCO_3$ solution (5 mL) and $NaHCO_3$ (500 mg) for 1 h. The aqueous layer was extracted with ether (500 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification by silica gel column chromatography gave epoxy alcohol **20** (590 mg, 1.98 mmol) as a 2.5:1 diastereomeric mixture**.** Colorless oil; ^{1}H-NMR ($CDCl_3$) δ: 4.17 (2.5H, m), 3.83 (1H, d, *J* = 8.0 Hz), 3.23 (1H, s), 3.12 (2.5H, s), 1.79-1.03 (45.5H, m), 0.89 (31.5H, m), 0.09 (21H, m); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 76.75, 75.01, 74.02, 68.08, 63.74, 44.26, 43.14, 32.33, 32.08, 25.87, 25.77, 22.55, 21.25, 20.84, 19.93, 18.08, 17.98, 14.03, 11.61, 11.22, -4.79, -4.87.

7-((tert-Butyldimethylsilyl)oxy)-8-hydroxy-1-methylbicyclo[4.2.1]nonan-9-one (21)



To a cooled (-78 °C) solution of epoxy alcohol **20** (89 mg, 0.30 mmol) in CH_2Cl_2（3 mL） was dropwise added $BF_3{\cdot}OEt_2$ (41 μL, 0.33 mmol). The reaction mixture was warmed up to room temperature immediately and was stirred for 3 min. A saturated aqueous $NaHCO_3$ solution (5 mL) was added, and the aqueous layer was extracted with ethyl acetate (10 mL). The solution was dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude product by silica gel column chromatography gave **21** (77 mg, 0.26 mmol, 78%) as a 2.5:1 diastereomeric mixture. Colorless oil; ^{1}H-NMR ($CDCl_3$) δ: 4.30 (1H, t, *J* = 4.0 Hz), 4.05 (5H, m), 3.95 (1H, t, *J* = 4.3 Hz), 3.11 (1H, d, *J* = 4.0 Hz), 2.67 (2.5H, dd, *J* = 10.6, 4.9 Hz), 2.38 (1H, t, *J* = 3.4 Hz), 2.06 (2.5H, s), 1.89-1.28 (13.5H, m), 1.13 (3H, d, *J* = 14.9 Hz), 1.02 (7.5H, s), 0.88 (31.5H, m), 0.12-0.06 (21H, m); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 219.15, 218.67, 83.20, 77.60, 76.44, 73.50, 54.22, 53.91, 53.55, 52.36, 38.69, 35.18, 25.77, 25.64, 25.52, 25.12, 25.00, 24.71, 24.63, 20.86, 18.07, 17.92, 17.66, 17.06, -4.48, -4.75, -4.94, -4.99.

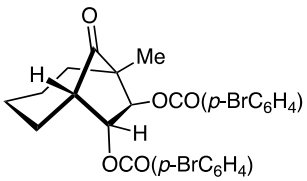
Bis(4-bromobenzoate) 23 (Determination of the configuration of **21**)



According to a similar procedure described for the synthesis of **18**, desilylation of **21** (110 mg 0.369 mmol) was conducted by using a 1 M THF solution of TBAF (1.08 mL, 1.08 mmol) and *N*-methylpyrrolidone (3.6 mL), giving rise to *cis*-diol (133 mg, 0.24 mmol, 66%) and *trans*-diol (53 mg, 0.096 mmol, 26%). Each isomer of the diol was then converted to the corresponding bis *p*-bromobenzoate *cis*-**23** and *trans*-**23**, respectively, according to a similar procedure described for the synthesis of **15**.

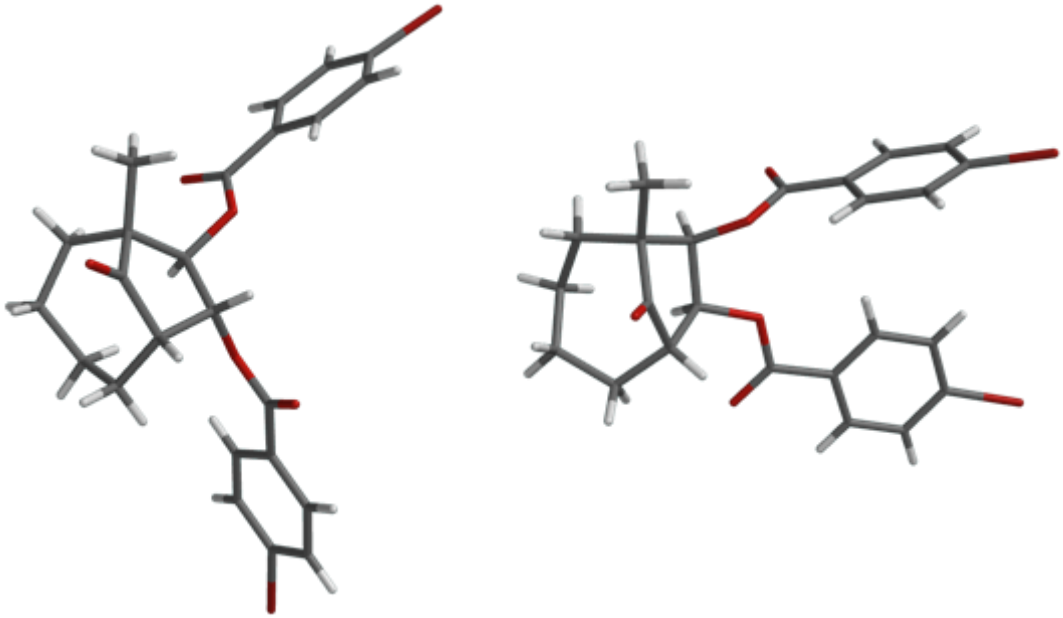
***cis*-23**: White solid; ^{1}H-NMR ($CDCl_3$) δ: 7.93 (4H, m), 7.61-7.53 (4H, m), 5.79 (1H, d, *J* = 6.3 Hz), 5.62 (1H, dd, *J* = 8.3, 6.3 Hz), 3.29 (1H, m), 2.04 (1H, m), 1.94-1.88 (1H, m), 1.79 (1H, m), 1.59 (6H, m), 1.08 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 214.99, 165.50, 164.96, 131.95, 131.90, 131.23, 131.2, 128.72, 128.02, 82.49, 76.16, 53.41, 50.29, 37.85, 24.82, 24.28, 22.38, 17.22.

