Review

Syntheses of Biologically Active Natural Products and Leading Compounds for New Pharmaceuticals Employing Effective Construction of a Polycyclic Skeleton

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Cascade reactions are useful methods for the construction of polycyclic skeletons, which are important cores for biological activities. A variety of cascade reactions carried out under multiple reaction conditions, such as pericyclic, polar, radical, and transition metal-catalyzed reaction conditions, have been investigated. Culmorin, pentalenene, pentalenic acid, deoxypentalenic acid, longiborneol, cedrandiol, 8,14-cedranoxide, atisirene, atisine, and estrane-type steroids were synthesized *via* the intramolecular double Michael reaction. Aza double Michael reaction was applied to the syntheses of tylophorine, epilupinine, tacamonine, and paroxetine. Furthermore, sequential Michael and aldol reactions were performed in both intramolecular and intermolecular manners, leading to the formation of polycyclic compounds fused to a four-membered ring. Synthesis of paesslerin A utilizing a multicomponent cascade reaction revealed an error in the proposed structure. Unique cascade reactions carried out under radical and transition metal-catalyzed reaction conditions were also investigated. With the combination of several cascade reactions, serofendic acids and methyl 7β-hydroxykaurenoate, both of which have neuroprotective activity, were synthesized in a selective manner.

Key words polycyclic compound; cascade reaction; polar reaction; radical reaction; transition metal-catalyzed reaction

1. Introduction

When various functional groups exist on a polycyclic skeleton, the three-dimensional relationships of the functional groups are restricted and a specific biological activity would be expected due to the rigid conformation (Chart 1). Therefore the development of an efficient method for the construction of polycyclic ring systems is highly desirable, particularly in the field of medicinal chemistry. Cascade reactions[2—7)] forming a number of bonds in one operation are useful for the creation of polycyclic compounds. Many stereogenic centers can be created at the same time. A reduction in the number of reaction steps save reagents and energy and reduce waste. Therefore cascade reactions are important from the economic and green chemistry points of view. In this context, we have been studying cascade reactions under various reaction conditions, such as pericyclic, polar, radical, and transition metal-catalyzed reaction conditions.

2. Cascade Reaction under Polar Conditions

2.1. Double Michael Reaction The bicyclo[2.2.2]octane skeleton is a framework of several natural products. We encountered difficulty in the stereoselective synthesis of the corresponding polycyclic systems using the intramolecular Diels–Alder reaction.[8)] The problem was solved by employing the intramolecular double Michael reaction, as shown in Chart 2. The treatment of cyclohexenones **1** and **3** with an α,β-unsaturated ester side chain at the 6 or 5 position with $LiN(TMS)_2$ provided the polycyclic bridged compounds **2** and **4** in highly stereoselective manners, respectively.[9,10)] The objective products were produced *via* ideal transition states, fixed by the coordination with lithium ion.

As a typical example of the application of this methodology, the synthesis of (±)-culmorin (**13**)[11)] is shown in Chart

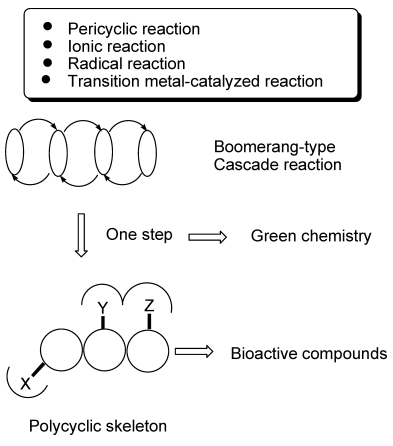

Chart 1. General Concepts for the Present Study

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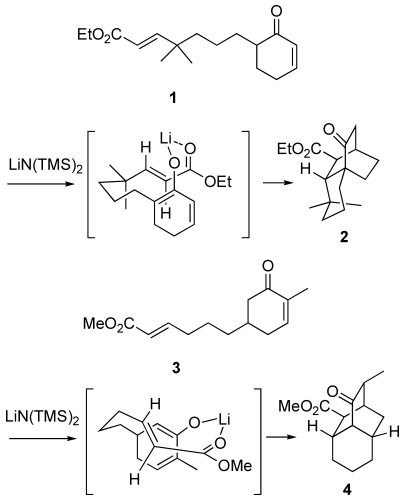

Chart 2. Intramolecular Double Michael Reaction

3. The substrate **9** of the key reaction was prepared by starting with the tricyclic compound **5**.[12] Alkylation of **5**, followed by the retro Diels–Alder reaction, gave the enone **7**. 1,2-Addition and successive oxidative rearrangement afforded the methylated enone **8**, which was then converted to **9** using a standard method. Treatment of **9** with $LiN(TMS)_2$ provided the tricyclic compound **10** as a single stereoisomer in quantitative yield.

The ester group of product **10** must be transformed into the hydroxyl group with the retention of the stereochemistry. Therefore, after hydrolysis of ester group, the oxidative decarboxylation of carboxylic acid **11** was examined under various conditions. The desired compound **12** was obtained in good yield when Garner *et al.*'s procedure[13] was applied. Reduction of the carbonyl group of **12** with metallic Li in liquid ammonia in the presence of MeOH gave **13** quantitatively. Thus a total synthesis of the racemate of culmorin (**13**) was accomplished in 46% overall yield in 11 steps from the known compound **5**.[14,15]

2.2. Aza Double Michael Reaction When the carbanion forming the α-position of the carbonyl group is replaced with nitrogen, the sequential Michael reaction (aza double Michael reaction) produces heterocyclic compounds, as shown in Chart 4.

