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DISSERTATION

Synthesis of Natural Terpenoids Using Anionic 8π Electrocyclic Reactions

(アニオン性 8π 系電子環状反応を利用した
テルペン系天然物の合成)

Ranmaru Kato

Hokkaido University

2025

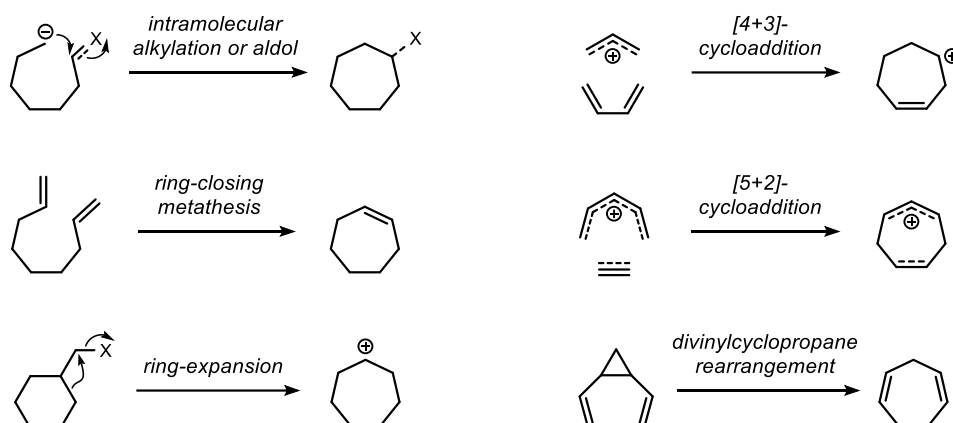
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General Introduction

1. Construction of Seven-Membered Carbocycles

A seven-membered carbocycle widely exists as the core structure of natural products. Notably, terpenoids are the most widespread class of natural products that contain a seven-membered carbocycle in their carbon skeleton. This type of terpenoids, especially which exhibit target-specific bioactivities, have attracted much attention from organic chemists as target compounds of total syntheses. To achieve efficient synthesis of these natural products, various methods for constructing seven-membered carbocycles have been established (Scheme 1). Similar with the formation of five- or six-membered rings, intramolecular C-C σ -bond forming reactions such as intramolecular alkylation or aldol reaction have widely been applied to construct seven-membered carbocycles. Recently, the ring-closing metathesis provided great improvement in constructing carbocycles including seven-membered ones. Since six-membered carbocycles are readily accessible by various synthetic methods, the one-carbon ring expansion reaction of them is useful for obtaining a seven-membered carbocycle. On the other hand, there are some methods for specific formation of seven-membered rings, such as [4+3] and [5+2] cycloaddition reactions^[1] or a divinylcyclopropane rearrangement reaction^[2]. It is noteworthy that these methods are classified as the pericyclic reactions which are expected to proceed in a stereospecific fashion.

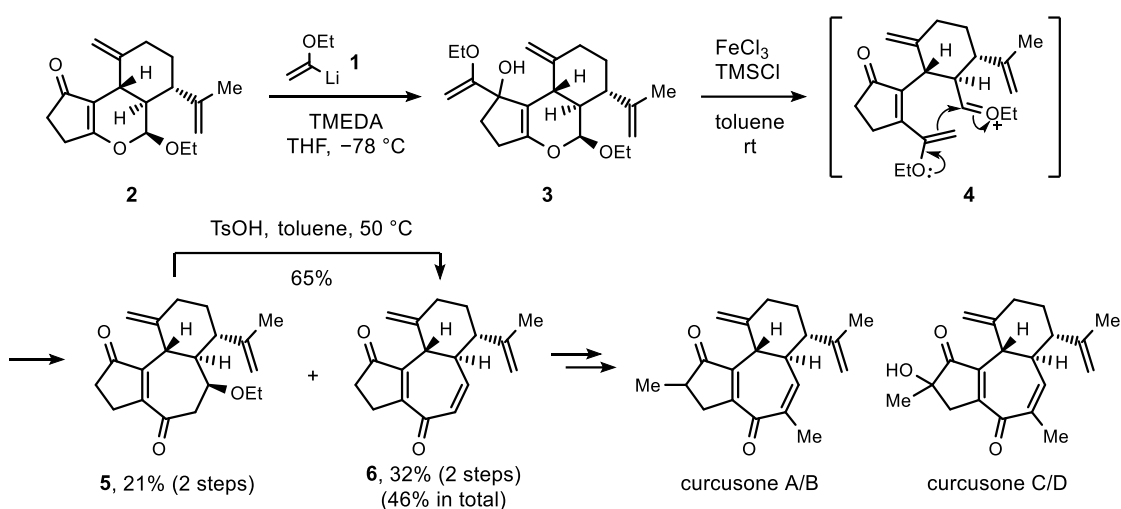


Scheme 1. General methods to construct seven-membered rings

In the next section, several recent examples of natural product synthesis are referenced, with the classification of each method for constructing the seven-membered ring.

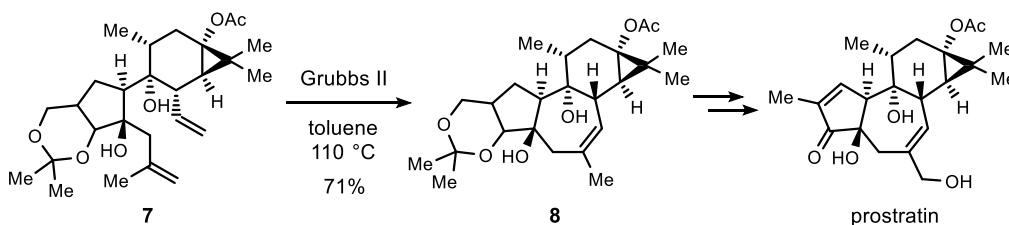
2. Construction of Seven-Membered Carbocycles in Total Synthesis

In 2021, Dai and coworkers reported a short-step total synthesis of curcusone diterpenoids using an intramolecular aldol reaction (Scheme 2).^[3] After 1,2-addition of vinyl lithium **1** to ketone **2**, the resulting compound **3** was subjected to a Lewis acid-mediated ring-opening to generate oxocarbenium ion **4**. This intermediate then underwent an intramolecular aldol reaction to afford tricyclic compounds **5** and **6**. Further acidic treatment of **5** afforded compound **6** which was obtained in 46% yield in total from ketone **2**.



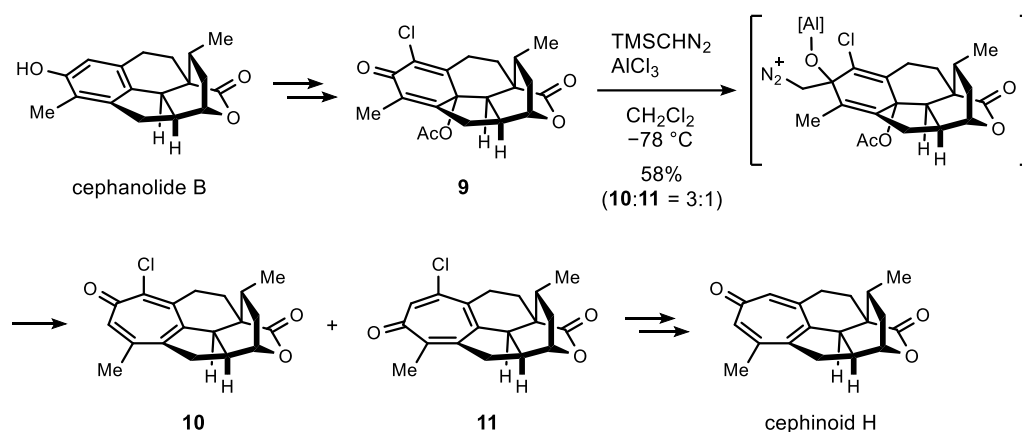
Scheme 2. Intramolecular aldol reaction in Dai's total synthesis of curcusone diterpenoids

It is also known that a similar tricyclic skeleton is accessible via ring-closing metathesis. Li and coworkers reported the total synthesis of prostratin in 2018 in which diene **7** was treated with Grubbs 2nd catalyst to afford tetracycle **8** in 71% yield (Scheme 3).^[4] Later, total synthesis of a related diterpenoid crotaphorbolone was also achieved by Liu and coworkers using a similar ring-closing metathesis strategy for constructing the seven-membered ring.^[5]



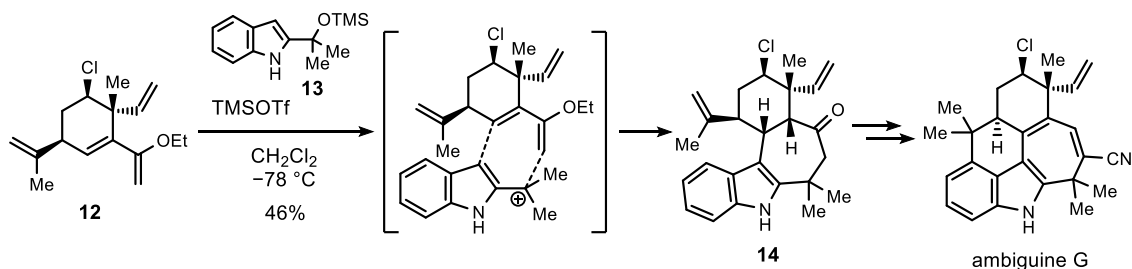
Scheme 3. Ring-closing metathesis in Li's total synthesis of prostratin

The ring-expansion strategy has recently come into fashion in total synthesis of *Cephalotaxus* diterpenoids. Zhao and coworkers, in 2024, reported the concise total syntheses of cephinoid H, fortalpinoid C, and cephanolide E using this strategy (Scheme 4).^[6] Starting with dienone **9**, which was prepared from cephanolide B, Lewis acid-mediated 1,2-addition of TMSCHN₂ followed by ring-expansion afforded a 3:1 regioisomeric mixture of **10** and **11** in 58% yield. Similar reaction conditions were also applied in the synthesis of harringtonolide reported by Sarpong and coworkers.^[7]



Scheme 4. One-carbon ring-expansion in Zhao's total synthesis of cephinoid H

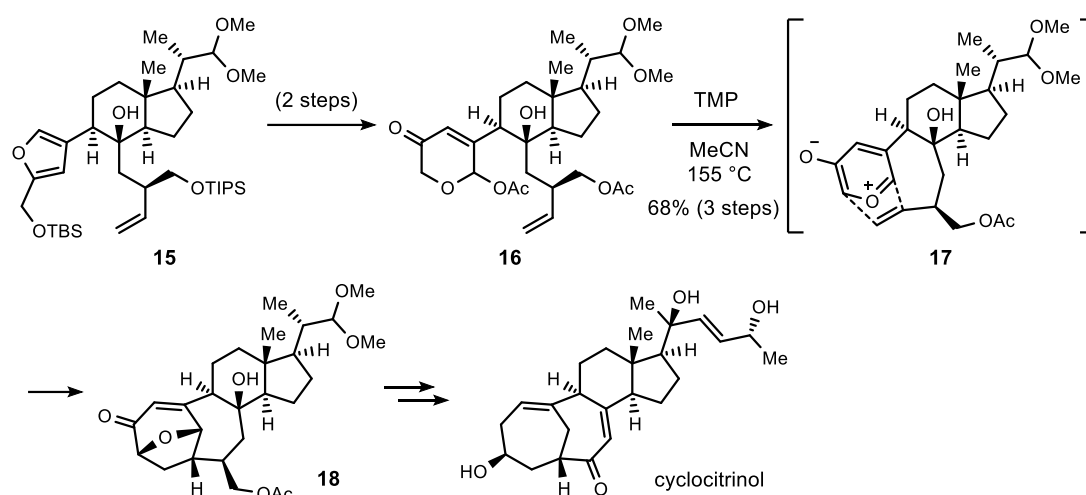
There are a number of examples applying pericyclic reactions in the total synthesis of seven-membered ring-containing natural products. In 2021, Rawal and coworkers achieved a concise total synthesis of ambiguine G using intermolecular [4+3] cycloaddition as the key step (Scheme 5).^[8] In this report, ethoxy diene **12** was subjected to the TMSOTf-promoted [4+3] cycloaddition reaction with indole derivative **13** to afford tetracycle **14** in 46% yield.



Scheme 5. The [4+3] cycloaddition reaction in Rawal's total synthesis of ambiguine G

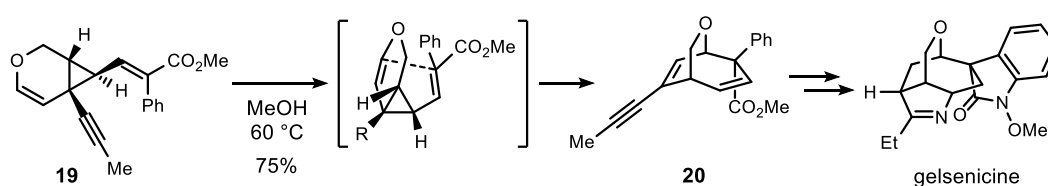
On the other hand, [5+2] cycloaddition reactions are usually performed in an intramolecular fashion. In 2018, Li and coworkers reported the first total synthesis of cyclocitrinol using this

reaction.^[9] After two-step transformation of furan derivative **15**, the precursor **16** was treated with TMP under reflux conditions to generate oxidopyrylium ion **17**. This intermediate underwent [5+2] cycloaddition to afford pentacyclic compound **18** having a bridgehead double bond in 68% yield from **15** (Scheme 6).



Scheme 6. The [5+2] cycloaddition reaction in Li's total synthesis of cyclocitrinol

In 2016, Ferreira and coworkers reported the first racemic total synthesis of gelsenicine via a divinylcyclopropane rearrangement reaction (Scheme 7).^[10] Upon heating in MeOH, substrate **19** underwent isomerization of the vinyl group to *cis*-configuration followed by a stereospecific Cope rearrangement to afford compound **20** in 75% yield.

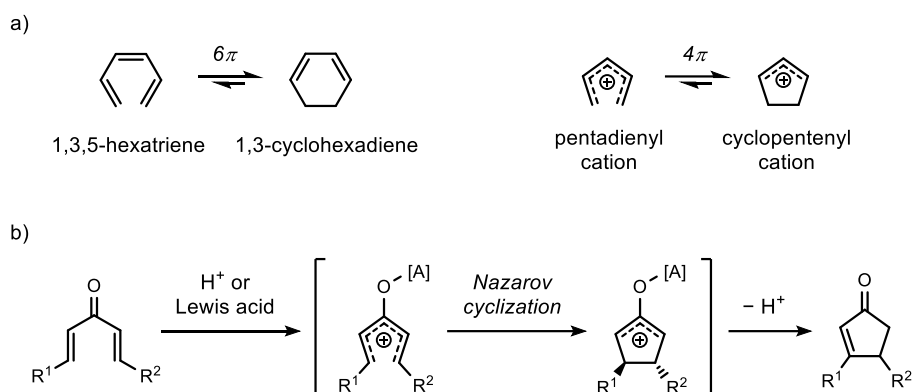


Scheme 7. Divinylcyclopropane rearrangement in Ferreira's total synthesis of gelsenicine

3. Electrocyclic Reaction

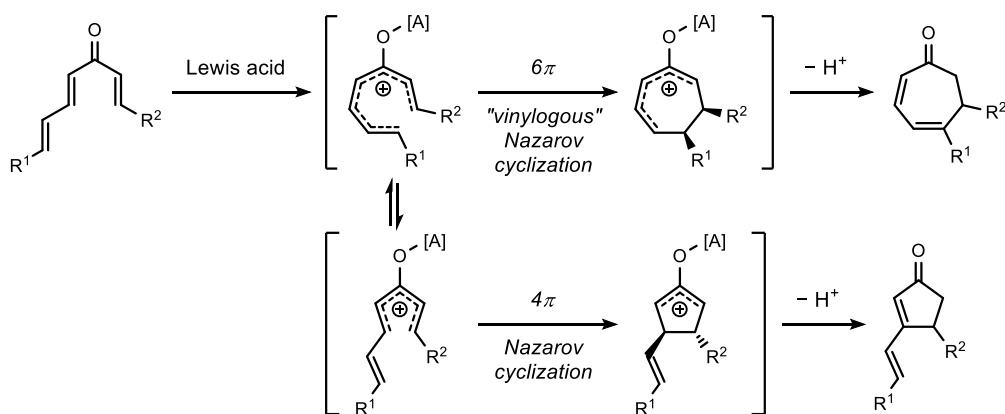
Electrocyclic reaction, which is classified as one of the pericyclic reactions, is known as a powerful tool to construct five- or six-membered carbocycles. The reaction proceeds both thermally and photochemically, and in line with other pericyclic reactions, even a cationic or anionic π -conjugation system can be involved. For example, a linear 1,3,5-hexatriene, which possesses a conjugated 6π -electron system, affords a 1,3-cyclohexadiene by a thermal

electrocyclization (Scheme 8a). In a similar way, a linear pentadienyl cation, possessing a 4π -electron system, gives rise to the corresponding cyclopentenyl cation. Especially, the cationic 4π -electrocyclization reaction of a divinyl ketone motif, which is known as the Nazarov cyclization, has frequently been used for preparing five-membered cyclic enones (Scheme 8b).^[11] It is noteworthy that these reactions have found widespread use in total synthesis of natural products.^[12]



Scheme 8. Typical electrocyclic reactions

Recently it was reported that a cationic 6π -electron system, which was prepared by introducing an additional vinyl group to a divinyl ketone, gives rise to a seven-membered carbocycle by 6π -electrocyclization (Scheme 9).^[13] The “vinylogous Nazarov cyclization” was however found to suffer from a competitive 4π -electrocyclization.

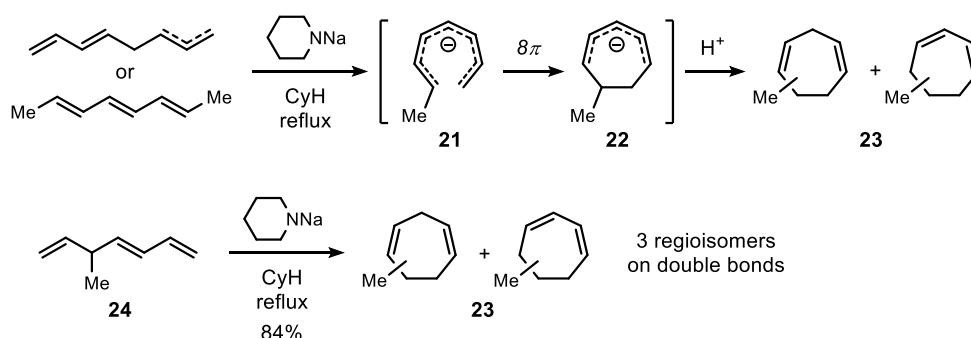


Scheme 9. Vinylogous Nazarov cyclization

On the other hand, construction of seven-membered carbocycles by an anionic electrocyclization reaction was first reported in 1968.

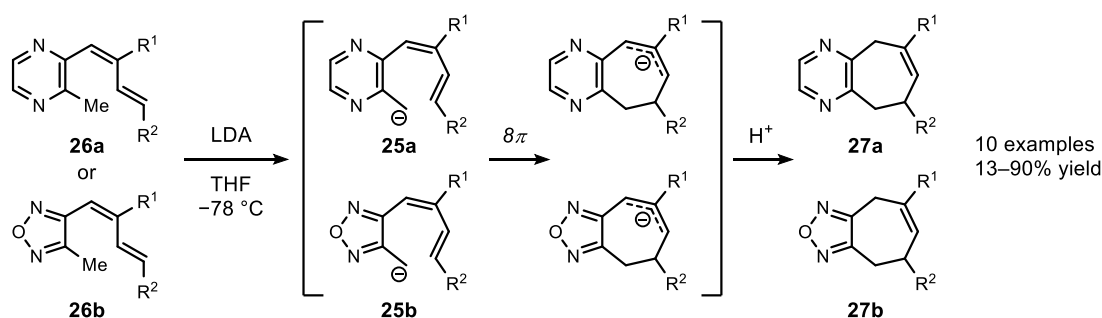
4. Anionic 8π -Electrocyclic Reaction

Thus, Kleinschmidt and coworkers found the cyclization reaction of a heptatrienyl anion generated from linear octatrienes (Scheme 10).^[14] This reaction is triggered by an allylic deprotonation of the substrate by sodium piperidide in boiling cyclohexane. The resulting linear-conjugate anion **21** undergoes an 8π -electrocyclization to form cyclic anion **22** which is protonated to afford cycloheptadienes **23**. The reaction of a skipped 1,3,6-triene **24** was found to give the cyclized product in high yield (84%), but the GLPC analysis indicated that the product was a mixture of three isomers of methylcycloheptadienes.

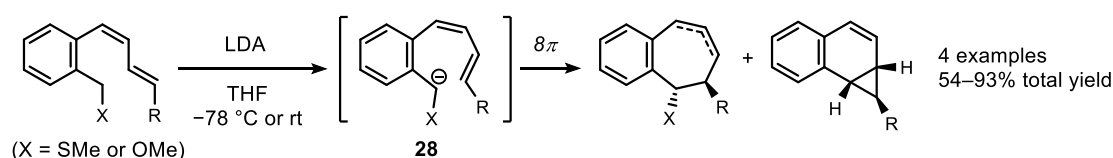


Scheme 10. The initial report of anionic 8π -electrocyclization (Kleinschmidt, 1968)

After the report by Kleinschmidt *et al.*, the anionic 8π -electrocyclization reactions have attracted little attention for over three decades.^[15] One serious drawback is the limitation of the reaction conditions, in which a strong base is required to deprotonate the non-activated allylic position of the substrate heptatrienes. In addition, the non-regioselective protonation of the arising cyclic anion species usually gives a mixture of double bond regioisomers. To overcome these drawbacks, several modified methods using heptatrienes with anion-stabilizing substructures were developed. In 2004, Matsumoto and coworkers reported the cyclization of pyrazine- or oxadiazole-fused heptatrienyl anions **25a** or **25b** (Scheme 11).^[16] They used LDA to generate the anion species at the activated methyl group of substrates **26a** or **26b**. The reaction proceeded at $-78\text{ }^\circ\text{C}$, which enabled the regioselective protonation to afford the products **27a** or **27b** almost as a single regioisomer. Later, in 2013, they also reported the cyclization of benzene-fused heptatrienyl anions **28** (Scheme 12).^[17] It should be noted that an additional functional group (MeS or MeO) was required to enhance the deprotonation at the benzylic position of the substrates.

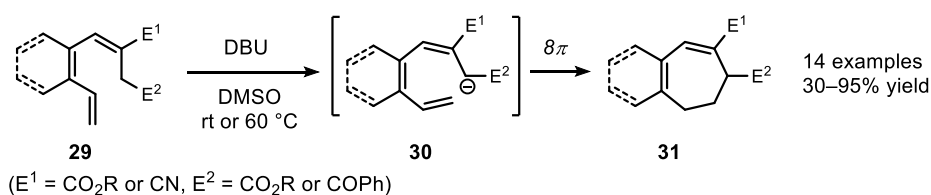


Scheme 11. Synthesis of pyrazine- or oxadiazole-fused cycloheptenes by anionic 8π -electrocyclization (Matsumoto, 2004)



Scheme 12. Synthesis of benzocycloheptenes by anionic 8π -electrocyclization (Matsumoto, 2013)

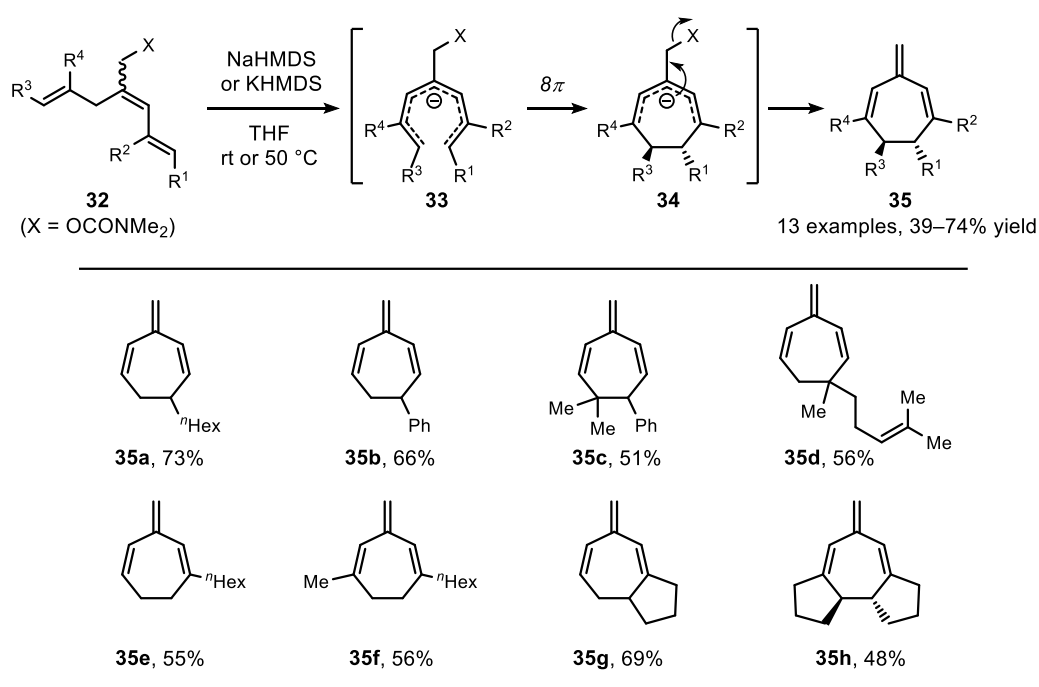
Recently, Orellana and coworkers reported the cyclization reaction of trienes **29** having two electron-withdrawing groups (Scheme 13).^[18] They used DBU, a mild amidine base, to generate a carbanion at the α -position of the electron-withdrawing group. The anion **30** cyclized to afford the corresponding bicyclic compounds **31** in good to high yields. They recognized the reaction as an 8π -electrocyclization, but it may be considered as an intramolecular vinylogous conjugate addition reaction.



Scheme 13. Anionic cyclization of trienes bearing two electron-withdrawing groups (Orellana, 2024)

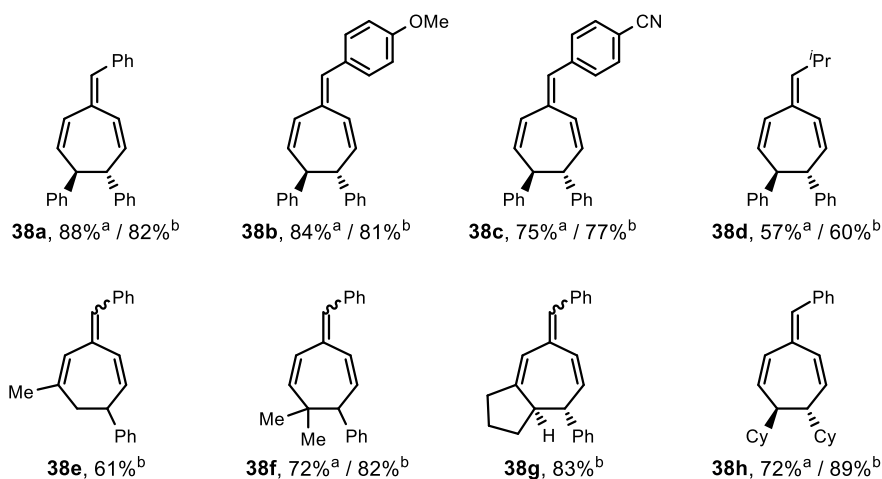
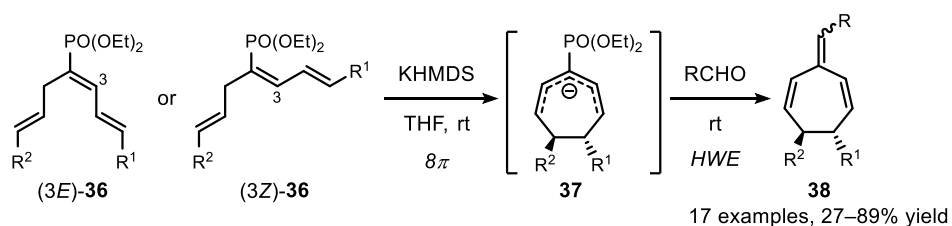
Since 2016, Tanino's research group (including the author) has been independently working on the anionic 8π -electrocyclic reactions. In the earliest publication paper in 2021, Uda and the author developed a tandem anionic cyclization/ β -elimination reaction of skipped heptatrienes **32** possessing a leaving group at the appropriate position (Scheme 14).^[19, 20] Upon treatment with NaHMDS or KHMDS as the base, the substrate was deprotonated at the bis-allylic position to

form 8π -conjugated anion **33**, which cyclized into anion **34**. This anion intermediate then underwent elimination of the leaving group to afford cross-conjugated cycloheptatriene **35** in complete regiocontrol of the double bonds. After exploring the substrate design, a carbamate was selected as the optimal leaving group for both facilitation of generating an 8π -conjugated anion and β -elimination. Using this method, a variety of cross-conjugated cycloheptatrienes including bicyclic or tricyclic motifs were obtained in medium to good yields.



Scheme 14. Anionic 8π -electrocyclization of trienes bearing a leaving group

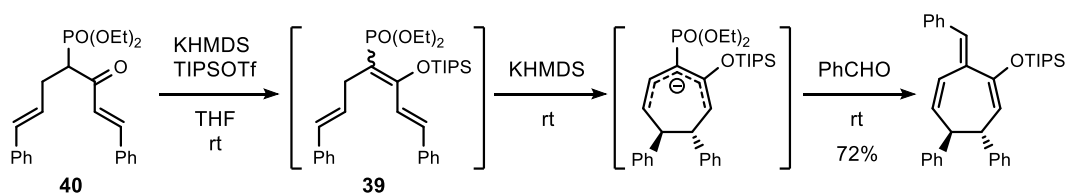
Subsequently, Saito in the same research group reported the anionic 8π -electrocyclic reaction of triene substrates **36** bearing a phosphonate group as the electron-withdrawing group (Scheme 15).^[19, 21] In this reaction, the phosphonate group not only facilitates deprotonation by the inductive effect but also stabilizes the cyclic anion intermediate **37** by the resonance effect. The resulting cyclic anion intermediate **37** was subjected to a one-pot Horner-Wadsworth-Emmons (HWE) reaction with aldehydes, giving rise to a variety of cyclic cross-conjugate cycloheptatrienes **38** in medium to high yields. It was also proved that the relative stereochemistry of the two adjacent substituents on the seven-membered ring clearly reflects the *E/Z* stereochemistry of both termini of the 8π -conjugation system, which was in good agreement with the Woodward-Hoffmann rules.



^a Yield from (3E)-36, ^b Yield from (3Z)-36

Scheme 15. Anionic 8π -electrocyclization of triene phosphonates and one-pot HWE reaction

Notably, a triene phosphonate **39** possessing a β -silyloxy group, which was prepared in situ from a β -ketophosphonate **40**, also underwent cyclization and HWE reaction under the same conditions (Scheme 16). Although the reaction went good with only limited examples, it offered a great opportunity to investigate further derivatizations of the cyclized products.



Scheme 16. Anionic 8π -electrocyclization/HWE reaction of β -ketophosphonate-derived triene **39**

In this dissertation, the author reports the progress of anionic 8π -electrocyclic reactions toward synthetically more useful seven-membered carbocyclic motifs. These findings are applied to the natural product synthesis which will clearly indicate the utilities of the new methods. In chapter 1, the development of a novel anionic cyclization reaction using β -ketoester-derived trienes and its application to the total synthesis of 6,11-epoxyisodaucane will be described. In chapter 2, the

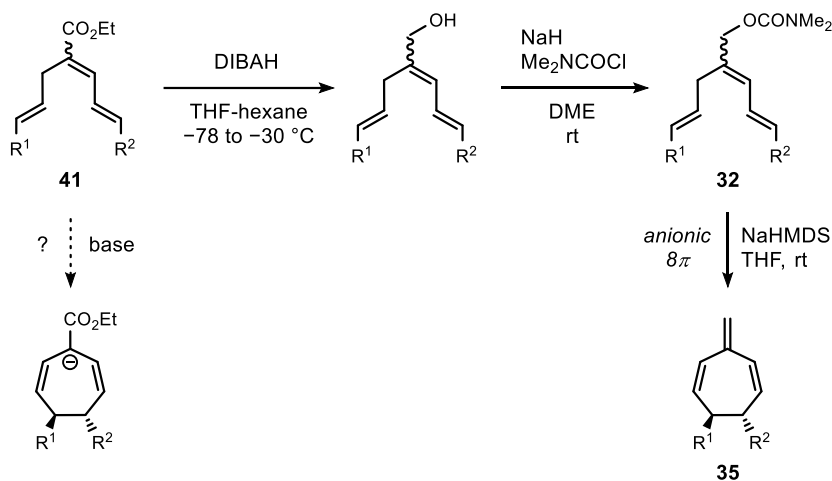
expansion of the substrate scope to β -ketoester-derived dienynes and its application to the asymmetric total synthesis of (-)-orobanone will be described. In chapter 3, new findings observed in the synthesis of alkyne-substituted seven-membered rings and synthetic progress toward natural product cyathin A₃ will be described.

Chapter 1

Anionic Cyclization of β -Ketoester-Derived Trienes: Application to Total Synthesis of 6,11-Epoxyisodaucane

Introduction

An ester ($-\text{CO}_2\text{R}$) is a highly useful compound that can be easily converted to related compounds such as an alcohol, aldehyde or carboxylic acid. Not only its convertibility, but also its electron-withdrawing character has been playing important roles as an anion or radical stabilizer in chemical reactions. The author's group previously explored the cascade anionic 8π -electrocyclization/elimination reactions, and carbamate-type triene substrates **32** were synthesized from the corresponding conjugated unsaturated esters **41** through two-step transformations (Scheme 17).^[20] On the other hand, the author's group had also discovered that an electron-withdrawing phosphonate group can facilitate the anionic 8π -electrocyclization.^[21] These results led the author to examine a similar cyclization reaction of ester-type triene substrates **41**, which are more easily accessible than carbamates **32**.

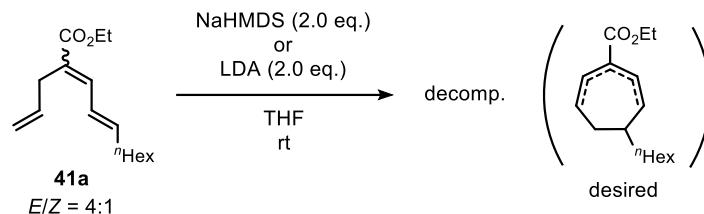


Scheme 17. Synthesis of triene carbamates and reaction hypothesis

Results and Discussion

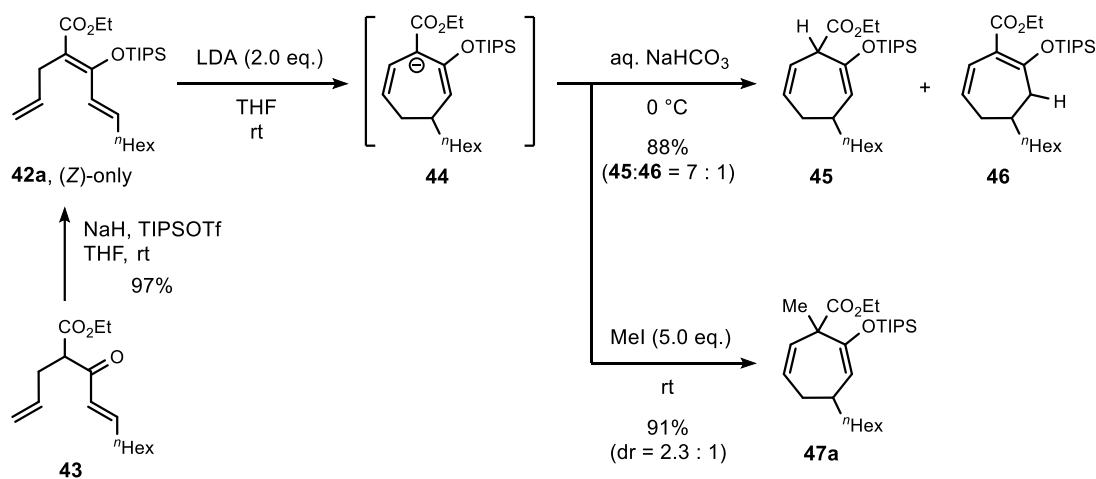
To test the hypothesis, ester substrate **41a**, which is a synthetic intermediate of carbocycle **35a** (See scheme 14 in general introduction), was subjected to the cyclization reaction using NaHMDS

as the base (Scheme 18). However, the substrate failed to give any desired carbocycle, resulting in complete decomposition. The use of LDA as the base also led to a similar result.



Scheme 18. Attempted anionic cyclization of triene ester **41a**

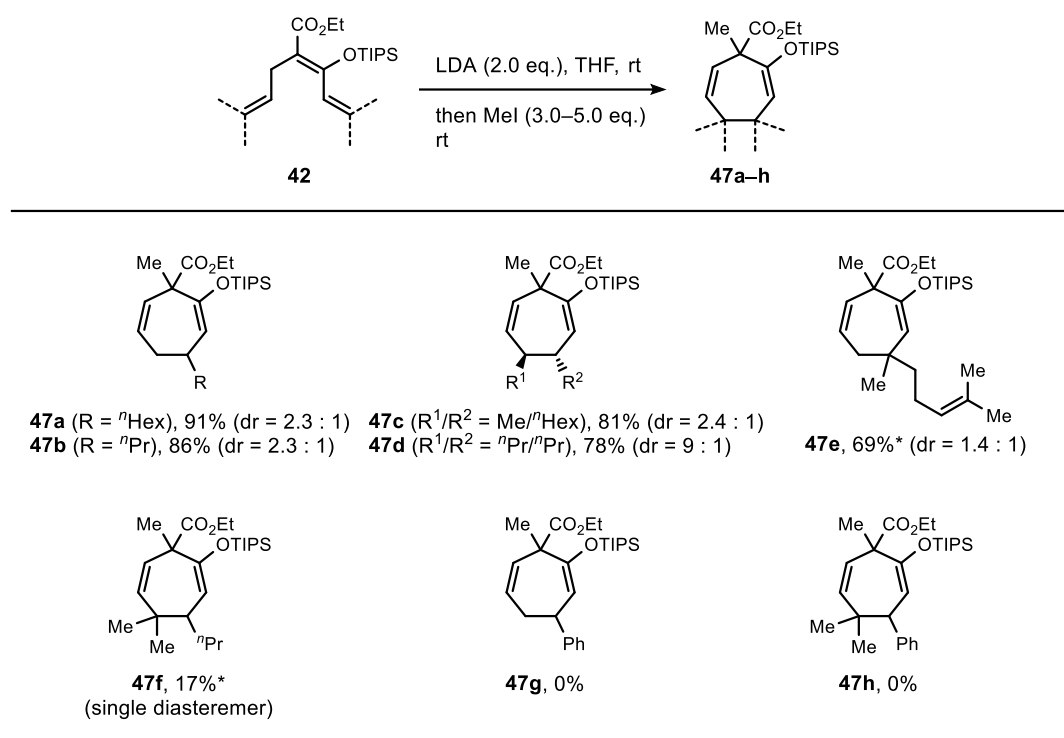
On the other hand, introduction of a bulky silyloxy group at the β -position of the ester group was found effective to suppress the decomposition of the substrates, presumably by blocking an undesired 1,4-addition of the base (Scheme 19). The new substrate **42a** with *Z*-configuration was synthesized by silylation of the corresponding β -ketoester **43** using NaH and TIPSOTf. Upon treatment with 2.0 equiv. of LDA, substrate **42a** underwent smooth anionic cyclization to form cyclic anion **44**. When the reaction was quenched with a saturated aqueous NaHCO₃ solution, seven-membered cyclic dienes **45** and **46** were obtained as a 7:1 mixture in 88% yield. Furthermore, when the anion intermediate **44** was trapped with 5.0 equiv. of iodomethane, a regioselective α -methylation reaction proceeded to afford cyclic ester **47a** in 91% yield.



Scheme 19. Anionic cyclization of β -ketoester-derived triene **42a**

Encouraged by these initial results, similar cyclization reactions of triene substrates with various substitution patterns were investigated (Scheme 20). Similar with *n*-hexyl-substituted triene **42a**, the substrate possessing an *n*-propyl group afforded the cyclized product **47b** in 86%

yield. Trienes possessing alkyl substituents on both alkene termini were also applicable, and the cyclized products **47c** and **47d** were obtained in around 80% yields. It was proved that the *gem*-dialkyl group is also tolerated, affording the cyclized product **47e** in 69% NMR yield. In contrast, a trisubstituted substrate was less suitable and afforded the cyclized product **47f** in only 17% NMR yield. Contrary to the previous works, replacing an alkyl group of the substrates with a phenyl group led to substrate decomposition, and the desired cyclized products **47g** and **47h** were not obtained at all.