***trans*-23**: White solid; ^{1}H-NMR δ: 7.70 (4H,m), 7.49 (4H, m), 5.76 (2H, s), 2.81 (1H, d, *J* = 6.3 Hz), 1.96 (1H, m), 1.79 (4H, m), 1.63-1.52 (4H, m), 1.18 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 215.66, 164.91, 131.88, 131.8, 131.06, 131.00, 128.68, 128.58, 128.13, 128.08, 74.10, 53.08, 51.87, 25.35, 24.91, 24.82, 17.78.

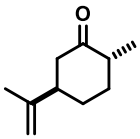


The structure of *cis*-23 determined by X-ray crystallographic analysis.

The structure of *trans*-23 determined by X-ray crystallographic analysis.

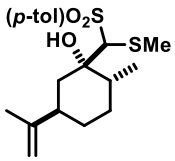


Trans-Dihydrocarvone (43)



Dyhydrocarvone (43) was prepared to follow the procedure described in Yadav group's report11).The product obtained from (R)-carvone (5.21 mL, 33.3 mmol) in 60% yield (3.07 g, 20.2 mmol). Colorless oil; 1H-NMR (500 MHz, CDCl3) δ 4.73 (2H, d, J=13.7 Hz), 2.43 (1H, dt, J=11.5, 2.29 Hz), 2.41-2.24 (3H, m), 2.15-2.08 (1H, m), 1.96-1.90 (1H, m), 1.72 (3H, s), 1.63 (1H, qd, J=13.1, 3.44 Hz), 1.36 (1H, qd, J=13.1, 3.44 Hz), 1.02 (1H, d, J=6.31); 13C-NMR (125 MHz, CDCl3) δ 212.71, 147.60, 109.58, 46.97, 46.83, 44.71, 34.86, 30.72, 20.46, 14.32.

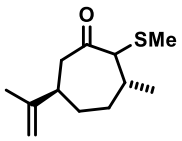
2-methyl-1-(-(methylthio)(tosyl)methyl)-5-(prop-1-en-2-yl)cyclohexan-1-ol (56)



To a THF (100 mL) solution of MT-sulfone (20 mmol) n-BuLi 2.69 M in Hexane (7.8 mL, 21 mmol) was added dropwise and stirred for 1 h. To the reaction mixture, dihydrocarvone (1.52 g, 10 mmol) in THF (10 mL) was added dropwise and stirred for 10 min. The reaction was quenched with saturated aq. NH4Cl (100 mL) at -78℃ and warmed to room temperature. The aqueous layer was extracted with ether (50 mL), dried over MgSO4, and concentrated vacuo. Purified through column chromatography gave hydoroxysulfone (2.94 g, 7.98 mmol) 79% and recovered starting material 20%. Pale yellow oil; 1H-NMR

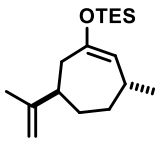
(500 MHz, CDCl3) δ 7.92 (2H, d, J = 8.59 Hz), 7.37 (2H, d, J= 8.02 Hz), 4.22 (1H, br), 3.92 (1H, s), 2.46 (3H, s), 2.38 (1H, tt, J = 12.6, 2.86 Hz), 2.30 (1H, bd, J = 13.7 Hz), 2.16-2.08 (1H. m), 1.87 (3H, s), 1.75-1.68 (4H, m), 1.62-1.42 (4H, m), 1.30-1.13 (2H, m), 0.87 (3H, d, J = 6.3 Hz).

3-methyl-2-(methylthio)-6-(prop-1-en-2-yl)cycloheptan-1-one (58)



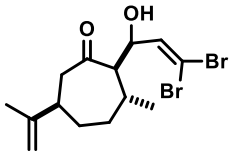
To a DME (80 mL) solution of hydroxysulfone (2.93 g, 7.98 mmol), EtAlCl2 1.05M in hexane (45.6 mL, 47.9 mmol) was added at 0 ℃. The reaction mixture was allowed to warmed up to room temperature and stirred for 1 h at the same temperature in a water bath. 10% aq, Rochelle solt solution (100 mL) was added slowly to stop the reaction, and stirred for 1 h. The aqueous layer was extracted with ether (100 mL) and dried over MgSO4.Concentraion in vacuo and purification through column chromatography gave thiomethylketone (1.28 g, 6.30 mmol) as a 10:3 diastereomer mixture in 79% yield. Colorless oil; 1H-NMR (500 MHz, CDCl3) δ 4.72-4.65 (2.6H, m), 3.83 (0.3H, s), 3.13 (1H, s), 2.97 (1H, t, J = 11.4 Hz), 2.79 (1H, dt, J = 18.3, 2.29 Hz), 2.59 (0.3H, d, J = 1.14 Hz), 2.49 (1H, dd, J = 17.7, 11.4 Hz), 2.24 (2H, d, J = 6.30 Hz), 2.09 (3H, s), 1.86 (1H, d, br), 1.75-1.51 (6.6H, m), 1.42-1.32 (1.3H, m), 1.20-1.15 (3.6H, m), 1.03 (0.3H, d, J = 5.72 Hz), 0.91 (1H, d, J = 8.01 Hz).