The desired intramolecular cascade reaction was successfully performed under several reaction conditions, such as heating with a mixture of TMSCl, Et_3N, and $ZnCl_2$,[16] treatment with TBSOTf in the presence of Et_3N,[17,18] treatment with TMSI in the presence of $(TMS)_2NH$,[19] and treatment with Bu_2BOTf in the presence of $(TMS)_2NH$.[19]

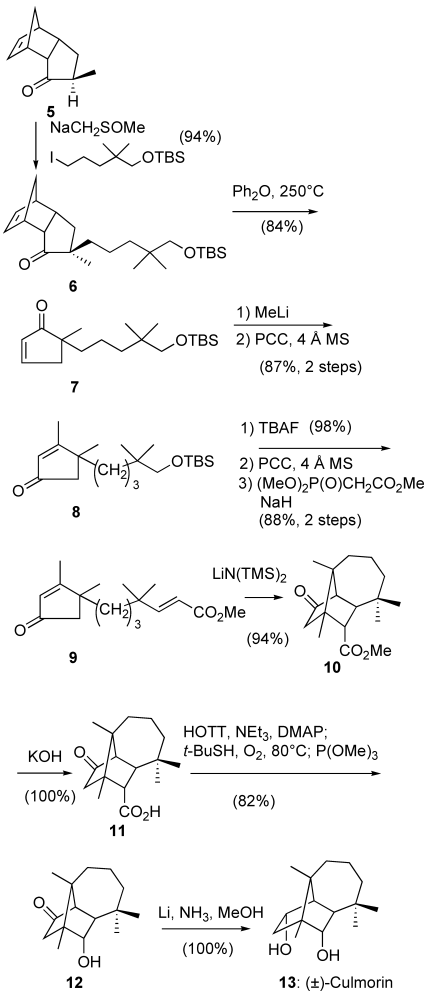

Chart 3. Synthesis of (±)-Culmorin

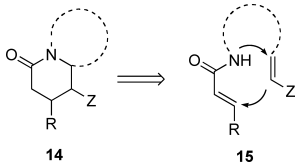

Chart 4. Aza Double Michael Reaction

The naturally occurring enantiomer of tylophorine (**23**)

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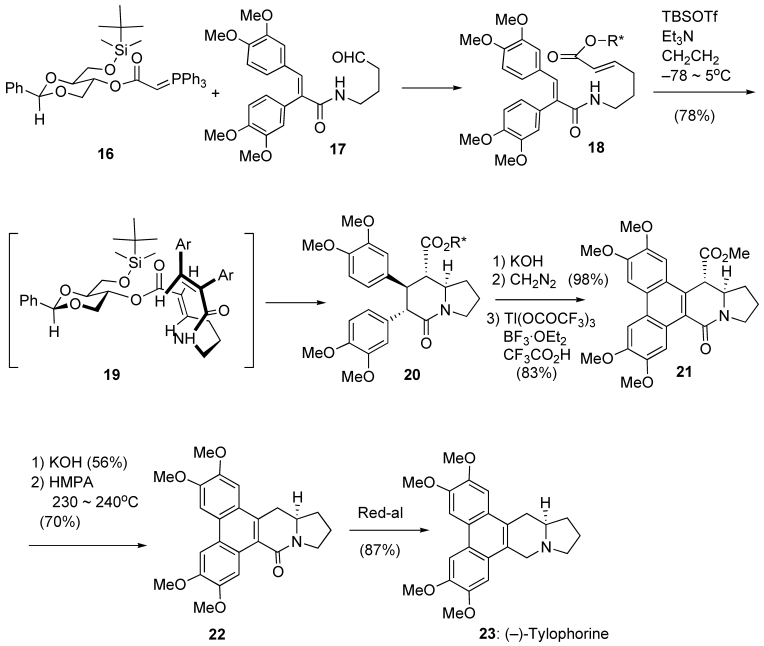


Chart 5. Synthesis of (−)-Tylophorine

was synthesized by the diastereofacially controlled intramolecular aza double Michael reaction. Prior to our studies, optically active tylophorine was synthesized starting with amino acids.[20,21] Therefore the naturally occurring (*R*)-enantiomer (**23**) had not been chemically prepared. We designed an asymmetric synthesis of tylophorine with the desired absolute configuration in the cascade reaction, for which the stereochemistry was controlled by a chiral auxiliary.

A novel chiral auxiliary was prepared from glucose and converted to the phosphorane **16**, which was reacted with the aldehyde **17** to afford the α,β-unsaturated ester **18**. Treatment of **18** with TBSOTf in the presence of Et_3N furnished the indolizidine **20** as a single diastereomer (Chart 5).

The presence of Lewis acid such as TBSOTf forces the α,β-unsaturated ester part to become a *s-trans* form, and the α,β-unsaturated amide part approaches from the less hindered side. Thus the desired compound with the (*R*)-configuration at the angular position could be preferentially formed *via* the transition state **19**. The result was confirmed by the transformation of product **20** into natural product **23**.