* NMR yield

Scheme 20. Substrate scope for anionic cyclization of β -ketoester-derived trienes

Despite the limited substrate scope, the current method has a large advantage in accessing multi-substituted seven-membered carbocycle motifs in short steps. To demonstrate the synthetic utility, a study toward the total synthesis of 6,11-epoxyisodaucane (**48**) based on the cyclization reaction was planned (Figure 1). 6,11-Epoxyisodaucane is a natural sesquiterpenoid that was first isolated from a liverwort *Tritomaria polita* in 2003.^[22] It was also detected from some geosmin-producing cyanobacteria or actinomycetes,^[23] suggesting some biosynthetic relationships between **48** and geosmin (**49**). Compound **48** has a unique tricyclic scaffold containing a THF ring fused on a hydroazulene skeleton (isodaucane skeleton) with five contiguous stereogenic

centers. Since cyclization product **47e** in Scheme 20 has the common carbon framework of compound **48**, the author planned its total synthesis by using **47e** as the key intermediate.

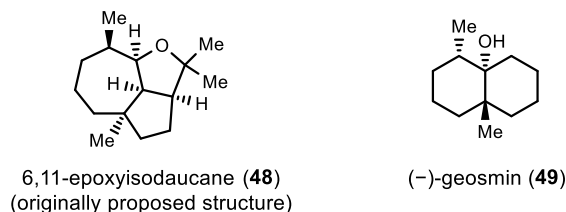
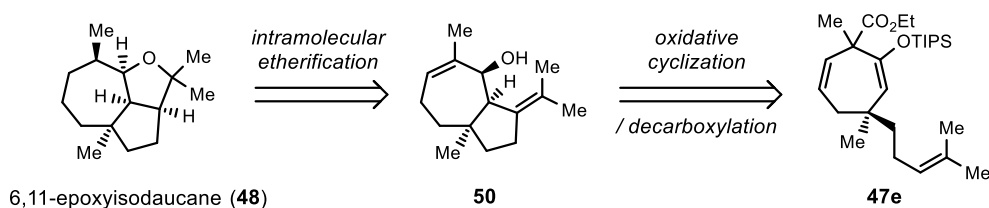


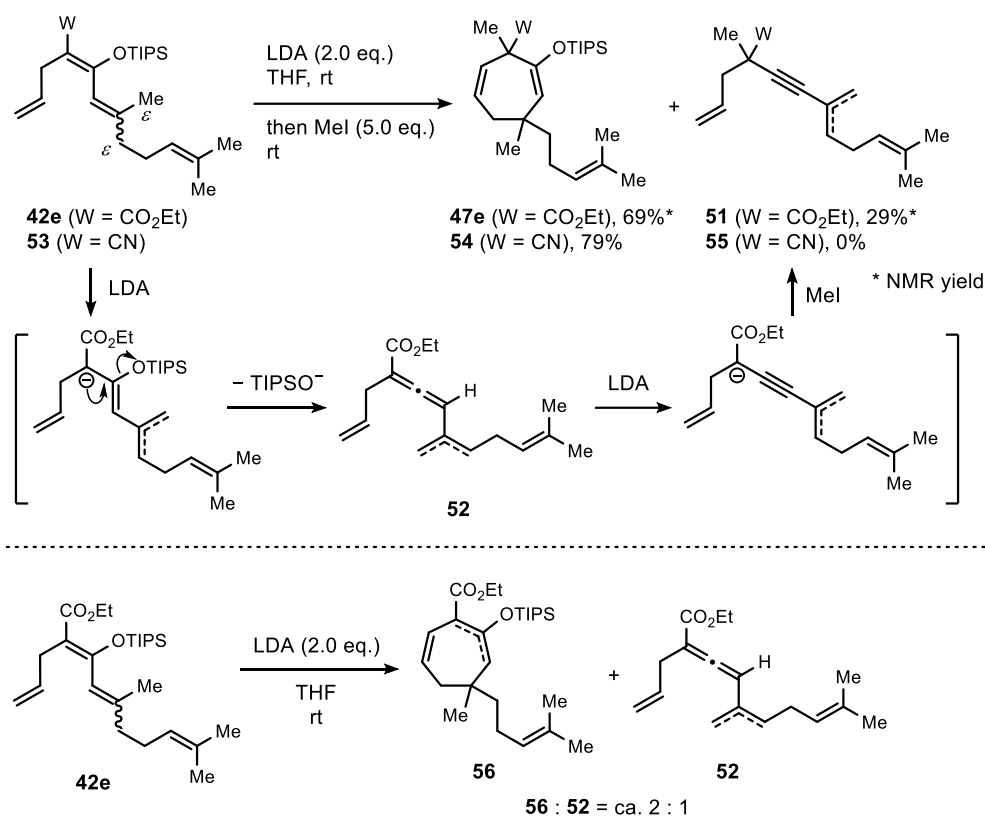
Figure 1. The structures of 6,11-epoxyisodaucane and geosmin

A retrosynthetic analysis for this natural product was conducted as follows (Scheme 21). The target compound **48** would be obtained through an intramolecular etherification from bicyclic alcohol **50**. This bicyclic compound was supposed to be accessible by an oxidative five-membered ring construction followed by decarboxylation from the cyclic ester **47e**.



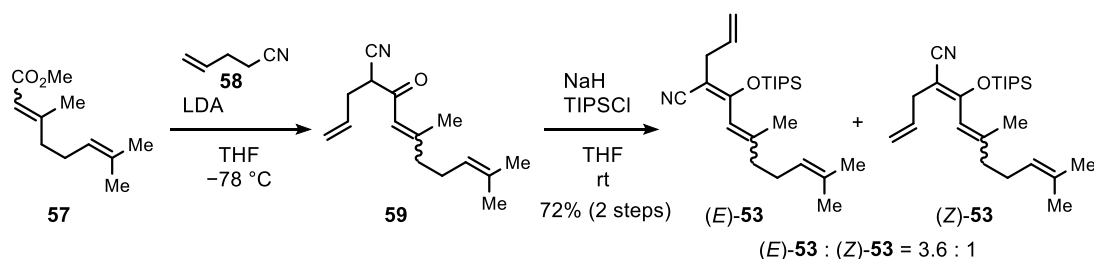
Scheme 21. Retrosynthetic analysis of 6,11-epoxyisodaucane

Upon working on the synthetic study, it became necessary to address a remaining problem with the preparation of cyclic ester **47e**. As described above, the cyclic ester **47e** was produced in 69% NMR yield under the standard conditions, but the crude product contained an inseparable alkyne byproduct **51** in 29% NMR yield (Scheme 22). The alkyne byproduct **51** seems to be formed through methylation of allene **52**, which would be generated via an undesired ε -deprotonation and elimination of the silyloxy group. This reaction pathway was also evidenced by the detection of allene **52** after aqueous quenching. In this reaction, the strong resonance stabilization effect of an ester group would enhance the acidity of ε -proton, suggesting that an alternative electron-withdrawing group like a cyano group may suppress the undesired ε -deprotonation. Fortunately, the reaction of nitrile substrate **53** was found to afford the corresponding cyclic diene **54** in 79% yield without producing any alkyne byproduct **55**.^[24]



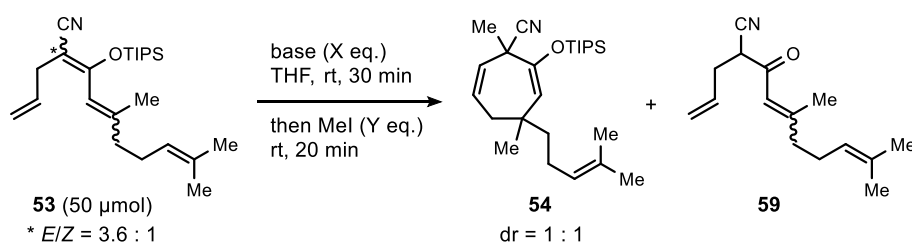
Scheme 22. Different reaction outcomes between ester and nitrile substrates

The nitrile substrate **53** was synthesized in 2 steps from commercial methyl geranate (**57**) (Scheme 23). The Claisen condensation of **57** with γ,δ -unsaturated nitrile **58** afforded β -ketonitrile **59** which was treated with NaH and TIPSCl to give silyloxy nitrile **53** as a 3.6:1 mixture of *E/Z*-isomers about the α,β -double bond. The *E/Z* stereochemistry was determined by subjecting the products to ring-closing metathesis conditions, under which the *Z*-isomer was fully converted to a cyclic compound.



Scheme 23. Preparation of the substrate nitrile **53**

With the nitrile substrate **53** in hand, an optimization study for the cyclization reaction was conducted (Table 1). As shown in entry 1, LHMDS (2.0 equiv.) as the base was not useful for the deprotonation step due to its low basicity. Contrary, the use of KHMDS (2.0 equiv.) effected full consumption of the substrate, but the product yield was very low (entry 2). The best result was obtained by using 2.0 equiv. of LDA, giving rise to the desired product **54** in 75% NMR yield (entry 4). On the other hand, decreasing the amount of LDA to 1.1 equiv. led to partial recovery of the substrate and partial desilylation (entry 5). The use of less bulky LiNEt₂ (entries 6 and 7) or bulky LiTMP (entries 8 and 9) instead of LDA did not improve the yield of **54** at all.



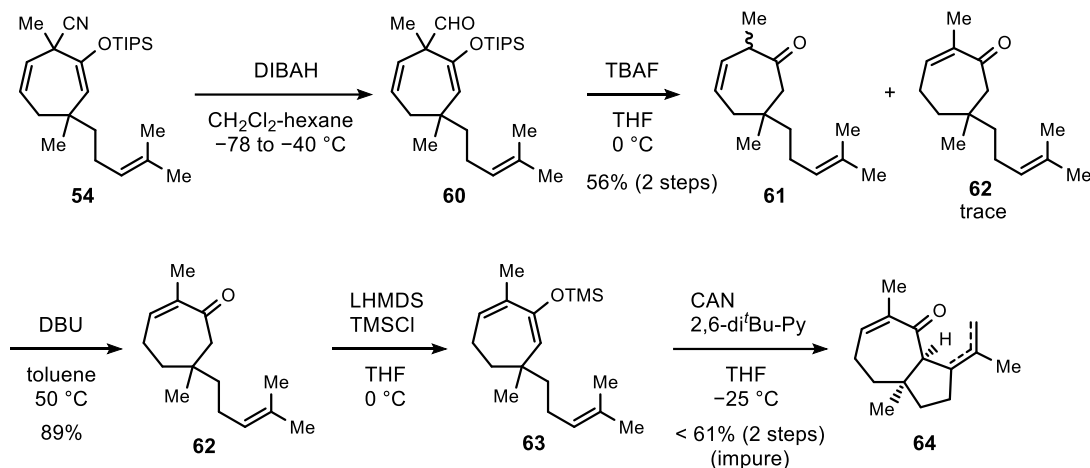
enrty	base	X (eq.)	Y (eq.)	NMR yield		
				54	59	53
1	LHMDS	2.0	5.0	-	-	91%
2	KHMDS	2.0	5.0	18%	-	-
3	KHMDS	1.1	1.5	18%	-	5%
4	LDA	2.0	5.0	75% (79%*)	-	-
5	LDA	1.1	1.5	56%	11%	14%
6	LiNEt ₂	2.0	5.0	70%	-	-
7	LiNEt ₂	1.1	1.5	66%	< 5%	-
8	LiTMP	2.0	5.0	56%	-	-
9	LiTMP	1.1	1.5	40%	11%	27%

* 2.5 mmol scale, isolated yield.

Table 1. Reaction condition optimization for the cyclization of nitrile **53**

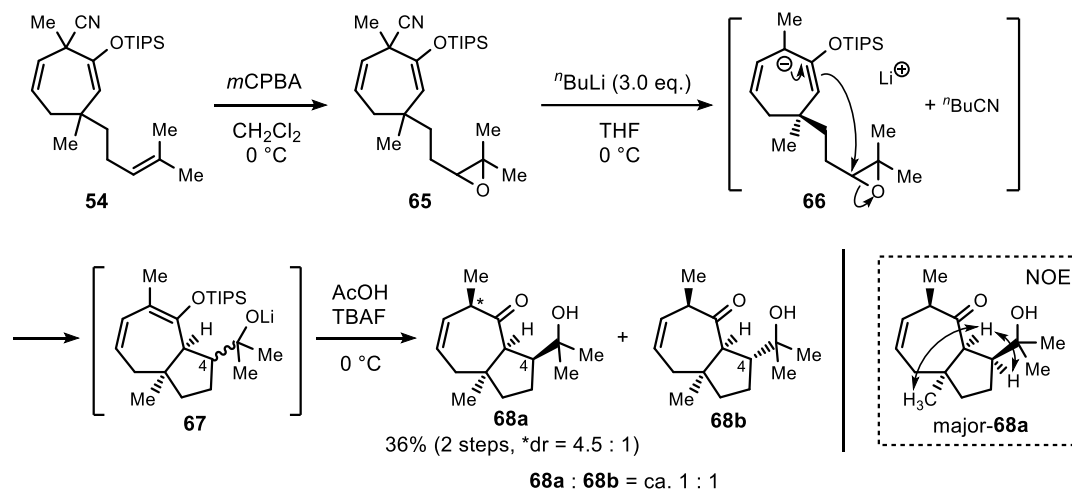
Next, the stage was set for the construction of a fused five-membered ring from nitrile **54** (Scheme 24). In accordance with the initial synthetic plan, an oxidative cyclization of **54** using ceric ammonium nitrate (CAN) as an oxidant was tested.^[25] It was expected that the single-electron transfer from the silyl enol ether moiety would form a radical species which might undergo an intramolecular addition reaction with the alkene side chain. However, the desired reaction did not proceed probably due to the steric hindrance of the TIPS group. Since the electron-withdrawing effect of the cyano group was also supposed to affect the reactivity of the enol ether, the cyano group was removed before constructing the five-membered ring. The DIBAH reduction of nitrile **54** gave the corresponding aldehyde **60** which was treated with TBAF, giving rise to a mixture of enone **61** and **62** through desilylation accompanied with deformylation.

After treatment of the mixture with DBU for inducing isomerization of the major product **61**, enone **62** was isolated in 50% yield for 3 steps. The enone was converted to TMS enol ether **63** which was subjected to the oxidative cyclization reaction using CAN, giving rise to the bicyclic product **64** as a mixture of alkenes in ca. 60% yield. However, the multi-step transformation of nitrile **54** into bicyclic compound **64** in low yield was not satisfactory to the author, and another efficient synthetic route of the bicyclic motif was explored.



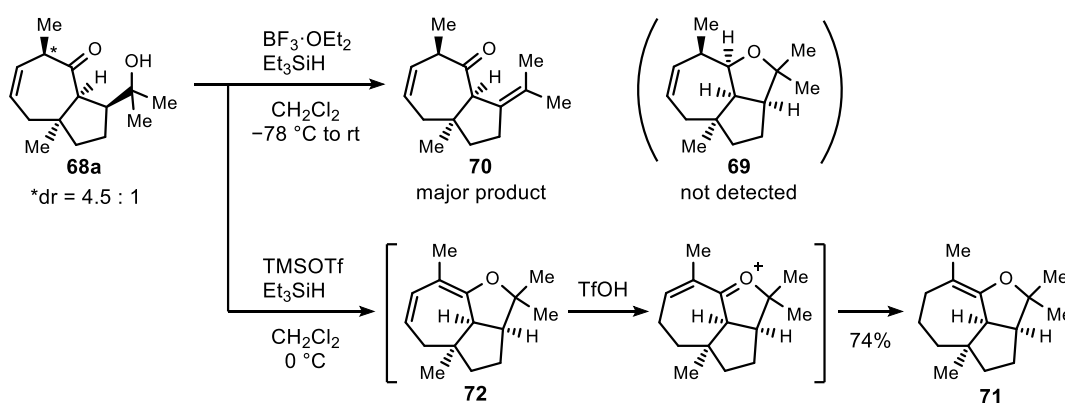
Scheme 24. Construction of a fused five-membered ring through oxidative cyclization

Afterwards, it was found that the trisubstituted alkene moiety on the side chain can be selectively oxidized with *m*CPBA (Scheme 25). The resulting epoxide moiety was expected to be a useful electrophile for five-membered ring construction by an intramolecular nucleophilic attack. Fortunately, exposure of epoxynitrile **65** to 3.0 equiv. of ^{*n*}BuLi successfully constructed the desired five-membered ring through removal of the cyano group at once. This reaction starts with the nucleophilic attack of ^{*n*}BuLi to the cyano group followed by the release of valeronitrile (pentanenitrile) to give a stabilized cyclic pentadienyl anion **66**. Then the anion moiety attacks on the epoxide moiety to form a five-membered ring, giving rise to alkoxide **67**. The TIPS group was removed by one-pot addition of acetic acid and TBAF, and the bicyclic ketone **68a** and **68b** were obtained in almost 1:1 diastereomeric ratio at the C4 position. After silica gel column purification, the diastereomers **68a** with the desired stereochemistry of the C4 position were isolated in 36% yield for 2 steps. The stereochemistry was confirmed by NOE correlation study for the major diastereomer.



Scheme 25. Novel decyanative cyclization to construct the fused five-membered ring

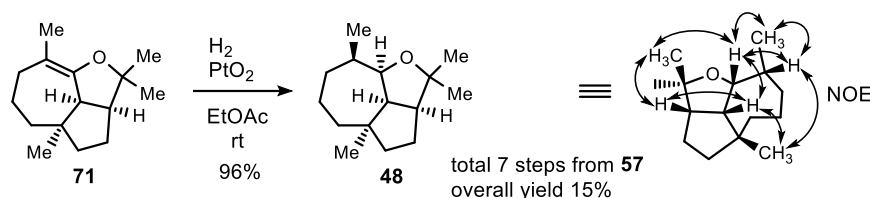
The remaining challenges were the construction of the cyclic ether and the stereocontrol of a methyl group directed toward the β -face. First, reductive etherification of hydroxyketone **68a** was attempted by the combined use of $\text{BF}_3 \cdot \text{OEt}_2$ as the Lewis acid and Et_3SiH as the reductant (Scheme 26). However, the desired tricyclic compound **69** was not produced, and ketone **70** was obtained as the major product through dehydration. On the other hand, the use of TMSOTf instead of $\text{BF}_3 \cdot \text{OEt}_2$ [26] led to formation of cyclic enol ether **71** in 74% yield. The reaction mechanism is presumed as follows. The substrate undergoes dehydration by TMSOTf to give dienol ether **72** which is then converted to product **71** through protonation by the in situ formed triflic acid followed by conjugate reduction with Et_3SiH .



Scheme 26. Construction of a tricycle under reductive etherification conditions

Finally, hydrogenation of the double bond of **71** with Adams' catalyst successfully introduced the two hydrogen atoms from the convex face, giving rise to the target compound **48** with the

originally proposed stereochemistry (Scheme 27). It was confirmed by an NOE correlation study that all five stereogenic centers were correctly constructed as desired. However, the NMR spectroscopic data for the synthetic compound **48** were not consistent with those reported in literature.^[22]



Scheme 27. Synthesis of the originally proposed structure of 6,11-epoxyisodaucane

As shown in figure 3, there were remarkable differences in both chemical shift and signal shape of the C6 proton between the two ^1H NMR charts. It was suspected that the relative stereochemistry around the C6 proton of the natural product might be opposite to that of the originally reported one. To estimate the relationship between the C6 stereochemistry and the coupling constants in ^1H NMR signals, structural optimizations of both C6 epimers using DFT methods were carried out (Figure 2). The optimal structure showed that the dihedral angle between the C6 and the C7 C-H bonds of the originally proposed structure was 69.4° , which suggests that the signal coupling between the C6 and the C7 protons is very small. This complies with the observation that the ^1H NMR signal of the C6 proton in synthetic 6,11-epoxyisodaucane appeared clearly as a doublet. In contrast, the dihedral angle values between the C5/C6 and the C6/C7 C-H bonds of the corresponding epimer are close to each other (170.4° and 158.7°), which complies with the almost equally split double-doublet of the C6 proton on the ^1H NMR chart of the natural 6,11-epoxyisodaucane.

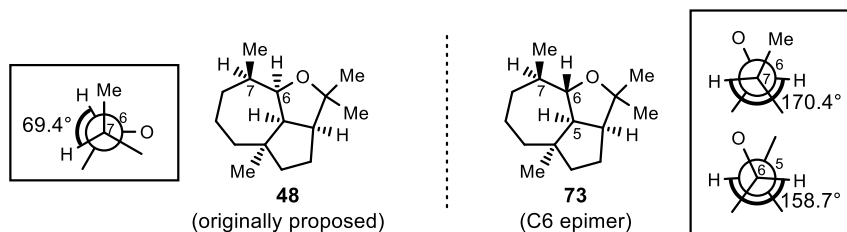


Figure 2. Conformational understanding of originally proposed 6,11-epoxyisodaucane and its C6 epimer

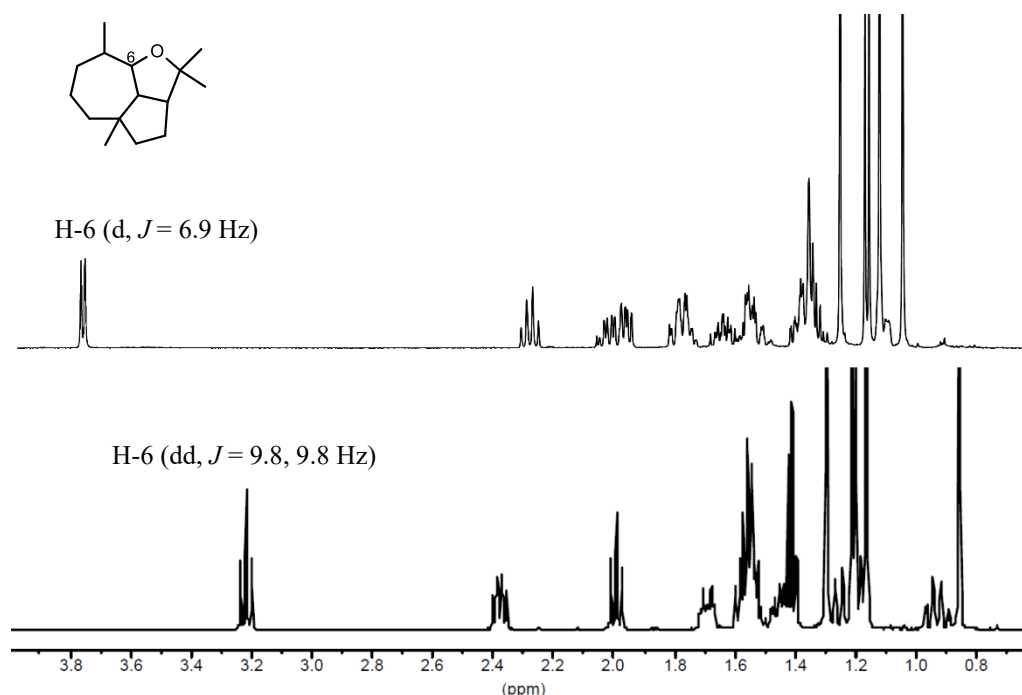
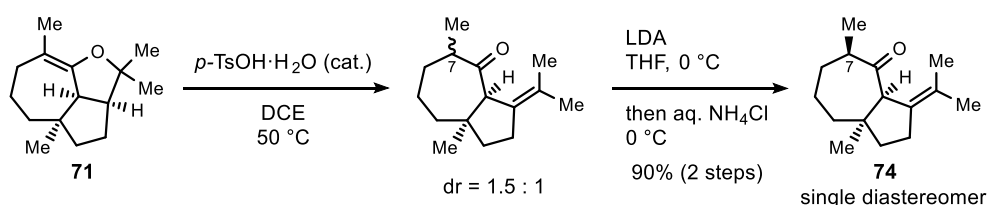


Figure 3. Comparison of ^1H NMR charts (500 MHz, C_6D_6) for synthetic (**48**, top) and natural (bottom) $^{[27]}$ 6,11-epoxyisodaucane

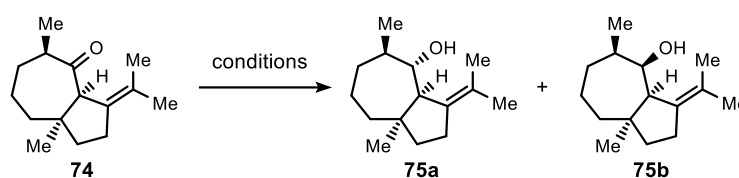
Based on this hypothesis, studies were continued by setting the C6 epimer **73** as the new synthetic target with a view to confirming the correct structure of natural 6,11-epoxyisodaucane. Since no hydrogenation method was expected to achieve stereoselective introduction of the desired *trans*-C6 and C7 protons to enol ether **71**, stepwise introduction of these hydrogen atoms was investigated. Starting from tricycle **71**, the ether ring was cleaved by acidic treatment using a catalytic amount of *p*-TsOH·H₂O (Scheme 28). Convergence of the C7 stereochemistry through an α -selective protonation of the corresponding lithium enolate afforded ketone **74** in 90% yield for 2 steps, as the single diastereomer.



Scheme 28. Stereoselective synthesis of bicyclic ketone **74**

Next, for obtaining the C6 alcohol with α -configuration, stereoselective reduction of the ketone moiety was investigated (Table 2). Since hydride reduction using DIBAH occurred only

from the convex face (entry 1), several single-electron reduction conditions were employed aiming for the reversed stereoselectivity. Mild single-electron reduction conditions using SmI₂ could hardly reduce the sterically congested C6 ketone moiety (entry 2). On the other hand, almost full conversion of ketone **74** was observed under Birch reduction conditions, but the desired α -alcohol **75a** was obtained as a minor product (entries 3–5).^[28] While the reaction under Bouveault-Blanc conditions (Na metal in ethanol) mainly gave alcohol **75a**, 40% of ketone **74** was recovered (entry 6). Further investigations revealed that the use of an excessive amount of Ca metal as the reductant in ethanol or methanol led to better results (entries 7–10). Consequently, Ca reduction in boiling ethanol was found optimal, and the secondary alcohols **75a** and **75b** were obtained as a 3:1 mixture (entry 8).



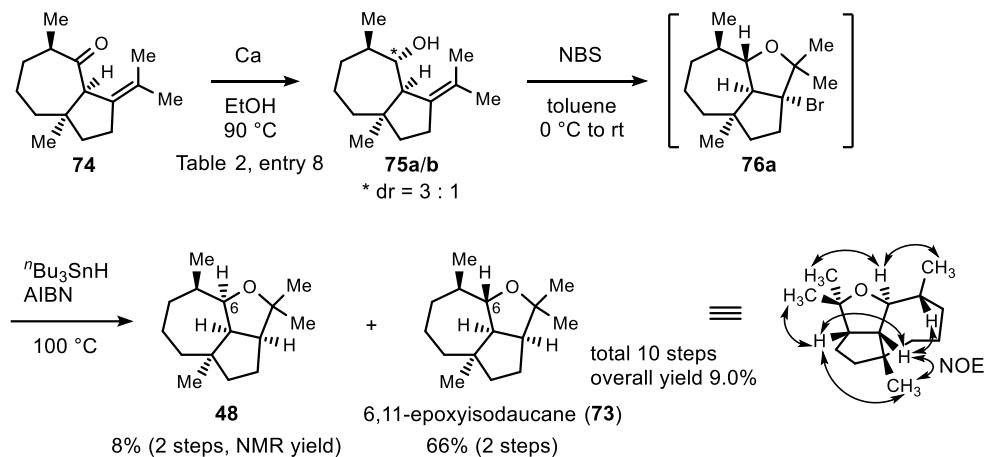
entry	conditions	result / NMR yield		
		75a	75b	74
1	DIBAH (3.0), CH ₂ Cl ₂ , -30 °C	-	97%	-
2	SmI ₂ (3.0), HMPA (15.0), THF, ^t BuOH, rt	almost no reaction		
3	Li (50), NH ₃ , THF, ^t BuOH, -78 °C	19%	71%	-
4	Ca (30), NH ₃ , THF, ^t BuOH, -78 °C	11%	89%	-
5	Li (50), ethylenediamine, THF, ^t BuOH, 0 °C to rt	27%	40%	9%
6	Na (30), EtOH, 0 °C	32%	12%	40%
7	Ca (30), EtOH, rt	65%	14%	9%
8	Ca (30), EtOH, 90 °C	73%	25%	-
9	Ca (30), MeOH, 0 °C	64%	19%	-
10	Ca (30), MeOH, 50 °C	27%	5%	49%
11	Li (50), EtOH, rt	-	-	76%

Values in parentheses are equivalents of reagents.

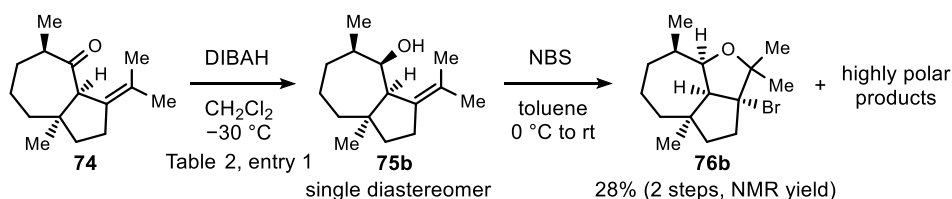
Table 2. Reaction condition optimization for stereoselective reduction of ketone **74**

With the desired alcohol **75a** containing a small amount of **75b** in hand, intramolecular bromoetherification with NBS was conducted (Scheme 29). The resulting bromoether **76a** was subjected to the one-pot radical debromination, and the desired compound **73** with the newly proposed stereochemistry was obtained in 66% yield for 2 steps. At this stage, the side product **48** arising from **75b**, the minor isomer of the 3:1 mixture, was separated in impure form (8% NMR yield). The low two-step yield of **48** is consistent with the result that bromoetherification of pure β -alcohol **75b** gave bromoether **76b** in only 28% NMR yield along with many byproducts

(Scheme 30). Thus, the reaction efficiency in bromoetherification depends on the configuration of the hydroxyl group in substrates **75a** and **75b**.



Scheme 29. Synthesis of the newly proposed structure of 6,11-epoxyisodaucane



Scheme 30. Bromoetherification of concave alcohol **75b**

Finally, the stereochemistry of the desired compound **73** was confirmed by the NOE correlation study (Scheme 29). The ^1H NMR and ^{13}C NMR spectroscopic data of the synthetic **73** were confirmed as identical to the natural product,^[22] by which the structural revision of 6,11-epoxyisodaucane was achieved.

Conclusion

In conclusion, an efficient synthetic method of multi-substituted seven-membered cyclic dienes using an anionic 8π -electrocyclic reaction of β -ketoester-derived trienes was developed. This synthetic method was applied to the first, concise total synthesis of natural sesquiterpenoid 6,11-epoxyisodaucane. The misassigned stereochemistry of the natural product was revised by synthesizing both the originally proposed structure and its C6 epimer. It is noteworthy that a new method for generating a pentadienyl anion species by the treatment of a nitrile derivative with $n\text{-BuLi}$ was also developed. In addition, Bouveault-Blanc type reaction using Ca metal and ethanol

was introduced to achieve the stereoselective reduction of a hindered ketone. These results would be useful for the total synthesis of various other terpenoids containing a seven-membered carbocycle.

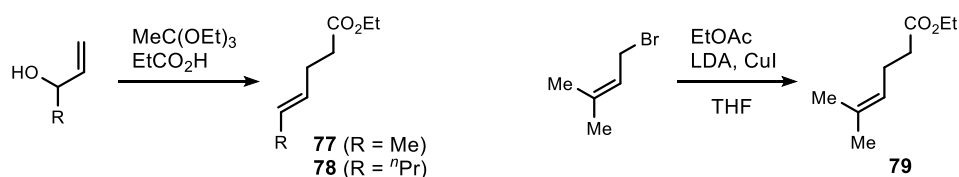
Experimental Section

General Information

All reactions were performed using flame-dried glassware under a positive pressure of argon unless otherwise noted. Reactions at elevated temperatures were performed under heating in an oil bath. THF was distilled from sodium benzophenone ketyl. Other anhydrous solvents were purchased from chemical companies. $i\text{Pr}_2\text{NH}$ and Et_3N were distilled from CaH_2 under argon and stored in the presence of NaOH (pellets). All other reagents were used as received from commercial sources without further purification.

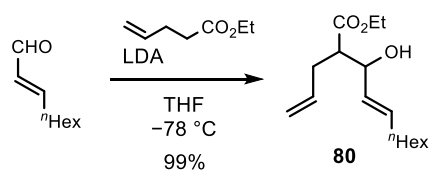
^1H NMR spectra were recorded on JEOL ECA-500 (500 MHz) in CDCl_3 (δ_{H} 7.26) or C_6D_6 (δ_{H} 7.15). Chemical shifts are reported in parts per million (ppm), and signals are expressed as broad (br), singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). Coupling constants are reported in Hz. ^{13}C NMR spectra were recorded on JEOL ECA-500 (126 MHz) in CDCl_3 (δ_{C} 77.0) or C_6D_6 (δ_{C} 128.0). HRMS were recorded on JEOL JMS-T100GCV (GC-TOFMS) at the GC-MS & NMR Laboratory, Faculty of Agriculture, Hokkaido University. FT-IR spectra were recorded on JASCO FT/IR-4100 spectrophotometer. Analytical TLC was performed using Silica Gel 60 F254 (E. Merck). Reaction components were visualized by illumination with ultraviolet light (254 nm) and by staining with 8% ethanolic phosphomolybdic acid, ceric ammonium molybdate in 10% sulfuric acid, or basic potassium permanganate aqueous solution. Flash column chromatography was performed on Chromatorex PSQ60B (Fuji Silysia Chemical Ltd.).

Ethyl esters **77**, **78**^[29] and **79**^[30] were prepared by known procedures.



Experimental and Characterization Details

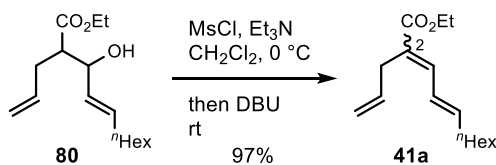
β -Hydroxyester **80**



To a solution of $i\text{Pr}_2\text{NH}$ (843 μL , 6.00 mmol) in THF (25 mL) was added $n\text{BuLi}$ (2.69 mol/L in hexane, 2.23 mL, 6.00 mmol) at 0 °C and stirred for 30 min. The reaction mixture was then cooled down to –78 °C and ethyl 4-pentenoate (854 μL , 6.00 mmol) in THF was added. After stirring for 30 min, *trans*-2-nonenal (825 μL , 5.00 mmol) was added and the resulting mixture was stirred at –78 °C for 10 min. The reaction was quenched with saturated aqueous NH_4Cl solution (25 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (20 mL $\times$ 3). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2 , hexane:EtOAc = 10:1 to 3:1) to afford **80** (dr = 1.2:1, 1.33 g, 4.96 mmol, 99% yield).

80: yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 5.83–5.69 (m, 2H), 5.49–5.41 (m, 1H), 5.09–5.01 (m, 2H), 4.27 (t, J = 6.3 Hz, 0.55H), 4.21–4.11 (m, 2H + 0.45H), 2.61 (dt, J = 10.3, 4.6 Hz, 0.55H), 2.53 (q, J = 7.1 Hz, 0.45H), 2.47–2.34 (m, 2H), 2.06–2.01 (m, 2H), 1.36–1.24 (m, 11H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.4, 173.8, 135.5, 134.7, 134.2, 134.1, 129.9, 128.9, 117.1, 116.7, 73.1, 72.9, 60.5, 60.5, 51.1, 51.1, 33.5, 32.2, 32.0, 32.0, 31.6, 29.0, 29.0, 28.8, 22.6, 14.2, 14.0 (only detected signals are recorded); FT-IR (ATR) ν 3449 (br), 3079, 2957, 2925, 2855, 1732, 1715, 1178 cm^{-1} ; HRMS (FI) calcd for $\text{C}_{16}\text{H}_{28}\text{O}_3$ (M^+): 268.2038, found: 268.2045.

Triene **41a**

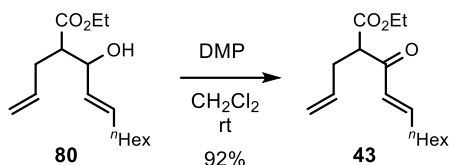


To a solution of **80** (1.33 g, 4.96 mmol) in CH_2Cl_2 (25 mL) were added successively Et_3N (2.08 mL, 14.9 mmol) and MsCl (772 μL , 9.92 mmol) at 0 °C. After stirring for 30 min, DBU (3.70 mL, 24.8 mmol) was added. The reaction mixture was then warmed up to room temperature and stirred for 13 h. The reaction was quenched with saturated aqueous NaHCO_3 solution (25 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (20 mL $\times$ 3). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2 , hexane:EtOAc = 20:1) to afford the **41a** (2E/2Z = 4:1, 1.21 g, 4.82 mmol, 97% yield).

41a: colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 7.23 (d, J = 10.9 Hz, 0.8H), 7.10–7.05 (m, 0.2H), 6.39–6.29 (m, 1H), 6.11 (dt, J = 14.7, 7.3 Hz, 0.8H), 5.95 (dt, J = 15.0, 7.4 Hz, 0.2H), 5.87–5.79 (m, 1H), 5.08–4.98 (m, 2H), 4.25–4.18 (m, 2H), 3.16 (d, J = 5.7 Hz, 0.8 $\times$ 2H), 3.04 (d, J = 6.3 Hz, 0.2 $\times$ 2H), 2.20–2.14 (m, 2H), 1.45–1.39 (m, 2H), 1.33–1.28 (m, 9H), 0.90–0.87 (m, 3H); ^{13}C

NMR (126 MHz, CDCl₃) δ 168.0, 167.3, 144.3, 142.9, 140.8, 139.8, 136.1, 135.6, 127.4, 126.9, 126.6, 125.6, 116.1, 115.1, 60.4, 60.2, 38.2, 33.3, 33.0, 31.7, 31.6, 30.8, 28.9, 28.8, 28.8, 22.6, 14.3, 14.2, 14.0 (only detected signals are recorded); FT-IR (ATR) ν 2956, 2926, 2856, 1703, 1638, 1205 cm⁻¹; HRMS (FD) calcd for C₁₆H₂₆O₂ (M⁺): 250.1933, found: 250.1943.

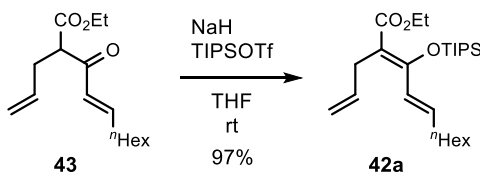
β -Ketoester **43**



To a solution of **80** (134 mg, 0.499 mmol) in CH₂Cl₂ (2.5 mL) was added Dess-Martin periodinane (255 mg, 0.601 mmol) at room temperature. After stirring for 15 min, the reaction was quenched with saturated aqueous NaHCO₃ solution (2.5 mL). Two layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (2.5 mL $\times$ 3). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, hexane:EtOAc = 20:1) to afford **43** (123 mg, 0.461 mmol, 92% yield).

43 (ketone:enol = 5:1): yellow oil; ¹H NMR (500 MHz, CDCl₃) δ 6.96 (dt, J = 15.4, 7.0 Hz, 0.83H), 6.70 (dt, J = 15.5, 6.8 Hz, 0.17H), 6.21 (d, J = 15.4 Hz, 0.83H), 6.18 (d, J = 15.5 Hz, 1H), 5.84–5.71 (m, 1H), 5.20–4.96 (m, 2H), 4.27–4.12 (m, 2H), 3.74 (t, J = 7.4 Hz, 0.83H), 3.03 (d, J = 5.7 Hz, 0.17 $\times$ 2H), 2.67–2.56 (m, 2H), 2.25–2.19 (m, 2H), 1.49–1.43 (m, 2H), 1.32–1.22 (m, 6H), 1.24 (t, J = 6.8 Hz, 3H), 0.88 (t, J = 6.9 Hz, 3H)

Triene **42a**

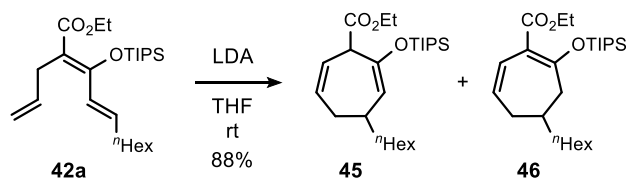


NaH (60% dispersion in mineral oil, 22.2 mg, 0.555 mmol) was washed with THF and suspended with THF (2.3 mL). To this mixture was added **43** (122 mg, 0.457 mmol) in THF (0.50 mL) via cannula at 0 °C. After stirring for 30 min, TIPSOTf (147 μ L, 0.548 mmol) was added. The reaction mixture was then warmed up to room temperature and stirred for 30 min. The reaction was quenched by the careful addition of saturated aqueous NaHCO₃ solution (2.0 mL), and the organic layer was diluted with EtOAc (2.0 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (2.0 mL $\times$ 4). The combined organic layers were dried over MgSO₄, filtered,

and concentrated under reduced pressure. The residue was purified by flash column chromatography [SiO_2 (neutralized by the elution of *N,N*-dimethylaniline), hexane:EtOAc = 50:1] to afford **42a** (188 mg, 0.445 mmol, 97% yield).