triethyl((-3-methyl-6-(prop-1-en-2-yl)cyclohept-1-en-1-yl)oxy)silane (63)



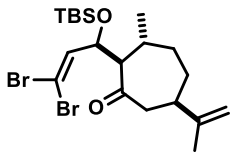
To a slurry of well washed lithium dispersion (15 mmol in theory) in THF (9 mL), TESCl (2.50 mL, 15 mmol) was added slowly and the mixture was sonicated for 5 min at room temperature and cooled to -78℃. A solution of methyl thioketone (657 mg, 3 mmol) in THF (3 mL) was added dropwise and stirred for 3 h. TEA (5 mL) was added drop wise then the solution was poured into excess ice for quenching the reaction. After all of lithium was quenched, the aqueous layer was extracted with hexane (60 mL) and dried over MgSO4. Concentration and passing a silica gel short pad (which was pre-deactivated with PhNMe2, EA, and conditioned with hexane) gave the almost pure product (759 mg, 2.71 mmol). Colorless oil; 1H-NMR (500 MHz, CDCl3) δ 4.73 (1H, m), 4.64 (2H, d, J = 13.1 Hz), 2.54 (1H, t, J = 12.6 Hz), 2.22 (1H, br), 2.07 (1H, t, J = 11.4 Hz), 2.02-1.88 (2H, m), 1.71-1.68 (4H, m), 1.65-1.58 (1H, m), 1.56 (1H, s), 1.53 (1H, d, J = 13.1 Hz), 1.24 (1H, q, J = 12.6 Hz), 1.02-0.95 (9H, m), 0.70-0.63 (6H, m).

2-(-3,3-dibromo-1-hydroxyallyl)-3-methyl-6-(prop-1-en-2-yl)cycloheptan-1-one (51)



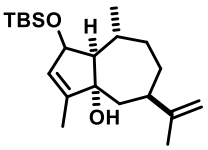
To mixture of TES enol ether (140 mg, 0.5 mmol) and dibromoacrorein (160 mg, 0.75 mmol) in CH2Cl2 (5 mL), BF3・OEt2 (69 μL, 0.55 mmol) was added at -78℃ and stirred for 2 min. The reaction was quenched with saturated aq. NaHCO3 (5 mL) and aqueous layer was extracted with ether (20 mL). The crude product was dried over MgSO4, concentrated in vacuo and purified through column chromatography. It gave aldol product (119 mg, 0.32 mmol) in 63% yield as a 2:1 diastereomer mixture. Colorless oil; 1H-NMR (CDCl3) δ 6.61 (0.5H, d, J = 8.6 Hz), 6.55 (1H, d, J = 8.0 Hz), 4.75-4.73 (3.5H, m),4.75 (0.5H, m) 4.43 (1H, td, J = 8.4, 3.1 Hz), 3.75 (1H, d, J = 9.2 Hz), 3.03 (0.5H, d, J = 5.7 Hz), 2.69 (0.5H, q, J = 4.2 Hz), 2.04-1.79 (4.5H, m), 1.71 (4.5H, m), 1.62-1.38 (3H, m), 1.16 (3H, d, J = 6.9 Hz), 1.10 (0.5H, dd, J = 11.2, 7.2 Hz), 0.97 (3H, q, J = 5.3 Hz), 0.88 (1H, t, J = 6.9 Hz), 0.59 (1.5H, q, J = 8.0 Hz).

2-(3,3-dibromo-1-((tert-butyldimethylsilyl)oxy)allyl)-3-methyl-6-(prop-1-en-2-yl)cycloheptan-1-one (40)



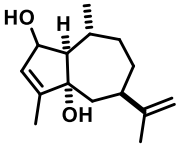
To a solution of aldol products (99 mg, 0.26 mmol) in DMF (2.6 mL) was added imidazole (106 mg, 1.56 mmol) and TBSCl (205 mg, 0.78 mmol) at 0℃. After stirring for 16 h at room temperature, the reaction was quenched with MeOH (0.5 mL) and stirred for 10 min. Then saturated aq. NH4Cl (20 mL) was added and aqueous layer was extracted hexane: EA = 1:1 (15 mL), dried over MgSO4,and concentrated in vacuo. Purification through column chromatography gave product (113 mg, 0.23 mmol) in 89% yield. Colorless oil; 1H-NMR (CDCl3) δ 6.39-6.34 (1.5H, m), 4.73 (3H,m), 4.68-4.63 (1.5H, m),2.62 (1H, t, J = 11.4 Hz) 2.53 (0.5H, s), 2.44 (0.5H, dd, J = 8.59, 5.15 Hz), 2.38 (0.5H, d, J = 12.0 Hz), 2.32 -2.21(2.5H, m), 2.19-2.11 (1.5H, m), 2.24-1.93 (2H, m), 1.96-1.81 (2.5H, m), 1.72 (1.5H, s), 1.70 (3H, m), 1.50-1.40 (1.5H, m), 1.12 (1.5H, d, J = 6.87 Hz), 1.60 (3H, d, J = 6.3 Hz), 0.92-0.82 (13.5H, m), 0.09-0.1 (9H, m),