After conversion of **20** to the corresponding methyl ester, the phenanthroindolizidine skeleton of **21** was constructed through oxidative aryl coupling. The removal of the ester function *via* the carboxylic acid, followed by the reduction with Red-al, produced (−)-tylophorine (**23**). Thus the first asymmetric synthesis of the natural enantiomer of tylophorine was effectively achieved.[22—24]

The intermolecular aza double Michael reaction was further elaborated after numerous trials.[25,26] The method was applied to the synthesis of paroxetine (**28**), a selective serotonin reuptake inhibitor (SSRI), as shown in Chart 6. Treatment of the mixture of the amide **24** and methyl acrylate with TBSOTf in the presence of Et_3N and *t*-BuOH provided the two stereoisomers **25** and **26**. The minor *cis* isomer **26** could be epimerized to **25** by treatment with NaOMe. The *trans* isomer **25** was reduced with $LiAlH_4$ to afford the piperidine **27**, which had been correlated with paroxetine (**28**). Thus the

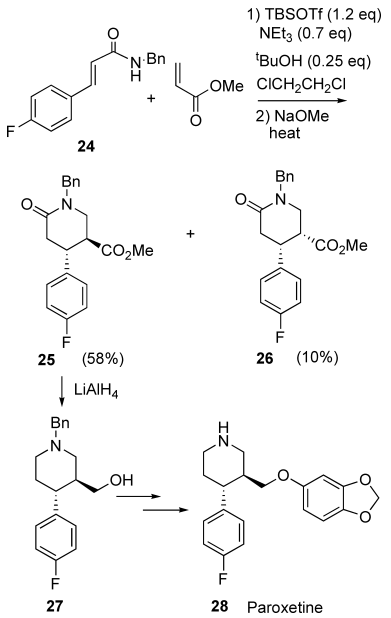


Chart 6. Synthesis of Paroxetine *via* Intermolecular Aza Double Michael Reaction

important antidepressant was prepared in short steps.[27,28]

The double Michael reaction was further applied to the syntheses of pentalenene (**29**),[29] pentalenic acid (**30**),[30] deoxypentalenic acid (**31**),[29] longiborneol (**32**),[15,31] cedrandiol (**33**),[32] 8,14-cedranoxide (**34**),[33] atisirene (**35**),[34,35] atisine (**36**),[36—38] estrane (**37**),[39] epilupinine (**38**),[40] and tacamonine (**39**)[41] (Fig. 1).

2.3. Michael–Aldol Reaction Four-membered ring systems are important structural units frequently found in biologically important compounds. Among the synthetic methods available for the synthesis of cyclobutanes, [2+2] cycloaddition is the most commonly used. As an extension of our study of the double Michael reaction, we envisaged the

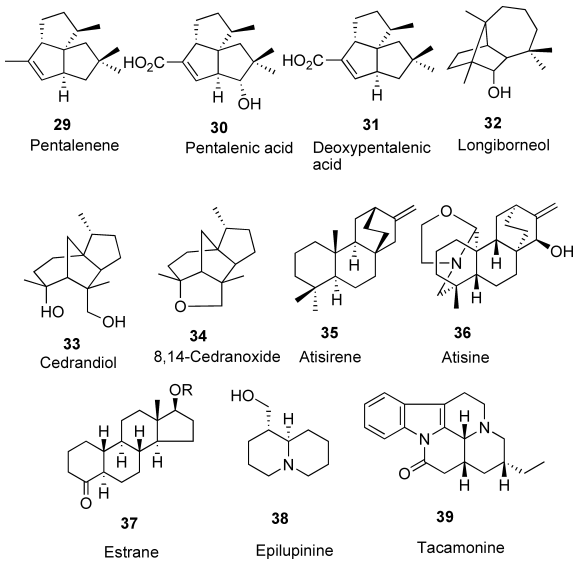


Fig. 1. Other Natural Products Synthesized *via* Double Michael Reaction

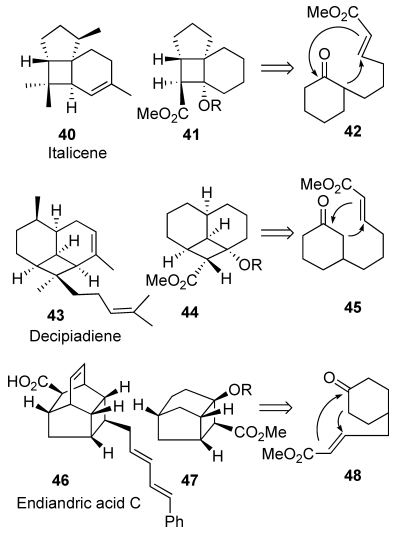


Chart 7. Plan of Intramolecular Michael–Aldol Reaction

formation of polycyclic ring systems fused to a cyclobutane by the sequential Michael and aldol reactions. That is, the cascade reactions of α-substituted **42**, β-substituted **45**, and γ-substituted cyclohexanones **48** would provide tricyclic compounds **41**, **44**, and **47**, which are the frameworks of italicene (**40**), decipiadiene (**41**), and endiandric acid C (**46**), respectively (Chart 7).

The intramolecular Michael–Aldol reaction can be performed under various reaction conditions, such as treatment with TBSOTf and Et_3N,[42] treatment with TMSI and $(TMS)_2NH$,[43] and treatment with Bu_2BOTf and $(TMS)_2NH$.[44] Thus treatment of the symmetrical ketone **48** with TBSOTf in the presence of Et_3N or TMSI in the presence of $(TMS)_2NH$ gave **49** in a good yields (Chart 8). Both (*E*)- and (*Z*)-unsaturated esters of **48** produced the same compound **49**.[42] The tetracyclic compound **51** was obtained in quantitative yield from **50**.[42] For the cascade reaction of **42** having two types of hydrogens, thermodynamically controlled reaction conditions, TMSI-$(TMS)_2NH$, were required. The same product **52** was provided from both (*E*)- and (*Z*)-**42**. Therefore the stepwise mechanism was clearly supported for the cascade process.[43]

The asymmetric cascade reaction was further studied in the presence of chiral amines.[45]