42a: colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 6.18 (dt, $J = 15.5, 7.1$ Hz, 1H), 6.10 (d, $J = 15.5$ Hz, 1H), 5.82 (ddt, $J = 17.3, 10.3, 5.8$ Hz, 1H), 5.04 (dd, $J = 17.3, 1.7$ Hz, 1H), 4.98 (dd, $J = 10.3, 1.7$ Hz, 1H), 4.15 (q, $J = 7.0$ Hz, 2H), 3.06 (d, $J = 6.3$ Hz, 2H), 2.14 (td, $J = 7.1, 7.1$ Hz, 2H), 1.39 (q, $J = 6.9$ Hz, 2H), 1.32–1.17 (m, 9H), 1.26 (t, $J = 7.0$ Hz, 3H), 1.09 (d, $J = 6.9$ Hz, 18H), 0.89 (t, $J = 6.6$ Hz, 3H)

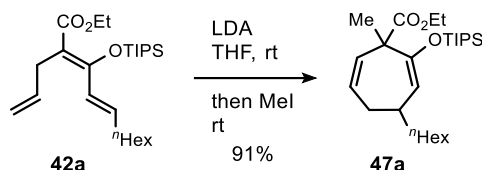
Cycloheptadienes **45** + **46**



An LDA solution (ca. 1.0 mol/L in THF-hexane) was prepared by the addition of $n\text{BuLi}$ (2.69 mol/L in hexane, 743 μL , 2.00 mmol) to a solution of $i\text{Pr}_2\text{NH}$ (281 μL , 2.00 mmol) in THF (1.26 mL) at 0 °C. The mixture was stirred for 30 min at the same temperature before the use. To another reaction vessel charged with **42a** (20.6 mg, 48.7 μmol) in THF (0.50 mL) was added the LDA solution (ca. 1.0 mol/L in THF-hexane, 100 μL , 0.100 mmol) via a syringe at room temperature. After stirring for 40 min, the reaction mixture was cooled down to 0 °C, and a catalytic amount of 3-*tert*-butyl-4-hydroxyanisole was added. The reaction was quenched with saturated aqueous NaHCO_3 solution (0.50 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (0.50 mL $\times$ 3). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography [SiO_2 (neutralized by the elution of *N,N*-dimethylaniline), hexane:EtOAc = 50:1] to afford a mixture of **45** and **46** (**45**:**46** = 7:1, 18.1 mg, 42.8 μmol , 88% yield).

45 + **46**: yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 6.14 (d, $J = 10.9$ Hz, 0.13H), 5.80–5.70 (m, $0.87 \times 2\text{H} + 0.13\text{H}$), 4.73 (d, $J = 5.2$ Hz, 0.87H), 4.30 (s, 0.87H), 4.22–4.09 (m, 2H), 2.41–2.36 (m, 0.87H), 2.28–2.01 (m, $0.87 \times 2\text{H} + 0.13 \times 4\text{H}$), 1.53 (s, 0.13H), 1.29–1.22 (m, 13H), 1.20–1.05 (m, 21H), 0.88 (t, $J = 6.9$ Hz, 3H)

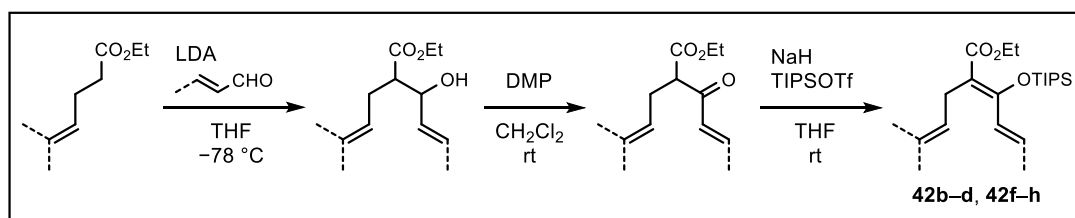
Cycloheptadiene **47a**



An LDA solution (ca. 1.0 mol/L in THF-hexane) was prepared by the addition of n BuLi (2.70 mol/L in hexane, 740 μ L, 2.00 mmol) to a solution of i Pr₂NH (281 μ L, 2.00 mmol) in THF (1.26 mL) at 0 °C. The mixture was stirred for 30 min at the same temperature before the use. To another reaction vessel charged with **42a** (21.2 mg, 50.2 μ mol) in THF (0.50 mL) was added the LDA solution (100 μ L, 100 μ mol) via a syringe at 0 °C. The reaction mixture was then warmed up to room temperature and stirred for 30 min. To this mixture was added MeI (15.6 μ L, 250 μ mol), and the reaction mixture was stirred for another 10 min at the same temperature. The reaction was quenched with saturated aqueous NaHCO₃ solution (0.50 mL), and the organic layer was diluted with EtOAc (0.50 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (0.50 mL $\times$ 3). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography [SiO₂ (neutralized by the elution of *N,N*-dimethylaniline), hexane:EtOAc = 100:1] to afford **47a** (dr = 2.3:1, 19.9 mg, 45.5 μ mol, 91% yield).

47a: colorless oil; ¹H NMR (500 MHz, CDCl₃) δ 5.80–5.72 (m, 1H), 5.35 (d, J = 11.5 Hz, 0.7H), 5.22 (d, J = 11.5 Hz, 0.3H), 4.80 (d, J = 4.6 Hz, 0.3H), 4.77 (d, J = 5.2 Hz, 0.7H), 4.21–4.11 (m, 1H), 4.09–3.97 (m, 1H), 2.29 (br, 1H), 2.21–1.95 (m, 2H), 1.49 (s, 0.3 $\times$ 3H), 1.48 (s, 0.7 $\times$ 3H), 1.30–1.13 (m, 16H), 1.11–1.06 (m, 18H), 0.88 (t, J = 6.6 Hz, 3H)

General procedure A: synthesis of trienes

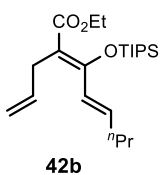


Step 1: An LDA solution (ca. 1.0 mol/L in THF-hexane) was prepared by the addition of n BuLi (2.69 mol/L in hexane, 1.86 mL, 5.00 mmol) to a solution of i Pr₂NH (703 μ L, 5.00 mmol) in THF (3.14 mL) at 0 °C. The mixture was stirred for 20–30 min at the same temperature before the use. To another reaction vessel charged with ethyl ester in THF (0.24 mol/L, 1.0 equiv.) was added the LDA solution (1.2 equiv.) via a syringe at –78 °C. After stirring for 30 min, aldehyde (1.2 equiv.) was added, and the reaction mixture was stirred for another 10–15 min at the same temperature.

The reaction was quenched with saturated aqueous NH_4Cl solution, and the organic layer was diluted with EtOAc. Two layers were separated, and the aqueous layer was extracted three times with EtOAc. The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2 , hexane:EtOAc = 10:1 to 3:1–2:1) to afford β -hydroxyester.

Step 2: To a solution of above β -hydroxyester in CH_2Cl_2 (0.2 mol/L, 1.0 equiv.) was added Dess-Martin periodinane (1.2 equiv.) at 0 °C. The reaction mixture was then warmed up to room temperature and stirred for 30 min. The reaction was quenched with saturated aqueous NaHCO_3 and $\text{Na}_2\text{S}_2\text{O}_3$ solution, and the biphasic mixture was stirred vigorously for 30 min. Two layers were separated, and the aqueous layer was extracted three times with EtOAc. The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2 , hexane:EtOAc = 20:1–5:1) to afford β -ketoester.

Step 3: NaH (60% dispersion in mineral oil, 1.2–2.0 equiv.) was washed with THF and suspended with THF. To this suspension was added above β -ketoester (1.0 equiv.) in THF via cannula at 0 °C (the final concentration of β -ketoester reached 0.2 mol/L). After stirring for 30 min, TIPSOTf (1.2–1.5 equiv.) was added. The reaction mixture was then warmed up to room temperature and stirred for 30 min. The reaction was quenched by the careful addition of saturated aqueous NaHCO_3 solution, and the organic layer was diluted with EtOAc. Two layers were separated, and the aqueous layer was extracted three times with EtOAc. The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography [SiO_2 (neutralized by the elution of *N,N*-dimethylaniline), hexane:EtOAc = 100:1–50:1] to afford the product triene.

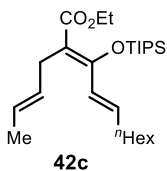


Step 1: According to the general procedure A, β -hydroxyester (200 mg, 0.883 mmol, 88% yield) was synthesized from LDA (ca. 1.0 mol/L in THF-hexane, 1.20 mL, 1.20 mmol), ethyl 4-pentenoate (142 μL , 1.00 mmol) and *trans*-2-hexenal (139 μL , 1.20 mmol).

Step 2, 3: **42b** (74.2 mg, 0.195 mmol, 97% yield for 2 steps) was synthesized from β -hydroxyester (45.3 mg, 0.200 mmol), Dess-Martin periodinane (101 mg, 0.238 mmol), NaH (60% dispersion in mineral oil, 16.3 mg, 0.408 mmol) and TIPSOTf (80.6 μL , 0.300 mmol).

42b: colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 6.18 (dt, J = 15.4, 6.9 Hz, 1H), 6.11 (d, J = 15.4 Hz, 1H), 5.82 (ddt, J = 17.3, 10.2, 6.2 Hz, 1H), 5.04 (dd, J = 17.3, 1.7 Hz, 1H), 4.98 (dd, J = 10.2, 1.7 Hz, 1H), 4.16 (q, J = 7.3 Hz, 2H), 3.06 (d, J = 6.2 Hz, 2H), 2.13 (dt, J = 7.1, 6.9 Hz, 2H),

1.48–1.40 (m, 2H), 1.26 (t, $J = 7.3$ Hz, 3H), 1.23–1.15 (m, 3H), 1.09 (d, $J = 7.4$ Hz, 18H), 0.93 (t, $J = 7.4$ Hz, 3H)

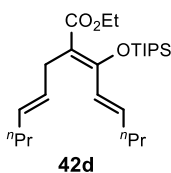


Step 1: According to the general procedure A, β -hydroxyester (366 mg, 1.29 mmol, 86% yield) was synthesized from i Pr₂NH (253 μ L, 1.80 mmol), n BuLi (2.69 mol/L in hexane, 669 μ L, 1.80 mmol), ethyl ester **77** (213 mg, 1.50 mmol) and *trans*-2-nonenal (297 μ L, 1.80 mmol). Enolate was prepared by the addition of **77** in THF to an LDA solution.

Step 2: β -ketoester (120 mg, 0.427 mmol, 85% yield) was synthesized from β -hydroxyester (141 mg, 0.500 mmol) and Dess-Martin periodinane (254 mg, 0.598 mmol).

Step 3: **42c** (166 mg, 0.380 mmol, 89% yield) was synthesized from NaH (60% dispersion in mineral oil, 20.9 mg, 0.523 mmol), β -ketoester (120 mg, 0.427 mmol) and TIPSOTf (138 μ L, 0.512 mmol).

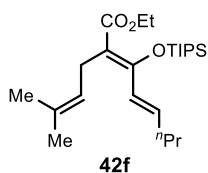
42c: colorless oil; ¹H NMR (500 MHz, CDCl₃) δ 6.17 (dt, $J = 15.8, 6.4$ Hz, 1H), 6.12 (d, $J = 15.8$ Hz, 1H), 5.47–5.37 (m, 2H), 4.15 (q, $J = 7.1$ Hz, 2H), 2.98 (d, $J = 4.6$ Hz, 2H), 2.14 (td, $J = 6.7, 6.4$ Hz, 2H), 1.63 (d, $J = 5.2$ Hz, 3H), 1.41–1.37 (m, 2H), 1.32–1.24 (m, 6H), 1.26 (t, $J = 7.0$ Hz, 3H), 1.23–1.16 (m, 3H), 1.09 (d, $J = 6.9$ Hz, 18H), 0.89 (t, $J = 6.9$ Hz, 3H)



Step 1: According to the general procedure A, β -hydroxyester (209 mg, 0.778 mmol, 78% yield) was synthesized from LDA (ca. 1.0 mol/L in THF-hexane, 1.20 mL, 1.20 mmol), ethyl ester **78** (171 mg, 1.00 mmol) and *trans*-2-hexenal (139 μ L, 1.20 mmol).

Step 2, 3: **42d** (77.1 mg, 0.182 mmol, 92% yield for 2 steps) was synthesized from β -hydroxyester (53.4 mg, 0.199 mmol), Dess-Martin periodinane (102 mg, 0.240 mmol), NaH (60% dispersion in mineral oil, 16.6 mg, 0.415 mmol) and TIPSOTf (80.6 μ L, 0.300 mmol).

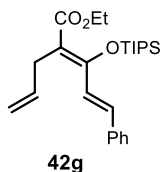
42d: colorless oil; ¹H NMR (500 MHz, CDCl₃) δ 6.17 (dt, $J = 15.5, 6.4$ Hz, 1H), 6.13 (d, $J = 15.5$ Hz, 1H), 5.45–5.35 (m, 2H), 4.15 (q, $J = 7.0$ Hz, 2H), 2.99 (d, $J = 4.6$ Hz, 2H), 2.12 (td, $J = 6.9, 6.9$ Hz, 2H), 1.94 (td, $J = 6.7, 6.4$ Hz, 2H), 1.47–1.40 (m, 2H), 1.37–1.30 (m, 2H), 1.25 (t, $J = 7.0$ Hz, 3H), 1.24–1.15 (m, 3H), 1.09 (d, $J = 6.9$ Hz, 18H), 0.93 (t, $J = 7.4$ Hz, 3H), 0.86 (t, $J = 7.2$ Hz, 3H)



Step 1: According to the general procedure A, β -hydroxyester (111 mg, 0.438 mmol, 88% yield) was synthesized from LDA (ca. 1.0 mol/L in THF-hexane, 600 μ L, 0.600 mmol), ethyl ester **79** (78.1 mg, 0.500 mmol) and *trans*-2-hexenal (69.3 μ L, 0.600 mmol).

Step 2, 3: **42f** (74.9 mg, 0.183 mmol, 92% yield for 2 steps) was synthesized from β -hydroxyester (49.9 mg, 0.196 mmol), Dess-Martin periodinane (102 mg, 0.241 mmol), NaH (60% dispersion in mineral oil, 16.3 mg, 0.408 mmol) and TIPSOTf (80.6 μ L, 0.300 mmol).

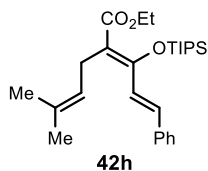
42f: colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 6.19–6.11 (m, 2H), 5.06 (t, J = 6.9 Hz, 1H), 4.15 (q, J = 7.3 Hz, 2H), 3.00 (d, J = 6.9 Hz, 2H), 2.14–2.10 (m, 2H), 1.66 (s, 3H), 1.64 (s, 3H), 1.48–1.40 (m, 2H), 1.26 (t, J = 7.3 Hz, 3H), 1.23–1.15 (m, 3H), 1.09 (d, J = 6.9 Hz, 18H), 0.93 (t, J = 7.4 Hz, 3H)



Step 1: According to the general procedure A, β -hydroxyester (118 mg, 0.455 mmol, 91% yield) was synthesized from LDA (ca. 1.0 mol/L in THF-hexane, 600 μ L, 0.600 mmol), ethyl 4-pentenoate (71.2 μ L, 0.500 mmol) and *trans*-cinnamaldehyde (75.5 μ L, 0.600 mmol).

Step 2, 3: **42g** (70.7 mg, 0.171 mmol, 86% yield for 2 steps) was synthesized from β -hydroxyester (51.8 mg, 0.199 mmol), Dess-Martin periodinane (102 mg, 0.239 mmol), NaH (60% dispersion in mineral oil, 16.4 mg, 0.410 mmol) and TIPSOTf (80.6 μ L, 0.300 mmol).

42g: pale yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 7.42 (d, J = 7.3 Hz, 2H), 7.36 (dd, J = 7.3, 7.3 Hz, 2H), 7.30 (t, J = 7.3 Hz, 1H), 7.07 (d, J = 15.8 Hz, 1H), 6.89 (d, J = 15.8 Hz, 1H), 5.88 (ddt, J = 17.3, 10.2, 6.1 Hz, 1H), 5.11 (dd, J = 17.3, 1.7 Hz, 1H), 5.03 (dd, J = 10.2, 1.7 Hz, 1H), 4.19 (q, J = 7.2 Hz, 2H), 3.18 (d, J = 6.1 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H), 1.31–1.23 (m, 3H), 1.13 (d, J = 6.9 Hz, 18H)

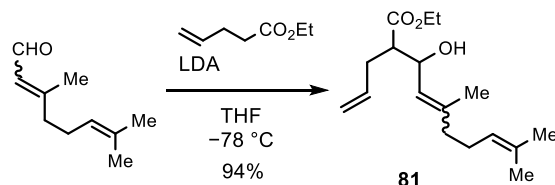


Step 1: According to the general procedure A, β -hydroxyester (44.5 mg, 0.154 mmol, 61% yield) was synthesized from LDA (ca. 1.0 mol/L in THF-hexane, 303 μ L, 0.303 mmol), ethyl ester **79** (39.5 mg, 0.253 mmol) and *trans*-cinnamaldehyde (38.1 μ L, 0.303 mmol).

Step 2, 3: **42h** (58.4 mg, 0.132 mmol, 88% yield for 2 steps) was synthesized from β -hydroxyester (43.4 mg, 0.150 mmol), Dess-Martin periodinane (76.7 mg, 0.181 mmol), NaH (60% dispersion in mineral oil, 12.1 mg, 0.303 mmol) and TIPSOTf (60.7 μ L, 0.226 mmol).

42h: pale yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 7.41 (d, $J = 7.2$ Hz, 2H), 7.36 (dd, $J = 7.2$, 7.2 Hz, 2H), 7.29 (t, $J = 7.2$ Hz, 1H), 7.05 (d, $J = 15.8$ Hz, 1H), 6.91 (d, $J = 15.8$ Hz, 1H), 5.12 (t, $J = 6.9$ Hz, 1H), 4.18 (q, $J = 7.2$ Hz, 2H), 3.12 (d, $J = 6.9$ Hz, 2H), 1.70 (s, 3H), 1.68 (s, 3H), 1.28 (t, $J = 7.2$ Hz, 3H), 1.28–1.21 (m, 3H), 1.13 (d, $J = 6.9$ Hz, 18H)

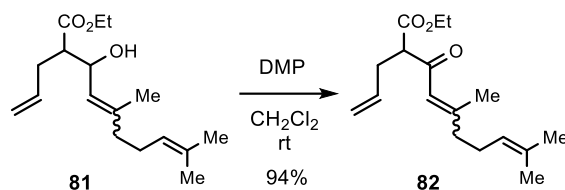
β -Hydroxyester **81**



To a solution of $i\text{Pr}_2\text{NH}$ (211 μL , 1.50 mmol) in THF (5.0 mL) was added $n\text{BuLi}$ (2.64 mol/L in hexane, 568 μL , 1.50 mmol) at 0 $^\circ\text{C}$, and the reaction mixture was stirred for 30 min. The reaction mixture was then cooled down to -78 $^\circ\text{C}$, and ethyl 4-pentenoate (171 μL , 1.20 mmol) was added. After stirring for 30 min, citral ($E/Z = 1.8:1$, 171 μL , 1.00 mmol) was added, and the reaction mixture was stirred for another 15 min at the same temperature. The reaction was quenched with saturated aqueous NH_4Cl solution (5.0 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (5.0 mL $\times$ 3). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2 , hexane: $\text{EtOAc} = 10:1$ to 3:1) to afford **81** (dr = 1.4:1, E/Z mixture, 264 mg, 0.941 mmol, 94% yield).

81: colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 5.81–5.69 (m, 1H), 5.26 (dd, $J = 19.3$, 8.8 Hz, 0.58 H), 5.18–5.00 (m, 3H + 0.42H), 4.57–4.46 (m, 1H), 4.21–4.11 (m, 2H), 2.63–2.56 (m, 0.58H), 2.53–2.38 (m, 1H + 0.42H), 2.31–2.27 (m, 1H), 2.22–2.00 (m, 5H), 1.75 (d, $J = 9.0$ Hz, $0.42 \times 3\text{H}$), 1.70–1.67 (m, $3\text{H} + 0.58 \times 3\text{H}$), 1.61 (s, $0.42 \times 3\text{H}$), 1.60 (s, $0.58 \times 3\text{H}$), 1.29–1.21 (m, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.5, 173.7, 140.9, 140.7, 140.6, 140.3, 135.6, 134.83, 134.79, 132.3, 131.74, 131.66, 125.9, 125.1, 125.0, 124.2, 123.8, 123.73, 123.71, 116.84, 116.82, 116.55, 116.50, 69.0, 68.71, 68.66, 68.3, 60.5, 60.43, 60.35, 60.30, 52.0, 51.9, 51.6, 39.59, 39.55, 33.6, 33.3, 32.32, 32.25, 32.23, 26.4, 26.3, 26.2, 25.6, 23.35, 23.33, 17.6, 16.73, 16.65, 14.25, 14.22 (only detected signals are recorded); FT-IR (ATR) ν 3443 (br), 2978, 2916, 1731, 1178, 1020 cm^{-1} ; HRMS (FI) calcd for $\text{C}_{17}\text{H}_{28}\text{O}_3$ (M^+): 280.2038, found: 280.2052.

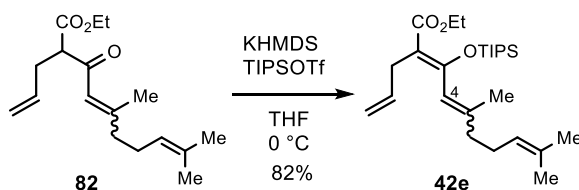
β -Ketoester **82**



To a solution of **81** (264 mg, 0.941 mmol) in CH_2Cl_2 (4.7 mL) was added Dess-Martin periodinane (481 mg, 1.13 mmol) at 0 °C. The reaction mixture was then warmed up to room temperature and stirred for 1 h. The reaction was quenched with saturated aqueous NaHCO_3 and $\text{Na}_2\text{S}_2\text{O}_3$ solution (5.0 mL), and the biphasic mixture was stirred vigorously for 10 min. Two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (5.0 mL $\times$ 3). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified through a short pad of SiO_2 (hexane:EtOAc = 5:1) to afford **82** (*E/Z* or *Z/E* = 2.0:1, 246 mg, 0.883 mmol, 94% yield).

82: pale yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 6.12 (s, 1H), 5.79–5.71 (m, 1H), 5.13–5.00 (m, 3H), 4.21–4.12 (m, 2H), 3.52–3.47 (m, 1H), 2.64–2.53 (m, 2H + 0.33 $\times$ 2H), 2.16–2.10 (m, 0.67 $\times$ 7H), 1.90 (s, 0.33 $\times$ 3H), 1.68–1.65 (m, 3H + 0.33 $\times$ 2H), 1.603 (s, 0.33 $\times$ 3H), 1.595 (s, 0.67 $\times$ 3H), 1.25–1.22 (m, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 193.9, 193.2, 169.73, 169.7, 162.6, 161.9, 134.7, 132.6, 132.2, 123.5, 122.8, 122.1, 121.5, 117.0, 61.1, 59.6, 59.5, 41.3, 34.2, 32.4, 26.7, 26.0, 25.9, 25.6, 19.8, 17.7, 17.6, 14.1 (only detected signals are recorded); FT-IR (ATR) ν 2979, 2918, 1736, 1686, 1614, 1439, 1178 cm^{-1} ; HRMS (FI) calcd for $\text{C}_{17}\text{H}_{26}\text{O}_3$ (M^+): 278.1882, found: 278.1870.

Triene **42e**

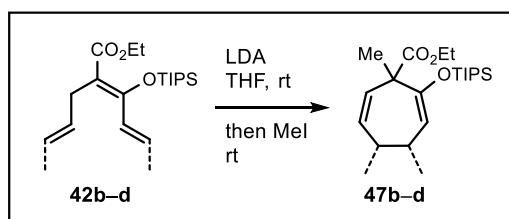


To a solution of **82** (112 mg, 0.401 mmol) in THF (2.0 mL) was added KHMDS (1.0 mol/L in THF, 480 μL , 0.480 mmol) at 0 °C. After stirring for 10 min, TIPSOTf (129 μL , 0.480 mmol) was added, and the reaction mixture was stirred for another 10 min at the same temperature. The reaction was quenched with saturated aqueous NaHCO_3 solution (2.0 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (2.0 mL $\times$ 3). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue

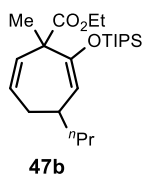
was purified by flash column chromatography [SiO_2 (neutralized by the elution of *N,N*-dimethylaniline), hexane:EtOAc = 50:1] to afford **42e** (4*E*/4*Z* or 4*Z*/4*E* = 2.2:1, 143 mg, 0.329 mmol, 82% yield).

42e: yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 5.80–5.71 (m, 1H), 5.65 (s, 1H), 5.10–5.07 (m, 1H), 4.99 (d, J = 17.2 Hz, 1H), 4.92 (d, J = 10.3 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 2.91 (d, J = 5.7 Hz, $0.31 \times 2\text{H}$), 2.88 (d, J = 5.7 Hz, $0.69 \times 2\text{H}$), 2.17–2.05 (m, 4H), 1.78 (s, $0.31 \times 3\text{H}$), 1.69–1.68 (m, $0.69 \times 6\text{H} + 0.31 \times 3\text{H}$), 1.61 (s, $0.69 \times 3\text{H}$), 1.60 (s, $0.31 \times 3\text{H}$), 1.26 (t, J = 7.2 Hz, 3H), 1.16–1.05 (m, 21H); ^{13}C NMR (126 MHz, CDCl_3) δ 168.3, 168.1, 153.9, 153.8, 143.0, 142.8, 136.5, 136.4, 132.1, 131.9, 123.9, 123.6, 121.9, 121.0, 114.7, 111.0, 110.9, 59.7, 59.6, 39.0, 33.94, 33.88, 33.7, 25.9, 25.72, 25.69, 25.67, 22.3, 18.7, 17.91, 17.88, 17.7, 17.6, 14.4, 13.3, 13.2 (only detected signals are recorded); FT-IR (ATR) ν 2943, 2867, 1716, 1197, 881, 682 cm^{-1} ; HRMS (FI) calcd for $\text{C}_{26}\text{H}_{46}\text{O}_3\text{Si}$ (M^+): 434.3216, found: 434.3214.

General procedure B: synthesis of cycloheptadienes

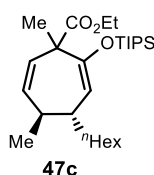


An LDA solution (ca. 1.0 mol/L in THF-hexane) was prepared by addition of $n\text{BuLi}$ (2.69 mol/L in hexane, 743 μL , 2.00 mmol) to a solution of $i\text{Pr}_2\text{NH}$ (281 μL , 2.00 mmol) in THF (1.26 mL) at 0 $^\circ\text{C}$. The mixture was stirred for 30 min at the same temperature before the use. To another reaction vessel charged with triene (1.0 equiv.) in THF (0.1 mol/L) was added the LDA solution (2.0 equiv.) via a syringe at 0 $^\circ\text{C}$. The reaction mixture was then warmed up to room temperature and stirred for 30 min. To this mixture was added MeI (3.0–5.0 equiv.), and the reaction mixture was stirred for another 20–30 min at the same temperature. The reaction was quenched with saturated aqueous NaHCO_3 solution, and the organic layer was diluted with EtOAc. Two layers were separated, and the aqueous layer was extracted three times with EtOAc. The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography [SiO_2 (neutralized by the elution of *N,N*-dimethylaniline), hexane:EtOAc = 200:1–50:1] to afford the product cycloheptadiene.



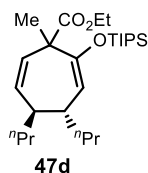
According to the general procedure B, **47b** (dr = 2.3:1, 17.0 mg, 43.1 μ mol, 86% yield) was synthesized from triene **42b** (19.0 mg, 49.9 μ mol), LDA (ca. 1.0 mol/L in THF-hexane, 100 μ L, 100 μ mol) and MeI (9.3 μ L, 150 μ mol).

47b: colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 5.80–5.72 (m, 1H), 5.35 (d, J = 12.0 Hz, 0.7H), 5.22 (d, J = 12.0 Hz, 0.3H), 4.80 (d, J = 4.6 Hz, 0.3H), 4.76 (d, J = 4.9 Hz, 0.7H), 4.21–4.13 (m, 1H), 4.09–3.96 (m, 1H), 2.31 (br, 1H), 2.21–2.09 (m, 1H + 0.3H), 2.00–1.94 (m, 0.7H), 1.49 (s, $0.3 \times 3\text{H}$), 1.48 (s, $0.7 \times 3\text{H}$), 1.36–1.25 (m, 4H), 1.24–1.13 (m, 6H), 1.09–1.06 (m, 18H), 0.91–0.87 (m, 3H)



According to the general procedure B, **47c** (dr = 2.4:1, 17.8 mg, 39.5 μ mol, 81% yield) was synthesized from triene **42c** (21.4 mg, 49.0 μ mol), LDA (ca. 1.0 mol/L in THF-hexane, 100 μ L, 100 μ mol) and MeI (15.6 μ L, 250 μ mol).

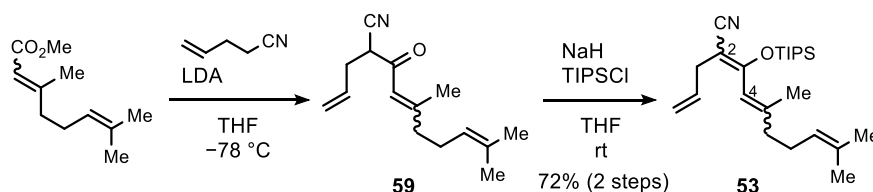
47c: yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 5.67–5.60 (m, 1H), 5.18 (d, J = 12.6 Hz, 0.71H), 5.12 (d, J = 12.0 Hz, 0.29H), 4.84–4.82 (m, 1H), 4.18–4.10 (m, 1H), 4.04–3.96 (m, 1H), 2.36–2.31 (m, 0.71H), 2.26–2.21 (m, 0.29H), 2.05–1.97 (m, 1H), 1.47 (s, $0.71 \times 3\text{H}$), 1.46 (s, $0.29 \times 3\text{H}$), 1.31–1.15 (m, 13H), 1.12–1.05 (m, 24H), 0.88 (t, J = 6.9 Hz, 3H)



According to the general procedure B, **47d** (dr = 9:1, 17.3 mg, 39.6 μ mol, 78% yield) was synthesized from triene **42d** (21.5 mg, 50.9 μ mol), LDA (ca. 1.0 mol/L in THF-hexane, 100 μ L, 100 μ mol) and MeI (9.3 μ L, 150 μ mol).

47d: yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 5.72–5.65 (m, 1H), 5.21 (d, J = 12.0 Hz, 0.9H), 5.09 (d, J = 12.0 Hz, 0.1H), 4.89–4.86 (m, 1H), 4.19–4.09 (m, 1H), 4.04–3.92 (m, 1H), 2.21–2.13 (m, 1H), 2.11–2.06 (m, 0.9H), 1.99–1.92 (m, 0.1H), 1.66–1.25 (m, 11H), 1.22–1.10 (m, 6H), 1.09–1.06 (m, 18H), 0.89–0.86 (m, 6H)

Triene 53



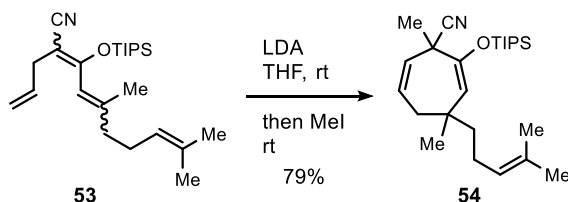
To a solution of $i\text{Pr}_2\text{NH}$ (1.51 mL, 11.0 mmol) in THF (25 mL) was added $n\text{BuLi}$ (2.70 mol/L in hexane, 4.07 mL, 11.0 mmol) at 0 $^\circ\text{C}$. After stirring for 30 min, the reaction mixture was cooled

down to $-78\text{ }^{\circ}\text{C}$ and 4-pentenitrile (1.06 mL, 11.0 mmol) was added. After stirring for 30 min, methyl geranate ($E/Z = 4.2:1$, 985 μL , 5.00 mmol) was added, and the reaction mixture was stirred for another 10 min at the same temperature. The reaction was quenched with saturated aqueous NH_4Cl solution (15 mL), and the organic layer was diluted with EtOAc (15 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (15 mL $\times$ 2). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure to afford crude **59**.

NaH (55% dispersion in paraffin, 659 mg, 15.1 mmol) was washed with hexane and suspended with THF (25 mL). To this suspension was added the crude **59** in THF (3.0 mL) via cannula at $0\text{ }^{\circ}\text{C}$. After stirring for 30 min, TIPSCl (1.27 mL, 6.00 mmol) was added. The reaction mixture was then warmed up to room temperature and stirred for 30 min. The reaction was quenched with saturated aqueous NaHCO_3 solution (20 mL), and the organic layer was diluted with EtOAc (15 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (15 mL $\times$ 3). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography [SiO_2 (neutralized by the elution of N,N -dimethylaniline), hexane:EtOAc = 100:1] to afford **53** [($2E$, $4E$) + ($2E$, $4Z$):[($2Z$, $4E$) + ($2Z$, $4Z$)] = 3.6:1, 1.39 g, 3.58 mmol, 72% yield for 2 steps).

53: colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 5.85–5.73 (m, 1H), 5.68 (s, 0.78H), 5.58 (s, 0.22H), 5.16–5.03 (m, 3H), 3.01–2.97 (m, $0.78 \times 2\text{H}$), 2.77–2.72 (m, $0.22 \times 2\text{H}$), 2.27–2.07 (m, 4H), 1.86–1.81 (m, 3H), 1.67 (d, $J = 2.9\text{ Hz}$, 3H), 1.60 (s, 3H), 1.20–1.11 (m, 3H), 1.09–1.01 (m, 18H); ^{13}C NMR (126 MHz, CDCl_3) δ 162.3, 162.0, 161.9, 147.5, 147.1, 146.3, 134.0, 133.85, 133.75, 132.4, 132.2, 131.9, 123.7, 123.3, 123.1, 120.4, 120.3, 119.2, 118.74, 118.66, 116.8, 116.6, 116.5, 93.62, 93.59, 92.0, 39.5, 39.0, 34.1, 33.1, 31.5, 31.4, 25.85, 25.78, 25.6, 25.3, 22.7, 19.4, 18.9, 17.8, 17.7, 17.61, 17.59, 17.4, 17.3, 13.3, 13.2, 13.02, 12.96 (only detected signals are recorded); FT-IR (ATR) ν 2945, 2868, 2206, 1602, 1250, 882, 685 cm^{-1} ; HRMS (FI) calcd for $\text{C}_{24}\text{H}_{41}\text{NOSi}$ (M^+): 387.2957, found: 387.2955.

Cycloheptadiene **54**

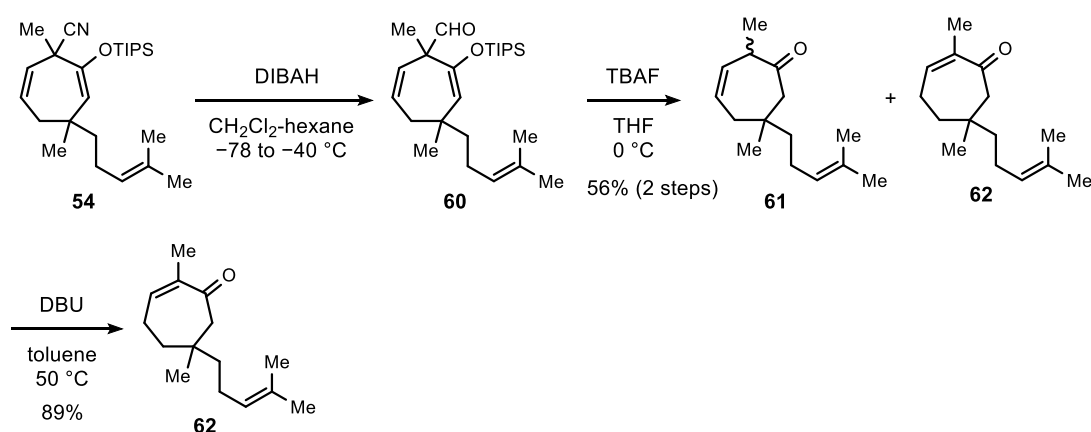


An LDA solution (ca. 1.0 mol/L in THF-hexane) was prepared by the addition of $n\text{-BuLi}$ (2.70 mol/L in hexane, 2.59 mL, 7.00 mmol) to a solution of $i\text{-Pr}_2\text{NH}$ (984 μL , 7.00 mmol) in THF (4.4

mL) at 0 °C. The mixture was stirred for 30 min at the same temperature before the use. To another reaction vessel charged with **53** [(2*E*, 4*E*) + (2*E*, 4*Z*):[(2*Z*, 4*E*) + (2*Z*, 4*Z*)] = 3.6:1, 967 mg, 2.49 mmol) in THF (12.5 mL) was added the LDA solution (5.00 mL, 5.00 mmol) via a syringe at 0 °C. The reaction mixture was then warmed up to room temperature and stirred for 30 min. To this mixture was added MeI (778 µL, 12.5 mmol), and the reaction mixture was stirred for 20 min at the same temperature. The reaction was quenched with saturated aqueous NaHCO₃ solution (10 mL), and the organic layer was diluted with EtOAc (10 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (10 mL × 3). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, hexane:EtOAc = 100:1) to afford **54** (dr = 1:1, 794 mg, 1.98 mmol, 79% yield).

54: yellow oil; ¹H NMR (500 MHz, CDCl₃) δ 5.89–5.84 (m, 1H), 5.61 (d, *J* = 11.5 Hz, 0.5H), 5.57 (d, *J* = 10.9 Hz, 0.5H), 5.08–5.04 (m, 1H), 4.79 (s, 0.5H), 4.77 (s, 0.5H), 2.39 (q, *J* = 7.3 Hz, 0.5H), 2.28 (q, *J* = 7.1 Hz, 0.5H), 2.18 (q, *J* = 7.3 Hz, 0.5H), 2.07 (q, *J* = 7.3 Hz, 0.5H), 1.99–1.90 (m, 2H), 1.69–1.67 (m, 6H), 1.61–1.57 (m, 2H), 1.40–1.20 (m, 6H), 1.16–0.95 (m, 21H); ¹³C NMR (126 MHz, CDCl₃) δ 144.8, 144.7, 131.4, 130.8, 130.7, 129.9, 129.5, 124.4, 122.5, 122.3, 117.21, 117.19, 43.3, 42.85, 42.79, 42.7, 37.4, 37.2, 36.9, 28.5, 28.3, 26.9, 26.6, 25.7, 23.2, 18.10, 18.08, 18.0, 17.9, 17.53, 17.50, 12.9 (only detected signals are recorded); FT-IR (ATR) ν 2944, 2867, 1461, 1211, 1163, 1127, 881, 731 cm⁻¹ (CN absorption bands were not detected due to the very weak intensity); HRMS (FI) calcd for C₂₅H₄₃NOSi (M⁺): 401.3113, found: 401.3096.

Cycloheptenone **62**



To a solution of **54** (1.14 g, 2.85 mmol) in CH₂Cl₂ (14 mL) was added DIBALH (1.02 mol/L in hexane, 4.19 mL, 4.27 mmol) at -78 °C. The reaction mixture was then warmed up to -40 °C and stirred for 30 min. The reaction was quenched with saturated aqueous Rochelle salt (potassium

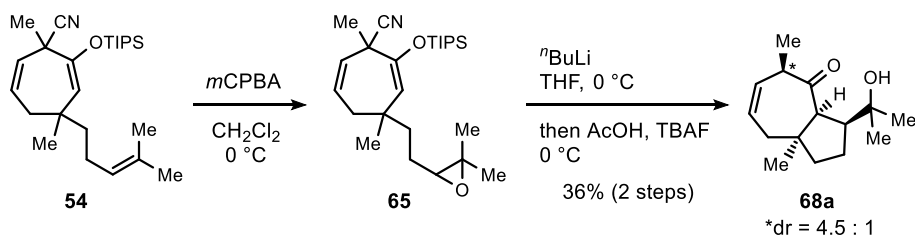
sodium (+)-tartrate) solution (12 mL), and the biphasic mixture was stirred vigorously overnight. Two layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (10 mL × 3). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure to afford crude **60**.