1-((tert-butyldimethylsilyl)oxy)-3,8-dimethyl-5-(prop-1-en-2-yl)-4,5,6,7,8,8a-**hexahydroazulen-3a(1H)-ol (39)**



To a slurry of CuI (219 mg, 1.15 mmol) in ether (2.3 mL), MeLi 1.17 M in ether (1.96 mL, 2.3 mmol) was added dropwise at -78℃. The reaction mixture was warmed up to 0℃ and stirred for 10 min. To the obtained clear solution, the precursor (113 mg, 0.23 mmol) in ether (0.2 mL) was added and warmed up to 0℃ immediately and stirred for 10 min at this temperature. The reaction was quenched with saturated aq. NH4Cl (10 mL) filtered with Celite, and aqueous layer was extracted with ether (15 mL). Concentration in vacuo and purification through column chromatography gave cyclopentenol (63 mg, 0.18 mmol) in 78% yield as a siastereomer mixture. Colorless oil; 1H-NMR (CDCl3) δ 5.36 (1.5H, m), 4.68 (4.5H,m), 429 (1H, t, J = 2.3 Hz),2.90 (0.5H, s) 2.58 (3H, m), 2.34-2.17 (3H, m), 2.17 (0.5H, s), 2.03 (2H, t, J = 10.9 Hz),1.91-1.60 (10.5H, m), 1.42 (3H, d, J = 11.5 Hz), 1.19 (5H, m),0.96-0.86 (13.5H, m), 0.03 (9H, m),

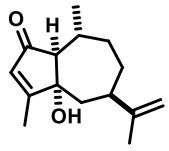
3,8-dimethyl-5-(prop-1-en-2-yl)-4,5,6,7,8,8a-hexahydroazulene-1,3a(1H)-diol (64)



The mixture of cyclopentenol (63 mg, 0.18 mmol) and TBAF 1M in THF (0.48 mL, 0.48 mmol) was evaporated to distill most of THF. To the obtained slurry, NMP (0.5 mL) was added and the reaction mixture was stirred at 80℃ for 1 h. The reaction was quenched with saturated aq. NH4Cl, and aqueous layer was extracted with ether (10 mL), dried over MgSO4, and concentrated in vacuo. The crude product was purified through column chromatography and it gave diol (25 mg, 0.105 mmol) in 59% yield as a diastereomer mixture. Colorless oil; 1H-NMR (CDCl3) δ 5.44 (2H, s), 4.85 (1H, s), 4.72-4.63 (4H, m),4.25 (2H, m) 2.57 (1H, t, J =13.1 Hz), 2.26 (1H, t, J =10.3 Hz), 2,10-1.08 (52H, m), 0.94-0.85 (9H, m).

3a-hydroxy-3,8-dimethyl-5-(prop-1-en-2-yl)-4,5,6,7,8,8a-hexahydroazulen-1(3aH)-one (38)

To a solution of diol (0.105 mmol) in CH2Cl2 (1.05 mL) was added 4A MS (1 tip), NMO (18.6 mg, 0.159 mmol) and TPAP (1.8 mg, 5 mol%) was added at 0℃. The reaction mixture was allowed to warm up to room temperature and stirred for 2 h. Silica gel (5 g) was added and the slurry was passed through silica gel short pad with EA (10 mL).



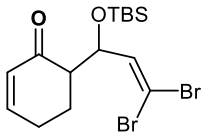
Resulted crude material was purified through columln chromatography and it gave the target material (21mg, 0.089 mmol) in 86% yield. Pale yellow oil; 1H-NMR (CDCl3) δ : 5.83 (1H, d, J = 1.1 Hz), 4.69 (3H, m), 2.18 (1H, d, J = 10.3 Hz), 2.06 (3H, s), 1.96-1.56 (10H, m), 1.39 (2H, tt, J = 17.8, 5.8 Hz), 1.03 (s).

General procedure for the lithium carbenoid reaction

To a cooled (-78 °C) suspension of ketone substitutes (0.2M), was added MeLi (1.11M in ether). The mixture was stirred vigorously for 10 minutes warmed up to 0 °C and stirred further 30 min. A saturated aqueous $NaHCO_3$ solution was added, and the aqueous layer was extracted with ether. The solution was dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude product by silica gel column chromatography gave target bromocyclopentenes.

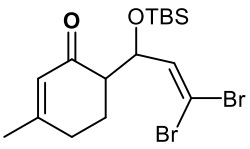
The aldol reactions of the enones ware conducted as above

6-(3,3-dibromo-1-((tert-butyldimethylsilyl)oxy)allyl)cyclohex-2-en-1-one



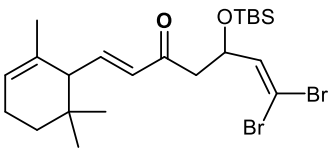
@ (753 mg, 1.72 mmol, 86%) was obtained as a 5:1 mixture of diastereomers from cyclopentenone (0.19 mL 2.00 mmol), diisopropylamine (0.31 mL, 2.2 mmol), *n*-BuLi 2.65 M in hexane (0.83 mL, 2.2 mmol), TBSCl (1.59 g, 10.5 mmol), and imidazole (0.82 g, 12 mmol) according to the general procedure described above. Yellow oil; ^1H -NMR ($CDCl_3$) δ: 6.61 (2H, d, *J* = 8.6 Hz), 6.47 (1H, d, *J* = 8.6 Hz), 5.28 (3H, d, *J* = 25.8 Hz), 5.04 (1H, d, *J* = 9.7 Hz), 4.64 (2H, q, *J* = 4.2 Hz), 3.82 (6H, q, *J* = 6.9 Hz), 2.46-2.33 (8H, m), 2.22 (1H, s), 2.11-2.03 (3H, m), 1.90 (3H, d, *J* = 16.6 Hz), 1.49 (22H, s), 1.33-1.20 (11H, m), 0.81 (37H, t, *J* = 22.9 Hz), 0.02 (22H, q, *J* = 6.3 Hz).