Although the intermolecular Michael–Aldol reaction between ketones and α,β-unsaturated carbonyl compounds has not yet been carried out, four-membered carbocyclic compounds could be prepared by the reaction of the silyl enol ethers with α,β-unsaturated carbonyl compounds in the presence of a catalytic amount of Lewis acids (Chart 9).[46—48] The best result was obtained when the reaction of **53** with methyl acrylate was carried out in the presence of Tf_2NH.[47] Use of the equivalent mole of Tf_2NH did not produce **54**, but the bicyclic compound **54** was provided in quantitative yield when using a catalytic amount of Tf_2NTBS. The results indicate that the actual reagent must be Tf_2NTBS, which is formed by the reaction of the silyl enol ether **53** with Tf_2NH.[48—53]

Cyclobutane derivatives **56**—**61** were prepared from **55**

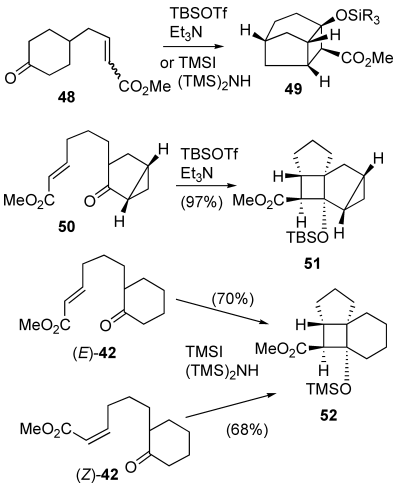
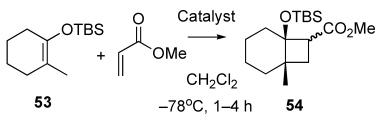


Chart 8. Intramolecular Michael–Aldol Reaction



Run	Catalyst (mol%)	Yield % (*trans* : *cis*)
1	$EtAlCl_2$ (20)	79 (95 : 5)
2	Tf_2NH (1.0)	92 (100 : trace)
3	Tf_2NH (0.1)	98 (100 : trace)
4	Tf_2NTBS (1.0)	99 (9 : 1)

Chart 9. Intermolecular Michael–Aldol Reaction

and **59** *via* similar reactions, as shown in Chart 10.[48]

The above procedure is a practical method for the preparation of cyclobutane and cyclobutene derivatives. Examples of gram-scale production are shown in Chart 11. Thus the bicyclic cyclobutane **56** and the bicyclic cyclobutene **61** were

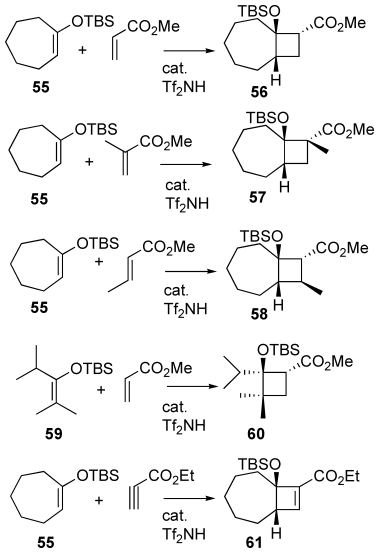


Chart 10. Syntheses of Cyclobutanes and Cyclobutene

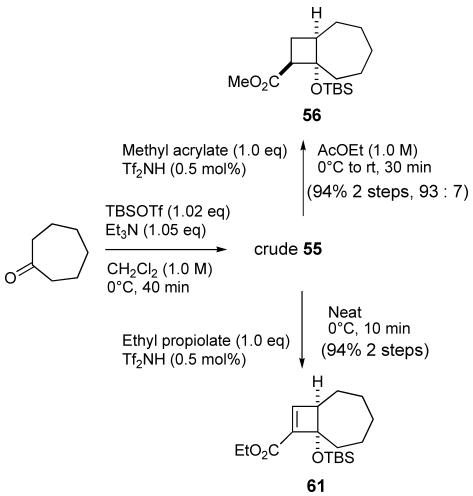


Chart 11. Practical Syntheses of Cyclobutane and Cyclobutene

synthesized in excellent yields from cycloheptanone *via* **55** in two steps under mild reaction conditions.[48,54]

Tf_2NH is a good catalyst for the Diels–Alder reaction. Thus bicyclic compound **64** was obtained by the cycloaddition of the enone **62** with diene **63**, catalyzed by Tf_2NH and then reacted with methyl acrylate in the presence of Tf_2NH to afford the tricyclic compound **65** as a mixture of diastereoisomers. The tricyclic structure is a skeleton of sterpurene-type sesquiterpenes **66** and **67** (Chart 12).[48]

On the basis of the above observations, we devised a three-component cascade reaction. The formation of tricyclic compound **69** was achieved by the reaction of one equivalent of the diene **68** and two equivalent of methyl propiolate. The cascade reaction was conducted with three different Lewis acids, as shown in Chart 13.[47]

Reduction of product **69** with DIBALH provided the unexpected alcohol **70**, which was then transformed into paesslerin A (**71**) (Chart 14), isolated from the soft coral *Alcyonium paessleri*.[55] The racemate of natural product **71** was totally synthesized in 34% overall yield in eight steps from a