To a solution of crude **60** in THF (14 mL) was added TBAF (1.0 mol/L in THF, 3.42 mL, 3.42 mmol) at 0 °C. After stirring for 30 min, the reaction was quenched with saturated aqueous NH₄Cl solution (10 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (10 mL × 3). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, hexane:EtOAc = 50:1) to afford **61** (along with a trace amount of **62**, 353 mg, 1.60 mmol, 56% yield for 2 steps).

To a solution of **61** (mixture with **62**, 353 mg, 1.60 mmol) in toluene (8.0 mL) was added DBU (1.20 mL, 8.01 mmol) at room temperature. The reaction mixture was then warmed up to 50 °C and stirred for 16 h. After cooling down to 0 °C, the reaction was quenched with saturated aqueous NaHCO₃ solution (8 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (8 mL × 3). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, hexane:EtOAc = 50:1) to afford **62** (312 mg, 1.42 mmol, 89% yield).

62: yellow oil; ¹H NMR (500 MHz, CDCl₃) δ 6.64 (td, *J* = 6.0, 1.3 Hz, 1H), 5.09 (t, *J* = 6.9 Hz, 1H), 2.49 (d, *J* = 11.5 Hz, 1H), 2.41 (d, *J* = 11.5 Hz, 1H), 2.35–2.32 (m, 2H), 2.02–1.89 (m, 2H), 1.80 (s, 3H), 1.67 (s, 3H), 1.60 (s, 3H), 1.57 (s, 2H), 1.58–1.47 (m, 1H), 1.36–1.26 (m, 1H), 0.99 (s, 3H)

Hydroxyketone **68a**



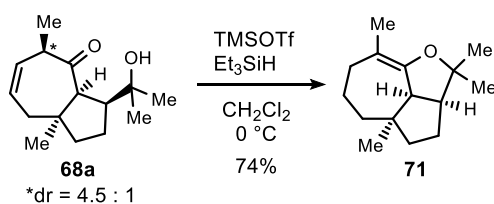
To a solution of **54** (dr = 1:1, 790 mg, 1.97 mmol) in CH₂Cl₂ (10 mL) was added *m*CPBA (contains ca. 30% water, 580 mg, 2.35 mmol) at 0 °C. After stirring for 30 min, the reaction was quenched by the addition of 2-methyl-2-butene (2.09 mL, 19.7 mmol) and saturated aqueous NaHCO₃ solution (10 mL), and the biphasic mixture was stirred vigorously for 30 min at 0 °C. Two layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (10 mL × 3). The combined

organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure to afford crude **65**.

To a solution of crude **65** in THF (10 mL) was added $n\text{BuLi}$ (2.70 mol/L in hexane, 2.19 mL, 5.91 mmol) at 0 °C. After stirring for 20 min, AcOH (1.13 mL, 19.7 mmol) was added dropwise to the reaction mixture, and TBAF (1.0 mol/L in THF, 9.85 mL, 9.85 mmol) was added successively. After stirring for 30 min at 0 °C, 1 M aqueous HCl solution (20 mL) was added, and the biphasic mixture was stirred vigorously for 10 min at the same temperature. The reaction mixture was neutralized by the addition of NaHCO_3 (powder), and the organic layer was diluted with EtOAc (10 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (10 mL $\times$ 3). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2 , hexane:EtOAc = 10:1 to 5:1) to afford **68a** (dr = 4.5:1, 168 mg, 0.712 mmol, 36% yield for 2 steps).

68a: yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 5.82–5.71 (m, 1H), 5.63 (ddd, J = 10.6, 5.3, 2.3 Hz, 0.82H), 5.47 (dt, J = 10.9, 2.4 Hz, 0.18H), 3.42 (d, J = 7.4 Hz, 0.18H), 3.11–3.05 (m, 0.82H), 2.94–2.85 (m, 1H), 2.82 (d, J = 6.9 Hz, 0.82H), 2.79 (d, J = 7.4 Hz, 0.18H), 2.13 (dd, J = 14.3, 6.3 Hz, 0.18H), 1.98 (dd, J = 14.6, 4.3 Hz, 0.82H), 1.87 (dd, J = 14.3, 8.3 Hz, 0.18H), 1.83–1.74 (m, $0.82 \times 2\text{H} + 0.18\text{H}$), 1.63–1.36 (m, 3H), 1.22 (d, J = 7.5 Hz, $0.18 \times 3\text{H}$) 1.16–1.12 (m, 9H), 1.09 (s, $0.82 \times 3\text{H}$); ^{13}C NMR (126 MHz, CDCl_3) δ 215.0, 213.5, 131.3, 130.6, 128.4, 127.1, 71.7, 71.3, 60.3, 58.8, 51.29, 51.26, 51.18, 51.15, 49.9, 48.2, 39.9, 39.5, 36.7 (2C), 29.6, 29.5, 26.8 (2C), 26.22, 26.19, 26.1, 26.0, 18.0, 15.1; FT-IR (ATR) ν 3508 (br), 2963, 2931, 2869, 1698, 1375, 732 cm^{-1} ; HRMS (FI) calcd for $\text{C}_{15}\text{H}_{24}\text{O}_2$ (M^+): 236.1776, found: 236.1765.

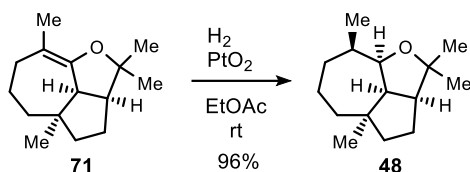
Enol ether **71**



To a solution of **68a** (dr = 4.5:1, 117 mg, 0.496 mmol) in CH_2Cl_2 (2.5 mL) were added successively Et_3SiH (158 μL , 0.993 mmol) and TMSOTf (179 μL , 0.993 mmol) at 0 °C. After stirring for 1.5 h at the same temperature, the reaction was quenched with saturated aqueous NaHCO_3 solution (2.5 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (2.5 mL $\times$ 3). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2 , hexane:EtOAc = 100:1) to afford **71** (80.7 mg, 0.366 mmol, 74% yield).

71: pale yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 2.92 (d, $J = 8.0$ Hz, 1H), 2.39 (ddd, $J = 8.0$, 8.0, 8.0 Hz, 1H), 2.11–2.05 (m, 1H), 1.80–1.75 (m, 1H), 1.64 (d, $J = 1.7$ Hz, 3H), 1.59–1.39 (m, 7H), 1.32–1.25 (m, 4H), 1.17 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 150.9, 99.5, 82.2, 55.7, 54.2, 43.6, 42.0, 36.2, 30.5, 28.8, 27.3, 26.6, 23.6, 20.2, 16.6; FT-IR (ATR) ν 2926, 2854, 1701, 1159 cm^{-1} ; HRMS (FI) calcd for $\text{C}_{15}\text{H}_{24}\text{O}$ (M^+): 220.1827, found: 220.1827.

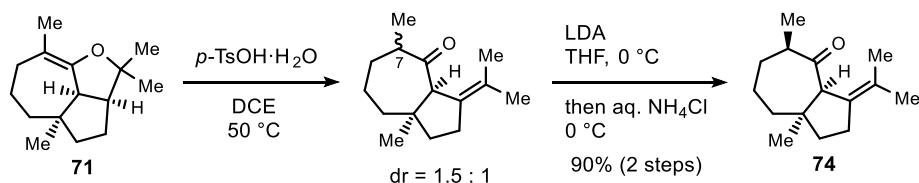
(±)-6-*epi*-6,11-epoxyisodaucane (48)



To a solution of enol ether **71** (21.8 mg, 98.9 μmol) in EtOAc (0.50 mL) was added PtO_2 (4.6 mg, 20 μmol) under Ar atmosphere. A balloon filled with H_2 gas was attached to the reaction vessel, and the reaction atmosphere was replaced with H_2 gas. After stirring for 14 h at room temperature, the reaction mixture was filtered through a pad of Celite[®], and the residue was washed with EtOAc. The filtrate was concentrated under reduced pressure to afford **48** (21.2 mg, 95.3 μmol , 96% yield).

48: colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 3.83 (d, $J = 6.9$ Hz, 1H), 2.50 (ddd, $J = 9.7$, 9.7, 9.7 Hz, 1H), 2.19 (dd, $J = 10.0$, 7.2 Hz, 1H), 1.92–1.86 (m, 1H), 1.76–1.63 (m, 3H), 1.56–1.48 (m, 3H), 1.44–1.33 (m, 3H), 1.25 (s, 3H), 1.16–1.13 (m, 4H), 1.09 (s, 3H), 1.04 (d, $J = 6.9$ Hz, 3H); (500 MHz, C_6D_6) δ 3.76 (d, $J = 6.7$ Hz, 1H), 2.28 (ddd, $J = 9.6$, 9.6, 9.6 Hz, 1H), 2.06–1.95 (m, 2H), 1.82–1.73 (m, 2H), 1.68–1.51 (m, 3H), 1.41–1.30 (m, 4H), 1.25 (s, 3H), 1.16 (d, $J = 6.9$ Hz, 3H), 1.12–1.09 (m, 4H), 1.04 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 81.6, 78.3, 58.3, 55.1, 47.1, 45.4, 36.7, 34.5, 31.8, 28.3, 28.1, 25.8, 25.0, 24.6, 24.2; (126 MHz, C_6D_6) δ 81.5, 78.2, 58.6, 55.5, 47.5, 45.6, 37.0, 35.0, 32.3, 28.3, 28.2, 26.1, 25.2, 25.0, 24.5; FT-IR (ATR) ν 2961, 2927, 1451, 991 cm^{-1} ; HRMS (FI) calcd for $\text{C}_{15}\text{H}_{26}\text{O}$ (M^+): 220.1984, found: 222.1994.

Bicyclic ketone 74

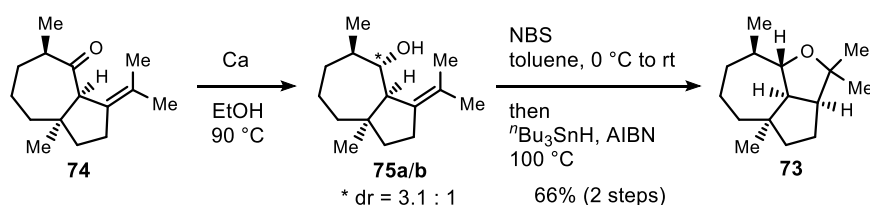


To a solution of **71** (44.4 mg, 0.201 mmol) in 1,2-dichloroethane (1.0 mL) was added $p\text{-TsOH}\cdot\text{H}_2\text{O}$ (3.8 mg, 20 μmol) at room temperature. The reaction mixture was then warmed up to 50 $^\circ\text{C}$ and stirred for 1 h. After cooling down to 0 $^\circ\text{C}$, the reaction was quenched with saturated

aqueous NaHCO₃ solution (1.0 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (1.0 mL × 3). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure to afford a crude mixture of **74** and 7-*epi*-**74** (dr = 1.5:1). An LDA solution (ca. 1.0 mol/L in THF-hexane) was prepared by the addition of ⁿBuLi (2.64 mol/L in hexane, 758 μL, 2.00 mmol) to a solution of ⁱPr₂NH (281 μL, 2.00 mmol) in THF (1.24 mL) at 0 °C. The mixture was stirred for 30 min at the same temperature before the use. To another reaction vessel charged with the crude mixture of **74** and 7-*epi*-**74** in THF (1.0 mL) was added the LDA solution (400 μL, ca. 0.400 mmol) via a syringe at 0 °C. After stirring for 20 min, the reaction was quenched with saturated aqueous NH₄Cl solution (1.0 mL), and the organic layer was diluted with EtOAc (1.0 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (1.0 mL × 3). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, hexane:EtOAc = 100:1) to afford **74** (39.9 mg, 0.181 mmol, 90% yield for 2 steps).

74: pale yellow oil; ¹H NMR (500 MHz, CDCl₃) δ 3.42 (s, 1H), 2.69–2.62 (m, 1H), 2.42 (dd, *J* = 16.5, 9.0 Hz, 1H), 2.32–2.24 (m, 1H), 2.04–1.98 (m, 1H), 1.75–1.69 (m, 2H), 1.67–1.54 (m, 4H), 1.48–1.44 (m, 4H), 1.29–1.09 (m, 3H), 1.04 (d, *J* = 6.5 Hz, 3H), 1.03 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 215.0, 135.9, 125.0, 64.7, 47.5, 44.6, 39.54, 39.46, 34.4, 28.9, 26.7, 22.0, 21.7, 20.9, 15.6; FT-IR (ATR) ν 2927, 2856, 1707, 1458, 1373 cm⁻¹; HRMS (FI) calcd for C₁₅H₂₄O (*M*⁺): 220.1827, found: 220.1824.

(±)-6,11-epoxyisodaucane (**73**)



To a solution of **74** (22.1 mg, 0.100 mmol) in EtOH (1.0 mL) was added Ca chips (cut into ca. 2 mm particles before the use, 122 mg, 3.04 mmol) at room temperature. The reaction vessel was equipped with a reflux condenser and warmed up to 90 °C. After stirring for 30 min, additional EtOH (1.0 mL) was added to disperse insoluble salts, and the reaction mixture was stirred for another 1.5 h at the same temperature. After cooling down to 0 °C, the reaction was quenched with saturated aqueous NH₄Cl solution (1.0 mL), and the organic layer was diluted with EtOAc (2.0 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (1.0 mL × 3). After evaporating the most part of organic solvents, brine (1.0 mL) was added, and the aqueous solution was again extracted with EtOAc (1.0 mL × 3). The combined organic layers were dried

over MgSO₄, filtered, and concentrated under reduced pressure to afford a crude mixture of **75a** and **75b** (**75a**:**75b** = 3.1:1).

To a solution of the crude mixture of **75a** and **75b** in toluene (0.50 mL) was added NBS (26.7 mg, 0.150 mmol) at 0 °C. After stirring for 10 min, the reaction mixture was warmed up to room temperature and stirred for 50 min. To this mixture were added successively ⁿBu₃SnH (80.9 μL, 0.300 mmol) and AIBN (3.8 mg, 23 μmol). The reaction mixture was then warmed up to 100 °C and stirred for 1 h. The solvent was evaporated, and the residue was dissolved with Et₂O (1.0 mL). To this mixture was added DBU (50 μL), and the suspension was filtered through a short pad of SiO₂ (Et₂O only). The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, hexane:CH₂Cl₂ = 10:1 to 5:1) to afford **73** (14.8 mg, 66.6 μmol, 66% yield for 2 steps).

73: colorless oil; ¹H NMR (500 MHz, CDCl₃) δ 3.23 (dd, *J* = 9.7, 9.7 Hz, 1H), 2.50 (ddd, *J* = 9.0, 9.0, 4.7 Hz, 1H), 2.05 (dd, *J* = 9.2, 9.2 Hz, 1H), 1.82–1.78 (m, 1H), 1.73–1.61 (m, 3H), 1.59–1.46 (m, 4H), 1.36 (ddd, *J* = 12.8, 12.8, 12.8 Hz, 1H), 1.30–1.25 (m, 4H), 1.17 (s, 3H), 1.03–0.94 (m, 7H); ¹H NMR (500 MHz, C₆D₆) δ 3.21 (dd, *J* = 9.5, 9.5 Hz, 1H), 2.39–2.35 (m, 1H), 1.98 (dd, *J* = 9.5, 9.5 Hz, 1H), 1.71–1.66 (m, 1H), 1.59–1.52 (m, 4H), 1.47–1.39 (m, 3H), 1.29–1.23 (m, 4H), 1.21–1.15 (m, 7H), 0.92 (ddd, *J* = 11.8, 11.8, 11.8 Hz, 1H), 0.85 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 82.6, 81.1, 62.3, 53.8, 42.5, 41.6, 41.1, 41.0, 38.3, 31.8, 28.0, 26.0, 23.5, 23.1, 20.0; ¹³C NMR (126 MHz, C₆D₆) δ 82.6, 81.0, 62.8, 54.1, 42.5, 41.9, 41.7, 41.2, 38.5, 32.1, 28.0, 26.3, 23.7, 23.5, 20.3; FT-IR (ATR) ν 2924, 2856, 1461, 1050 cm⁻¹; HRMS (FI) calcd for C₁₅H₂₆O (M⁺): 222.1984, found: 222.1979.

Computational Study

DFT calculations were performed using Gaussian 16 software on the Hokkaido University High Performance Intercloud at the Information Initiative Center, Hokkaido University. Both structures were optimized at the B3LYP/6-31++G(d,p) level of theory using the IEFPCM (benzene) solvent model. Frequency analyses were performed on both optimized structures to confirm that they have no imaginary frequencies.

6-*epi*-6,11-epoxyisodaucane (48)

Charge: 0

Spin: singlet

E(RB3LYP): -662.537180 hartrees

atom	x	y	z
C1	1.0659350	1.5461260	1.0845900
C2	0.1513410	1.7192810	-0.1553130
C3	-0.1620250	0.4172990	-0.9949460
C4	0.4746980	-0.9460630	-0.6805140
C5	1.9904780	-1.1239100	-0.4974160
C6	2.5954370	-0.5013000	0.7705010
C7	2.4954120	1.0239160	0.8803160
C8	-1.6649180	0.0835110	-0.7832460
C9	-1.6631270	-1.1151740	0.2447280
O10	-0.2577090	-1.4253360	0.4552560
C11	-1.2455700	2.2119070	0.3577350
C12	-2.3238590	1.4180710	-0.3991710
C13	-2.3518410	-2.3458120	-0.3692050
C14	-2.2597000	-0.8315590	1.6241070
C15	0.7518270	2.7802930	-1.1041000
C16	2.3550590	-2.6193000	-0.5739260
H17	1.1171220	2.5346390	1.5626230
H18	0.5660260	0.8873530	1.8048630
H19	0.0224050	0.6459770	-2.0513940
H20	0.2178120	-1.5807040	-1.5489910
H21	2.4456490	-0.6262250	-1.3683470
H22	3.6556220	-0.7861480	0.8039510
H23	2.1250870	-0.9586870	1.6508490
H24	3.0975270	1.3392140	1.7425740
H25	2.9635070	1.4932280	0.0042970
H26	-2.1049700	-0.2900640	-1.7143120
H27	-1.3622660	3.2936050	0.2238080
H28	-1.3282560	2.0259570	1.4338410
H29	-3.2470990	1.3029030	0.1787860
H30	-2.5985460	1.9415200	-1.3233480
H31	-2.3005930	-3.1961450	0.3184380
H32	-3.4063860	-2.1331180	-0.5802900
H33	-1.8736710	-2.6357970	-1.3105680
H34	-3.3366940	-0.6468900	1.5559430
H35	-2.1069870	-1.7026630	2.2691410

H36	-1.7877340	0.0279710	2.1039640
H37	1.6775610	2.4323180	-1.5753150
H38	0.0476610	3.0239440	-1.9086000
H39	0.9768290	3.7077710	-0.5640910
H40	3.4415780	-2.7566710	-0.5471890
H41	1.9819800	-3.0762370	-1.4975790
H42	1.9236200	-3.1680880	0.2700630

6,11-epoxyisodaucane (73)

Charge: 0

Spin: singlet

E(RB3LYP): -662.545379 hartrees

atom	x	y	z
C1	-2.2614070	-1.0634150	0.6584870
C2	-0.9517000	-1.5605680	-0.0008130
C3	-0.0904510	-0.4250330	-0.6167600
C4	-0.0878470	0.9285410	0.1178410
C5	-1.1807730	1.9100350	-0.3221290
C6	-2.5743330	1.4715310	0.1792790
C7	-3.0320910	0.0297780	-0.1144130
C8	1.3989870	-0.8830740	-0.5459110
C9	2.1813690	0.3951020	-0.0746950
O10	1.2078970	1.4667090	-0.1719610
C11	0.0229580	-2.1957600	1.0251310
C12	1.4071090	-2.1562250	0.3478680
C13	3.3190500	0.7571450	-1.0312270
C14	2.7078570	0.3428150	1.3687510
C15	-1.2971630	-2.5857450	-1.1039410
C16	-0.8877500	3.3427150	0.1514650
H17	-2.9155930	-1.9331000	0.8038370
H18	-2.0468360	-0.6841310	1.6668110
H19	-0.3871480	-0.2344970	-1.6548460
H20	-0.1737030	0.7779680	1.2082540
H21	-1.1902100	1.9099420	-1.4226960
H22	-3.3091610	2.1648380	-0.2501710

H23	-2.6152580	1.6280500	1.2680070
H24	-4.0921930	-0.0354310	0.1609010
H25	-2.9940560	-0.1650610	-1.1947620
H26	1.7653960	-1.1417660	-1.5437960
H27	-0.2794550	-3.2076840	1.3199750
H28	0.0349770	-1.5880910	1.9393600
H29	2.2240630	-2.1734720	1.0739520
H30	1.5405140	-3.0407240	-0.2842170
H31	3.7815250	1.7056530	-0.7390700
H32	4.0917640	-0.0195070	-1.0214590
H33	2.9409100	0.8586380	-2.0532750
H34	3.5173330	-0.3866910	1.4740220
H35	3.1014740	1.3278600	1.6377790
H36	1.9242360	0.0831810	2.0866970
H37	-1.9787990	-2.1528440	-1.8447680
H38	-0.4056050	-2.9247370	-1.6419950
H39	-1.7857650	-3.4681400	-0.6739800
H40	-1.6844430	4.0236090	-0.1699200
H41	0.0610920	3.7065230	-0.2489980
H42	-0.8311250	3.3888820	1.2464490

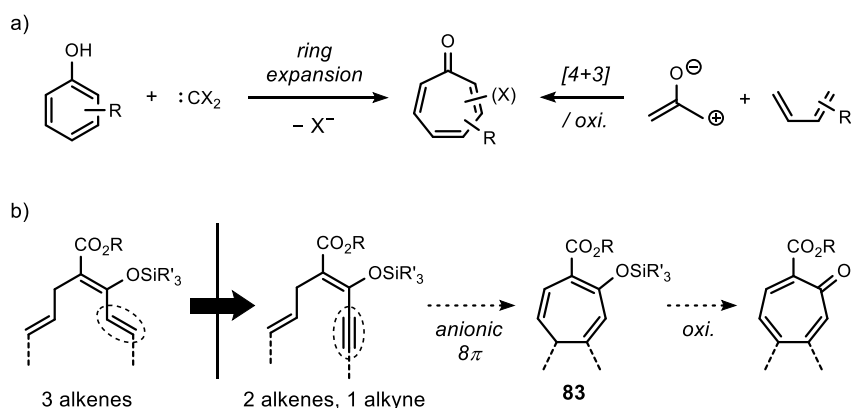
Chapter 2

Anionic Cyclization of β -Ketoester-Derived Dienynes: Asymmetric Total Synthesis of (–)-Orobanone

Introduction

As described in chapter 1, the author established a unique method for accessing multi-substituted seven-membered cyclic motifs using β -ketoester-derived triene derivatives as the precursor for anionic 8π -electrocyclization. The utility of the new method was clearly demonstrated by achieving the total synthesis of 6,11-epoxyisodaucane. The double bonds on the seven-membered ring, however, had to be finally reduced to access the fully saturated target molecule. This experience led the author to address the next issue, namely, effective use of these double bonds after cyclization, and an even more unsaturated (or oxidized) seven-membered cyclic motif was set as the synthetic target.

Tropone is one of the important synthetic motifs, which possesses a non-benzenoid aromatic seven-membered ring. It is also known as the substructure of natural products,^[31] and many synthetic studies of these natural products have focused on how effectively to construct the tropone substructure.^[32] Conventionally, these tropone derivatives have been synthesized through a ring expansion/elimination cascade of phenol derivatives or an oxidation of [4+3] cycloadducts (Scheme 31a). These methods have great advantages in accessing tropone derivatives in short steps; however, the regiocontrolled introduction of substituents, simply by the steric or electronic factors, is sometimes difficult.

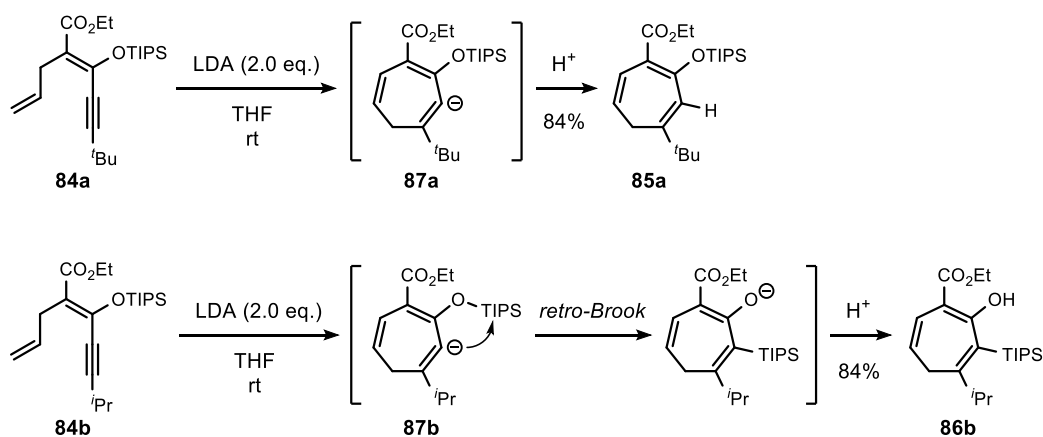


Scheme 31. Synthetic strategies of tropone derivatives

Here, based on the author's achievements on the anionic 8π -electrocyclization of β -ketoester-derived trienes, a new synthetic method to access such tropone derivatives in a regioselective fashion was established (Scheme 31b). By replacing a double bond of the triene substrate with a triple bond, a highly unsaturated compound **83** would be obtained through an anionic 8π -electrocyclization. The seven-membered ring product would serve as a useful precursor of substituted tropone derivatives.

Results and Discussion

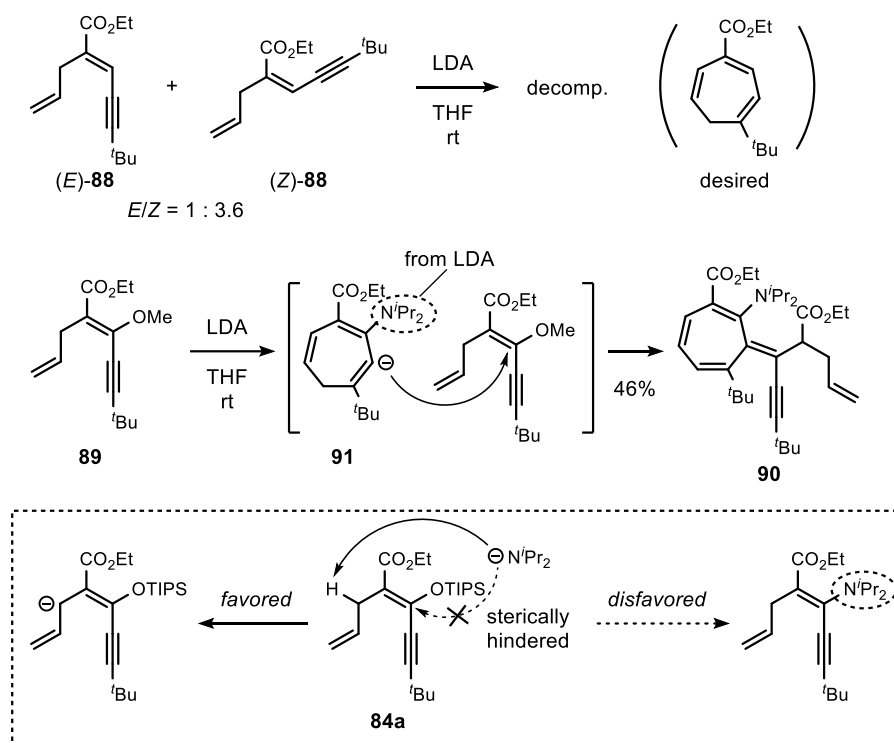
The research started with the investigation of the cyclization reaction of dienyne **84a** possessing a *tert*-butyl group at the alkyne terminus (Scheme 32). According to the previous study, 2.0 equiv. of LDA was added as the base to induce cyclization at room temperature. As the result, the cyclization reaction smoothly proceeded and the expected cycloheptatriene **85a** was obtained as the sole product in 84% yield. Subsequently, the cyclization of substrate **84b** possessing an isopropyl group was investigated under the same conditions; however, the expected triene was not obtained, but a silyl-migrated one **86b** was obtained as the sole product in 84% yield. The different reaction outcomes can be explained by the different steric hindrances of the substituents. In the reaction intermediate **87b**, the sterically less hindered isopropyl group allows the TIPS group to migrate onto the sp^2 carbon through *retro*-Brook rearrangement, while the sterically hindered *tert*-butyl group in **87a** prevents such reaction pathway.



Scheme 32. Different reaction outcomes in cyclization of β -ketoester-derived dienyne

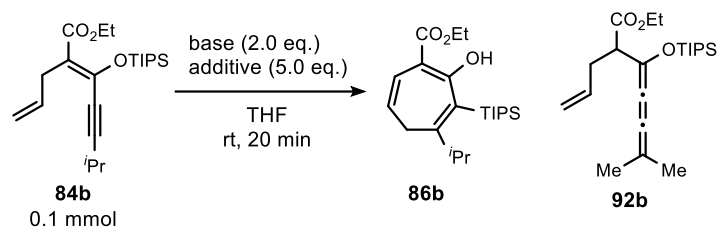
Next, the necessity of the β -silyloxy group was investigated by modifying the β -substituents on the substrate **84a** (Scheme 33). A dienyne substrate **88** without a silyloxy group was synthesized and subjected to the standard conditions, but the reaction resulted in substrate

decomposition. On the other hand, the reaction of substrate **89**, which possesses a methoxy group instead of a silyloxy group, afforded an unexpected dimer **90** having a diisopropylamino group. This product was supposedly formed through a 1,4-addition-elimination of LDA followed by an anionic cyclization to form cyclic anion **91**, which underwent further 1,4-addition to remaining substrate **89**. These results imply that a bulky silyloxy group is essential to the desired cyclization for protecting substrates from undesired 1,4-addition of the base.



Scheme 33. Reaction of dienyne substrates with modified β -substituents

Then, a brief screening of bases was conducted using an isopropyl containing substrate **84b** (Table 3). When LHMDS was used as the base, the reaction did not proceed at all due to its low basicity (entry 1). On the other hand, the use of KHMDS afforded cumulene **92b** as the major product, which was generated through deprotonation from the ϵ -position (the isopropyl methine group) of the substrate (entry 2). A similar result was observed when LDA combined with HMPA was used, suggesting that the coordination of the substrate to a lithium ion is necessary for the regioselective deprotonation (entry 3). Among the bases tested, LDA without any additives was the sole base that can induce the desired cyclization reaction from substrate **84b** (entry 4).

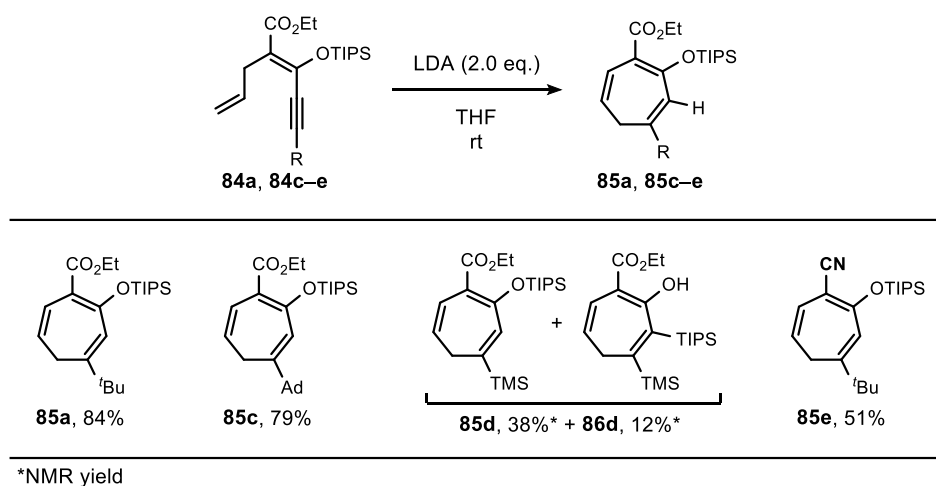


entry	base	additive	result (NMR yield)
1	LHMDS	-	no reaction (84b , 99%)
2	KHMDS	-	92b (58%)
3	LDA	HMPA	92b (51%)
4	LDA	-	86b (84%*)

* isolated yield

Table 3. Brief screening of bases in cyclization of dienyne **84b**

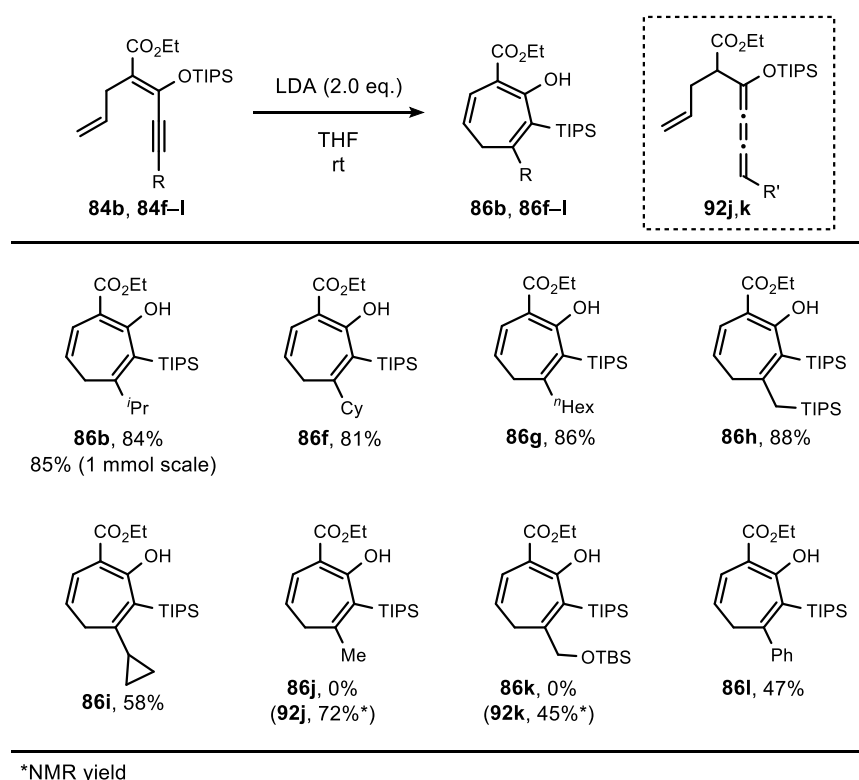
Based on these preliminary results, substrate scope of the current cyclization method was investigated (Scheme 34). Cycloheptatriene **85c** possessing a bulky adamantyl group was obtained in 79% yield as a silyl ether, similarly with the *tert*-butyl derivative **85a**. The substrate possessing a TMS group was also applicable, but the products were obtained as a mixture of silyl ether **85d** and vinylsilane **86d** probably due to the decreased steric hindrance by a long C-Si σ -bond. It proved to be possible to use a cyano group instead of an ester group, and the corresponding nitrile-derivative **85e** was obtained in 51% yield.



Scheme 34. Substrate scope of dienynes possessing a bulky substituent

Other dienyne substrates possessing a less bulky alkyne terminal substituents afforded the products as vinylsilanes through *retro*-Brook rearrangement (Scheme 35). Not only the

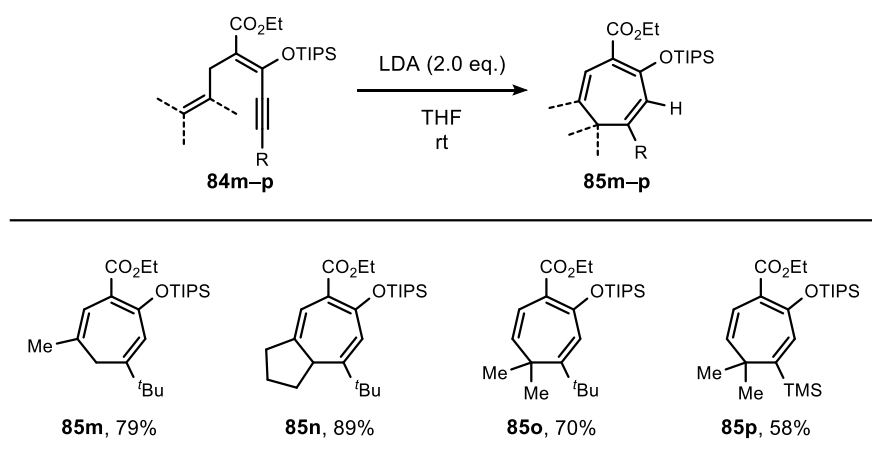
aforementioned isopropyl group, but also the substrates possessing a cyclohexyl, *n*-hexyl, or TIPS-methyl group afforded the desired cycloheptatrienes **86f**, **86g**, or **86h** in high yields, respectively. The substrate possessing a cyclopropyl group partially allowed an undesired ε -deprotonation; therefore, the product cycloheptatriene **86i** was obtained in a slightly decreased yield. For substrates possessing a methyl or (silyloxy)methyl group, the deprotonation occurred at the undesired ε -position predominantly. As the result, the desired cyclized products **86j** and **86k** were not observed but the corresponding cumulene byproducts **92j** and **92k** were detected in 72% and 45% NMR yield, respectively. It is noteworthy that the substrate possessing a phenyl group afforded cycloheptatriene **86l** in 47% yield, which clearly contrasts with the unsuccessful cyclization from the corresponding triene substrate (See scheme 20 in chapter 1).



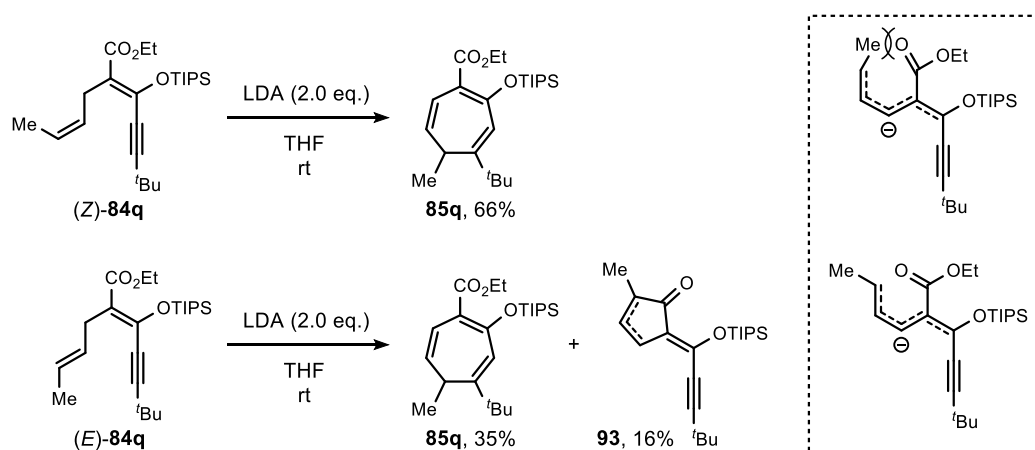
Scheme 35. Substrate scope of dienynes possessing a less bulky substituent

Next, the scope of substituents on the alkene moiety was investigated (Scheme 36). An internal methyl group and a fused five-membered ring were tolerated, and the products **85m** and **85n** were obtained in 79% and 89% yield, respectively. Also, introducing terminal dimethyl group led to construction of a quaternary carbon center, and the cycloheptatrienes **85o** and **85p** were obtained in 70% and 58% yield. On the other hand, the substrates possessing a terminal mono-methyl group exhibited some unique reactivities depending on their *E/Z* stereochemistry. To compare the

reactivity, both (*E*)- and (*Z*)-methylated substrates **84q** were prepared in stereoselective manners (Scheme 37). When these substrates were subjected to the same cyclization conditions, the (*Z*)-substrate afforded the desired cycloheptatriene **85q** in 66% yield, while the (*E*)-substrate afforded the same product in only 35% yield. In the reaction of diyne (*E*)-**84q**, cyclopentenone **93** was also obtained as a minor product in 16% yield. This suggests that an undesired intramolecular addition to the ester center occurred from this substrate. It was speculated that the undesired cyclopentenone formation was suppressed in the reaction of diyne (*Z*)-**84q** because of the large steric repulsion between the methyl group and the ester moiety.