6-(3,3-dibromo-1-((tert-butyldimethylsilyl)oxy)allyl)-3-methylcyclohex-2-en-1-one



@ (736 mg, 1.95 mmol, 84%) was obtained as a 5:1 mixture of diastereomers from 3-methylcyclopentanone (0.18 mL 2.00 mmol), diisopropylamine (0.31 mL, 2.2 mmol), *n*-BuLi 2.65 M in hexane (0.83 mL, 2.2 mmol), TBSCl (1.59 g, 10.5 mmol), and imidazole (0.82 g, 12 mmol) according to the general procedure described above. Yellow oil; ^1H-NMR ($CDCl_3$) δ ^1H -NMR ($CDCl_3$) δ: 7.16 (2H, d, *J* = 8.0 Hz), 6.59 (4H, dt, *J* = 52.9, 20.5 Hz), 5.14 (1H, d, *J* = 7.4 Hz), 4.84 (10H, ddd, *J* = 62.4, 35.2, 14.3 Hz), 4.47-4.35 (4H, m), 3.44 (2H, s), 3.11 (1H, t, *J* = 7.2 Hz), 2.87 (4H, dt, *J* = 30.0, 11.7 Hz), 2.62-2.30 (13H, m), 1.77-1.24 (55H, m), 1.00-0.68 (65H, m), 0.12--0.08 (40H, m).

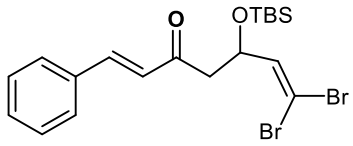
(E)-7,7-dibromo-5-((tert-butyldimethylsilyl)oxy)-1-(2,6,6-trimethylcyclohex-2-en-1-yl)hepta-1,6-dien-3-one



@ (832 mg, 1.60 mmol, 80%) was obtained as a 4:1 mixture of diastereomers from ionone (0.19 mL 2.00 mmol), diisopropylamine (0.31 mL, 2.2 mmol), *n*-BuLi 2.65 M in hexane (0.83 mL, 2.2 mmol), TBSCl (1.59 g, 10.5 mmol), and

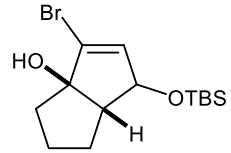
imidazole (0.82 g, 12 mmol) according to the general procedure described above. Yellow oil; ^{1}H-NMR ($CDCl_3$) ^{1}H δ: 6.31 (1H, dt, *J* = 53.1, 18.6 Hz), 5.20-5.06 (1H, m), 4.49 (1H, tt, *J* = 37.5, 8.3 Hz), 3.60 (4H, dt, *J* = 47.3, 14.6 Hz), 2.99 (3H, ddt, *J* = 61.5, 32.6, 12.4 Hz), 2.54 (1H, dq, *J* = 41.1, 4.8 Hz), 1.92 (0H, d, *J* = 7.4 Hz), 1.45 (3H, d, *J* = 29.8 Hz), 1.10-0.77 (28H, m), 0.03 (9H, ddd, *J* = 24.2, 14.5, 9.0 Hz)..

(E)-7,7-dibromo-5-((tert-butyldimethylsilyl)oxy)-1-phenylhepta-1,6-dien-3-one



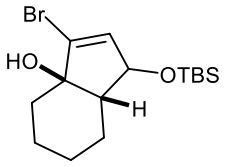
Ketone **13b** (970 mg, 1.88 mmol, 94%) was obtained as a 1.5:1 mixture of diastereomers from methylstilyl ketone (2.00 mL 2.00 mmol), diisopropylamine (0.31 mL, 2.2 mmol), *n*-BuLi 2.65 M in hexane (0.83 mL, 2.2 mmol), TBSCl (1.59 g, 10.5 mmol), and imidazole (0.82 g, 12 mmol) according to the general procedure described above. Yellow oil; ^{1}H -NMR ($CDCl_3$) δ: (some peaks are missing due to the solvent to be measured again).64-6.57 (1H, m), 6.40 (1H, d, *J* = 8.0 Hz), 6.02 (1H, d, *J* = 15.5 Hz), 5.44 (1H, s), 4.80 (1H, td, *J* = 8.2, 3.8 Hz), 3.42 (1H, q, *J* = 6.9 Hz), 2.82 (1H, dd, *J* = 14.6, 8.3 Hz), 2.52 (1H, dd, *J* = 14.3, 3.4 Hz), 2.23-1.98 (3H, m), 1.55 (4H, d, *J* = 47.0 Hz), 1.43-1.38 (1H, m), 1.20 (2H, dq, *J* = 41.5, 8.3 Hz), 0.81 (18H, tt, *J* = 30.9, 22.3 Hz), -0.05 (7H, t, *J* = 30.1 Hz).