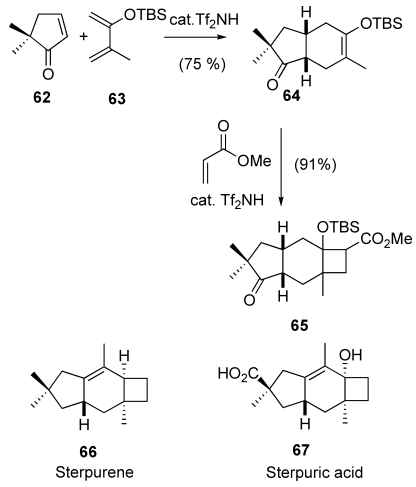
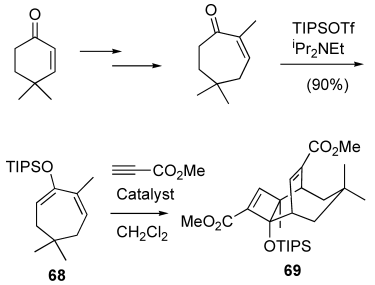


Chart 12. Consecultive [4+2] and [2+2] Cycloadditions: Construction of a Stepurane Skeleton



Run	Catalyst (mol%)	Conditions	Yield %
1	$EtAlCl_2$ (50)	-40°C – rt, 24 h	92
2	$AgNTf_2$ (1)	0°C, 40 min	93
3	$HNTf_2$ (3)	0°C – rt, 11 h	70

Chart 13. Synthesis of Proposed Paesslerin A (1)

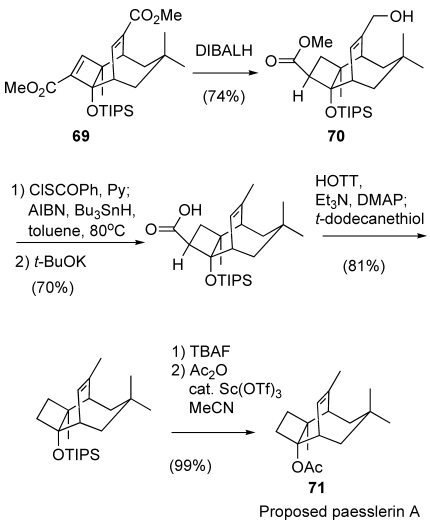


Chart 14. Synthesis of Proposed Paesslerin A (2)

known compound. However, the spectral data of the synthetic compound were not consistent with the reported ones for the natural product. The structure of the synthetic compound was verified by X-ray analysis. The result clearly indicates that a

revision of the structure of natural paesslerin A is required.[47)]

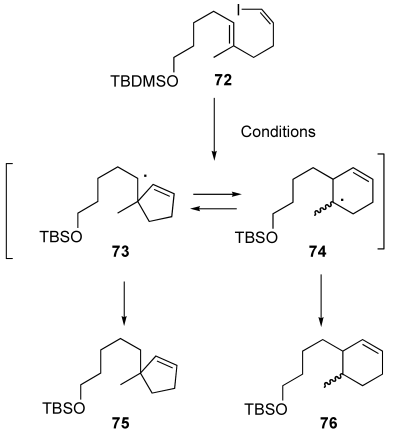
3. Cascade Reaction under Radical Conditions

Cascade radical cyclization starting with vinyl radical was studied, and radical cyclization of vinyl iodide **72** was first examined (Chart 15). When the reaction was carried out in refluxing benzene, only six-membered compounds **76** were obtained as a mixture of two stereoisomers. On the other hand, treatment with tin hydride in the presence of triethylborane at −40 °C produced a mixture of five-membered compound **75** and six-membered compounds **76** in a ratio of 2 : 1. These results indicates that 5-*exo* cyclization would take place in a kinetic controlled manner. The resulting five-membered homoallyl radical **73** would be rearranged to six-membered radical **74** under thermodynamically controlled reaction conditions.[56)]

Very similar results were obtained in the case of radical cyclization of polyene **77**, as shown in Chart 16. Thus the desired tricyclic compounds **78** were produced from **77** as a mixture of stereoisomers by the reaction carried out in refluxing benzene, while monocyclic five-membered compound **79** was obtained at −40 °C. The result confirmed that 5-*exo* cyclization is a kinetically controlled reaction, and 6-*endo* cyclization is a thermodynamically controlled reaction.[56)]

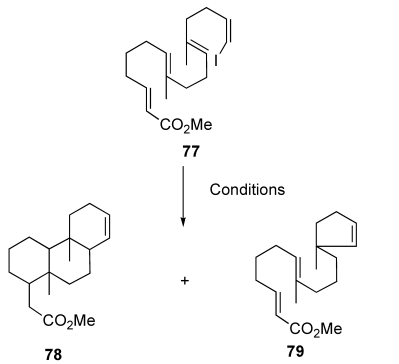
It is interesting that when bromo triene **80** was subjected to radical cyclization, linear triquinane-type compounds **81** and **82** were produced as a mixture of stereoisomers at a higher temperature, with refluxing benzene, and at room temperature (Chart 17). *Cis-syn-cis* and *cis-anti-cis* isomers were isolated upon column chromatography.[57,58)] Similar results were recently reported by Curran and coworkers.[59)]

The different reactivity of vinyl radicals **83** and **84** could be explained as shown in Chart 18. Since further cyclization of the initially formed five-membered radical **85** is not possible, homoallyl-homoallyl rearrangement under thermody-



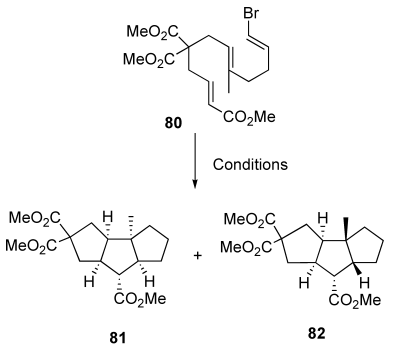
Run	Conditions	Ratio of **75** and **76**
1	Bu_3SnH, AIBN, benzene, reflux	0 : 1
2	Bu_3SnH, Et_3B, toluene, O_2, –40°C	2 : 1