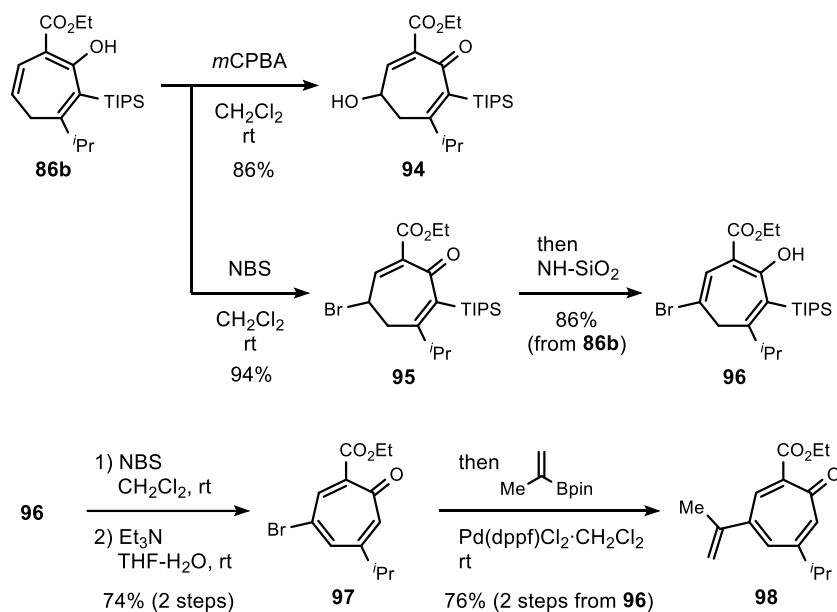
Scheme 36. Substrate scope of diynes with modified alkene substituents



Scheme 37. Different reaction outcomes between (*E*)- and (*Z*)-methylated substrates

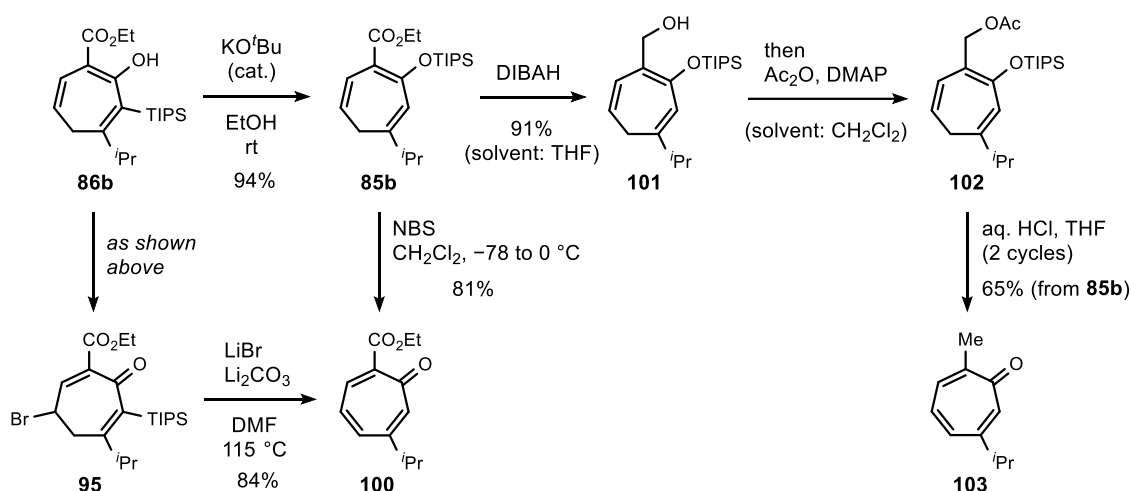
With the synthesized cycloheptatriene **86b** in hand, further synthetic applications were investigated. The regioselective γ -hydroxylation or γ -bromination was achieved using *m*CPBA or NBS affording ketoesters **94** and **95** in high yields (Scheme 38). From bromide **95**, enolization

was induced by purifying the crude product through an NH-silica gel, giving rise to cycloheptatriene **96** in 86% yield from **86b**. This cycloheptatriene was further brominated with NBS, then treated with triethylamine in wet THF to afford bromotropone **97** in 74% yield for 2 steps. Furthermore, one-pot addition of isopropenyl boronate and Pd(II) catalyst to the reaction mixture containing **97** gave rise to a Suzuki coupling product **98** in 76% yield for 2 steps.



Scheme 38. Selective γ -functionalization and further transformations of cycloheptatriene **86b**

The vinylsilane moiety of **86b** was readily converted to the corresponding silyl ether by treatment with a catalytic amount of KO^tBu in ethanol (Scheme 39, Table 4). This transformation was further applied to vinylsilanes **86g**, **86l** and **96** to obtain the corresponding silyl ethers **85g**, **85l** and **99** in high yields. Interestingly, the reaction rate differed by the steric bulkiness or electronic effect of the substituents. Oxidation of the resulting silyl ether **85b** with NBS afforded disubstituted tropone **100** in 81% yield. This tropone **100** was also found to be accessible by the elimination reaction of γ -bromide **95** in 84% yield. In addition, the ester moiety of **85b** was chemoselectively reduced by DIBAH to afford alcohol **101** in 91% yield. It was also possible to trap the intermediate alkoxide as an acetate **102**. The following treatment with hydrochloric acid induced both desilylation and elimination of the acetoxy group to afford tropone **103** in 65% overall yield.



Scheme 39. Synthesis of disubstituted tropones

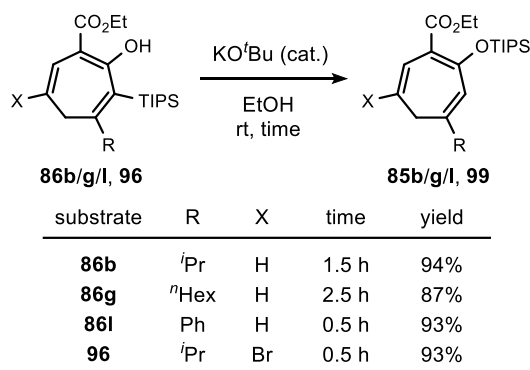
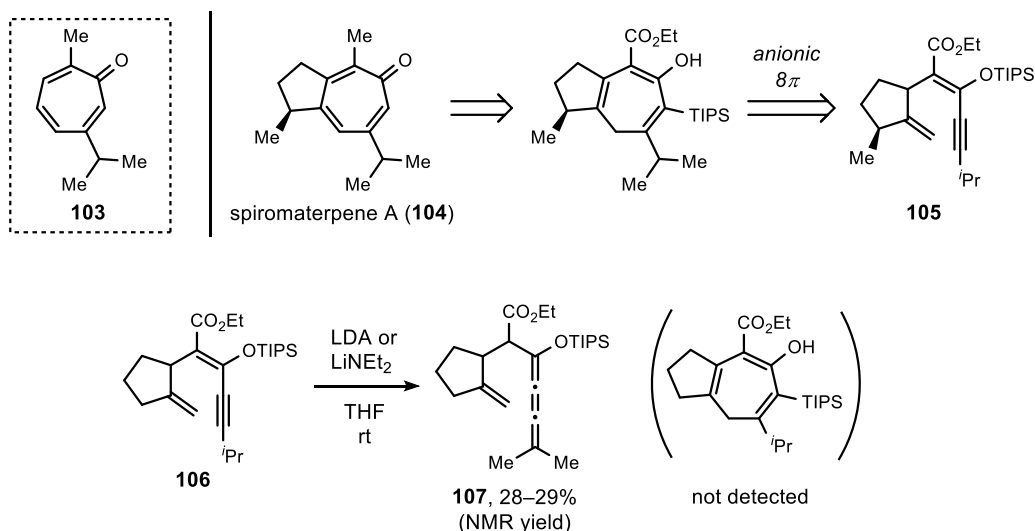


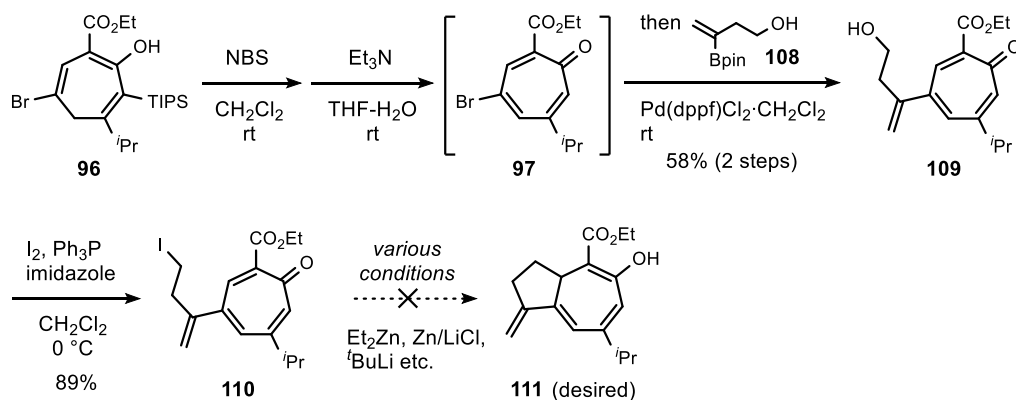
Table 4. KO^tBu-catalyzed Brook-rearrangement of vinylsilanes

To demonstrate the synthetic utility of current method, the application to total synthesis of a tropone-containing natural product was planned. Since it was proved that tropone derivative **103** is accessible, spiromaterpene A (**104**),^[33] a bicyclic sesquiterpenoid possessing a common substructure with **103**, was selected as the first synthetic target (Scheme 40). Initially, the target molecule **104** was expected to be synthesized through an anionic cyclization of dienyn **105** having a fused five-membered ring. The model study using substrate **106**, however, revealed that the synthetic plan is not feasible. Upon treatment with LDA or LiNEt₂ as the base, **106** afforded a complex mixture containing undesired cumulene byproduct **107** in 28–29% NMR yield. These results indicated that the fused five-membered ring of the target molecule should be constructed after anionic 8 π -electrocyclization.



Scheme 40. Initial synthetic plan of spiromaterpene A and model investigation

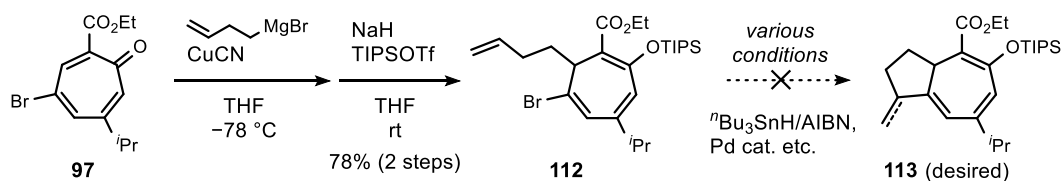
As a new strategy for constructing the five-membered ring, an intramolecular conjugate addition route was planned (Scheme 41). Suzuki coupling of bromotropone **97** with vinyl boronate **108** afforded the desired product **109** in 58% yield from substrate **96**. After conversion of the alcohol moiety to an iodide (**110**), various reductive cyclization conditions were tested.^[34] However, none of them afforded the desired bicyclic compound **111**.



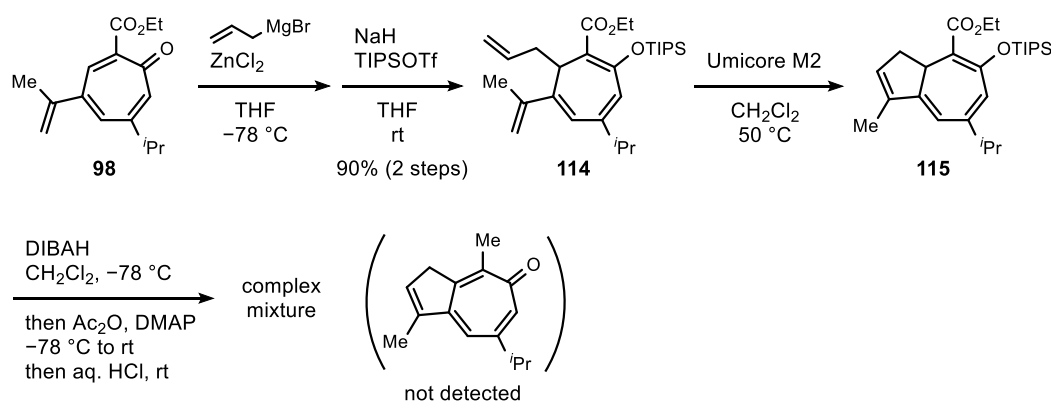
Scheme 41. 1st generation synthesis toward spiromaterpene A

In contrast to the failed intramolecular addition reaction, an intermolecular conjugate addition reaction was found to be feasible. Thus, a homoallylcopper reagent smoothly reacted with bromotropone **97**, and adduct **112** was obtained in good yield through protection of the enol moiety with TIPS group (Scheme 42). The product was then subjected to several cyclization conditions (including radical cyclization or Heck reaction), but the desired bicyclic product **113**

was not obtained at all. On the other hand, conjugate addition of allylzinc with tropone **98** proceeded efficiently, and adduct **114** was obtained in 90% yield after TIPS protection (Scheme 43). The product was subjected to the ring-closing metathesis to give the desired bicyclic product **115**, but efforts for converting it to a tropone derivative led to the formation of unidentified azulene-like aromatized products. These unsuccessful results led the author to focus on another tropone natural product as the synthetic target.

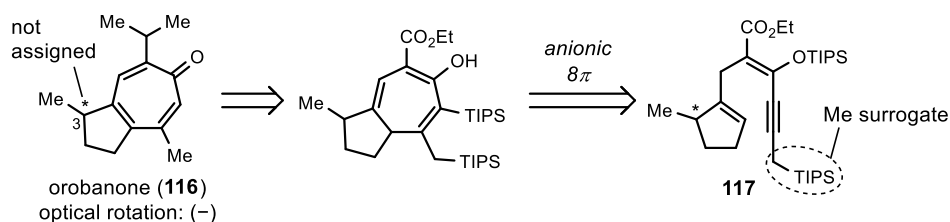


Scheme 42. 2nd generation synthesis toward spiromaterpene A



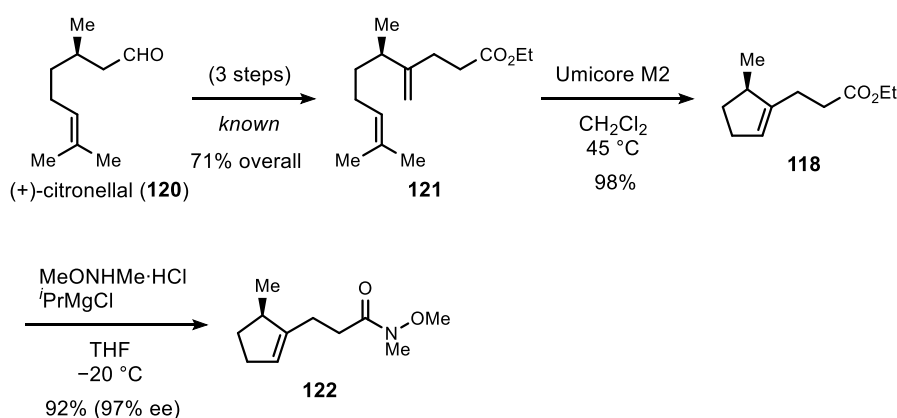
Scheme 43. 3rd generation synthesis toward spiromaterpene A

Instead of spiromaterpene A, a closely related natural sesquiterpenoid orobanone (**116**) was selected as the new synthetic target (Scheme 44). Orobanone was first isolated from a broomrape *Orobanche rapum-genistae* in 1981^[35] and known to exhibit antibacterial activity against *Bacillus cereus* (100 µg/disk).^[36] Although several reports described the isolation of this natural product, the absolute stereochemistry of the C3 position has remained undetermined.^[37] To access this compound, an anionic cyclization of dienynyl ester **117** possessing a chiral five-membered ring was designed. Since it had already been known that a methyl group at the alkyne terminus is not tolerated in the anionic cyclization (as described in Scheme 35), a TIPS-methyl group was selected as the surrogate for a methyl group.

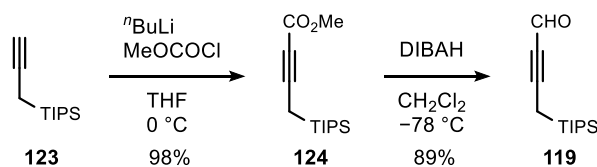


Scheme 44. Retrosynthetic analysis of orobanone

Based on this synthetic plan, fragments **118** and **119** as the precursors for dienyne **117** were prepared (Scheme 45, 46). The optically active cyclic ester **118** was synthesized from (+)-citronellal (**120**) through known three-step transformation^[38] and ring-closing metathesis. The enantiomeric purity of cyclic ester **118** was determined as 97% ee (by HPLC analysis) after conversion into the corresponding Weinreb amide **122**. Alkynyl aldehyde **119** was synthesized from known propargylsilane **123**^[39] via an addition reaction with methyl chloroformate followed by DIBAH reduction.



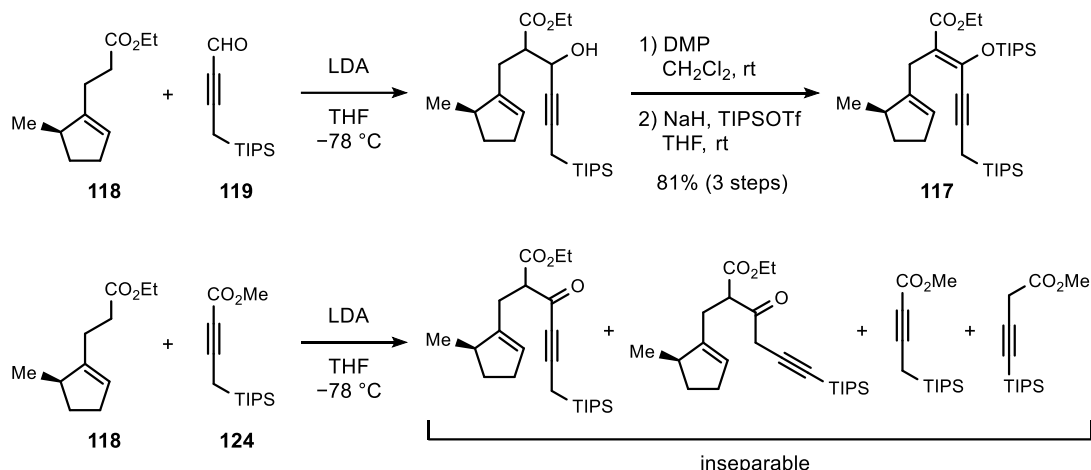
Scheme 45. Synthesis of cyclic ester **118**



Scheme 46. Synthesis of alkynyl aldehyde **119**

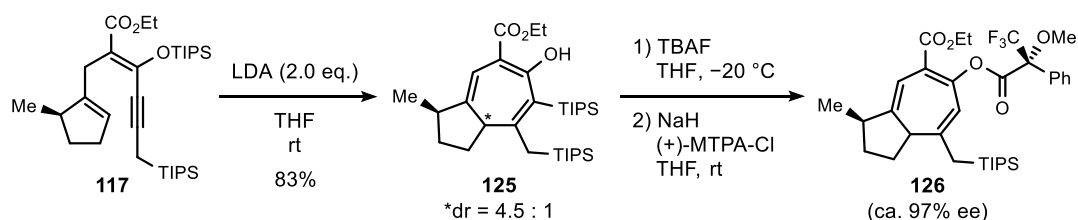
These fragments were coupled to each other by an aldol reaction, and the resulting alcohol was subjected to Dess-Martin oxidation followed by silylation using NaH and TIPSOTf, giving rise to dienyne **117** in 81% yield for 3 steps (Scheme 47). It is noteworthy that Claisen condensation

of esters **118** and **124** suffered from an undesired γ -deprotonation of ester **124**, affording an inseparable mixture containing alkyne isomers.



Scheme 47. Synthesis of the cyclization precursor by different approaches

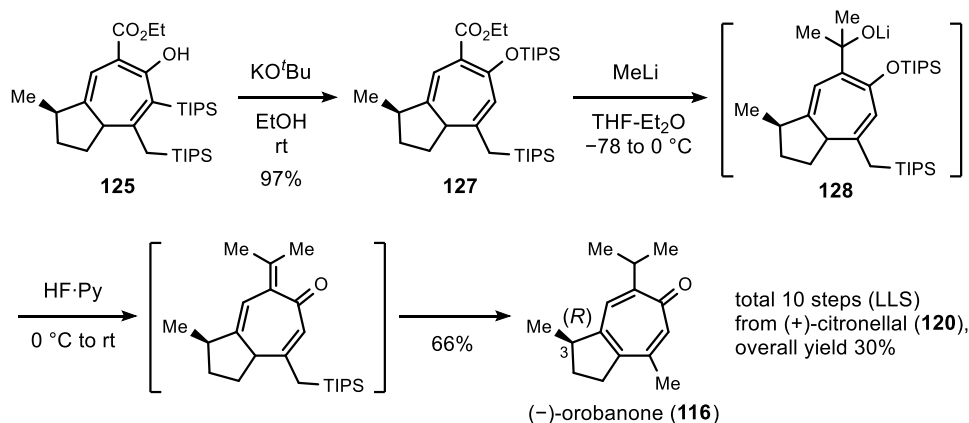
The anionic cyclization of dienyne **117** proceeded smoothly under the standard conditions, and the desired bicyclic triene **125** was obtained in 83% yield (Scheme 48). The enantiomeric purity of product **125** was determined after selective removal of the TIPS group and conversion to chiral enol ester **126**. The ^1H NMR analysis of crude **126** indicated ca. 97% ee, which was consistent with the ee value of the intermediate ester **118**.



Scheme 48. Anionic cyclization and determination of enantiomeric excess

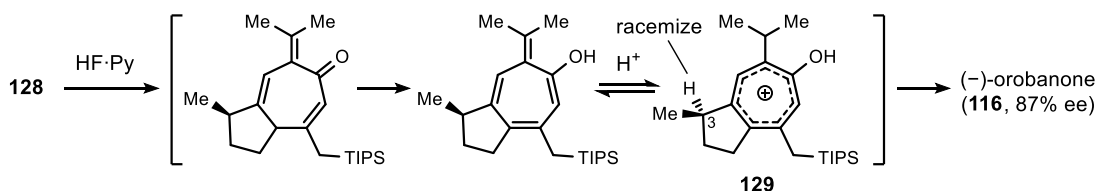
The vinylsilane **125** was transformed into the natural product as shown below (Scheme 49). Under the influence of an equimolar of KO^tBu in ethanol, vinylsilane **125** was isomerized to the corresponding silyl ether **127** in 97% yield. Then, the ester moiety was converted to a tertiary alkoxide **128** by treatment with an excessive amount of MeLi . Subsequent one-pot addition of $\text{HF}\cdot\text{pyridine}$ facilitated both desilylation and dehydration to afford the target compound **116** in 66% yield. The optical rotation value of the final compound was in good agreement with that reported in the literature,^[37] which led to assignment of the absolute stereochemistry of the natural

product as (3*R*)-configuration (shown). After all, the target compound (–)-orobanone was obtained in 30% overall yield for 10 steps (LLS) from commercial (+)-citronellal.



Scheme 49. Synthesis of (–)-orobanone

The HPLC analysis of the synthetic (–)-orobanone indicated that the enantiomeric purity slightly decreased to 87% ee, compared with that of the intermediate ester **125**. It was supposed that a partial racemization of the C3 position would have occurred via cation intermediate **129** under acidic conditions (Scheme 50).



Scheme 50. Proposed racemization mechanism

Conclusion

In conclusion, a novel synthetic method of functionalized cycloheptatrienes using an anionic 8π -electrocyclic reaction of β -ketoester-derived dienyne derivatives was developed. The product cycloheptatrienes were suitable for a variety of chemical transformations including tropone synthesis. Using this method, a concise, first total synthesis of (–)-orobanone, a natural tropone-containing sesquiterpenoid was achieved.

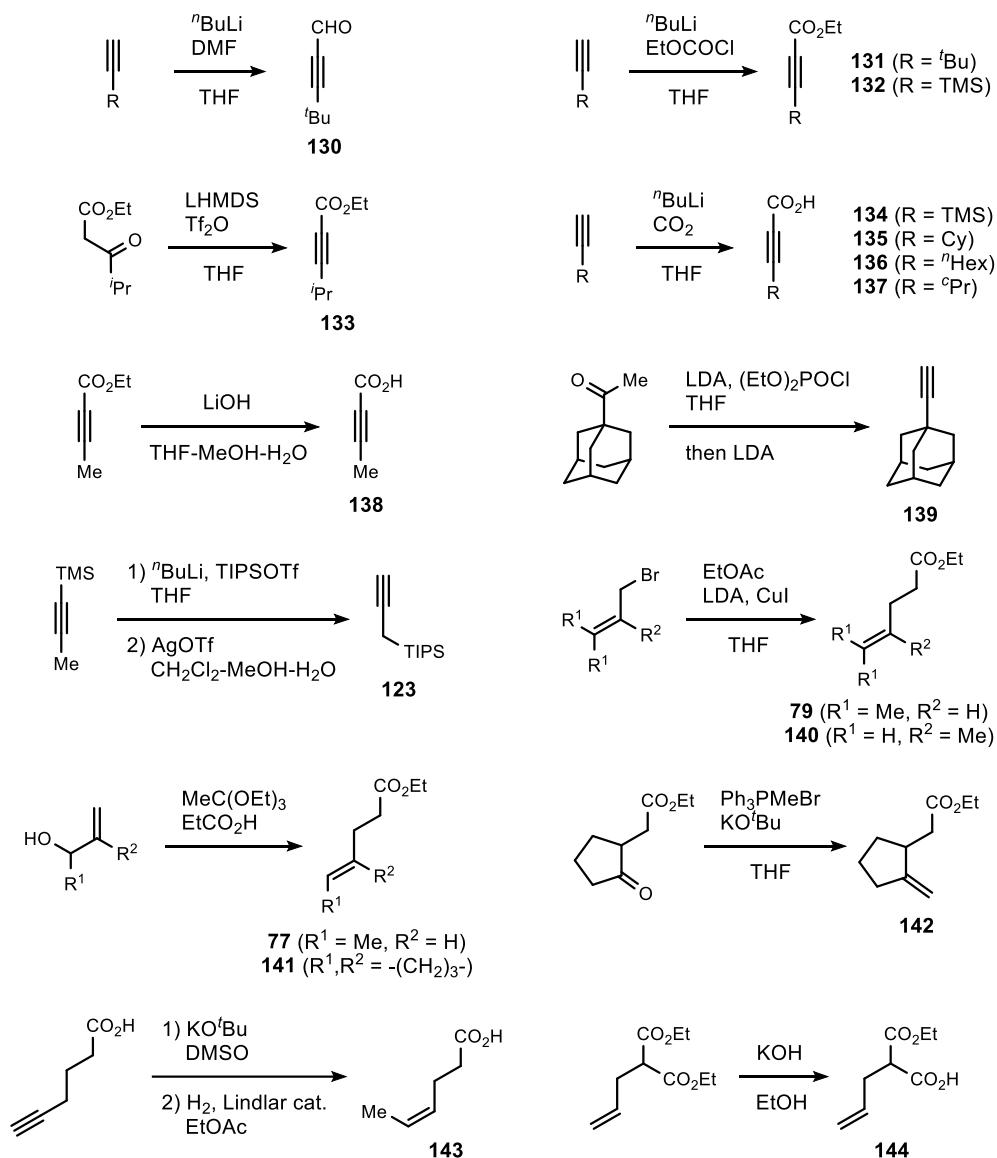
Experimental Section

General Information

All reactions were performed using flame-dried glassware under a positive pressure of argon unless otherwise noted. Reactions at elevated temperatures were performed under heating in an oil bath. THF was distilled from sodium benzophenone ketyl. Other anhydrous solvents were purchased from chemical companies. $i\text{-Pr}_2\text{NH}$ and Et_3N were distilled from CaH_2 under argon and stored in the presence of NaOH (pellets). All other reagents were used as received from commercial sources without further purification.

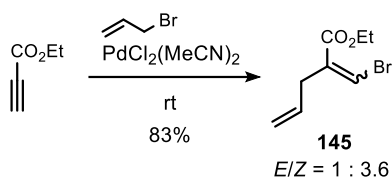
The melting points were measured using ASONE ATM-02 apparatus and uncorrected. Specific optical rotations were determined using JASCO P-2200 polarimeter with a 100 mm cell at 589 nm. Enantiomeric excesses were determined by HPLC analyses using JASCO PU-2089 Plus pump, UV-2075 Plus detector, and DAICEL CHIRALPAK AS-H column (0.46 cm $\phi \times$ 25 cm). ^1H NMR spectra were recorded on JEOL ECA-500 (500 MHz) in CDCl_3 (δ_{H} 7.26). Chemical shifts are reported in parts per million (ppm), and signals are expressed as broad (br), singlet (s), doublet (d), triplet (t), quartet (q), septet (sept), and multiplet (m). Coupling constants are reported in Hz. ^{13}C NMR spectra were recorded on JEOL ECA-500 (126 MHz) in CDCl_3 (δ_{C} 77.0). HRMS were recorded on JEOL JMS-T100GCV (GC-TOFMS) at the GC-MS & NMR Laboratory, Faculty of Agriculture, Hokkaido University. FT-IR spectra were recorded on JASCO FT/IR-4100 spectrophotometer. Analytical TLC was performed using Silica Gel 60 F₂₅₄ (E. Merck), and PTLC was performed using PLC Silica Gel 60 F₂₅₄ (E. Merck). Reaction components were visualized by illumination with UV light (254 nm) and by staining with 8% ethanolic phosphomolybdic acid, ceric ammonium molybdate in 10% sulfuric acid, or basic potassium permanganate aqueous solution. Flash column chromatography was performed on Chromatorex PSQ60B (Fuji Silysia Chemical Ltd.) or Chromatorex NH-DM2035 (Fuji Silysia Chemical Ltd.).

Alkynyl aldehyde **130**,^[40] alkynyl ester **131–133**,^[41] alkynyl carboxylic acid **134–138**,^[42] alkyne **139**, **123**,^[43, 39] alkenyl ester **140–142**, **77**, **79**,^[44, 20, 30] alkenyl carboxylic acid **143**,^[45] and alkenyl malonic acid monoester **144**^[46] were prepared by known procedures.



Experimental and Characterization Details

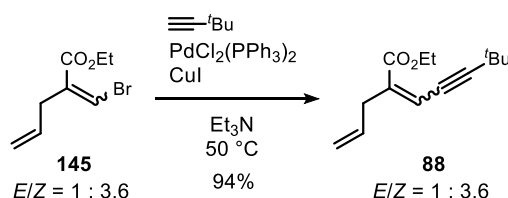
Bromoester 145



To a solution of $\text{PdCl}_2(\text{MeCN})_2$ (37.0 mg, 0.143 mmol) in allyl bromide (3.0 mL) was added dropwise ethyl propiolate (307 μL , 3.00 mmol) at room temperature over 1 h. After stirring for another 1 h, the reaction mixture was filtered through a pad of Celite[®], and the residue was washed

with CH₂Cl₂. The filtrate was concentrated under reduced pressure and purified by flash column chromatography (SiO₂, hexane:EtOAc = 50:1) to afford **145** (*E/Z* = 1:3.6, 543 mg, 2.48 mmol, 83% yield). The spectral data matched with those reported in literature. [47]

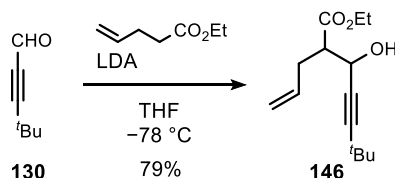
Dienyne **88**



To a solution of **145** (103 mg, 0.469 mmol) in Et₃N (2.0 mL) were added successively PdCl₂(PPh₃)₂ (6.9 mg, 9.8 μmol), CuI (1.7 mg, 8.9 μmol) and 3,3-dimethyl-1-butene (73.6 μL, 0.600 mmol) at room temperature. The reaction mixture was then warmed up to 50 °C and stirred for 13 h. After cooling down to room temperature, the mixture was filtered, and the residue was washed with Et₂O. The filtrate was concentrated under reduced pressure and diluted with Et₂O (1.0 mL) and saturated aqueous NH₄Cl solution (1.0 mL). Two layers were separated, and the aqueous layer was washed with Et₂O (1.0 mL × 3). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, hexane:EtOAc = 100:1) to afford **88** (*E/Z* = 1:3.6, 97.6 mg, 0.443 mmol, 94% yield).

88: colorless oil; ¹H NMR (500 MHz, CDCl₃) δ 6.67 (s, 0.22H), 5.96 (t, *J* = 2.0 Hz, 0.78H), 5.88–5.75 (m, 1H), 5.13–4.99 (m, 2H), 4.26 (q, *J* = 7.2 Hz, 0.78 × 2H), 4.20 (q, *J* = 7.2 Hz, 0.22 × 2H), 3.23 (ddd, *J* = 6.7, 1.5, 1.5 Hz, 0.22 × 2H), 3.07 (dddd, *J* = 6.7, 2.0, 2.0, 2.0 Hz, 0.78 × 2H), 1.34 (t, *J* = 7.2 Hz, 3H), 1.28 (s, 0.22 × 9H), 1.27 (s, 0.78 × 9H)

β-Hydroxyester **146**

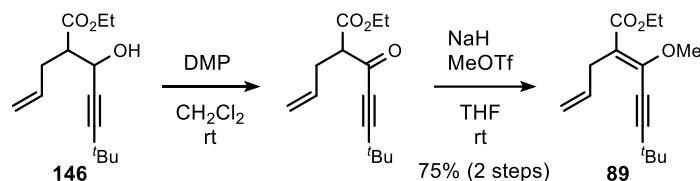


To a solution of ^{*i*}Pr₂NH (528 μL, 3.76 mmol) in THF (9.4 mL) was added ^{*n*}BuLi (2.66 mol/L in hexane, 1.41 mL, 3.76 mmol) at 0 °C, and the reaction mixture was stirred for 20 min. The reaction mixture was then cooled down to −78 °C, and ethyl 4-pentenoate (535 μL, 3.76 mmol) was added. After stirring for 25 min, **130** (207 mg, 1.88 mmol) in THF (0.50 mL) was added via cannula and the resulting mixture was stirred for another 10 min at the same temperature. The reaction was

quenched with saturated aqueous NH_4Cl solution (10 mL), and the organic layer was diluted with EtOAc (10 mL). Two layers were separated, and the aqueous layer was washed with EtOAc (10 mL $\times$ 3). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2 , hexane:EtOAc = 30:1 to 5:1) to afford **146** (dr = 1.5:1, 355 mg, 1.49 mmol, 79% yield).

146: pale yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 5.87–5.72 (m, 1H), 5.13 (d, J = 1.7 Hz, 0.6H), 5.10 (d, J = 1.7 Hz, 0.6H), 5.06 (s, 0.4H), 5.04 (s, 0.4H), 4.54 (dd, J = 7.4, 5.2 Hz, 0.6H), 4.48 (dd, J = 7.6, 7.2 Hz, 0.4H), 4.195 (q, J = 7.2 Hz, $0.6 \times 2\text{H}$), 4.190 (q, J = 7.2 Hz, $0.4 \times 2\text{H}$), 2.83 (d, J = 7.4 Hz, 0.6H), 2.74 (d, J = 7.6 Hz, 0.4H), 2.72–2.66 (m, 1H), 2.59–2.42 (m, 2H), 1.29 (t, J = 7.2 Hz, $0.6 \times 3\text{H}$), 1.28 (t, J = 7.2, Hz, $0.4 \times 3\text{H}$), 1.21 (s, $0.4 \times 9\text{H}$), 1.20 (s, $0.6 \times 9\text{H}$)

Dienyne **89**

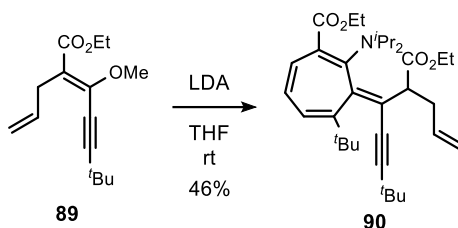


To a solution of **146** (47.5 mg, 0.199 mmol) in CH_2Cl_2 (0.40 mL) was added Dess-Martin periodinane (101 mg, 0.239 mmol) at 0 °C. The reaction mixture was then warmed up to room temperature and stirred for 45 min. The reaction was quenched with saturated aqueous NaHCO_3 and $\text{Na}_2\text{S}_2\text{O}_3$ solution (0.50 mL), and the biphasic mixture was stirred vigorously for 40 min. Two layers were separated, and the aqueous layer was extracted with EtOAc (0.50 mL $\times$ 3). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was filtered through a short pad of SiO_2 (hexane:EtOAc = 5:1) to afford β -ketoester along with a small amount of impurities.

NaH (60% dispersion in mineral oil, 15.8 mg, 0.395 mmol) was washed with hexane and suspended with THF (0.50 mL). To this suspension was added above β -ketoester in THF (0.50 mL) via cannula at 0 °C. After stirring for 15 min, MeOTf (32.8 μL , 0.300 mmol) was added. The reaction mixture was then warmed up to room temperature and stirred for 10 min. The reaction was quenched by the careful addition of saturated aqueous NaHCO_3 solution (1.0 mL), and the organic layer was diluted with EtOAc (1.0 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (1.0 mL $\times$ 3). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2 , hexane:EtOAc = 50:1 to 20:1) to afford **89** (37.6 mg, 0.150 mmol, 75% yield for 2 steps).

89: colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 5.82 (ddt, $J = 17.1, 10.0, 6.5$ Hz, 1H), 5.06 (dd, $J = 17.1, 1.1$ Hz, 1H), 4.96 (d, $J = 10.0$ Hz, 1H), 4.18 (q, $J = 7.2$ Hz, 2H), 3.80 (s, 3H), 3.14 (d, $J = 6.5$ Hz, 2H), 1.31 (s, 9H), 1.26 (t, $J = 7.2$ Hz, 3H)

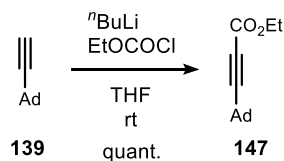
Dimer 90



An LDA solution (ca. 1.0 mol/L in THF-hexane) was prepared by the addition of $^n\text{BuLi}$ (2.65 mol/L in hexane, 755 μL , 2.00 mmol) to a solution of $i\text{Pr}_2\text{NH}$ (281 μL , 2.00 mmol) in THF (1.25 mL) at 0 $^\circ\text{C}$. The mixture was stirred for 20 min at the same temperature before the use. To another reaction vessel charged with **89** (25.4 mg, 0.101 mmol) in THF (1.0 mL) was added the LDA solution (200 μL , 0.200 mmol) via a syringe at 0 $^\circ\text{C}$. The reaction mixture was then warmed up to room temperature and stirred for 20 min. The reaction was quenched with saturated aqueous NaHCO_3 solution (1.0 mL), and the organic layer was diluted with EtOAc (1.0 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (1.0 mL $\times$ 3). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2 , hexane:EtOAc = 30:1) to afford **90** (12.5 mg, 23.2 μmol , 46% yield).

90: orange oil; ^1H NMR (500 MHz, CDCl_3) δ 6.87 (d, $J = 15.8$ Hz, 1H), 6.58 (dd, $J = 15.8, 10.9$ Hz, 1H), 6.34 (d, $J = 10.9$ Hz, 1H), 5.74 (dddd, $J = 17.1, 10.1, 7.2, 7.0$ Hz, 1H), 5.08 (dd, $J = 17.1, 1.7$ Hz, 1H), 5.00 (dd, $J = 10.1, 1.7$ Hz, 1H), 4.26 (q, $J = 7.0$ Hz, 2H), 4.13 (q, $J = 7.0$ Hz, 2H), 3.32 (sept, $J = 6.4$ Hz, 2H), 3.12 (dd, $J = 7.4, 7.3$ Hz, 1H), 2.60 (ddd, $J = 14.7, 7.4, 7.2$ Hz, 1H), 2.46 (ddd, $J = 14.3, 7.3, 7.0$ Hz, 1H), 1.36 (t, $J = 7.0$ Hz, 3H), 1.25 (s, 18H), 1.25 (t, $J = 7.0$ Hz, 3H), 1.09 (d, $J = 6.4$ Hz, 12H)

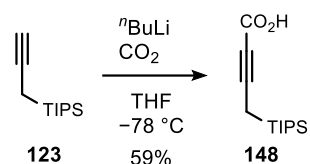
Alkynyl ester 147



To a solution of **139** (320 mg, 2.00 mmol) in THF (10 mL) was added $^n\text{BuLi}$ (2.65 mol/L in hexane, 792 μL , 2.10 mmol) at -78 $^\circ\text{C}$. The reaction mixture was then warmed up to 0 $^\circ\text{C}$ and stirred for

20 min. To this mixture was added ethyl chloroformate (381 μ L, 4.00 mmol), and the reaction mixture was warmed up to room temperature. After stirring for 20 min, the reaction was quenched with saturated aqueous NaHCO_3 solution (10 mL), and the organic layer was diluted with EtOAc (10 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (10 mL $\times$ 3). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2 , hexane:EtOAc = 30:1) to afford **147** (480 mg, > 2.00 mmol, quant.). The spectral data matched with those reported in literature.^[48]

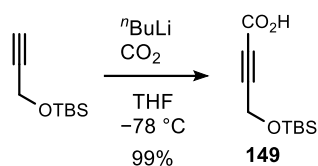
Alkenyl carboxylic acid **148**



To a solution of **123** (331 mg, 1.68 mmol) in THF (7.5 mL) was added $n\text{BuLi}$ (2.65 mol/L in hexane, 582 μ L, 1.54 mmol) at -78°C . After stirring for 20 min, crushed dry ice (excess.) was added, and the reaction mixture was stirred under ambient temperature until the evolution of CO_2 gas ceased. The reaction was quenched with saturated aqueous NH_4Cl solution (5 mL), and the organic layer was diluted with Et_2O (5.0 mL). Two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (5.0 mL $\times$ 3). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2 , hexane only, then EtOAc only) to afford **148** (238 mg, 0.991 mmol, 59% yield).