4-bromo-6-((tert-butyldimethylsilyl)oxy)-2,3,6,6a-tetrahydropentalen-3a(1H)-ol



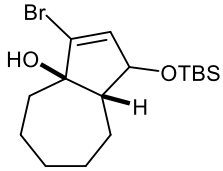
The reaction of a 2:1 diastereomeric mixture of **13b** (82 mg, 0.20 mmol) by using 1.11 M ethereal solution of MeLi (0.27 mL, 0.30 mmol) according to the general procedure described above afforded a 2:1 diastereomeric mixture of **14b** (264 mg, 0.192 mmol, 96%). Yellow oil; ^{1}H-NMR ($CDCl_3$) δ: 6.36 (0.5H, s), 6.33 (1H, s), 4.86 (1H, dt, *J* = 7.4, 1.7 Hz), 4.14 (0.5H, d, *J* = 1.1 Hz), 2.41 (1H, td, *J* = 8.3, 4.6 Hz), 2.16 (0.5H, t, *J* = 4.6 Hz), 2.03 (1H, dt, *J* = 10.7, 3.6 Hz), 1.90-1.80 (3H, m), 1.74 (1H, t, *J* = 1.4 Hz), 1.72 (3H, dd, *J* = 4.9, 3.7 Hz), 1.70-1.47 (3H, m), 0.88 (13.5H, m), 0.07 (3H, t, *J* = 3.2 Hz), 0.05 (6H, s).

3-bromo-1-((tert-butyldimethylsilyl)oxy)-1,4,5,6,7,7a-hexahydro-3aH-inden-3a-ol



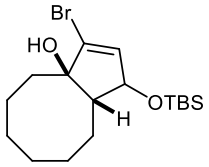
The reaction of a 3:1 diastereomeric mixture of **13b** (85 mg, 0.20 mmol) by using 1.11 M ethereal solution of MeLi (0.27 mL, 0.30 mmol) according to the general procedure described above afforded a 3:1 diastereomeric mixture of **14b** (60 mg, 0.172 mmol, 86%). Yellow oil; ^{1}H-NMR ($CDCl_3$) δ: 6.88 (1.5H, d, *J* = 8.0 Hz), 6.41 (1H, d, *J* = 8.0 Hz), 4.82 (1H, dd, *J* = 8.0, 2.3 Hz), 4.43 (1.5H, dd, *J* = 8.0, 3.8 Hz), 2.32-1.92 (14H, m), 1.78-1.72 (3.5H, m), 0.88-0.80 (22.5H, m), 0.04 (15H, m)

3-bromo-1-((tert-butyldimethylsilyl)oxy)-4,5,6,7,8,8a-hexahydroazulen-3a(1H)-ol



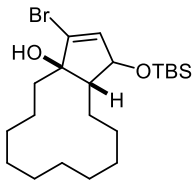
The reaction of a 3:1 diastereomeric mixture of **13b** (85 mg, 0.20 mmol) by using 1.11 M ethereal solution of MeLi (0.27 mL, 0.30 mmol) according to the general procedure described above afforded a 3:1 diastereomeric mixture of **14b** (62 mg, 0.172 mmol, 86%). Yellow oil; ^{1}H-NMR ($CDCl_3$) δ: 6.44 (2.2H, s), 4.67 (1H, d, *J* = 6.3 Hz), 4.24 (1.2H, d, *J* = 1.7 Hz), 2.17-2.14 (1.2H, m), 1.99 (1.2H, m), 1.91-1.27 (30.6H, m), 0.88 (19.8H, m), 0.09-0.03 (13.2H, m).

3-bromo-1-((tert-butyldimethylsilyl)oxy)-1,4,5,6,7,8,9,9a-octahydro-3aH-cyclopenta[8]annulen-3a-ol



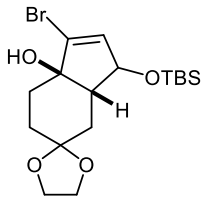
The reaction of a 2:1 diastereomeric mixture of **13b** (91 mg, 0.20 mmol) by using 1.11 M ethereal solution of MeLi (0.27 mL, 0.30 mmol) according to the general procedure described above afforded a 2:1 diastereomeric mixture of **14b** (69 mg, 0.184 mmol, 92%). Yellow oil; ^{1}H-NMR ($CDCl_3$) δ: 5.61 (1H, s), 6.46 (1H, s), 4.30 (1H, q, *J* = 2.3 Hz), 4.15 (1H, s), 2.15 (1H, s), 1.95 (1H, m), 1.91-1.35 (24H, m), 0.88 (18H, t, *J* = 9.5 Hz), 0.08-0.04 (12H, m).

3-bromo-1-((tert-butyldimethylsilyl)oxy)-1,4,5,6,7,8,9,10,11,12,13,13a-dodecahydro-3aH-cyclopenta[12]annulen-3a-ol



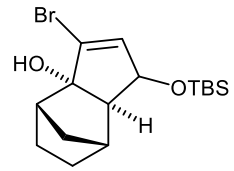
The reaction of a 2.5:1 diastereomeric mixture of **13b** (102 mg, 0.20 mmol) by using 1.11 M ethereal solution of MeLi (0.27 mL, 0.30 mmol) according to the general procedure described above afforded a 2.5:1 diastereomeric mixture of **14b** (56 mg, 0.130 mmol, 65%). Yellow oil.