Chart 15. Cyclization Starting with Vinyl Radical



Run	Conditions	Yield (%) **78**	Yield (%) **79**
1	$(TMS)_3SiH$, AIBN, benzene, reflux	77	0
2	Bu_3SnH, Et_3B, toluene, O_2, –40°C	0	99

Chart 16. Cascade Reaction Starting with Vinyl Radical (1)



Run	Conditions	Yield (%)	Ratio of **81** and **82**
1	TMS_3SiH, AIBN benzene, reflux	80	4 : 3
2	Bu_3SnH, Et_3B O_2, benzene, rt	83	4 : 3

Chart 17. Cascade Reaction Starting with Vinyl Radical (2)

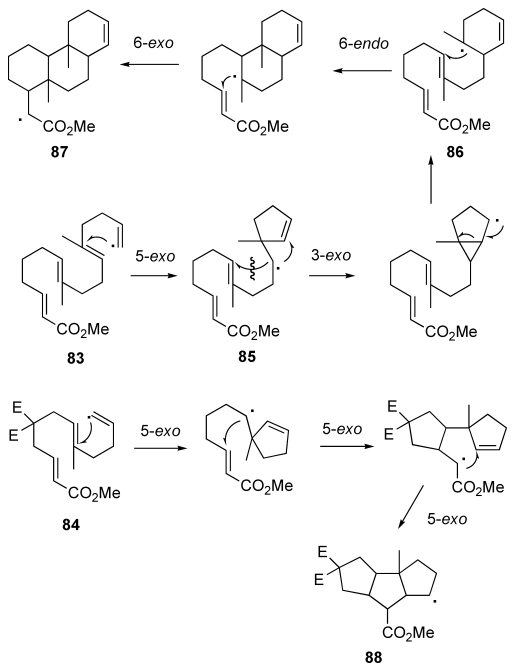
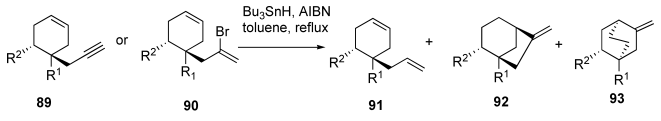


Chart 18. Mechanism of Cascade Radical Cyclization



Run	Substrate	R^1	R^2	Yield (%)	Ratio of products 91 : 92 : 93
1	89	CO_2Me	H	80	0 : 39 : 61
2	89	CO_2Me	Me	69	0 : 32 : 68
3	90	CO_2Me	Me	61	6 : 12 : 82
4	90	CO_2Me	CO_2Me	80	13 : 11 : 76
5	90	—COOCH$_2$—		77	0 : 90 : 10

Chart 19. Selective Construction of Bicyclo[3.2.1]octane and Bicyclo[2.2.2]octane

namically controlled reaction conditions affords the six-membered homoallyl radical **86**, of which 6-*endo*, followed by 6-*exo* cyclization, provides tricyclic radicals **87**. On the other hand, in the case of the other vinyl radical **84**, sequential 5-*exo* cyclizations would easily take place to give linear triquinane radicals **88**.[58]

It was made clear that the regioselectivity of the cyclization of vinyl radical could be controlled by the reaction temperature and also by the structure of substrates. The results of cyclization for the synthesis of bridged compounds are shown in Chart 19. When R^2 was a methyl or methoxycarbonyl group, the major products were bicyclo[2.2.2]octane derivatives **93**, as shown in entries 1—4. On the other hand, bicyclo[3.2.1]octane **92** was obtained as a major product in the case of lactone, as shown in entry 5. It was considered that reduction of the initially formed homoallyl radical with tin hydride was hindered by the presence of the R^2 group. Therefore further rearrangement led to the thermodynamically more stable bicyclo[2.2.2]octane derivatives **93** as major products. In the case of lactone, the bicyclo[3.2.1]octane **92** would be more stable.[60] It was thus established that selective formation of bicyclo[2.2.2]octane and bicyclo[3.2.1]octane could be controlled depending on the substrate.

On the basis of the above findings, syntheses of atisane and kaurene using radical cyclization were planed, and methyl 7β-hydroxykaurenoate (**94**) and methyl gummifolate (**97**) were selected as target molecules. The synthetic plans for the two diterpenes are shown in Chart 20. The bicyclo[3.2.1]octane **95**, a synthetic intermediate of methyl 7β-hydroxykaurenoate (**94**), would be obtained by radical cyclization of the acetylene **96**, and bicyclo[2.2.2]octane **98**, an intermediate of methyl gummiferolate (**97**), would be synthesized from **99**. Substrates of radical cyclization could be prepared from anhydride **100**. It is known that gummiferolic acid shows a plant growth-regulatory activity similar to or greater than that of gibberellic acid. 7β-Hydroxykaurenoic acid is known to be the biosynthetic precursor of gibberellic acid. It is interesting that both structurally different diterpenoids could be synthesized starting with the same compound using a similar strategy.[61]

Substrate **96** of radical cyclization was prepared in both racemic and optically active forms and then subjected to the key reaction. The desired compound **95** was obtained in a highly selective manner and converted into tetracyclic compound **102** through the intramolecular Diels–Alder reaction of **101** (Chart 21).[61] (−)- and (±)-Methyl 7β-hydroxykaurenoate (**94**) were stereoselectively synthesized *via* **103**.[61,62] In a similar manner, (±)-methyl gummiferolate (**97**) was synthesized.[61] It has been observed that methyl 7β-hydroxykaurenoate (**94**) shows potent neuroprotective activity and optically active **94** displays about twice the activity of the corresponding racemate.[62]