148: white solid; ^1H NMR (500 MHz, CDCl_3) δ 1.73 (s, 2H), 1.22–1.14 (m, 3H), 1.09 (d, J = 6.9 Hz, 18H); ^{13}C NMR (126 MHz, CDCl_3) δ 158.6, 93.7, 72.3, 18.4 (6C), 11.0 (3C), 0.2; FT-IR (ATR) ν 2943, 2867, 2225, 1676, 1283 cm^{-1} ; HRMS (FD) calcd for $\text{C}_{13}\text{H}_{25}\text{O}_2\text{Si}$ ($[\text{M} + \text{H}]^+$): 241.1624, found: 241.1615; m.p. (hexane) $52\text{--}55^\circ\text{C}$.

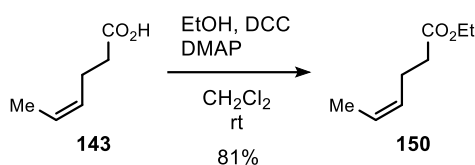
Alkynyl carboxylic acid **149**



To a solution of *tert*-butyldimethyl(2-propynyloxy)silane (601 μ L, 3.00 mmol) in THF (10 mL) was added $n\text{BuLi}$ (2.65 mol/L in hexane, 1.19 mL, 3.15 mmol) at -78°C . After stirring for 30

min, crushed dry ice (excess.) was added, and the reaction mixture was stirred under ambient temperature until the evolution of CO₂ gas ceased. The reaction was quenched with saturated aqueous NaHCO₃ solution (5.0 mL) and water (10 mL). Two layers were separated, and the aqueous layer was washed with CH₂Cl₂ (5.0 mL × 2). The aqueous layer was then neutralized with 3 M aqueous HCl solution and extracted with CH₂Cl₂ (5.0 mL × 4). The combined organic extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure to afford **149** (634 mg, 2.96 mmol, 99% yield). The spectral data matched with those reported in literature.^[49]

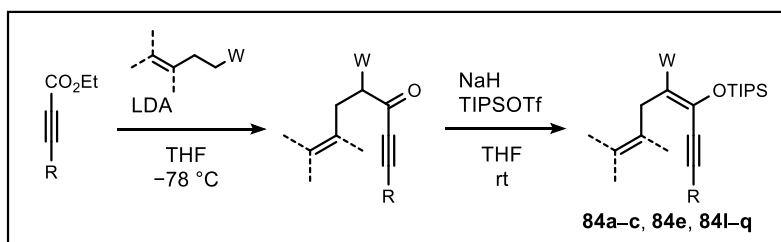
Alkenyl ester **150**



To a solution of **143** (116 mg, 1.01 mmol) in CH₂Cl₂ (5.0 mL) were added successively EtOH (294 μL, 5.05 mmol), 4-dimethylaminopyridine (11.7 mg, 95.8 μmol), and *N,N'*-dicyclohexylcarbodiimide (228 mg, 1.10 mmol) at room temperature. After stirring for 14 h, AcOH (578 μL, 10.1 mmol) was added, and the mixture was stirred for 1 h at the same temperature. The reaction was quenched with saturated aqueous NaHCO₃ solution (5.0 mL). Two layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (5.0 mL × 3). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, pentane:Et₂O = 10:1) to afford **150** (117 mg, 0.823 mmol, 81% yield).

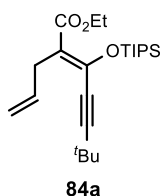
150: colorless oil; ¹H NMR (500 MHz, CDCl₃) δ 5.52–5.45 (m, 1H), 5.38–5.32 (m, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 2.38–2.31 (m, 4H), 1.62 (dd, *J* = 5.7, 1.1 Hz, 3H), 1.24 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 173.3, 128.3, 125.3, 60.2, 34.2, 22.4, 14.2, 12.7; FT-IR (ATR) ν 2980, 2927, 1735, 1161 cm⁻¹; HRMS (FI) calcd for C₈H₁₄O₂ (M⁺): 142.0994, found: 142.0989.

General procedure A: synthesis of dienynes



Step 1: An LDA solution (ca. 1.0 mol/L in THF-hexane) was prepared by the addition of ⁿBuLi (2.65 mol/L in hexane, 755 μ L, 2.00 mmol) to a solution of ⁱPr₂NH (281 μ L, 2.00 mmol) in THF (1.25 mL) at 0 °C. The mixture was stirred for 20 min at the same temperature before the use. To another reaction vessel charged with alkenyl ester (1.2 equiv.) in THF (0.2 mol/L) was added the LDA solution (2.4 equiv.) via a syringe at -78 °C. After stirring for 20 min, alkynyl ester (1.0 equiv.) in THF was added via cannula, and the mixture was stirred for 10 min at the same temperature. [For synthesis of **84p** and (*E*)-**84q**, alkynyl ester (1.2 equiv.) and LDA solution (2.4 equiv.) based on alkenyl ester (1.0 equiv.) were used]. Crushed dry ice was added to trap the excessive enolate, and the mixture was stirred under ambient temperature until the evolution of CO₂ gas ceased. The reaction was quenched with saturated aqueous NaHCO₃ solution, and the organic layer was diluted with EtOAc. Two layers were separated, and the aqueous layer was extracted three times with EtOAc. The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. Highly polar components were filtered off through a short pad of SiO₂ (hexane:EtOAc = 10:1) to afford β -ketoester along with a small amount of impurities.

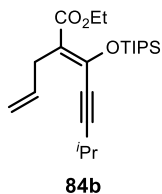
Step 2: NaH (60% dispersion in mineral oil, 2.0 equiv.) was washed with hexane and suspended with THF. To this suspension was added above β -ketoester (1.0 equiv.) in THF via cannula at 0 °C (The final concentration of β -ketoester reached 0.2 mol/L). After stirring for 10 min, TIPSOTf (1.5 equiv.) was added. The reaction mixture was then warmed up to room temperature and stirred for 10 min. The reaction was quenched by the careful addition of saturated aqueous NaHCO₃ solution, and the organic layer was diluted with EtOAc. Two layers were separated, and the aqueous layer was extracted three times with EtOAc. The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, hexane:EtOAc = 100:1) to afford the product dienyne.



According to the general procedure A, **84a** (154 mg, 0.392 mmol, 79% yield for 2 steps) was synthesized from LDA (ca. 1.0 mol/L in THF-hexane, 1.20 mL, 1.20 mmol), ethyl 4-pentenoate (85.4 μ L, 0.600 mmol), alkynyl ester **131** (76.6 mg, 0.497 mmol), NaH (60% in mineral oil, 40.2 mg, 1.01 mmol), and TIPSOTf (202 μ L, 0.750 mmol).

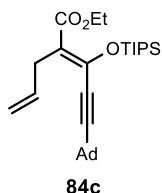
84a: colorless oil; ¹H NMR (500 MHz, CDCl₃) δ 5.82 (ddt, *J* = 17.1, 10.1, 6.4 Hz, H), 5.06 (ddt, *J* = 17.1, 1.7, 1.6 Hz, 1H), 4.95 (ddt, *J* = 10.1, 1.7, 1.6 Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.13 (ddd, *J* = 6.4, 1.6, 1.6 Hz, 2H), 1.36–1.28 (m, 3H), 1.26 (s, 9H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.11 (d, *J* = 7.4 Hz, 18H); ¹³C NMR (126 MHz, CDCl₃) δ 167.1, 140.7, 136.0, 115.8, 114.8, 104.7, 76.0,

59.9, 34.6, 30.2 (3C), 28.2, 17.9 (6C), 14.4, 13.0 (3C); FT-IR (ATR) ν 2969, 2945, 2867, 2216, 1716, 1318, 1197 cm^{-1} ; HRMS (FD) calcd for $\text{C}_{23}\text{H}_{40}\text{O}_3\text{Si}$ (M^+): 392.2747, found: 392.2759.



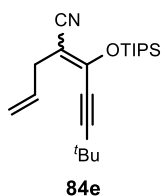
According to the general procedure A, **84b** (933 mg, 2.46 mmol, 60% yield for 2 steps) was synthesized from $i\text{Pr}_2\text{NH}$ (1.39 mL, 9.91 mmol), $n\text{BuLi}$ (2.65 mol/L in hexane, 3.74 mL, 9.91 mmol), ethyl 4-pentenoate (706 μL , 4.96 mmol), alkynyl ester **133** (579 mg, 4.13 mmol), NaH (60% in mineral oil, 249 mg, 6.21 mmol), and TIPSOTf (1.33 mL, 4.96 mmol). Enolate was prepared by the addition of ethyl 4-pentenoate to an LDA solution.

84b: pale yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 5.82 (ddt, $J = 17.1, 10.2, 6.4$ Hz, 1H), 5.06 (ddt, $J = 17.1, 1.7, 1.6$ Hz, 1H), 4.95 (ddt, $J = 10.2, 1.7, 1.5$ Hz, 1H), 4.17 (q, $J = 7.3$ Hz, 2H), 3.14 (ddd, $J = 6.4, 1.6, 1.5$ Hz, 2H), 2.73 (sept, $J = 6.9$ Hz, 1H), 1.34–1.28 (m, 3H), 1.25 (t, $J = 7.3$ Hz, 3H), 1.20 (d, $J = 6.9$ Hz, 6H), 1.10 (d, $J = 7.4$ Hz, 18H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.1, 140.7, 136.0, 115.7, 114.9, 102.3, 76.5, 59.9, 34.6, 22.1 (2C), 21.2, 17.9 (6C), 14.4, 13.0 (3C); FT-IR (ATR) ν 2944, 2867, 2216, 1715, 1322, 1207 cm^{-1} ; HRMS (FD) calcd for $\text{C}_{22}\text{H}_{38}\text{O}_3\text{Si}$ (M^+): 378.2590, found: 378.2607.



According to the general procedure A, **84c** (172 mg, 0.365 mmol, 73% yield for 2 steps) was synthesized from LDA (ca. 1.0 mol/L in THF-hexane, 1.20 mL, 1.20 mmol), ethyl 4-pentenoate (85.4 μL , 0.600 mmol), alkynyl ester **147** (116 mg, 0.501 mmol), NaH (60% in mineral oil, 41.0 mg, 1.03 mmol), and TIPSOTf (202 μL , 0.750 mmol).

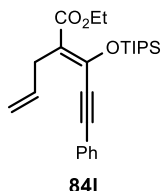
84c: colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 5.82 (ddt, $J = 16.9, 10.1, 6.5$ Hz, 1H), 5.07 (ddt, $J = 16.9, 1.9, 1.9$ Hz, 1H), 4.95 (ddt, $J = 10.1, 1.9, 1.9$ Hz, 1H), 4.17 (q, $J = 7.3$ Hz, 2H), 3.13 (d, $J = 6.5$ Hz, 2H), 1.98 (br, 3H), 1.88 (br-d, $J = 2.9$ Hz, 6H), 1.70 (br, 6H), 1.36–1.28 (m, 3H), 1.25 (t, $J = 7.3$ Hz, 3H), 1.11 (d, $J = 7.4$ Hz, 18H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.1, 141.0, 136.1, 115.6, 114.8, 104.5, 76.2, 59.9, 42.0 (3C), 36.2 (3C), 34.7, 30.3, 27.7 (3C), 17.9 (6C), 14.4, 13.1 (3C); FT-IR (ATR) ν 2906, 2865, 2213, 1715, 1322, 1133 cm^{-1} ; HRMS (FD) calcd for $\text{C}_{29}\text{H}_{46}\text{O}_3\text{Si}$ (M^+): 470.3216, found: 470.3232.



According to the general procedure A, **84e** (E/Z or $Z/E = 3.9:1$, 118 mg, 0.342 mmol, 69% yield for 2 steps) was synthesized from LDA (ca. 1.0 mol/L in THF-hexane, 1.20 mL, 1.20 mmol), 4-pentenitrile (57.9 μL , 0.600 mmol), alkynyl

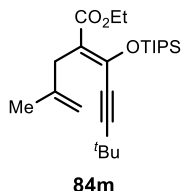
ester **131** (76.6 mg, 0.497 mmol), NaH (60% in mineral oil, 40.6 mg, 1.01 mmol), and TIPSOTf (202 μ L, 0.750 mmol).

84e (*E/Z* mixture): pale yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 5.82–5.72 (m, 1H), 5.17–5.08 (m, 2H), 2.98 (dt, $J = 6.5, 1.4$ Hz, 2H), 1.37–1.28 (m, 3H), 1.28 (s, $0.20 \times 9\text{H}$), 1.27 (s, $0.80 \times 9\text{H}$), 1.12 (d, $J = 7.4$ Hz, $0.80 \times 18\text{H}$), 1.09 (d, $J = 7.4$ Hz, $0.20 \times 18\text{H}$); ^{13}C NMR (126 MHz, CDCl_3) δ 146.4, 145.9, 133.4, 133.0, 120.0, 117.9, 117.0, 116.9, 109.0, 104.5, 99.1, 97.2, 74.6, 73.7, 33.7, 31.2, 30.0 (3C, major), 29.9 (3C, minor), 28.3, 28.2, 17.8 (6C, major + minor), 12.73 (3C, minor), 12.68 (3C, major); FT-IR (ATR) ν 2947, 2868, 2204, 1588, 1313, 1190 cm^{-1} ; HRMS (FD) calcd for $\text{C}_{21}\text{H}_{35}\text{NOSi}$ (M^+): 345.2488, found: 345.2481.



According to the general procedure A, **84l** (260 mg, 63.0 mmol, 63% yield for 2 steps) was synthesized from $i\text{Pr}_2\text{NH}$ (337 μL , 2.40 mmol), $n\text{BuLi}$ (2.66 mol/L, 902 μL , 2.40 mmol), ethyl 4-pentenoate (171 μL , 1.20 mmol), ethyl phenylpropiolate (164 μL , 1.00 mmol), NaH (60% in mineral oil, 80.0 mg, 2.00 mmol), and TIPSOTf (403 μL , 1.50 mmol). Enolate was prepared by the addition of ethyl 4-pentenoate to an LDA solution.

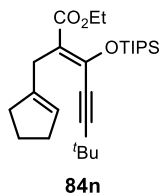
84l: yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 7.45–7.43 (m, 2H), 7.39–7.35 (m, 3H), 5.89 (ddt, $J = 17.1, 10.2, 6.4$ Hz, 1H), 5.12 (ddt, $J = 17.1, 1.6, 1.6$ Hz, 1H), 5.00 (ddt, $J = 10.2, 1.6, 1.5$ Hz, 1H), 4.22 (q, $J = 7.3$ Hz, 2H), 3.27 (ddd, $J = 6.4, 1.6, 1.5$ Hz, 2H), 1.43–1.33 (m, 3H), 1.29 (t, $J = 7.3$ Hz, 3H), 1.15 (d, $J = 7.4$ Hz, 18H); ^{13}C NMR (126 MHz, CDCl_3) δ 166.9, 140.1, 135.8, 131.4 (2C), 129.3, 128.6 (2C), 121.8, 117.3, 115.3, 95.2, 85.6, 60.1, 34.7, 17.9 (6C), 14.4, 13.1 (3C); FT-IR (ATR) ν 2944, 2867, 2203, 1714, 1325, 1186 cm^{-1} ; HRMS (FD) calcd for $\text{C}_{25}\text{H}_{36}\text{O}_3\text{Si}$ (M^+): 412.2434, found: 412.2444.



According to the general procedure A, **84m** (136 mg, 0.335 mmol, 67% yield for 2 steps) was synthesized from LDA (ca. 1.0 mol/L in THF-hexane, 1.20 mL, 1.20 mmol), alkenyl ester **140** (85.5 mg, 0.602 mmol), alkynyl ester **131** (77.4 mg, 0.502 mmol), NaH (60% in mineral oil, 40.5 mg, 1.01 mmol), and TIPSOTf (202 μL , 0.750 mmol).

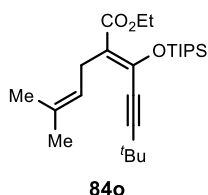
84m: colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 4.70 (s, 2H), 4.16 (q, $J = 7.3$ Hz, 2H), 3.11 (s, 2H), 1.73 (s, 3H), 1.36–1.28 (m, 3H), 1.243 (s, 9H), 1.242 (t, $J = 7.3$ Hz, 3H), 1.11 (d, $J = 7.4$ Hz, 18H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.4, 143.7, 140.2, 116.2, 110.5, 104.2, 76.0, 59.9, 38.3,

30.2 (3C), 28.1, 22.4, 17.9 (6C), 14.3, 13.0 (3C); FT-IR (ATR) ν 2968, 2945, 2867, 2217, 1715, 1200, 1060 cm^{-1} ; HRMS (FD) calcd for $\text{C}_{24}\text{H}_{42}\text{O}_3\text{Si}$ (M^+): 406.2903, found: 406.2911.



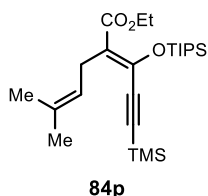
According to the general procedure A, **84n** (149 mg, 0.343 mmol, 68% yield for 2 steps) was synthesized from LDA (ca. 1.0 mol/L in THF-hexane, 1.20 mL, 1.20 mmol), alkenyl ester **141** (101 mg, 0.600 mmol), alkynyl ester **131** (77.4 mg, 0.502 mmol), NaH (60% in mineral oil, 39.9 mg, 0.998 mmol), and TIPSOTf (202 μL , 0.750 mmol).

84n: colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 5.34 (br, 1H), 4.16 (q, $J = 7.2$ Hz, 2H), 3.16 (s, 2H), 2.30–2.22 (m, 4H), 1.86–1.80 (m, 2H), 1.37–1.28 (m, 3H), 1.243 (s, 9H), 1.241 (t, $J = 7.2$ Hz, 3H), 1.11 (d, $J = 7.4$ Hz, 18H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.5, 142.4, 139.9, 124.2, 116.4, 104.3, 76.0, 59.9, 34.9, 32.4, 32.1, 30.2 (3C), 28.1, 23.4, 17.9 (6C), 14.3, 13.0 (3C); FT-IR (ATR) ν 2945, 2867, 2218, 1715, 1327, 1203, 1055 cm^{-1} ; HRMS (FD) calcd for $\text{C}_{26}\text{H}_{44}\text{O}_3\text{Si}$ (M^+): 432.3060, found: 432.3053.



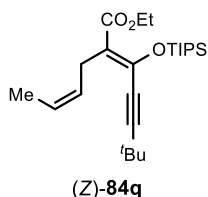
According to the general procedure A, **84o** (135 mg, 0.322 mmol, 64% yield for 2 steps) was synthesized from LDA (ca. 1.0 mol/L in THF-hexane, 1.20 mL, 1.20 mmol), alkenyl ester **79** (93.2 mg, 0.597 mmol), alkynyl ester **131** (77.0 mg, 0.499 mmol), NaH (60% in mineral oil, 39.7 mg, 0.993 mmol), and TIPSOTf (202 μL , 0.750 mmol).

84o: colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 5.14–5.10 (m, 1H), 4.16 (q, $J = 7.2$ Hz, 2H), 3.09 (d, $J = 7.4$ Hz, 2H), 1.67 (s, 6H), 1.34–1.28 (m, 3H), 1.251 (s, 9H), 1.251 (t, $J = 7.2$ Hz, 3H), 1.10 (d, $J = 7.4$ Hz, 18H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.4, 139.0, 132.1, 121.9, 117.7, 104.3, 76.0, 59.9, 30.2 (3C), 29.3, 28.1, 25.7, 18.0, 17.9 (6C), 14.3, 13.0 (3C); FT-IR (ATR) ν 2968, 2867, 2217, 1715, 1316, 1200, 1054 cm^{-1} ; HRMS (FD) calcd for $\text{C}_{25}\text{H}_{44}\text{O}_3\text{Si}$ (M^+): 420.3060, found: 420.3074.



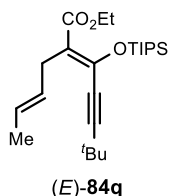
According to the general procedure A, **84p** (265 mg, 0.607 mmol, 61% yield for 2 steps) was synthesized from $^i\text{Pr}_2\text{NH}$ (337 μL , 2.40 mmol), $^n\text{BuLi}$ (2.69 mol/L, 892 μL , 2.40 mmol), alkenyl ester **79** (155 mg, 0.995 mmol), alkynyl ester **132** (204 mg, 1.20 mmol), NaH (60% in mineral oil, 80.7 mg, 2.02 mmol), and TIPSOTf (403 μL , 1.50 mmol). Enolate was prepared by the addition of **81** in THF to an LDA solution.

84p: pale yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 5.12 (t, $J = 7.1$ Hz, 1H), 4.17 (q, $J = 7.2$ Hz, 2H), 3.13 (d, $J = 7.1$ Hz, 2H), 1.67 (s, 6H), 1.35–1.28 (m, 3H), 1.26 (t, $J = 7.2$ Hz, 3H), 1.10 (d, $J = 7.4$ Hz, 18H), 0.19 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.2, 137.8, 132.4, 121.5, 119.7, 101.6, 100.6, 60.1, 29.4, 25.7, 18.0, 17.9 (6C), 14.3, 13.0 (3C), -0.7 (3C); FT-IR (ATR) ν 2945, 2868, 2148, 1718, 1204, 843 cm^{-1} ; HRMS (FD) calcd for $\text{C}_{24}\text{H}_{44}\text{O}_3\text{Si}_2$ (M^+): 436.2829, found: 436.2834.



According to the general procedure A, (*Z*)-**84q** (137 mg, 0.336 mmol, 68% yield for 2 steps) was synthesized from LDA (ca. 1.0 mol/L in THF-hexane, 1.48 mL, 1.48 mmol), alkenyl ester **150** (105 mg, 0.738 mmol), alkynyl ester **131** (75.6 mg, 0.490 mmol), NaH (60% in mineral oil, 39.2 mg, 0.980 mmol), and TIPSOTf (198 μL , 0.738 mmol).

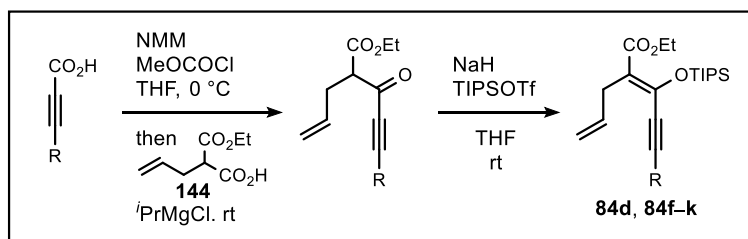
(*Z*)-**84q**: colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 5.49–5.36 (m, 2H), 4.16 (q, $J = 7.0$ Hz, 2H), 3.15 (d, $J = 6.9$ Hz, 2H), 1.68 (d, $J = 6.9$ Hz, 3H), 1.35–1.28 (m, 3H), 1.26 (s, 9H), 1.25 (t, $J = 7.0$ Hz, 3H), 1.10 (d, $J = 7.4$ Hz, 18H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.2, 139.6, 128.0, 124.4, 117.1, 104.5, 76.0, 59.9, 30.2 (3C), 28.21, 28.15, 18.0, 17.9 (6C), 14.4, 13.0 (3C); FT-IR (ATR) ν 2968, 2945, 2867, 2216, 1715, 1328, 1190 cm^{-1} ; HRMS (FD) calcd for $\text{C}_{24}\text{H}_{42}\text{O}_3\text{Si}$ (M^+): 406.2903, found: 406.2918.



According to the general procedure A, (*E*)-**84q** (135 mg, 0.331 mmol, 66% yield for 2 steps) was synthesized from LDA (ca. 1.0 mol/L in THF-hexane, 1.20 mL, 1.20 mmol), alkenyl ester **77** (71.2 mg, 0.501 mmol), alkynyl ester **131** (92.5 mg, 0.600 mmol), NaH (60% in mineral oil, 40.5 mg, 1.01 mmol), and TIPSOTf (202 μL , 0.750 mmol).

(*E*)-**84q**: colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 5.52–5.39 (m, 2H), 4.17 (q, $J = 7.1$ Hz, 2H), 3.05 (d, $J = 6.3$ Hz, 2H), 1.63 (d, $J = 5.7$ Hz, 3H), 1.35–1.28 (m, 3H), 1.26 (s, 9H), 1.25 (t, $J = 7.1$ Hz, 3H), 1.10 (d, $J = 8.0$ Hz, 18H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.3, 140.0, 128.3, 125.6, 116.8, 104.5, 76.0, 59.9, 33.5, 30.2 (3C), 28.2, 17.9 (6C), 17.8, 14.4, 13.0 (3C); FT-IR (ATR) ν 2968, 2944, 2867, 2216, 1715, 1317, 1191 cm^{-1} ; HRMS (FD) calcd for $\text{C}_{24}\text{H}_{42}\text{O}_3\text{Si}$ (M^+): 406.2903, found: 406.2890.

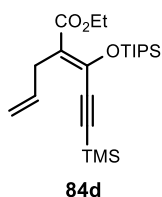
General procedure B: synthesis of dienynes



Step 1: This procedure is based on the method originally reported by Presset *et al.* [50]

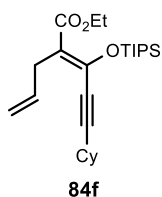
A solution of mixed anhydride in THF was prepared by the addition of *N*-methylmorpholine (1.1 equiv.) and MeOCOC(=O)Cl (1.1 equiv.) successively to a solution of alkynyl carboxylic acid (1.0 equiv.) in THF (0.5 mol/L) at 0 °C. The mixture was stirred for 15 min at the same temperature before the use. To another reaction vessel charged with malonic acid monoester **144** (1.5 equiv.) in THF (0.75 mol/L) was added *i*PrMgCl (2.0 mol/L in THF, 3.0 equiv.) at 0 °C. After stirring for 5 min, the solution of mixed anhydride in THF was transferred via cannula to this mixture. The resulting mixture was then warmed up to room temperature and stirred overnight. The reaction was quenched with saturated aqueous NH₄Cl solution, and the organic layer was diluted with EtOAc. Two layers were separated, and the aqueous layer was extracted three times with EtOAc. The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. Highly polar components were filtered off through a short pad of SiO₂ (hexane:EtOAc = 10:1) to afford β-ketoester along with a small amount of impurities.

Step 2: NaH (60% dispersion in mineral oil, 2.0 equiv.) was washed with hexane and suspended with THF. To this suspension was added above β-ketoester (1.0 equiv.) in THF via cannula at 0 °C (The final concentration of β-ketoester reached 0.2 mol/L). After stirring for 10 min, TIPSOTf (1.5 equiv.) was added. The reaction mixture was then warmed up to room temperature and stirred for 10 min. The reaction was quenched by the careful addition of saturated aqueous NaHCO₃ solution, and the organic layer was diluted with EtOAc. Two layers were separated, and the aqueous layer was extracted three times with EtOAc. The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, hexane:EtOAc = 100:1) to afford the product diene.



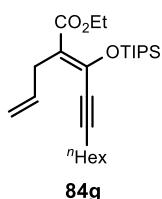
According to the general procedure B, **84d** (751 mg, 1.84 mmol, 73% yield for 2 steps) was synthesized from alkynyl carboxylic acid **134** (356 mg, 2.50 mmol), *N*-methylmorpholine (275 μL, 2.50 mmol), MeOCOC(=O)Cl (192 μL, 2.50 mmol), malonic acid monoester **144** (646 mg, 3.75 mmol), *i*PrMgCl (2.0 mol/L in THF, 3.75 mL, 7.50 mmol), NaH (60% in mineral oil, 149 mg, 3.73 mmol), and TIPSOTf (806 μL, 3.00 mmol).

84d: colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 5.81 (ddt, $J = 17.1, 10.2, 6.5$ Hz, 1H), 5.06 (ddt, $J = 17.1, 1.6, 1.6$ Hz, 1H), 4.97 (ddt, $J = 10.2, 1.6, 1.5$ Hz, 1H), 4.18 (q, $J = 7.2$ Hz, 2H), 3.16 (ddd, $J = 6.5, 1.6, 1.5$ Hz, 2H), 1.36–1.29 (m, 3H), 1.26 (t, $J = 7.2$ Hz, 3H), 1.10 (d, $J = 8.0$ Hz, 18H), 0.20 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 166.9, 139.4, 135.6, 117.7, 115.2, 102.2, 100.3, 60.1, 34.6, 17.9 (6C), 14.3, 13.0 (3C), -0.7 (3C); FT-IR (ATR) ν 2945, 2868, 2150, 1717, 1200, 842 cm^{-1} ; HRMS (FD) calcd for $\text{C}_{22}\text{H}_{40}\text{O}_3\text{Si}_2$ (M^+): 408.2516, found: 408.2535.



According to the general procedure B, **84f** (160 mg, 0.381 mmol, 76% yield for 2 steps) was synthesized from alkynyl carboxylic acid **135** (76.2 mg, 0.501 mmol), *N*-methylmorpholine (57.7 μL , 0.525 mmol), MeOCOCCl (40.3 μL , 0.525 mmol), malonic acid monoester **144** (129 mg, 0.750 mmol), $i\text{PrMgCl}$ (2.0 mol/L in THF, 750 μL , 1.50 mmol), NaH (60% in mineral oil, 36.4 mg, 0.910 mmol), and TIPSOTf (183 μL , 0.679 mmol).

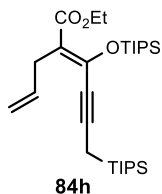
84f: colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 5.83 (ddt, $J = 17.1, 10.4, 6.4$ Hz, 1H), 5.06 (ddt, $J = 17.1, 1.7, 1.7$ Hz, 1H), 4.95 (ddt, $J = 10.4, 1.7, 1.7$ Hz, 1H), 4.17 (q, $J = 7.2$ Hz, 2H), 3.15 (d, $J = 6.4$ Hz, 2H), 2.57–2.52 (m, 1H), 1.85–1.80 (m, 2H), 1.74–1.68 (m, 2H), 1.50–1.43 (m, 2H), 1.35–1.29 (m, 7H), 1.26 (t, $J = 7.2$ Hz, 3H), 1.11 (d, $J = 7.4$ Hz, 18H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.1, 140.8, 136.1, 115.7, 114.9, 101.2, 77.1, 59.9, 34.6, 31.9 (2C), 29.7, 25.7, 24.8 (2C), 17.9 (6C), 14.4, 13.1 (3C); FT-IR (ATR) ν 2932, 2866, 2213, 1715, 1321, 1204 cm^{-1} ; HRMS (FD) calcd for $\text{C}_{25}\text{H}_{42}\text{O}_3\text{Si}$ (M^+): 418.2903, found: 418.2917.



According to the general procedure B, **84g** (62.6 mg, 0.149 mmol, 74% yield for 2 steps) was synthesized from alkynyl carboxylic acid **136** (31.0 mg, 0.201 mmol), *N*-methylmorpholine (24.2 μL , 0.220 mmol), MeOCOCCl (16.9 μL , 0.220 mmol), malonic acid monoester **144** (51.5 mg, 0.299 mmol), $i\text{PrMgCl}$ (2.0 mol/L in THF, 300 μL , 0.600 mmol), NaH (60% in mineral oil, 16.1 mg, 0.403 mmol), and TIPSOTf (80.6 μL , 0.300 mmol).

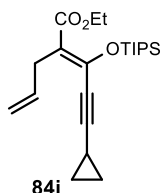
84g: colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 5.82 (ddt, $J = 17.1, 10.3, 6.4$ Hz, 1H), 5.05 (ddt, $J = 17.1, 1.7, 1.7$ Hz, 1H), 4.95 (ddt, $J = 10.3, 1.7, 1.7$ Hz, 1H), 4.17 (q, $J = 7.2$ Hz, 2H), 3.15 (d, $J = 6.4$ Hz, 2H), 2.36 (t, $J = 7.2$ Hz, 2H), 1.57–1.51 (m, 2H), 1.43–1.37 (m, 2H), 1.33–1.25 (m, 7H), 1.26 (t, $J = 7.2$ Hz, 3H), 1.11 (d, $J = 7.4$ Hz, 18H), 0.89 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.1, 140.6, 136.1, 115.7, 114.9, 97.7, 59.9, 34.5, 31.3, 28.6, 28.0, 22.5, 19.4, 17.9 (6C), 14.4, 14.0, 13.0 (3C) (1 signal overlapped with the solvent signals δ 77.2, 77.0, 76.7);

FT-IR (ATR) ν 2934, 2867, 2220, 1715, 1334, 1205 cm^{-1} ; HRMS (FD) calcd for $\text{C}_{25}\text{H}_{44}\text{O}_3\text{Si}$ (M^+): 420.3060, found: 420.3040.



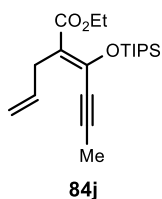
According to the general procedure B, **84h** (59.1 mg, 0.117 mmol, 78% yield for 2 steps) was synthesized from alkynyl carboxylic acid **148** (35.9 mg, 0.149 mmol), *N*-methylmorpholine (18.1 μL , 0.165 mmol), MeOCOCCl (12.7 μL , 0.165 mmol), malonic acid monoester **144** (39.1 mg, 0.227 mmol), $i\text{PrMgCl}$ (2.0 mol/L in THF, 225 μL , 0.450 mmol), NaH (60% in mineral oil, 12.3 mg, 0.308 mmol), and TIPSOTf (60.5 μL , 0.225 mmol).

84h: colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 5.79 (ddt, $J = 17.0, 10.1, 6.3$ Hz, 1H), 5.03 (ddt, $J = 17.0, 1.8, 1.8$ Hz, 1H), 4.94 (ddt, $J = 10.1, 1.8, 1.8$ Hz, 1H), 4.16 (q, $J = 7.3$ Hz, 2H), 3.15 (d, $J = 6.3$ Hz, 2H), 1.73 (s, 2H), 1.33–1.26 (m, 3H), 1.25 (t, $J = 7.3$ Hz, 3H), 1.18–1.12 (m, 3H), 1.11 (d, $J = 7.5$ Hz, 18H), 1.08 (d, $J = 7.0$ Hz, 18H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.3, 141.1, 136.3, 114.8, 114.7, 97.1, 76.4, 59.8, 34.2, 18.5 (6C), 17.9 (6C), 14.4, 13.1 (3C), 11.1 (3C), 0.4; FT-IR (ATR) ν 2943, 2867, 2204, 1715, 1205, 1163, 881 cm^{-1} ; HRMS (FD) calcd for $\text{C}_{29}\text{H}_{54}\text{O}_3\text{Si}_2$ (M^+): 506.3612, found: 506.3607.



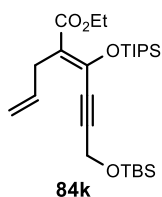
According to the general procedure B, **84i** (129 mg, 0.341 mmol, 68% yield for 2 steps) was synthesized from alkynyl carboxylic acid **137** (54.9 mg, 0.499 mmol), *N*-methylmorpholine (57.7 μL , 0.525 mmol), MeOCOCCl (40.3 μL , 0.525 mmol), malonic acid monoester **144** (129 mg, 0.751 mmol), $i\text{PrMgCl}$ (2.0 mol/L in THF, 750 μL , 1.50 mmol), NaH (60% in mineral oil, 34.0 mg, 0.850 mmol), and TIPSOTf (174 μL , 0.646 mmol).

84i: colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 5.81 (ddt, $J = 17.0, 10.2, 6.4$ Hz, 1H), 5.05 (ddt, $J = 17.0, 1.7, 1.6$ Hz, 1H), 4.96 (ddt, $J = 10.2, 1.7, 1.6$ Hz, 1H), 4.17 (q, $J = 7.2$ Hz, 2H), 3.13 (ddd, $J = 6.4, 1.6, 1.6$ Hz, 2H), 1.43–1.38 (m, 1H), 1.31–1.26 (m, 3H), 1.25 (t, $J = 7.2$ Hz, 3H), 1.10 (d, $J = 7.4$ Hz, 18H), 0.91–0.87 (m, 2H), 0.78–0.75 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.1, 140.7, 136.1, 115.6, 114.8, 100.5, 72.4, 59.9, 34.5, 17.9 (6C), 14.4, 13.0 (3C), 8.5 (2C), 0.1; FT-IR (ATR) ν 2945, 2867, 2217, 1714, 1208, 1184, 1126 cm^{-1} ; HRMS (FD) calcd for $\text{C}_{22}\text{H}_{36}\text{O}_3\text{Si}$ (M^+): 376.2434, found: 376.2420.



According to the general procedure B, **84j** (59.8 mg, 0.171 mmol, 63% yield for 2 steps) was synthesized from alkynyl carboxylic acid **138** (75% in Et₂O, 30.2 mg, 0.270 mmol), *N*-methylmorpholine (32.7 μ L, 0.297 mmol), MeOCOC₂H₅ (22.8 μ L, 0.297 mmol), malonic acid monoester **144** (69.2 mg, 0.402 mmol), *i*PrMgCl (2.0 mol/L in THF, 406 μ L, 0.811 mmol), NaH (60% in mineral oil, 19.6 mg, 0.490 mmol), and TIPSOTf (96.8 μ L, 0.360 mmol).

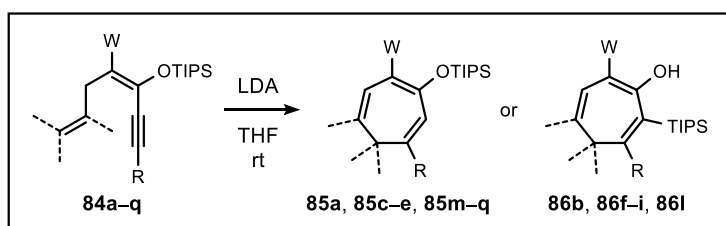
84j: colorless oil; ¹H NMR (500 MHz, CDCl₃) δ 5.82 (ddt, J = 17.0, 9.9, 6.4 Hz, 1H), 5.05 (ddt, J = 17.0, 1.7, 1.7 Hz, 1H), 4.96 (ddt, J = 9.9, 1.7, 1.7 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 3.14 (d, J = 6.4 Hz, 2H), 2.01 (s, 3H), 1.31–1.26 (m, 3H), 1.25 (t, J = 7.1 Hz, 3H), 1.10 (d, J = 7.4 Hz, 18H); ¹³C NMR (126 MHz, CDCl₃) δ 167.1, 140.5, 136.2, 115.6, 114.9, 93.2, 76.6, 59.9, 34.4, 17.9 (6C), 14.4, 13.0 (3C), 4.3; FT-IR (ATR) ν 2945, 2867, 2228, 1715, 1589, 1206 cm⁻¹; HRMS (FI) calcd for C₂₀H₃₄O₃Si (M⁺): 350.2277, found: 350.2268.



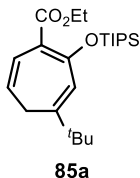
According to the general procedure B, **84k** (146 mg, 0.303 mmol, 61% yield for 2 steps) was synthesized from alkynyl carboxylic acid **149** (107 mg, 0.499 mmol), *N*-methylmorpholine (57.7 μ L, 0.525 mmol), MeOCOC₂H₅ (40.3 μ L, 0.525 mmol), malonic acid monoester **144** (129 mg, 0.750 mmol), *i*PrMgCl (2.0 mol/L in THF, 750 μ L, 1.50 mmol), NaH (60% in mineral oil, 34.5 mg, 0.863 mmol), and TIPSOTf (175 μ L, 0.651 mmol).

84k: colorless oil; ¹H NMR (500 MHz, CDCl₃) δ 5.80 (ddt, J = 16.9, 10.3, 6.4 Hz, 1H), 5.06 (ddt, J = 16.9, 1.6, 1.6 Hz, 1H), 4.96 (ddt, J = 10.3, 1.6, 1.6 Hz, 1H), 4.45 (s, 2H), 4.17 (q, J = 7.2 Hz, 2H), 3.15 (d, J = 6.4 Hz, 2H), 1.34–1.28 (m, 3H), 1.25 (t, J = 7.2 Hz, 3H), 1.10 (d, J = 7.4 Hz, 18H), 0.90 (s, 9H), 0.10 (s, 6H); ¹³C NMR (126 MHz, CDCl₃) δ 166.9, 139.3, 135.7, 117.2, 115.2, 94.2, 80.6, 60.1, 51.8, 34.4, 25.6 (3C), 18.2, 17.9 (6C), 14.3, 13.0 (3C), -5.4 (2C); FT-IR (ATR) ν 2947, 2867, 1717, 1207, 1093, 833, 777 cm⁻¹ (C $\equiv$ C absorption band was not detected due to the very weak intensity); HRMS (FI) calcd for C₂₆H₄₈O₄Si₂ (M⁺): 480.3091, found: 480.3078.