1-bromo-3-((tert-butyldimethylsilyl)oxy)-3a,4,6,7-tetrahydrospiro[indene-5,2'-[1,3]dioxolan]-7a(3H)-ol



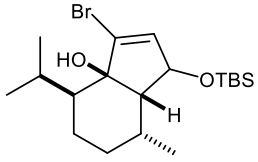
The reaction of a 2:1 diastereomeric mixture of **13e** (97 mg, 0.20 mmol) by using a 1.11 M ethereal solution of MeLi (0.27 mL, 0.300 mmol) according to the general procedure described above afforded a 2:1 diastereomeric mixture of **14e** (81 mg, 0.200 mmol, 99%). Yellow oil; ^{1}H-NMR ($CDCl_3$) δ: 6.66 (2.5H, s), 6.47 (1H, s), 4.41 (2.5H, s), 4.19 (1H, s), 2.46 (1H, dd, *J* = 12.6, 4.0 Hz), 1.97 (2.5H, q, *J* = 5.0 Hz), 1.84 (1H, d, *J* = 8.6 Hz), 1.77-1.66 (20.5H, m), 1.55-1.26 (60H, m), 1.07-0.98 (2.5H, m), 0.97-0.80 (31.5H, m), 0.78-0.72 (1H, m), 0.12--0.01 (21H, m).

3-bromo-1-((tert-butyldimethylsilyl)oxy)-1,4,5,6,7,7a-hexahydro-3aH-4,7-methanoinden-3a-ol



The reaction of a 2:1 diastereomeric mixture of **13e** (87 mg, 0.20 mmol) by using a 1.11 M ethereal solution of MeLi (0.27 mL, 0.300 mmol) according to the general procedure described above afforded a 2.:1 diastereomeric mixture of **14e** (81 mg, 0.174 mmol, 87%). Yellow oil.

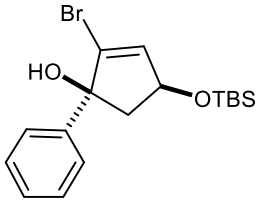
3-bromo-1-((tert-butyldimethylsilyl)oxy)-4-isopropyl-7-methyl-1,4,5,6,7,7a-hexahydro-3aH-inden-3a-ol



The reaction of a >10:1 diastereomeric mixture of **13e** (96 mg, 0.20 mmol) by using a 1.11 M ethereal solution of MeLi (0.27 mL, 0.300 mmol) according to the general procedure described above afforded a >10:1 diastereomeric mixture of **14e** (69 mg, 0.17 mmol, 85%). Yellow oil; ^{1}H-NMR (CDCl3) δ: (some peaks are missing due to the solvent to be measured again) 6.46 (1H, s), 5.40 (2H, s), 4.96 (2H, d, *J* = 8.0 Hz), 4.04 (1H, s), 2.34

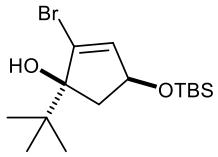
(2H, d, *J* = 4.6 Hz), 2.17-2.10 (5H, m), 2.00 (2H, m), 1.88 (2H, m), 1.80 (2H, s), 1.72-1.25 (19H, m), 1.05 (5H, m), 0.90 (27H, m), 0.06 (18H, m);.

2-bromo-4-((tert-butyldimethylsilyl)oxy)-1-phenylcyclopent-2-en-1-ol



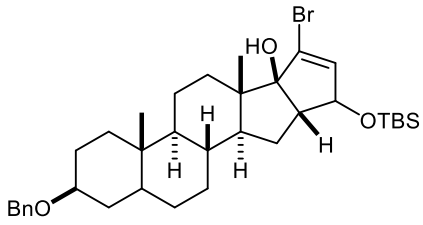
The reaction of a 3:1 diastereomeric mixture of **13e** (96 mg, 0.20 mmol) by using a 1.11 M ethereal solution of MeLi (0.27 mL, 0.300 mmol) according to the general procedure described above afforded a 3:1 diastereomeric mixture of **14e** (70 mg, 0.19 mmol, 95%). Yellow oil; ^{1}H-NMR ($CDCl_3$) δ: (some peaks are missing due to the solvent)5.61 (1H, s), 4.40 (1H, t, *J* = 3.2 Hz), 2.48-2.43 (1H, m), 2.25 (1H, s), 1.99-1.63 (5H, m), 1.50-1.47 (1H, m), 1.36 (1H, t, *J* = 6.9 Hz), 1.12 (2H, ddd, *J* = 27.5, 16.0, 5.4 Hz), 0.98 (3H, d, *J* = 6.9 Hz), 0.90 (6H, t, *J* = 6.3 Hz), 0.85 (9H, m), 0.03 (6H, m);

2-bromo-1-(tert-butyl)-4-((tert-butyldimethylsilyl)oxy)cyclopent-2-en-1-ol



The reaction of a 3:1 diastereomeric mixture of **13e** (86 mg, 0.20 mmol) by using a 1.11 M ethereal solution of MeLi (0.27 mL, 0.300 mmol) according to the general procedure described above afforded a 3:1 diastereomeric mixture of **14e** (59 mg, 0.17mmol, 86%). Yellow oil; ^{1}H -NMR ($CDCl_3$) δ: (some peaks are missing due to the solvent)7.14 (1H, dt, *J* = 42.2, 6.4 Hz), 6.39 (0H, d, *J* = 8.0 Hz), 5.98 (1H, d, *J* = 20.0 Hz), 4.75 (1H, tt, *J* = 34.7, 4.0 Hz), 4.46 (1H, t, *J* = 5.7 Hz), 2.89-2.57 (2H, m), 2.31-1.98 (3H, m), 1.69-1.61 (1H, m), 1.23-0.68 (40H, m), 0.07 (12H, dt, *J* = 55.9, 26.5 Hz).