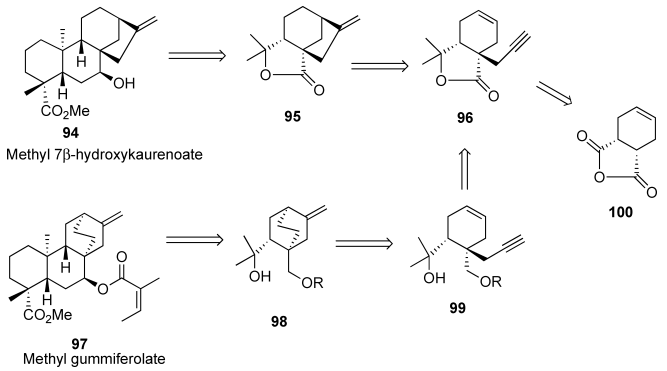


Chart 20. Synthetic Plan of Methyl 7β-Hydroxykaurenoate and Methyl Gummiferolate

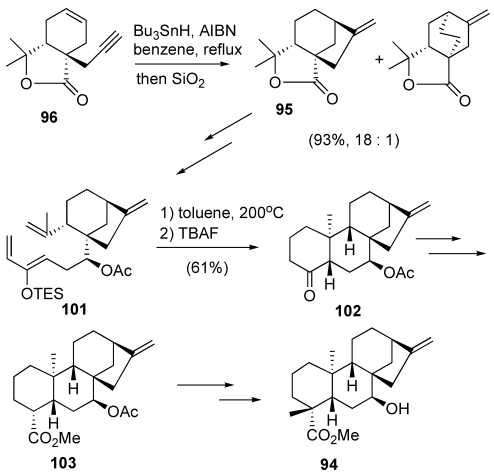


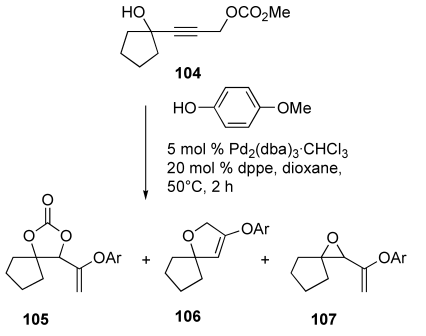
Chart 21. Synthesis of (±)- and (−)-Methyl 7β-Hydroxykaurenoate

Various cascade reactions carried out under radical reaction conditions were studied further.[63—67]

4. Cascade Reaction under Transition Metal-Catalyzed Conditions

Several cascade reactions carried out in the presence of a palladium or ruthenium catalyst have been developed[68–74] and a novel cascade reaction forming cyclic carbonates has been further devised, as depicted in Chart 22. When propargylic carbonate **104** was treated with *p*-methoxyphenol in the presence of a catalytic amount of zero valence of palladium catalyst under an Ar atmosphere, cyclic carbonate **105** was obtained together with dihydrofuran **106** and epoxide **107**. The reaction carried out under a CO_2 atmosphere gave cyclic carbonate **105** in quantitative yield. On the other hand, bubbling with Ar during the reaction to remove CO_2 resulted in the increased formation of dihydrofuran **106** and the epoxide **107**.[75]

On the basis of the above observations, a possible mechanism for the transformation is considered, as shown in Chart



Run	Conditions	Yield (%) 105	106	107
1	Under Ar	85	5	Trace
2	Under CO_2 (1 atm)	96	0	0
3	Bubbling Ar	21	32	11

Chart 22. Synthesis of Cyclic Carbonates

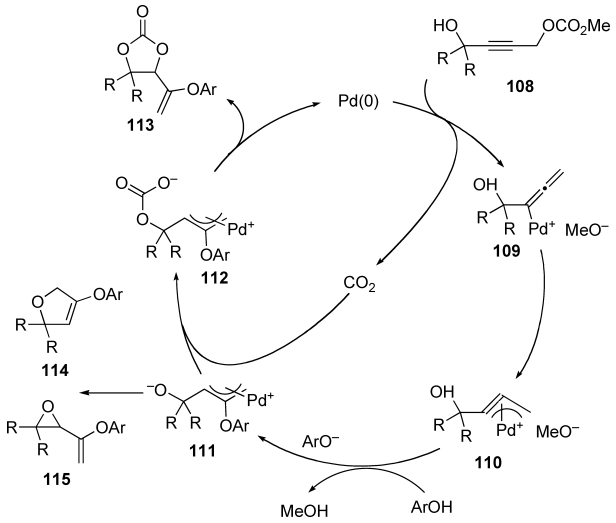


Chart 23. Mechanism of Recycling of CO_2

23. Reaction of propargylic carbonate **108** with palladium catalyst would afford CO_2 and the allenylpalladium complex **109**, which is in equilibrium with π-propargylpalladium complex **110**. Attack of the phenol against **110** yields the π-allylpalladium complex **111**, which could trap CO_2 to provide the cyclic carbonate **113** *via* **112** and zero-valence palladium. Dihydrofuran **114** and epoxide **115** are directly formed from π-allylpalladium complex **111**.[76)]

Various cyclic carbonates were prepared in good yields using this procedure. It was noteworthy that when *p*-methoxyphenylcarbonate **116** was used as a substrate, cyclic carbonate **117** was quantitatively obtained in the absence of the phenol (Chart 24). The reaction must be performed *via* splitting into three components, followed by their recombination without any loss of atoms.[75)]