General procedure C: synthesis of cycloheptatrienes

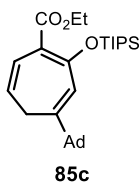


An LDA solution (ca. 1.0 mol/L in THF-hexane) was prepared by the addition of n BuLi (2.65 mol/L in hexane, 755 μ L, 2.00 mmol) to a solution of i Pr₂NH (281 μ L, 2.00 mmol) in THF (1.25 mL) at 0 °C. The mixture was stirred for 20 min at the same temperature before the use. To another reaction vessel charged with dienyne (1.0 equiv.) in THF (0.1 mol/L) was added the LDA solution (2.0 equiv.) via a syringe at 0 °C. The reaction mixture was then warmed up to room temperature and stirred for 20 min. The reaction was quenched with saturated aqueous NaHCO₃ solution, and the organic layer was diluted with EtOAc. Two layers were separated, and the aqueous layer was extracted three times with EtOAc. The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, hexane:EtOAc = 100:1) to afford the product cycloheptatriene.



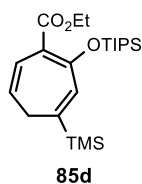
According to the general procedure C, **85a** (33.0 mg, 84.0 μ mol, 84% yield) was synthesized from dienyne **84a** (39.1 mg, 99.6 μ mol) and LDA (ca. 1.0 mol/L in THF-hexane, 200 μ L, 0.200 mmol).

85a: yellow oil; ¹H NMR (500 MHz, CDCl₃) δ 6.41 (d, J = 9.5 Hz, 1H), 5.86 (s, 1H), 5.28 (dt, J = 9.5, 6.7 Hz, 1H), 4.23 (q, J = 7.3 Hz, 2H), 2.35 (d, J = 6.7 Hz, 2H), 1.30 (t, J = 7.3 Hz, 3H), 1.27–1.20 (m, 3H), 1.12 (s, 9H), 1.10 (d, J = 7.4 Hz, 18H); ¹³C NMR (126 MHz, CDCl₃) δ 168.1, 157.9, 153.7, 125.1, 118.6, 117.5, 116.7, 60.2, 36.1, 29.24 (3C), 29.16, 17.9 (6C), 14.4, 13.3 (3C); FT-IR (ATR) ν 2946, 2867, 1720, 1195, 1058, 881 cm⁻¹; HRMS (FD) calcd for C₂₃H₄₀O₃Si (M⁺): 392.2747, found: 392.2762.



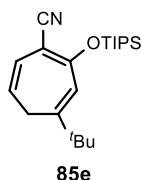
According to the general procedure C, **85c** (37.3 mg, 79.2 μ mol, 79% yield) was synthesized from dienyne **84c** (47.1 mg, 0.100 mmol) and LDA (ca. 1.0 mol/L in THF-hexane, 200 μ L, 0.200 mmol).

85c: yellow semisolid; ¹H NMR (500 MHz, CDCl₃) δ 6.41 (d, J = 9.4 Hz, 1H), 5.76 (s, 1H), 5.23 (ddd, J = 9.4, 7.0, 7.0 Hz, 1H), 4.22 (q, J = 7.2 Hz, 2H), 2.32 (br, 2H), 2.04 (br, 3H), 1.75–1.65 (m, 12H), 1.30 (t, J = 7.2 Hz, 3H), 1.27–1.20 (m, 3H), 1.10 (d, J = 7.4 Hz, 18H); ¹³C NMR (126 MHz, CDCl₃) δ 168.2, 158.1, 153.8, 125.0, 118.2, 117.6, 116.6, 60.2, 41.2 (3C), 37.7, 36.7 (3C), 28.3 (3C), 28.0, 17.9 (6C), 14.4, 13.3 (3C); FT-IR (ATR) ν 2903, 2865, 2849, 1713, 1204, 1064 cm⁻¹; HRMS (FD) calcd for C₂₉H₄₆O₃Si (M⁺): 470.3216, found: 470.3207.



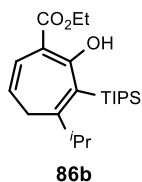
According to the general procedure C, **85d** (38% NMR yield) and **86d** (12% NMR yield) was synthesized from dienyne **84d** (39.4 mg, 96.4 μ mol) and LDA (ca. 1.0 mol/L in THF-hexane, 193 μ L, 0.193 mmol). The major product **85d** was partially isolated by PTLC purification.

85d: yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 6.41 (d, $J = 9.3$ Hz, 1H), 6.22 (s, 1H), 5.29 (dt, $J = 9.3, 6.9$ Hz, 1H), 4.24 (q, $J = 7.2$ Hz, 2H), 2.32 (d, $J = 6.9$ Hz, 2H), 1.31 (t, $J = 7.2$ Hz, 3H), 1.26–1.18 (m, 3H), 1.10 (d, $J = 6.9$ Hz, 18H), 0.13 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 168.1, 158.0, 144.8, 131.7, 125.0, 118.8, 117.9, 60.4, 30.2, 17.9 (6C), 14.3, 13.2 (3C), -1.9 (3C); FT-IR (ATR) ν 2946, 2867, 1723, 1206, 1053, 834 cm^{-1} ; HRMS (FD) calcd for $\text{C}_{22}\text{H}_{40}\text{O}_3\text{Si}_2$ (M^+): 408.2516, found: 408.2506.



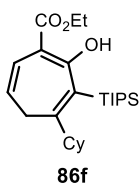
According to the general procedure C, **85e** (17.3 mg, 50.1 μ mol, 51% yield) was synthesized from dienyne **84e** (34.1 mg, 98.7 μ mol) and LDA (ca. 1.0 mol/L in THF-hexane, 200 μ L, 0.200 mmol).

85e: yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 6.12 (d, $J = 9.1$ Hz, 1H), 5.92 (s, 1H), 5.31 (dt, $J = 9.1, 7.4$ Hz, 1H), 2.40 (d, $J = 7.4$ Hz, 2H), 1.28–1.21 (m, 3H), 1.132 (s, 9H), 1.125 (d, $J = 6.9$ Hz, 18H); ^{13}C NMR (126 MHz, CDCl_3) δ 165.0, 156.7, 124.1, 120.4, 118.7, 116.9, 97.1, 36.6, 29.2, 29.1 (3C), 17.8 (6C), 13.0 (3C); FT-IR (ATR) ν 2947, 2868, 2209, 1308, 1228, 878, 837 cm^{-1} ; HRMS (FD) calcd for $\text{C}_{21}\text{H}_{35}\text{NOSi}$ (M^+): 345.2488, found: 345.2484.



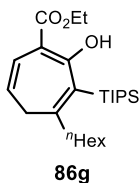
According to the general procedure C, **86b** (451 mg, 1.19 mmol, 85% yield) was synthesized from dienyne **84b** (530 mg, 1.40 mmol) and LDA (ca. 1.0 mol/L in THF-hexane, 2.80 mL, 2.80 mmol).

86b: yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 6.33 (dd, $J = 9.3, 1.4$ Hz, 1H), 5.45 (ddd, $J = 9.3, 7.4, 6.4$ Hz, 1H), 4.31–4.22 (m, 2H), 2.89 (dd, $J = 12.2, 7.4$ Hz, 1H), 2.80 (sept, $J = 6.8$ Hz, 1H), 1.87 (ddd, $J = 12.2, 6.4, 1.4$ Hz, 1H), 1.42–1.34 (m, 3H), 1.34 (t, $J = 7.3$ Hz, 3H), 1.12 (d, $J = 6.8$ Hz, 3H), 1.08 (d, $J = 6.8$ Hz, 3H), 1.07 (d, $J = 7.4$ Hz, 9H), 1.03 (d, $J = 7.4$ Hz, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 178.8, 172.8, 167.5, 124.5, 123.6, 122.7, 103.4, 60.6, 34.3, 29.8, 22.2, 21.6, 19.4 (3C), 19.3 (3C), 14.2, 13.6 (3C); FT-IR (ATR) ν 2946, 2866, 1637, 1533, 1226, 1067 cm^{-1} ; HRMS (FD) calcd for $\text{C}_{22}\text{H}_{38}\text{O}_3\text{Si}$ (M^+): 378.2590, found: 378.2576; m.p. (Et_2O) 57–62 $^\circ\text{C}$.



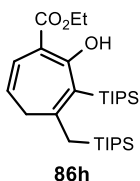
According to the general procedure C, **86f** (33.1 mg, 79.1 μmol , 81% yield) was synthesized from dienyne **84f** (41.1 mg, 98.2 μmol) and LDA (ca. 1.0 mol/L in THF-hexane, 200 μL , 0.200 mmol).

86f: yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 6.33 (dd, $J = 9.0, 1.4$ Hz, 1H), 5.44 (ddd, $J = 9.0, 7.4, 6.4$ Hz, 1H), 4.31–4.21 (m, 2H), 2.90 (dd, $J = 12.1, 7.4$ Hz, 1H), 2.46 (tt, $J = 11.4, 3.1$ Hz, 1H), 1.84 (ddd, $J = 12.1, 6.4, 1.4$ Hz, 1H), 1.82–1.70 (m, 3H), 1.65–1.61 (m, 2H), 1.53–1.19 (m, 8H), 1.34 (t, 7.0 Hz, 3H), 1.08 (d, $J = 7.4$ Hz, 9H), 1.03 (d, $J = 7.4$ Hz, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 178.8, 172.8, 166.4, 124.7, 123.1, 122.7, 103.5, 60.6, 45.2, 32.2, 31.4, 31.1, 26.05, 26.00, 25.8, 19.5 (3C), 19.4 (3C), 14.2, 13.7 (3C); FT-IR (ATR) ν 2927, 2864, 1636, 1316, 1228, 1070 cm^{-1} ; HRMS (FD) calcd for $\text{C}_{25}\text{H}_{42}\text{O}_3\text{Si}$ (M^+): 418.2903, found: 418.2922; m.p. (Et_2O) 96–101 $^\circ\text{C}$.



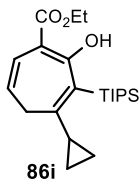
According to the general procedure C, **86g** (36.7 mg, 87.2 μmol , 86% yield) was synthesized from dienyne **84g** (42.5 mg, 0.101 mmol) and LDA (ca. 1.0 mol/L in THF-hexane, 200 μL , 0.200 mmol).

86g: yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 6.33 (d, $J = 9.1$ Hz, 1H), 5.52 (ddd, $J = 9.1, 7.4, 6.4$ Hz, 1H), 4.29–4.23 (m, 2H), 2.78 (dd, $J = 12.1, 7.4$ Hz, 1H), 2.38–2.32 (m, 1H), 2.26–2.20 (m, 1H), 2.05 (ddd, $J = 12.1, 6.4, 1.4$ Hz, 1H), 1.55–1.46 (m, 2H), 1.42–1.29 (m, 12H), 1.05 (d, $J = 7.4$ Hz, 9H), 1.02 (d, $J = 7.4$ Hz, 9H), 0.90 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 178.9, 172.8, 162.0, 125.1, 123.0, 122.6, 103.3, 60.6, 38.4, 35.1, 31.7, 29.9, 29.3, 22.5, 19.34 (3C), 19.30 (3C), 14.2, 14.0, 13.5 (3C); FT-IR (ATR) ν 2928, 2864, 1636, 1315, 1226, 1068 cm^{-1} ; HRMS (FD) calcd for $\text{C}_{25}\text{H}_{44}\text{O}_3\text{Si}$ (M^+): 420.3060, found: 420.3045.



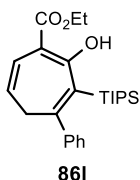
According to the general procedure C, **86h** (22.4 mg, 44.2 μmol , 88% yield) was synthesized from dienyne **84h** (25.4 mg, 50.1 μmol) and LDA (ca. 1.0 mol/L in THF-hexane, 100 μL , 0.100 μmol).

86h: pale yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 6.33 (d, $J = 9.3$ Hz, 1H), 5.56 (ddd, $J = 9.3, 7.0, 7.0$ Hz, 1H), 4.28–4.23 (m, 2H), 2.68 (br, 1H), 2.21 (br, 1H), 2.03 (br-d, $J = 12.3$ Hz, 1H), 1.95 (br-d, $J = 12.3$ Hz, 1H), 1.52–1.43 (m, 3H), 1.33 (t, $J = 7.2$ Hz, 3H), 1.25–1.14 (m, 3H), 1.11–1.04 (m, 36H); ^{13}C NMR (126 MHz, CDCl_3) δ 179.4, 172.7, 161.0, 125.1, 123.5, 122.7, 102.9, 60.5, 37.9, 21.5, 19.5 (6C), 19.0 (6C), 14.3, 14.0 (3C), 11.8 (3C); FT-IR (ATR) ν 2943, 2866, 1637, 1316, 1227, 1070 cm^{-1} ; HRMS (FD) calcd for $\text{C}_{29}\text{H}_{54}\text{O}_3\text{Si}_2$ (M^+): 506.3612, found: 506.3625; m.p. (Et_2O) 64–69 $^\circ\text{C}$.



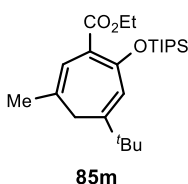
According to the general procedure C, **86i** (21.8 mg, 57.9 μ mol, 58% yield) was synthesized from diyne **84i** (37.6 mg, 99.8 μ mol) and LDA (ca. 1.0 mol/L in THF-hexane, 200 μ L, 0.200 mmol).

86i: yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 6.35 (d, $J = 9.3$ Hz, 1H), 5.33 (ddd, $J = 9.3, 7.1, 7.1$ Hz, 1H), 4.31–4.21 (m, 2H), 2.14 (dd, $J = 12.6, 7.1$ Hz, 1H), 1.77–1.71 (m, 2H), 1.47–1.38 (m, 3H), 1.33 (t, $J = 7.2$ Hz, 3H), 1.04 (d, $J = 7.5$ Hz, 18H), 0.95–0.87 (m, 2H), 0.85–0.79 (m, 1H), 0.68–0.63 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 178.8, 172.8, 162.0, 124.7, 123.5, 122.0, 103.1, 60.6, 27.6, 19.3 (3C), 19.1 (3C), 17.1, 14.2, 13.3 (3C), 9.5, 7.3; FT-IR (ATR) ν 2944, 2865, 1635, 1299, 1227, 1072 cm^{-1} ; HRMS (FD) calcd for $\text{C}_{22}\text{H}_{36}\text{O}_3\text{Si}$ (M^+): 376.2434, found: 376.2420.



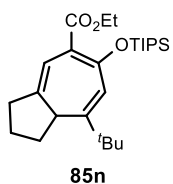
According to the general procedure C, **86l** (19.3 mg, 46.8 μ mol, 47% yield) was synthesized from diyne **84l** (40.7 mg, 98.6 μ mol) and LDA (ca. 1.0 mol/L in THF-hexane, 200 μ L, 0.200 mmol).

86l: yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 7.27–7.22 (m, 5H), 6.51 (d, $J = 9.2$ Hz, 1H), 5.72 (ddd, $J = 9.2, 6.8, 6.8$ Hz, 1H), 4.31 (q, $J = 7.3$ Hz, 2H), 2.86 (br, 1H), 2.34 (br, 1H), 1.37 (t, $J = 7.3$ Hz, 3H), 1.25–0.86 (m, 21H); ^{13}C NMR (126 MHz, CDCl_3) δ 178.0, 172.9, 159.2, 144.3, 127.9 (2C), 127.8, 127.5 (2C), 127.2, 123.4, 121.5, 104.1, 60.9, 40.2, 19.5 (6C), 14.2, 13.0 (3C); FT-IR (ATR) ν 2946, 2865, 1637, 1315, 1226, 1081 cm^{-1} ; HRMS (FD) calcd for $\text{C}_{25}\text{H}_{36}\text{O}_3\text{Si}$ (M^+): 412.2434, found: 412.2426; m.p. (Et_2O) 79–81 $^\circ\text{C}$.



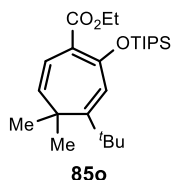
According to the general procedure C, **85m** (32.5 mg, 79.9 μ mol, 79% yield) was synthesized from diyne **84m** (41.0 mg, 0.101 mmol) and LDA (ca. 1.0 mol/L in THF-hexane, 200 μ L, 0.200 mmol).

85m: colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 6.13 (d, $J = 1.1$ Hz, 1H), 5.83 (s, 1H), 4.22 (q, $J = 7.2$ Hz, 2H), 2.41 (s, 2H), 1.97 (d, $J = 1.1$ Hz, 3H), 1.30 (t, $J = 7.2$ Hz, 3H), 1.26–1.17 (m, 3H), 1.14 (s, 9H), 1.09 (d, $J = 7.4$ Hz, 18H); ^{13}C NMR (126 MHz, CDCl_3) δ 168.5, 156.3, 152.6, 129.9, 120.7, 118.1, 116.8, 60.2, 36.1, 34.2, 28.8 (3C), 23.5, 17.9 (6C), 14.4, 13.3 (3C); FT-IR (ATR) ν 2945, 2867, 1720, 1223, 1194, 883 cm^{-1} ; HRMS (FD) calcd for $\text{C}_{24}\text{H}_{42}\text{O}_3\text{Si}$ (M^+): 406.2903, found: 406.2907.



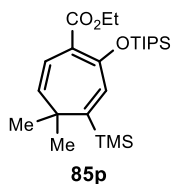
According to the general procedure C, **85n** (38.2 mg, 88.3 μmol , 89% yield) was synthesized from dienyne **84n** (43.1 mg, 99.6 μmol) and LDA (ca. 1.0 mol/L in THF-hexane, 200 μL , 0.200 mmol).

85n: pale yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 6.23 (s, 1H), 5.84 (s, 1H), 4.30–4.23 (m, 1H), 4.21–4.14 (m, 1H), 2.65–2.57 (m, 1H), 2.46–2.33 (m, 3H), 2.12–2.06 (m, 1H), 2.04–1.99 (m, 1H), 1.66–1.56 (m, 1H), 1.30 (t, $J = 6.9$ Hz, 3H), 1.25–1.18 (m, 3H), 1.20 (s, 9H), 1.11 (d, $J = 7.4$ Hz, 9H), 1.08 (d, $J = 6.9$ Hz, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 168.7, 155.9, 152.3, 143.9, 118.9, 117.3, 115.1, 60.3, 45.3, 36.5, 33.5, 30.2 (3C), 29.0, 26.6, 18.0 (3C), 17.9 (3C), 14.4, 13.3 (3C); FT-IR (ATR) ν 2946, 2867, 1721, 1272, 1200, 883 cm^{-1} ; HRMS (FD) calcd for $\text{C}_{26}\text{H}_{44}\text{O}_3\text{Si}$ (M^+): 432.3060, found: 432.3039.



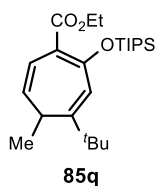
According to the general procedure C, **85o** (29.3 mg, 69.6 μmol , 70% yield) was synthesized from dienyne **84o** (42.0 mg, 99.8 μmol) and LDA (ca. 1.0 mol/L in THF-hexane, 200 μL , 0.200 mmol).

85o: yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 6.44 (d, $J = 10.3$ Hz, 1H), 5.99 (s, 1H), 4.91 (d, $J = 10.3$ Hz, 1H), 4.23 (q, $J = 7.2$ Hz, 2H), 1.30 (t, $J = 7.2$ Hz, 3H), 1.27–1.20 (m, 18H), 1.11 (d, $J = 7.4$ Hz, 18H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.8, 157.0, 152.7, 124.2, 122.7, 118.8, 115.3, 60.1, 38.9, 38.5 (2C), 32.0 (3C), 27.2, 18.0 (6C), 14.4, 13.4 (3C); FT-IR (ATR) ν 2946, 2867, 1720, 1204, 1068, 882 cm^{-1} ; HRMS (FD) calcd for $\text{C}_{25}\text{H}_{44}\text{O}_3\text{Si}$ (M^+): 420.3060, found: 420.3041.



According to the general procedure C, **85p** (12.7 mg, 29.1 μmol , 58% yield) was synthesized from dienyne **84p** (21.9 mg, 50.1 μmol) and LDA (ca. 1.0 mol/L in THF-hexane, 100 μL , 0.100 mmol).

85p: yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 6.37 (d, $J = 10.3$ Hz, 1H), 6.25 (s, 1H), 5.06 (d, $J = 10.3$ Hz, 1H), 4.23 (q, $J = 7.2$ Hz, 2H), 1.30 (t, $J = 7.2$ Hz, 3H), 1.26–1.19 (m, 3H), 1.12 (s, 6H), 1.11 (d, $J = 7.5$ Hz, 18H), 0.21 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 168.1, 157.4, 153.1, 132.1, 129.5, 122.3, 117.4, 60.4, 38.8 (2C), 26.3, 17.9 (6C), 14.4, 13.4 (3C), 1.8 (3C); FT-IR (ATR) ν 2947, 2867, 1722, 1203, 835 cm^{-1} ; HRMS (FD) calcd for $\text{C}_{24}\text{H}_{44}\text{O}_3\text{Si}_2$ (M^+): 436.2829, found: 436.2830.

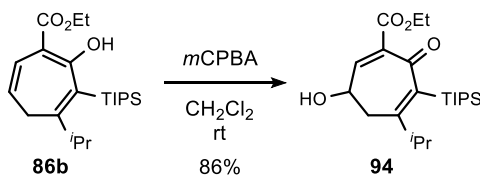


From (Z)-84q: According to the general procedure C, **85q** (26.5 mg, 65.2 μ mol, 66% yield) was synthesized from dienyne (Z)-**84q** (40.3 mg, 99.1 μ mol) and LDA (ca. 1.0 mol/L in THF-hexane, 200 μ L, 0.200 mmol).

From (E)-84q: According to the general procedure C, **85q** (14.2 mg, 34.9 μ mol, 35% yield) and **93** (isomeric mixture, 5.8 mg, 16 μ mol, 16% yield) was synthesized from dienyne (E)-**84q** (40.2 mg, 98.8 μ mol) and LDA (ca. 1.0 mol/L in THF-hexane, 200 μ L, 0.200 mmol).

85q: yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 6.41 (d, J = 10.2 Hz, 1H), 5.92 (d, J = 1.1 Hz, 1H), 5.39 (dd, J = 10.2, 8.9 Hz, 1H), 4.30–4.24 (m, 1H), 4.20–4.13 (m, 1H), 3.30 (dq, J = 8.9, 7.4 Hz, 1H), 1.30 (t, J = 7.3 Hz, 3H), 1.29–1.21 (m, 3H), 1.13 (s, 9H), 1.12 (d, J = 7.0 Hz, 9H), 1.10 (d, J = 7.0 Hz, 9H), 0.80 (d, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 168.3, 157.7, 156.2, 124.1, 122.8, 117.0, 115.6, 60.2, 37.5, 32.7, 29.3 (3C), 17.9 (6C), 14.4, 13.5, 13.3 (3C); FT-IR (ATR) ν 2946, 2868, 1719, 1197, 1068, 881 cm^{-1} ; HRMS (FD) calcd for $\text{C}_{24}\text{H}_{42}\text{O}_3\text{Si}$ (M^+): 406.2903, found: 406.2911.

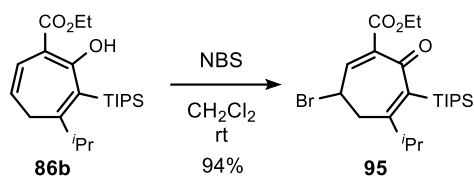
Ketoester **94**



To a solution of **86b** (18.9 mg, 49.9 μ mol) in CH_2Cl_2 (0.25 mL) was added *m*CPBA (contains ca. 30% water, 12.5 mg, 50.7 μ mol) at room temperature. After stirring for 20 min, the reaction was quenched by the addition of saturated aqueous NaHCO_3 solution (0.50 mL) and $\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$ (90 mg). After vigorous stirring for 1 h, the two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (0.50 mL $\times$ 3). The combined organic layers were washed with saturated aqueous NaHCO_3 solution (1.0 mL $\times$ 2), then dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2 , hexane: Et_2O = 10:1 to 1:1 gradient) to afford **94** (16.9 mg, 42.8 μ mol, 86% yield).

94: pale yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 7.21 (s, 1H), 4.35 (d, J = 11.8 Hz, 1H), 4.26–4.17 (m, 2H), 2.70 (sept, J = 6.8 Hz, 1H), 2.64 (dd, J = 13.6, 11.8 Hz, 2H), 2.48 (d, J = 13.6 Hz, 1H), 2.30 (br, 1H), 1.28 (t, J = 7.0 Hz, 3H), 1.29–1.23 (m, 3H), 1.12 (d, J = 6.8 Hz, 3H), 1.10 (d, J = 7.2 Hz, 9H), 1.05 (d, J = 7.2 Hz, 9H), 1.02 (d, J = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 199.9, 164.2, 154.4, 149.6, 144.5, 134.7, 68.3, 61.5, 35.7, 35.3, 20.9, 20.8, 19.2 (3C), 19.0 (3C), 13.9, 12.8 (3C); FT-IR (ATR) ν 3464 (br), 2947, 2867, 1720, 1661, 1243, 1042 cm^{-1} ; HRMS (FD) calcd for $\text{C}_{22}\text{H}_{39}\text{O}_4\text{Si}$ ($[\text{M} + \text{H}]^+$): 395.2618, found: 395.2607.

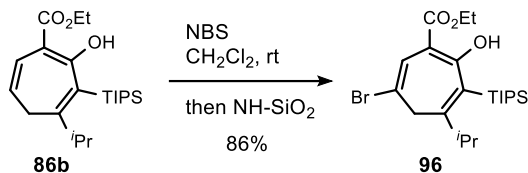
Ketoester **95**



To a solution of **86b** (37.7 mg, 99.6 μ mol) in CH₂Cl₂ (0.50 mL) was added NBS (26.7 mg, 0.150 mmol) at room temperature. After stirring for 30 min, the mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography (SiO₂, hexane:EtOAc = 50:1 to 20:1) to afford **95** (42.6 mg, 93.1 μ mol, 94% yield).

95: pale yellow oil; ¹H NMR (500 MHz, CDCl₃) δ 7.30 (dd, J = 3.4, 1.7 Hz, 1H), 4.78 (dt, J = 11.6, 3.4 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.03 (dd, J = 14.5, 11.6 Hz, 1H), 2.81 (dd, J = 14.5, 1.7 Hz, 1H), 2.69 (sept, J = 6.7 Hz, 1H), 1.28 (t, J = 7.1 Hz, 3H), 1.30–1.22 (m, 3H), 1.10 (d, J = 7.4 Hz, 12H), 1.06 (d, J = 7.4 Hz, 12H); ¹³C NMR (126 MHz, CDCl₃) δ 199.8, 163.4, 154.4, 146.5, 145.8, 133.8, 61.7, 44.9, 36.6, 35.0, 21.5, 20.6, 19.1 (3C), 19.0 (3C), 13.9, 12.8 (3C); FT-IR (ATR) ν 2946, 2867, 1720, 1672, 1248, 1042 cm⁻¹; HRMS (FD) calcd for C₂₂H₃₇BrO₃Si (M⁺): 456.1695, found: 456.1682.

Cycloheptatriene **96**

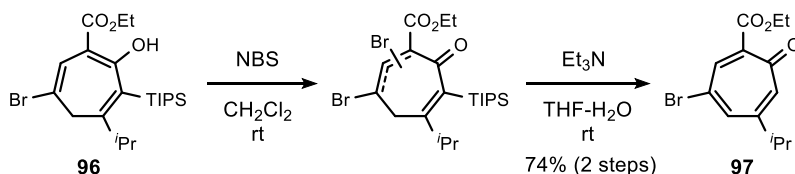


To a solution of **86b** (379 mg, 1.00 mmol) in CH₂Cl₂ (5.0 mL) was added NBS (215 mg, 1.21 mmol) at room temperature. After stirring for 30 min, hexane (5.0 mL) was added, and the resulting precipitate was filtered and washed with hexane. The filtrate was concentrated under reduced pressure and purified by flash column chromatography [SiO₂ (NH-functionalized), hexane:EtOAc = 200:1] to afford **96** (396 mg, 0.866 mmol, 86% yield).

96: white solid; ¹H NMR (500 MHz, CDCl₃) δ 6.65 (s, 1H), 4.31–4.22 (m, 2H), 3.11 (dd, J = 14.2, 1.4 Hz, 1H), 2.83 (sept, J = 6.7 Hz, 1H), 2.69 (dd, J = 14.2, 1.1 Hz, 1H), 1.43–1.35 (m, 3H), 1.34 (t, J = 7.3 Hz, 3H), 1.21 (d, J = 6.7 Hz, 3H), 1.09 (d, J = 6.7 Hz, 3H), 1.07 (d, J = 7.5 Hz, 9H), 1.04 (d, J = 7.5 Hz, 9H); ¹³C NMR (126 MHz, CDCl₃) δ 178.6, 171.6, 166.6, 127.0, 124.7, 112.9, 103.3, 61.0, 38.9, 34.6, 21.7, 20.9, 19.4 (3C), 19.3 (3C), 14.2, 13.5 (3C); FT-IR (ATR) ν 2966,

2946, 2867, 1639, 1226, 1067 cm^{-1} ; HRMS (FD) calcd for $\text{C}_{22}\text{H}_{37}\text{BrO}_3\text{Si}$ (M^+): 456.1695, found: 456.1697; m.p. (EtOAc) 100–105 $^\circ\text{C}$.

Tropone 97

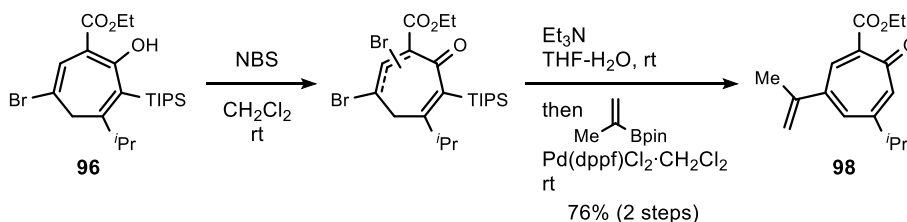


To a solution of **96** (230 mg, 0.502 mmol) in CH_2Cl_2 (5.0 mL) was added NBS (178 mg, 1.00 mmol) at room temperature. After stirring for 1 h, hexane (5.0 mL) was added, and the resulting precipitate was filtered and washed with hexane. The filtrate was concentrated under reduced pressure and purified through a short pad of SiO_2 (hexane:EtOAc = 10:1) to afford dibromide.

To a solution of above dibromide in THF (4.0 mL) and H_2O (1.0 mL) was added Et_3N (347 μL , 2.50 mmol) at room temperature. After stirring for 15 h, the reaction was quenched with saturated aqueous NH_4Cl solution (5.0 mL), and the organic layer was diluted with EtOAc (5.0 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (5.0 mL $\times$ 3). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2 , hexane:EtOAc = 20:1 to 5:1) to afford **97** (111 mg, 0.372 mmol, 74% yield for 2 steps).

97: yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 7.64 (d, J = 1.7 Hz, 1H), 7.37 (dd, J = 1.7, 1.1 Hz, 1H), 6.91 (d, J = 1.1 Hz, 1H), 4.35 (q, J = 7.3 Hz, 2H), 2.70 (sept, J = 6.9 Hz, 1H), 1.35 (t, J = 7.3 Hz, 3H), 1.21 (d, J = 6.9 Hz, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ 183.3, 165.9, 154.6, 141.5, 140.3, 139.3, 137.5, 127.2, 62.2, 37.7, 22.5 (2C), 14.1; FT-IR (ATR) ν 2965, 1730, 1624, 1584, 1234 cm^{-1} ; HRMS (FD) calcd for $\text{C}_{13}\text{H}_{15}\text{BrO}_3$ (M^+): 298.0205, found: 298.0214.

Tropone 98



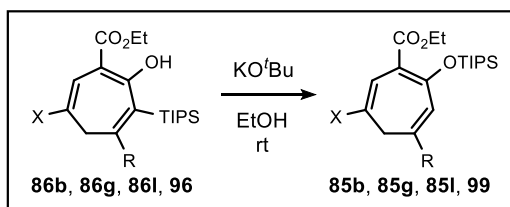
To a solution of **96** (196 mg, 0.428 mmol) in CH_2Cl_2 (4.3 mL) was added NBS (152 mg, 0.853 mmol) at room temperature. After stirring for 45 min, hexane (5.0 mL) was added, and the resulting precipitate was filtered and washed with hexane. The filtrate was concentrated under

reduced pressure and purified through a short pad of SiO₂ (hexane:EtOAc = 10:1) to afford dibromide.

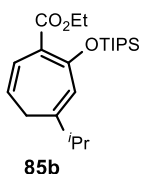
To a solution of above dibromide in THF (3.4 mL) and H₂O (0.85 mL) was added Et₃N (297 μL, 2.14 mmol) at room temperature. After stirring for 15 h, (isopropenyl)Bpin (121 μL, 0.643 mmol) and Pd(dppf)Cl₂·CH₂Cl₂ (16.9 mg, 20.7 μmol) were added successively, and the reaction mixture was stirred for another 1 h. The reaction was quenched with H₂O (3.0 mL), and the organic layer was diluted with EtOAc (3.0 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (3.0 mL × 3). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, hexane:EtOAc = 10:1 to 3:1) to afford **98** (85.2 mg, 0.327 mmol, 76% yield for 2 steps).

98: dark orange oil; ¹H NMR (500 MHz, CDCl₃) δ 7.62 (d, *J* = 1.1 Hz, 1H), 6.97 (dd, *J* = 1.7, 1.1 Hz, 1H), 6.90 (d, *J* = 1.7 Hz, 1H), 5.29 (s, 1H), 5.23 (s, 1H), 4.33 (q, *J* = 7.3 Hz, 2H), 2.73 (sept, *J* = 6.9 Hz, 1H), 2.09 (s, 3H), 1.33 (t, *J* = 7.3 Hz, 3H), 1.20 (d, *J* = 6.9 Hz, 6H); ¹³C NMR (126 MHz, CDCl₃) δ 184.2, 167.5, 155.8, 145.2, 144.8, 141.7, 137.0, 135.3, 133.9, 117.1, 61.7, 38.3, 22.7 (2C), 22.0, 14.0; FT-IR (ATR) ν 2964, 1726, 1634, 1579, 1233, 1044 cm⁻¹; HRMS (FD) calcd for C₁₆H₂₀O₃ (M⁺): 260.1412, found: 260.1402.

General procedure D: Brook rearrangement

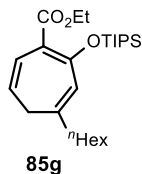


To a solution of vinylsilane in EtOH (0.2 mol/L, 1.0 equiv.) was added KO^tBu (1.0 mol/L in THF, 0.20 equiv.) at room temperature. The reaction mixture was stirred until full consumption of starting material was observed by TLC (indicated). The reaction was quenched with saturated aqueous NH₄Cl solution, and the resulting mixture was extracted four times with Et₂O. The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, hexane:EtOAc = 100:1) to afford the product silylether.



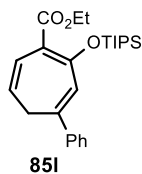
According to the general procedure D, **85b** (35.7 mg, 94.3 μmol, 94% yield) was synthesized from vinylsilane **86b** (38.0 mg, 0.100 mmol) and KO^tBu (1.0 mol/L in THF, 20.0 μL, 20.0 μmol). Reaction time: 1.5 h.

85b: colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 6.41 (d, $J = 9.5$ Hz, 1H), 5.79 (s, 1H), 5.27 (dt, $J = 9.5, 6.9$ Hz, 1H), 4.22 (q, $J = 7.3$ Hz, 2H), 2.47 (sept, $J = 6.7$ Hz, 1H), 2.33 (d, $J = 6.9$ Hz, 2H), 1.30 (t, $J = 7.3$ Hz, 3H), 1.27–1.19 (m, 3H), 1.10 (d, $J = 7.0$ Hz, 18H), 1.08 (d, $J = 6.7$ Hz, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ 168.2, 157.7, 151.3, 125.3, 118.4, 118.0, 116.7, 60.2, 35.6, 30.4, 21.9 (2C), 17.9 (6C), 14.4, 13.2 (3C); FT-IR (ATR) ν 2959, 2944, 2867, 1721, 1206 cm^{-1} ; HRMS (FD) calcd for $\text{C}_{22}\text{H}_{38}\text{O}_3\text{Si}$ (M^+): 378.2590, found: 378.2573.



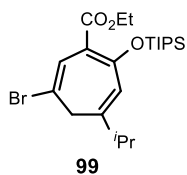
According to the general procedure D, **85g** (18.0 mg, 42.8 μmol , 87% yield) was synthesized from vinylsilane **86g** (20.6 mg, 49.0 μmol) and KO^tBu (1.0 mol/L in THF, 10.0 μL , 10.0 μmol). Reaction time: 2.5 h.

85g: pale yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 6.41 (d, $J = 9.1$ Hz, 1H), 5.77 (s, 1H), 5.28 (dt, $J = 9.1, 7.0$ Hz, 1H), 4.22 (q, $J = 7.2$ Hz, 2H), 2.34 (d, $J = 7.0$ Hz, 2H), 2.23 (t, $J = 7.2$ Hz, 2H), 1.50–1.43 (m, 2H), 1.41–1.20 (m, 9H), 1.30 (t, $J = 7.2$ Hz, 3H), 1.10 (d, $J = 7.0$ Hz, 18H), 0.88 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 168.2, 157.6, 145.2, 125.4, 120.6, 117.6, 116.9, 60.2, 38.0, 32.1, 31.7, 28.9, 28.6, 22.6, 17.9 (6C), 14.4, 14.1, 13.3 (3C); FT-IR (ATR) ν 2928, 2866, 1721, 1207, 1060, 882 cm^{-1} ; HRMS (FD) calcd for $\text{C}_{25}\text{H}_{44}\text{O}_3\text{Si}$ (M^+): 420.3060, found: 420.3050.



According to the general procedure D, **85l** (17.0 mg, 41.2 μmol , 93% yield) was synthesized from vinylsilane **86l** (18.2 mg, 44.1 μmol) and KO^tBu (1.0 mol/L in THF, 8.8 μL , 8.8 μmol). Reaction time: 0.5 h.

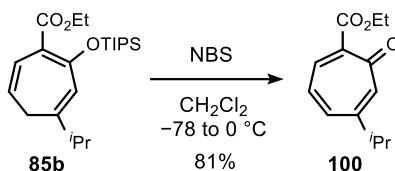
85l: pale yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 7.48–7.45 (m, 2H), 7.39–7.36 (m, 2H), 7.33–7.30 (m, 1H), 6.53 (d, $J = 9.3$ Hz, 1H), 6.30 (s, 1H), 5.43 (dt, $J = 9.3, 7.0$ Hz, 1H), 4.27 (q, $J = 7.2$ Hz, 2H), 2.81 (d, $J = 7.0$ Hz, 2H), 1.33 (t, $J = 7.2$ Hz, 3H), 1.30–1.23 (m, 3H), 1.12 (d, $J = 7.4$ Hz, 18H); ^{13}C NMR (126 MHz, CDCl_3) δ 168.1, 157.2, 139.9, 139.2, 128.7 (2C), 128.1, 127.3 (2C), 125.9, 121.4, 118.3, 117.7, 60.4, 31.4, 17.9 (6C), 14.4, 13.3 (3C); FT-IR (ATR) ν 2944, 2866, 1718, 1207, 1061 cm^{-1} ; HRMS (FD) calcd for $\text{C}_{25}\text{H}_{36}\text{O}_3\text{Si}$ (M^+): 412.2434, found: 412.2451.



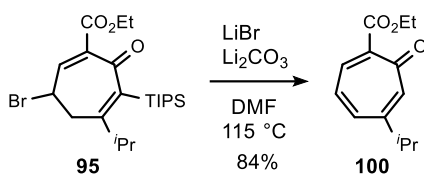
According to the general procedure D, **99** (37.8 mg, 82.6 μmol , 93% yield) was synthesized from vinylsilane **96** (40.6 mg, 88.7 μmol) and KO^tBu (1.0 mol/L in THF, 17.7 μL , 17.7 μmol). Reaction time: 0.5 h.

99: pale yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 6.73 (s, 1H), 5.82 (s, 1H), 4.22 (q, $J = 7.2$ Hz, 2H), 2.88 (s, 2H), 2.49 (sept, $J = 6.9$ Hz, 1H), 1.30 (t, $J = 7.2$ Hz, 3H), 1.25–1.17 (m, 3H), 1.14 (d, $J = 6.9$ Hz, 6H), 1.09 (d, $J = 7.4$ Hz, 18H)

Tropone **100**



From 85b: To a solution of **85b** (35.6 mg, 94.0 μmol) in CH_2Cl_2 (0.47 mL) was added NBS (20.2 mg, 0.113 mmol) at -78°C . The reaction mixture was then warmed up to 0°C and stirred for 10 min. The mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography (SiO_2 , hexane:EtOAc = 10:1 to 3:1) to afford **100** (16.8 mg, 76.3 μmol , 81% yield).