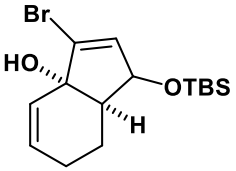
3-benzyloxy 16, 17-bromocycloepiandrostane (14k)



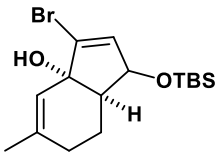
The reaction of **13e** (89 mg, 0.142mmol) by using a 1.11 M ethereal solution of MeLi (0.27 mL, 0.300 mmol) according to the general procedure described above afforded **14e** (141 mg, 0.20 mmol, 71%). Yellow oil.

3-bromo-1-((tert-butyldimethylsilyl)oxy)-1,6,7,7a-tetrahydro-3aH-inden-3a-ol

The reaction of of a 5:1 diastereomeric mixture **13e** (57 mg, 0.166mmol) by using a 1.11 M ethereal solution of MeLi (0.27 mL, 0.300 mmol) according to the general procedure described above afforded a 5:1 diastereomeric mixture of **14e** (84 mg, 0.20 mmol,83%). Yellow oil; ^{1}H -NMR ($CDCl_3$) δ: (some peaks are missing due to the solvent)7.11 (1H, dd, *J* = 27.8, 20.9 Hz), 5.95 (1H, t, *J* = 4.9 Hz), 5.83 (1H, d, *J* = 9.7 Hz), 5.60 (2H, dd, *J* = 81.0, 9.5 Hz), 4.94 (1H, t, *J* = 8.3 Hz), 4.34 (0H, d, *J* = 5.7 Hz), 3.57 (0H, d, *J* = 14.9 Hz), 2.37 (1H, dd, *J* = 14.9, 6.3 Hz), 2.28 (1H, t, *J* = 6.0 Hz), 2.05 (4H, tt, *J* = 42.7, 15.5 Hz), 1.81-1.71 (3H, m), 1.46 (3H, ddd, *J* = 51.5, 35.5, 12.9 Hz), 1.25 (3H, ddd, *J* = 44.8, 22.5, 15.3 Hz), 0.94-0.68 (18H, m), 0.12 (2H, dd, *J* = 33.2, 19.5 Hz), -0.02 (8H, d, *J* = 18.3 Hz).

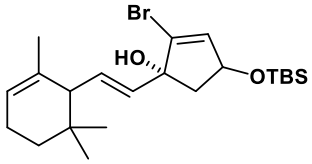


3-bromo-1-((tert-butyldimethylsilyl)oxy)-5-methyl-1,6,7,7a-tetrahydro-3aH-inden-3a-ol



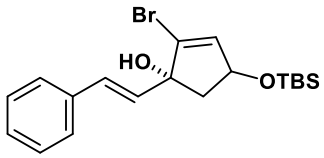
The reaction of a 5:1 diastereomeric mixture of **13e** (87 mg, 0.20 mmol) by using a 1.11 M ethereal solution of MeLi (0.27 mL, 0.300 mmol) according to the general procedure described above afforded a 5:1 diastereomeric mixture of **14e** (50 mg, 0.14 mmol, 69%). Yellow oil; ^{1}H-NMR ($CDCl_3$) δ: 6.61 (1H, s), 4.40 (1H, t, *J* = 3.2 Hz), 2.48-2.43 (1H, m), 2.25 (1H, s), 1.99-1.63 (5H, m), 1.50-1.47 (1H, m), 1.36 (1H, t, *J* = 6.9 Hz), 1.12 (2H, ddd, *J* = 27.5, 16.0, 5.4 Hz), 0.98 (3H, d, *J* = 6.9 Hz), 0.90 (6H, t, *J* = 6.3 Hz), 0.85 (9H, m), 0.03 (6H, m);

2-bromo-4-((tert-butyldimethylsilyl)oxy)-1-((E)-2-(2,6,6-trimethylcyclohex-2-en-1-yl)vinyl)cyclopent-2-en-1-ol



The reaction of a 4:1 diastereomeric mixture of **13e** (87 mg, 0.20 mmol) by using a 1.11 M ethereal solution of MeLi (0.27 mL, 0.300 mmol) according to the general procedure described above afforded a 4:1 diastereomeric mixture of **14e** (83 mg, 0.19 mmol, 96%). Yellow oil; ^{1}H -NMR ($CDCl_3$) (some peaks are missing due to the solvent) δ: 5.96 (2H, d, *J* = 5.2 Hz), 5.55-5.26 (10H, m), 4.81 (1H, s), 4.57 (1H, s), 2.52 (1H, q, *J* = 6.5 Hz), 2.38 (2H, q, *J* = 6.9 Hz), 2.29 (24H, s), 2.09 (4H, dd, *J* = 27.8, 17.5 Hz), 1.95 (11H, t, *J* = 13.7 Hz), 1.46 (21H, ddd, *J* = 81.8, 26.2, 15.6 Hz), 1.17 (11H, dq, *J* = 56.7, 11.7 Hz), 0.81 (59H, tt, *J* = 26.1, 18.5 Hz), 0.15-0.00 (20H, m).

2-bromo-4-((tert-butyldimethylsilyl)oxy)-1-((E)-styryl)cyclopent-2-en-1-ol



The reaction of a 4:1 diastereomeric mixture of **13e** (95 mg, 0.20 mmol) by using a 1.11 M ethereal solution of MeLi (0.27 mL, 0.300 mmol) according to the general procedure described above afforded a 4:1 diastereomeric mixture of **14e** (69.3 mg, 0.176 mmol, 88%). Yellow oil.

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