Catalytic asymmetric synthesis was easily applied to the above CO_2 fixation reaction. Thus highly optically active product **119** was produced from the symmetrical compound **118** in the presence of a catalytic amount of a chiral ligand (Chart 25). The preferred formation of one enantiomer could be explained by the favorable transition state **120** over **121**.[77)]

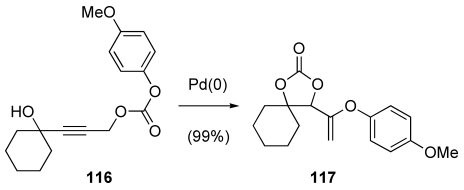


Chart 24. Three-Component Splitting and Reconstruction Reaction

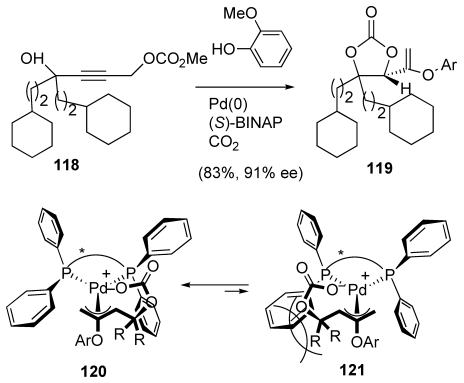


Chart 25. Asymmetric Synthesis of Cyclic Carbonate

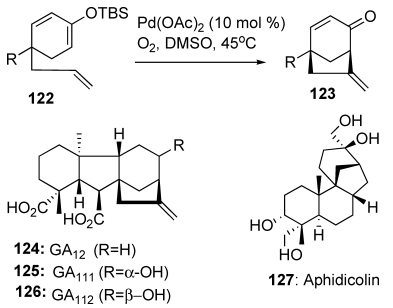


Chart 26. Palladium-Catalyzed Cycloalkenylation Reaction

The chirality transfer reaction was also studied.[78)] Furthermore, formation of cyclic carbonates was performed using allylic carbonates.[79)]

In relation to the transition metal-catalyzed reaction, palladium-catalyzed cycloalkenylation reaction of silyl enol ethers **122** forming bridged compounds **123** were developed by Ito *et al.*[80)] and Kende *et al.*[81)] independently. However, the original method requires a stoichiometric amount of divalent palladium, which is a serious drawback for large-scale preparation. Recently, we have performed the reaction using a catalytic amount of palladium when the reaction is carried out in DMSO under an oxygen atmosphere (Chart 26).[82,83)] With this method, gibberellins **124**—**126**[84)] and aphidicolin (**127**)[85)] were effectively synthesized.

Finally, syntheses of serofendic acids (**136**) using the above methodologies are discussed. Serofendic acids, recently isolated from fetal calf serum,[86)] show a potent protective action against the neurotoxicity induced by glutamate and an NO donor. The quaternary carbon of **129** was constructed starting with **128** in good yield with high optical purity using d'Angelo *et al.*'s method[87)] (Chart 27). Siloxydiene **130**, derived from ketone **129**, was subjected to the palladium-catalyzed cycloalkenylation reaction carried out under

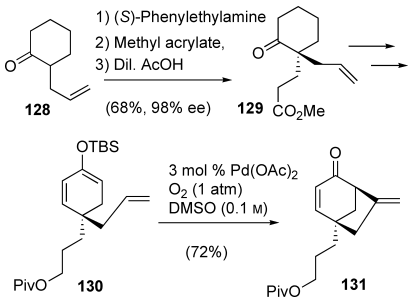


Chart 27. Synthesis of Serofendic Acids (1)

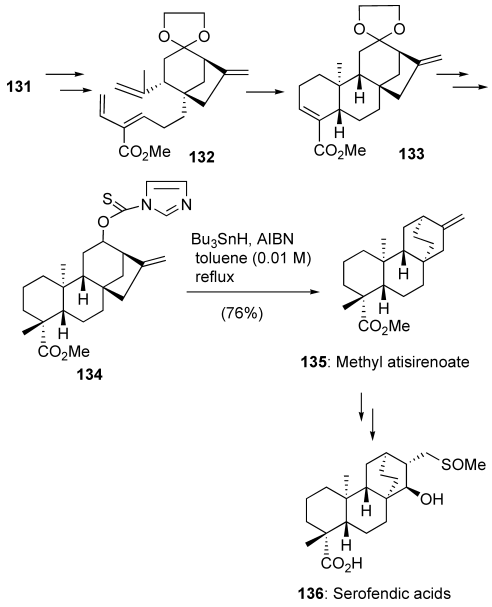


Chart 28. Synthesis of Serofendic Acids (2)

the above conditions. The desired compound **131** was obtained in a large quantity.[88,89)]

The AB ring of kaurene was constructed by the intramolecular Diels–Alder reaction of **132**. The presence of the ester function on the diene is important for the stereoselective production of the desired compound **133**. After conversion to thioimidazolide **134**, the reductive radical reaction was carried out using tin hydride and AIBN. The resulting homoallyl radical was rearranged to methyl atisirenoate (**135**) *via* a cyclopropyl carbinyl radical. No formation of kaurene derivative was observed (Chart 28).[88,89)] Methyl atisirenoate (**135**) was converted into serofendic acids (**136**) in 5 steps. Recently, serofendic acids (**136**) have alternatively been synthesized without use of the toxic tin hydride.[90)]

5. Summary

The usefulness of cascade reactions for syntheses of polycyclic compounds carried out by all chemical means has been demonstrated. These methodologies could be applied for the efficient preparation of various pharmacologically active compounds.

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