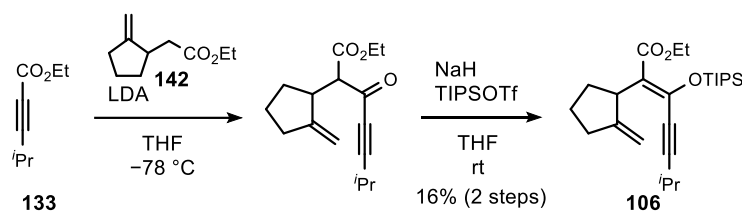
From 95: To a solution of **95** (44.2 mg, 96.6 μmol) in DMF (0.50 mL) were added successively Li_2CO_3 (21.6 mg, 0.292 mmol) and LiBr (25.8 mg, 0.297 mmol) at room temperature. The reaction mixture was then warmed up to 115°C and stirred for 1 h. After cooling down to room temperature, the reaction was quenched with brine (1.5 mL). Two layers were separated, and the aqueous layer was extracted with Et_2O (0.50 mL $\times$ 5). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2 , hexane:EtOAc = 3:1) to afford **100** (17.8 mg, 80.8 μmol , 84% yield).

100: yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 7.44–7.42 (dd, $J = 8.6, 1.0$ Hz, 1H), 6.99–6.97 (m, 2H), 6.91 (dd, $J = 12.0, 8.6$ Hz, 1H), 4.34 (q, $J = 7.2$ Hz, 2H), 2.73 (sept, $J = 6.9$ Hz, 1H), 1.34 (t, $J = 7.2$ Hz, 3H), 1.20 (d, $J = 6.9$ Hz, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ 184.4, 167.3, 155.7, 143.0, 139.0, 138.6, 135.3, 131.3, 61.7, 37.7, 22.6 (2C), 14.1; FT-IR (ATR) ν 2964, 1726, 1633, 1579, 1287, 1230 cm^{-1} ; HRMS (FD) calcd for $\text{C}_{13}\text{H}_{16}\text{O}_3$ (M^+): 220.1099, found: 220.1108.

Alcohol **101**

103: pale yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 7.23–7.21 (m, 1H), 7.01 (s, 1H), 6.88–6.83 (m, 2H), 2.75 (sept, $J = 6.9$ Hz, 1H), 2.24 (d, $J = 1.4$ Hz, 3H), 1.21 (d, $J = 6.9$ Hz, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ 187.2, 156.1, 151.8, 136.6, 134.5, 134.1, 132.5, 38.0, 22.9 (2C), 22.6; FT-IR (ATR) ν 2962, 1632, 1565, 1471, 794 cm^{-1} ; HRMS (FI) calcd for $\text{C}_{11}\text{H}_{14}\text{O}$ (M^+): 162.1045, found: 162.1046.

Dienyne 106

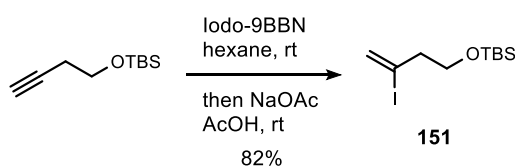


An LDA solution (ca. 1.0 mol/L in THF-hexane) was prepared by the addition of $n\text{BuLi}$ (2.65 mol/L in hexane, 755 μL , 2.00 mmol) to a solution of $i\text{Pr}_2\text{NH}$ (281 μL , 2.00 mmol) in THF (1.25 mL) at 0 $^\circ\text{C}$. The mixture was stirred for 20 min at the same temperature before the use. To another reaction vessel charged with alkenyl ester **142** (100.7 mg, 0.599 mmol) in THF (2.5 mL) was added the LDA solution (1.20 mL, 1.20 mmol) via a syringe at -78 $^\circ\text{C}$. After stirring for 10 min, alkynyl ester **133** (69.6 mg, 0.497 mmol) in THF (0.50 mL) was added via cannula, and the mixture was stirred for 30 min at the same temperature. Crushed dry ice was added to trap the excessive enolate, and the mixture was stirred under ambient temperature until the evolution of CO_2 gas ceased. The reaction was quenched with saturated aqueous NaHCO_3 solution (2.5 mL), and the organic layer was diluted with EtOAc (2.5 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (2.5 mL $\times$ 3). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2 , hexane: EtOAc = 10:1) to afford β -ketoester (31.8 mg, < 0.121 mmol) along with byproducts.

NaH (60% dispersion in mineral oil, 10.1 mg, 0.253 mmol) was washed with hexane and suspended with THF (0.50 mL). To this suspension was added above β -ketoester in THF (0.50 mL) via cannula at 0 $^\circ\text{C}$. After stirring for 10 min, TIPSOTf (48.9 μL , 0.182 mmol) was added. The reaction mixture was then warmed up to room temperature and stirred for 15 min. The reaction was quenched by the careful addition of saturated aqueous NaHCO_3 solution (1.0 mL), and the organic layer was diluted with EtOAc (1.0 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (1.0 mL $\times$ 3). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2 , hexane: EtOAc = 200:1) to afford **106** (33.9 mg, 81.0 μmol , 16% yield for 2 steps).

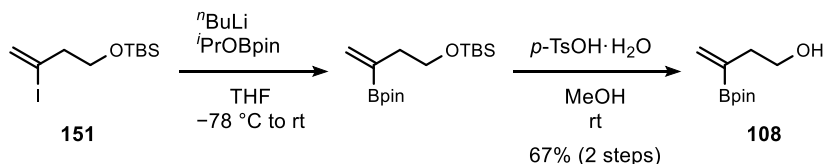
106: colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 4.86 (s, 1H), 4.80 (s, 1H), 4.18–4.05 (m, 2H), 3.63 (dd, $J = 8.0, 8.0$ Hz, 1H), 2.71 (sept, $J = 6.9$ Hz, 1H), 2.42–2.35 (m, 2H), 2.02–1.97 (m, 1H), 1.90–1.80 (m, 2H), 1.59–1.48 (m, 1H), 1.33–1.26 (m, 3H), 1.23 (t, $J = 7.2$ Hz, 3H), 1.19 (d, $J = 6.9$ Hz, 6H), 1.11 (dd, $J = 7.7, 1.4$ Hz, 18H)

Vinyl iodide **151**



To a solution of 4-(*tert*-butyldimethylsilyloxy)-1-butyne (439 μL , 2.00 mmol) in hexane (7.6 mL) was added dropwise *B*-iodo-9-BBN (1.0 mol/L in hexane, 2.40 mL, 2.40 mmol) at room temperature. After stirring for 12 h, NaOAc (197.4 mg, 2.41 mmol) and AcOH (400 μL , 7.0 mmol) were added, and the reaction mixture was stirred for 1 h at the same temperature. The reaction mixture was washed with water (10 mL), saturated aqueous NaHCO_3 solution (10 mL), and again with water (10 mL). The organic layer was dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified through a short pad of SiO_2 (hexane) to afford **151** (514.9 mg, 1.65 mmol, 82% yield). The spectral data matched with those reported in literature.
[51]

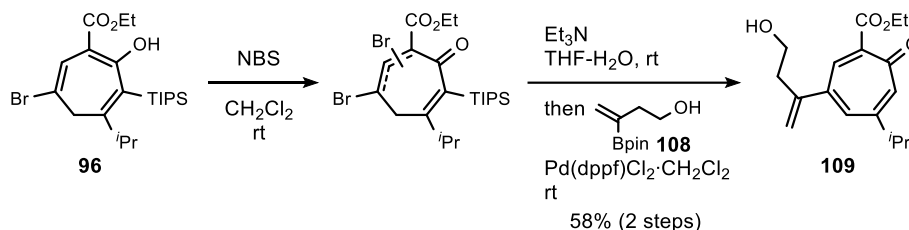
Vinyl boronate **108**



To a solution of **151** (248 mg, 0.795 mmol) in THF (4.0 mL) was added $n\text{-BuLi}$ (2.65 mol/L in hexane, 453 μL , 1.20 mmol) at -78°C . After stirring for 20 min, $i\text{PrOBpin}$ (243 μL , 1.20 mmol) was added. The reaction mixture was then warmed up to room temperature and stirred for 30 min. The reaction was quenched with saturated aqueous NH_4Cl solution (5.0 mL), and the organic layer was diluted with EtOAc (5.0 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (5.0 mL $\times$ 3). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. Highly polar components were filtered off through a short pad of SiO_2 (hexane: EtOAc = 10:1) to afford silyloxy vinyl boronate along with a small amount of impurities.

To a solution of above silyloxy vinyl boronate in MeOH (4.0 mL) was added *p*-TsOH·H₂O (30.2 mg, 0.159 mmol) at room temperature. After stirring for 15 min, the reaction mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography (SiO₂, hexane:EtOAc = 3:1) to afford **108** (105 mg, 0.531 mmol, 67% yield for 2 steps). The spectral data matched with those reported in literature.^[52]

Tropone 109

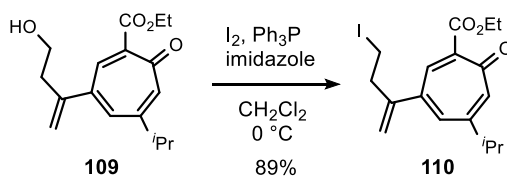


To a solution of **96** (60.2 mg, 0.132 mmol) in CH₂Cl₂ (1.3 mL) was added NBS (46.3 mg, 0.260 mmol) at room temperature. After stirring for 1 h, hexane (2.5 mL) was added, and the resulting precipitate was filtered and washed with hexane. The filtrate was concentrated under reduced pressure and purified through a short pad of SiO₂ (hexane:EtOAc = 10:1) to afford dibromide.

To a solution of above dibromide in THF (1.2 mL) and H₂O (0.24 mL) was added Et₃N (91.2 μL, 0.658 mmol) at room temperature. After stirring for 14 h, vinyl boronate **108** (38.7 mg, 0.195 mmol) in THF (0.20 mL) was added via cannula, and Pd(dppf)Cl₂·CH₂Cl₂ (11.0 mg, 13.5 μmol) was added successively. After stirring for 1 h, the reaction was quenched with H₂O (1.0 mL), and the organic layer was diluted with EtOAc (1.0 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (1.0 mL × 3). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, hexane:EtOAc = 2:1 to 1:1) to afford **109** (22.1 mg, 76.1 μmol, 58% yield for 2 steps).

109: dark orange oil; ¹H NMR (500 MHz, CDCl₃) δ 7.53 (d, *J* = 1.7 Hz, 1H), 6.99 (t, *J* = 1.7, 1.4 Hz, 1H), 6.94 (d, *J* = 1.4 Hz, 1H), 5.33 (s, 1H), 5.29 (s, 1H), 4.35 (q, *J* = 7.3 Hz, 2H), 3.76 (dt, *J* = 6.0, 6.0 Hz, 2H), 2.75 (sept, *J* = 6.9 Hz, 1H), 2.69 (t, *J* = 6.0 Hz, 2H), 1.42 (br, 1H), 1.35 (t, *J* = 7.3 Hz, 3H), 1.22 (d, *J* = 6.9 Hz, 6H)

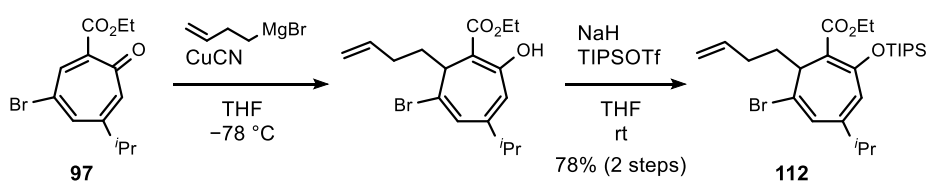
Tropone 110



To a solution of **109** (22.1 mg, 76.1 μ mol) in CH_2Cl_2 (0.76 mL) were added successively imidazole (7.9 mg, 0.12 mmol), Ph_3P (24.1 mg, 91.9 μ mol), and I_2 (23.1 mg, 91.0 μ mol) at 0 $^\circ\text{C}$. After stirring for 15 min, the reaction mixture was quenched with saturated aqueous NH_4Cl solution (1.0 mL), and the organic layer was diluted with Et_2O (1.0 mL). Two layers were separated, and the aqueous layer was extracted with Et_2O (1.0 mL $\times$ 3). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2 , hexane: EtOAc = 3:1) to afford **110** (27.2 mg, 68.0 μ mol, 89% yield).

110: yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 7.44 (d, J = 1.4 Hz, 1H), 6.96 (dd, J = 1.9, 1.4 Hz, 1H), 6.95 (d, J = 1.9 Hz, 1H), 5.33 (s, 1H), 5.25 (s, 1H), 4.36 (q, J = 7.1 Hz, 2H), 3.19 (t, J = 7.1 Hz, 2H), 2.97 (t, J = 7.1 Hz, 2H), 2.76 (sept, J = 6.9 Hz, 1H), 1.36 (t, J = 7.1 Hz, 3H), 1.24 (d, J = 6.9 Hz, 6H)

Cycloheptatriene **112**



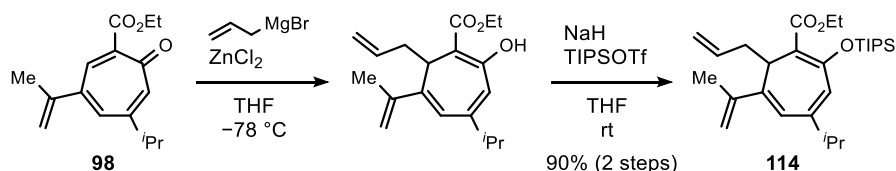
A (3-butenyl) MgBr solution (ca. 1.0 mol/L in THF) was prepared by the dropwise addition of 4-bromo-1-butene (202 μL , 2.00 mmol) in THF (0.50 mL) to a mixture containing Mg turning (48.9 mg, 2.01 mmol) and 1,2-dibromoethane (1.7 μL , 20 μmol) in THF (1.5 mL). The mixture was warmed up to 70 $^\circ\text{C}$ and stirred for 40 min before the use. To another reaction vessel charged with CuCN (66.6 mg, 0.744 mmol) in THF (2.0 mL) was added the (3-butenyl) MgBr solution (744 μL , 0.744 mmol) via a syringe at $-30\text{ }^\circ\text{C}$. After stirring for 10 min, the reaction mixture was cooled down to $-78\text{ }^\circ\text{C}$, and **97** (111 mg, 0.372 mmol) in THF (0.50 mL) was added via cannula. After stirring for 10 min, the reaction was quenched with saturated aqueous NH_4Cl solution (2.5 mL), and the organic layer was diluted with EtOAc (2.5 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (2.5 mL $\times$ 3). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2 , hexane: EtOAc = 100:1 to 50:1) to afford 1,4-adduct (ketone/enol mixture, 104 mg, 0.292 mmol).

NaH (60% dispersion in mineral oil, 24.1 mg, 0.603 mmol) was washed with hexane and suspended with THF (1.0 mL). To this suspension was added above 1,4-adduct (104 mg, 0.292 mmol) in THF (0.50 mL) via cannula at 0 $^\circ\text{C}$. After stirring for 15 min, TIPSOTf (118 μL , 0.438 mmol) was added. The reaction mixture was then warmed up to room temperature and stirred for

10 min. The reaction was quenched by the careful addition of saturated aqueous NaHCO₃ solution (1.5 mL), and the organic layer was diluted with EtOAc (1.5 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (1.5 mL × 3). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, hexane:EtOAc = 50:1) to afford **112** (148 mg, 0.289 mmol, 78% yield for 2 steps).

112: pale yellow oil; ¹H NMR (500 MHz, CDCl₃) δ 6.98 (s, 1H), 6.09 (s, 1H), 5.74 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H), 4.99 (dt, *J* = 17.2, 1.7 Hz, 1H), 4.95 (dd, *J* = 10.2, 1.7 Hz, 1H), 4.22–4.13 (m, 2H), 3.03 (dd, *J* = 8.0, 8.0 Hz, 1H), 2.29 (sept, *J* = 6.9 Hz, 1H), 1.98 (ddd, *J* = 7.1, 7.1, 7.0 Hz, 2H), 1.50–1.42 (m, 1H), 1.34–1.20 (m, 7H), 1.16 (d, *J* = 6.9 Hz, 3H), 1.11–1.07 (m, 21H)

Cycloheptatriene **114**

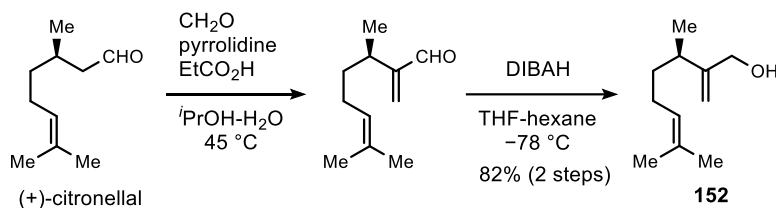


To a solution of ZnCl₂ (1.0 mol/L in THF, 150 μL, 0.150 mmol) in THF (0.50 mL) was added (allyl)MgBr (0.7 mol/L in Et₂O, 214 μL, 0.150 mmol) at room temperature. After stirring for 5 min, the reaction mixture was cooled down to −78 °C, and **98** (25.6 mg, 98.3 μmol) in THF (0.30 mL) was added via cannula. After stirring for 5 min, the reaction was quenched with 1 M aqueous HCl solution (1.0 mL), and the organic layer was diluted with Et₂O (1.0 mL). Two layers were separated, and the aqueous layer was extracted with Et₂O (1.0 mL × 3). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was filtered through a short pad of SiO₂ (hexane:EtOAc = 10:1) to afford 1,4-adduct along with a small amount of impurities.

To a solution of above 1,4-adduct in THF (0.50 mL) was added NaH (60% dispersion in mineral oil, 8.1 mg, 0.20 mmol) at 0 °C. After stirring for 10 min, TIPSOTf (40.3 μL, 0.150 mmol) was added, and the reaction mixture was warmed up to room temperature. After stirring for 10 min, the reaction was quenched by the careful addition of saturated aqueous NaHCO₃ solution (0.50 mL), and the organic layer was diluted with EtOAc (0.50 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (0.50 mL × 3). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, hexane:EtOAc = 50:1) to afford **114** (40.8 mg, 88.9 μmol, 90% yield for 2 steps).

114: yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 6.12 (s, 1H), 6.11 (s, 1H), 5.70–5.62 (m, 1H), 5.52 (s, 1H), 5.07 (s, 1H), 4.87 (s, 1H), 4.84 (d, $J = 4.6$ Hz, 1H), 4.22–4.13 (m, 3H), 2.54 (sept, $J = 6.9$ Hz, 1H), 2.11–1.99 (m, 2H), 1.97 (s, 3H), 1.27 (t, $J = 7.2$ Hz, 3H), 1.23–1.17 (m, 3H), 1.14 (d, $J = 6.9$ Hz, 3H), 1.13 (d, $J = 6.9$ Hz, 3H), 1.08 (d, $J = 7.4$ Hz, 9H), 1.05 (d, $J = 7.4$ Hz, 9H)

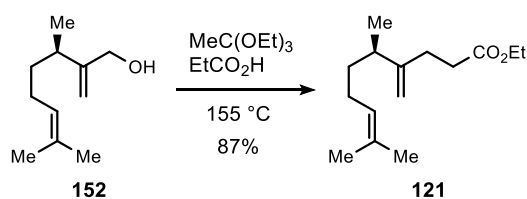
Alcohol 152



To a solution of (+)-citronellal (907 μL , 5.00 mmol) in $i\text{PrOH}$ (0.50 mL) were added successively CH_2O (37% in H_2O , 387 μL , 5.25 mmol), propionic acid (37.0 μL , 0.500 mmol), and pyrrolidine (41.3 μL , 0.500 mmol) at room temperature. The reaction mixture was then warmed up to 45 $^\circ\text{C}$ and stirred for 3 h. After cooling down to room temperature, the reaction was quenched with saturated aqueous NaHCO_3 solution (2.0 mL), and the organic layer was diluted with Et_2O (2.0 mL). Two layers were separated, and the aqueous layer was extracted with Et_2O (2.0 mL $\times$ 4). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was filtered through a short pad of SiO_2 (hexane: $\text{EtOAc} = 10:1$) to afford aldehyde along with a small amount of impurities.

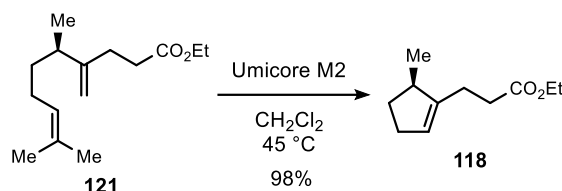
To a solution of above aldehyde in THF (15 mL) was added DIBAH (1.0 mol/L in hexane, 6.00 mL, 6.00 mmol) at -78 $^\circ\text{C}$. After stirring for 10 min, the reaction was quenched with saturated aqueous Rochelle salt solution (20 mL). The biphasic mixture was warmed up to room temperature and stirred vigorously overnight. Two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (10 mL $\times$ 3). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2 , hexane: $\text{EtOAc} = 10:1$ to 3:1) to afford **152** (694 mg, 4.12 mmol, 82% yield). The spectral data matched with those reported in literature. ^[38]

Alkenyl ester 121



To a solution of **152** (694 mg, 4.12 mmol) in triethyl orthoacetate (7.52 mL, 41.2 mmol) was added propionic acid (30.6 μ L, 0.412 mmol) at room temperature. The reaction mixture was warmed up to 155 °C and stirred under reflux for 3 h with removal of EtOH by distillation. After cooling down to room temperature, the mixture was diluted with Et₂O (5 mL), and the reaction was quenched with 1 M aqueous HCl solution (5.0 mL). After stirring overnight, the mixture was extracted with Et₂O (10 mL $\times$ 4). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, hexane:EtOAc = 50:1 to 30:1) to afford **121** (853 mg, 3.58 mmol, 87% yield). The spectral data matched with those reported in literature. [38]

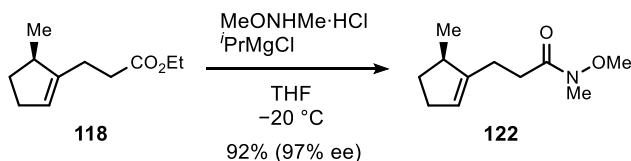
Alkenyl ester **118**



To a solution of **121** (853 mg, 3.58 mmol) in CH₂Cl₂ (10 mL) was added Grubbs catalyst[®] M2 (Umicore, 38.5 mg, 40.6 μ mol) at room temperature. The reaction mixture was then warmed up to 45 °C and stirred for 14 h. After cooling down to room temperature, the mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography (SiO₂, hexane:EtOAc = 50:1) to afford **118** (641 mg, 3.52 mmol, 98% yield).

118: pale yellow oil; ¹H NMR (500 MHz, CDCl₃) δ 5.30 (d, J = 1.7 Hz, 1H), 4.13 (q, J = 7.0 Hz, 2H), 2.60–2.53 (m, 1H), 2.52–2.37 (m, 3H), 2.30–2.13 (m, 3H), 2.12–2.05 (m, 1H), 1.42–1.35 (m, 1H), 1.25 (t, J = 7.0 Hz, 3H), 1.00 (d, J = 6.9 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 173.5, 147.2, 123.0, 60.3, 41.4, 32.74, 32.69, 30.6, 24.2, 19.2, 14.2; FT-IR (ATR) ν 2953, 2849, 1736, 1156 cm⁻¹; HRMS (FI) calcd for C₁₁H₁₈O₂ (M⁺): 182.1307, found: 182.1311; [α]_D²² = +17.55 (c 0.315, CHCl₃).

Amide **122**

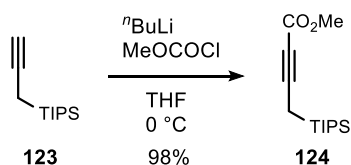


To a suspension of **118** (17.6 mg, 96.6 μ mol) and MeONHMe·HCl (14.6 mg, 0.150 mmol) in THF (0.50 mL) was added dropwise ^{*i*}PrMgCl (2.0 mol/L in THF, 0.300 mL, 0.600 mmol) at

–20 °C. After stirring for 10 min, the reaction was quenched with saturated aqueous NH_4Cl solution (0.50 mL), and the organic layer was diluted with EtOAc (0.50 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (0.50 mL $\times$ 3). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2 , hexane:EtOAc = 3:1) to afford **122** (17.5 mg, 88.7 μmol , 92% yield, 97% ee).

122: colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 5.32 (d, J = 1.7 Hz, 1H), 3.70 (s, 3H), 3.19 (s, 3H), 2.65–2.52 (m, 3H), 2.44–2.38 (m, 1H), 2.32–2.15 (m, 3H), 2.14–2.07 (m, 1H), 1.43–1.37 (m, 1H), 1.02 (d, J = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.4, 147.9, 122.7, 61.2, 41.5, 32.8, 32.2, 30.6, 30.2, 23.8, 19.3; FT-IR (ATR) ν 2951, 2848, 1664, 1415, 1384, 990 cm^{-1} ; HRMS (FD) calcd for $\text{C}_{11}\text{H}_{19}\text{NO}_2$ (M^+): 197.1416, found: 197.1415; $[\alpha]_D^{21}$ = +13.51 (c 0.345, CHCl_3).

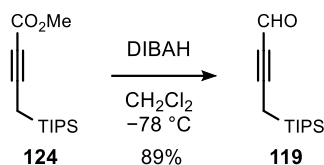
Alkynyl ester **124**



To a solution of **123** (819 mg, 4.17 mmol) in THF (12.5 mL) was added $n\text{-BuLi}$ (2.65 mol/L in hexane, 1.57 mL, 4.17 mmol) at –78 °C. After stirring for 20 min, MeOCOC1 (384 μL , 5.00 mmol) was added. The reaction mixture was then warmed up to 0 °C and stirred for 10 min. The reaction was quenched with saturated aqueous NaHCO_3 solution (10 mL), and the organic layer was diluted with EtOAc (10 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (10 mL $\times$ 3). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2 , hexane:EtOAc = 50:1 to 20:1) to afford **124** (1.04 g, 4.08 mmol, 98% yield).

124: colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 3.72 (s, 3H), 1.69 (s, 2H), 1.21–1.14 (m, 3H), 1.08 (d, J = 6.9 Hz, 18H); ^{13}C NMR (126 MHz, CDCl_3) δ 154.5, 90.5, 72.4, 52.3, 18.4 (6C), 11.0 (3C), –0.2; FT-IR (ATR) ν 2944, 2867, 2225, 1711, 1261, 1073 cm^{-1} ; HRMS (FI) calcd for $\text{C}_{14}\text{H}_{26}\text{O}_2\text{Si}$ (M^+): 254.1702, found: 254.1690.

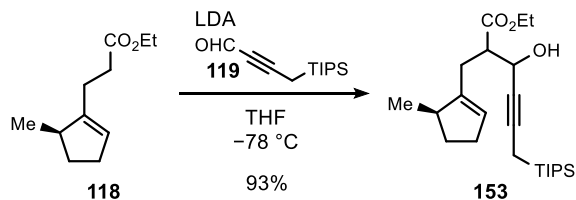
Alkynyl aldehyde **119**



To a solution of **124** (871 mg, 3.42 mmol) in CH₂Cl₂ (12.5 mL) was added DIBALH (1.0 mol/L in hexane, 4.11 mL, 4.11 mmol) at -78 °C. After stirring for 10 min, the reaction was quenched with saturated aqueous Rochelle salt solution (12.5 mL). The biphasic mixture was warmed up to room temperature and stirred vigorously for 2 h. Two layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (10 mL × 3). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, hexane:EtOAc = 50:1 to 20:1) to afford **119** (687 mg, 3.06 mmol, 89% yield).

119: colorless oil; ¹H NMR (500 MHz, CDCl₃) δ 9.12 (s, 1H), 1.80 (s, 2H), 1.22–1.14 (m, 3H), 1.09 (d, *J* = 6.9 Hz, 18H); ¹³C NMR (126 MHz, CDCl₃) δ 176.9, 101.4, 82.4, 18.4 (6C), 11.1 (3C), 0.9; FT-IR (ATR) ν 2943, 2867, 2184, 1666, 822 cm⁻¹; HRMS (FI) calcd for C₁₃H₂₄OSi (M⁺): 224.1596, found: 224.1588.

β-Hydroxyester **153**

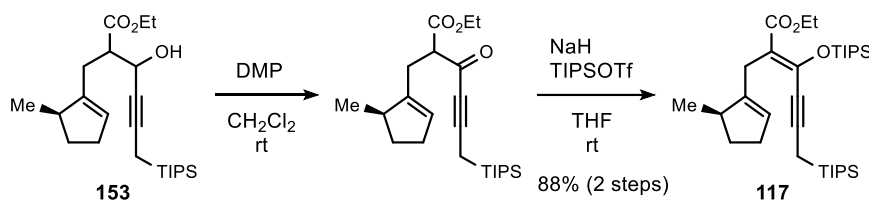


An LDA solution (ca. 1.0 mol/L in THF-hexane) was prepared by the addition of ^{*n*}BuLi (2.65 mol/L in hexane, 755 μL, 2.00 mmol) to a solution of ^{*i*}Pr₂NH (281 μL, 2.00 mmol) in THF (1.25 mL) at 0 °C. The mixture was stirred for 20 min at the same temperature before the use. To another reaction vessel charged with **118** (183 mg, 1.00 mmol) in THF (5.0 mL) was added the LDA solution (1.20 mL, 1.20 mmol) via a syringe at -78 °C. After stirring for 20 min, aldehyde **119** (269 mg, 1.20 mmol) in THF (0.50 mL) was added via cannula, and the mixture was stirred for another 10 min at the same temperature. The reaction was quenched with saturated aqueous NH₄Cl solution (5.0 mL), and the organic layer was diluted with EtOAc (5.0 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (5.0 mL × 3). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The

residue was purified by flash column chromatography (SiO₂, hexane:EtOAc = 20:1 to 3:1) to afford the product **153** (diastereomeric mixture, 379 mg, 0.931 mmol, 93% yield).

153: yellow oil; ¹H NMR (500 MHz, CDCl₃) δ 5.43–5.35 (m, 1H), 4.58–4.38 (m, 1H), 4.22–4.06 (m, 2H), 3.06 (d, *J* = 8.6 Hz, 0.3H), 2.83–2.70 (m, 1.7H), 2.67–2.48 (m, 2H), 2.45–2.25 (m, 2H), 2.19–2.05 (m, 2H), 1.57–1.54 (m, 1H), 1.43–1.35 (m, 1H), 1.33–1.21 (m, 3H), 1.20–1.06 (m, 21H), 1.03–0.99 (m, 3H) (The signal of a secondary alcohol was not assigned due to the signal overlapping)

Dienyne 117

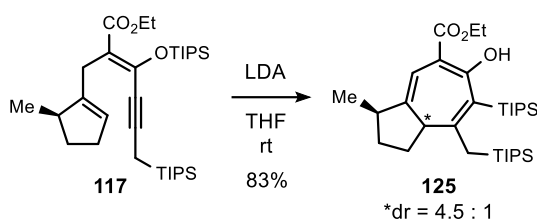


To a solution of **153** (379 mg, 0.931 mmol) in CH₂Cl₂ was added Dess-Martin periodinane (473 mg, 1.12 mmol) at 0 °C. The reaction mixture was then warmed up to room temperature and stirred for 30 min. At this time, additional Dess-Martin periodinane (118 mg, 0.279 mmol) was added, and the reaction mixture was stirred for 20 min at the same temperature. The reaction was quenched by the addition of saturated aqueous NaHCO₃ solution (5.0 mL) and Na₂S₂O₃·5H₂O (770 mg). After stirring vigorously for 50 min, the two layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (5.0 mL × 3). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was filtered through a short pad of SiO₂ (hexane:EtOAc = 10:1) to afford β -ketoester along with a small amount of impurities.

NaH (60% dispersion in mineral oil, 74.7 mg, 1.87 mmol) was washed with hexane (4.0 mL) and suspended with THF (4.0 mL). To this suspension was added above β -ketoester in THF (1.0 mL) via cannula at 0 °C. After stirring for 15 min, TIPSOTf (375 μ L, 1.40 mmol) was added. The reaction mixture was then warmed up to room temperature and stirred for 15 min. The reaction was quenched by the careful addition of saturated aqueous NaHCO₃ solution (5.0 mL), and the organic layer was diluted with EtOAc (5.0 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (5.0 mL $\times$ 3). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, hexane:EtOAc = 100:1) to afford **117** (458 mg, 0.817 mmol, 88% yield for 2 steps).

117: yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 5.24 (s, 1H), 4.13 (q, $J = 7.2$ Hz, 2H), 3.15 (d, $J = 16.0$ Hz, 1H), 3.02 (d, $J = 16.0$ Hz, 1H), 2.56–2.51 (m, 1H), 2.26–2.21 (m, 1H), 2.15–2.03 (m, 2H), 1.71 (s, 2H), 1.41–1.26 (m, 4H), 1.21 (t, $J = 7.2$ Hz, 3H), 1.17–1.08 (m, 3H), 1.11 (d, $J = 6.9$ Hz, 18H), 1.06 (d, $J = 6.9$ Hz, 18H), 1.02 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.5, 146.8, 139.9, 123.2, 115.8, 96.0, 76.4, 59.7, 41.7, 32.9, 30.5, 30.0, 19.3, 18.51 (3C), 18.49 (3C), 18.0 (6C), 14.3, 13.1 (3C), 11.0 (3C), 0.4; FT-IR (ATR) ν 2943, 2866, 2205, 1716, 1462, 1173, 881 cm^{-1} ; HRMS (FD) calcd for $\text{C}_{33}\text{H}_{60}\text{O}_3\text{Si}_2$ (M^+): 560.4081, found: 560.4068; $[\alpha]_D^{21} = +30.72$ (c 1.02, CHCl_3).

Bicyclic ester **125**

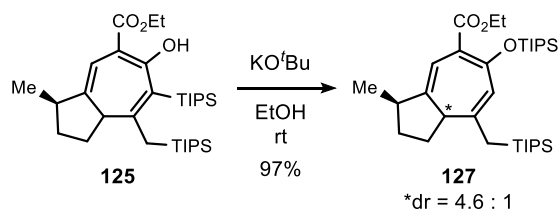


An LDA solution (ca. 1.0 mol/L in THF-hexane) was prepared by the addition of $n\text{BuLi}$ (2.65 mol/L in hexane, 755 μL , 2.00 mmol) to a solution of $i\text{Pr}_2\text{NH}$ (281 μL , 2.00 mmol) in THF (1.25 mL) at 0 $^\circ\text{C}$. The mixture was stirred for 20 min at the same temperature before the use. To another reaction vessel charged with **117** (282 mg, 0.502 mmol) in THF (5.0 mL) was added the LDA solution (1.00 mL, 1.00 mmol) via a syringe at 0 $^\circ\text{C}$. The reaction mixture was then warmed up to room temperature and stirred for 20 min. The reaction was quenched with saturated aqueous NaHCO_3 solution (5.0 mL), and the organic layer was diluted with EtOAc (5.0 mL). Two layers were separated, and the aqueous layer was extracted three times with EtOAc (5.0 mL $\times$ 3). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2 , hexane: EtOAc = 100:1) to afford **125** ($\text{dr} = 4.5:1$, 234 mg, 0.416 mmol, 83% yield). The diastereomers were inseparable even after PTLC, and the characterization data were collected as the mixture.

125: yellow semisolid; ^1H NMR (500 MHz, CDCl_3) δ 6.03 (t, $J = 1.7$ Hz, $0.82 \times 1\text{H}$), 5.92 (t, $J = 2.0$ Hz, $0.18 \times 1\text{H}$), 4.32–4.26 (m, 1H), 4.25–4.19 (m, 1H), 2.80–2.76 (m, 1H), 2.66–2.59 (m, $0.82 \times 1\text{H}$), 2.34–2.29 (m, $0.18 \times 1\text{H}$), 2.10–1.90 (m, 4H), 1.74–1.66 (m, 1H), 1.48–1.40 (m, 3H), 1.35–1.21 (m, 7H), 1.14–1.02 (m, 39H); ^{13}C NMR (126 MHz, CDCl_3) δ 177.8, 177.5, 172.4, 172.3, 168.1, 167.0, 151.3, 150.8, 127.1, 125.6, 113.1, 110.9, 103.8, 103.4, 60.4, 60.3, 48.6, 48.5, 38.0, 35.9, 35.1, 28.2, 27.3, 22.0, 20.7, 20.2, 19.9, 19.7, 19.4, 19.30, 19.26, 19.22, 17.2, 14.34, 14.31, 13.6, 13.5 (only detected signals are recorded); FT-IR (ATR) ν 2944, 2865, 1634, 1370, 1218,

1068, 880 cm^{-1} ; HRMS (FD) calcd for $\text{C}_{33}\text{H}_{60}\text{O}_3\text{Si}_2$ (M^+): 560.4081, found: 560.4069; $[\alpha]_D^{22} = +81.62$ (c 0.99, CHCl_3).

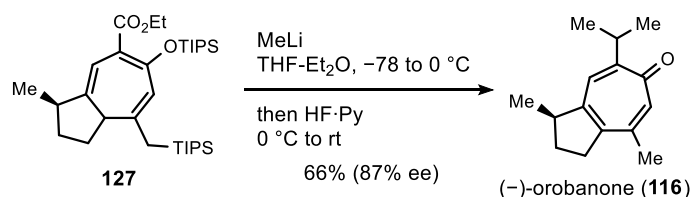
Bicyclic ester **127**



To a suspension of **125** (dr = 4.5:1, 84.5 mg, 0.151 mmol) in EtOH (0.75 mL) was added KO^tBu (1.0 mol/L in THF, 150 μL , 0.150 mmol) at room temperature. After stirring for 1.5 h, the reaction was quenched with saturated aqueous NH_4Cl solution (1.0 mL), and the resulting mixture was extracted with Et_2O (1.0 mL $\times$ 4). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2 , hexane:EtOAc = 100:1) to afford **127** (dr = 4.6:1, 81.4 mg, 0.145 mmol, 97% yield). The diastereomers were inseparable even after PTLC, and the characterization data were collected as the mixture.

127: yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 6.24 (s, $0.82 \times 1\text{H}$), 6.13 (s, $0.18 \times 1\text{H}$), 5.71 (s, 1H), 4.31–4.25 (m, 1H), 4.19–4.13 (m, 1H), 2.82–2.75 (m, $0.82 \times 1\text{H}$), 2.44–2.39 (m, $0.18 \times 1\text{H}$), 2.35 (dd, $J = 6.9, 6.9$ Hz, $0.18 \times 1\text{H}$), 2.28 (d, $J = 8.0$ Hz, $0.82 \times 1\text{H}$), 2.19 (dd, $J = 13.8, 6.3$ Hz, $0.82 \times 1\text{H}$), 2.09–1.95 (m, $1\text{H} + 0.18 \times 2\text{H}$), 1.88–1.79 (m, $1\text{H} + 0.82 \times 1\text{H}$), 1.67 (d, $J = 14.3$ Hz, $0.82 \times 1\text{H}$), 1.62 (d, $J = 13.7$ Hz, $0.18 \times 1\text{H}$), 1.40–1.29 (m, 4H), 1.26–1.15 (m, 6H), 1.11–1.06 (m, 39H); ^{13}C NMR (126 MHz, CDCl_3) δ 169.3, 169.0, 155.1, 154.7, 144.4, 143.7, 142.2, 120.1, 119.4, 117.7, 117.1, 115.2, 114.1, 60.2, 47.0, 46.6, 38.8, 38.5, 35.9, 35.2, 27.6, 26.4, 20.2, 18.7, 18.3, 18.04, 18.00, 15.3, 14.4, 13.8, 13.7, 13.4, 11.53, 11.48 (only detected signals are recorded); FT-IR (ATR) ν 2942, 2865, 1717, 1462, 1213, 881 cm^{-1} ; HRMS (FD) calcd for $\text{C}_{33}\text{H}_{60}\text{O}_3\text{Si}_2$ (M^+): 560.4081, found: 560.4080; $[\alpha]_D^{22} = -7.397$ (c 1.02, CHCl_3).

(–)-Orobanone (**116**)



To a solution of **127** (40.5 mg, 72.2 μmol) in THF (0.72 mL) was added MeLi (1.13 mol/L in Et₂O, 0.319 mL, 0.361 mmol) at $-78\text{ }^{\circ}\text{C}$. The reaction mixture was then warmed up to $0\text{ }^{\circ}\text{C}$ and stirred for 10 min. To this mixture was added dropwise HF·pyridine (HF: 67%, 0.180 mL), and the resulting suspension was stirred vigorously for 30 min at $0\text{ }^{\circ}\text{C}$. The mixture was then warmed up to room temperature and stirred for 21 h. The reaction was quenched by the careful addition of saturated aqueous NaHCO₃ solution (1.0 mL), and the mixture was neutralized with additional NaHCO₃ (powder). The organic layer was diluted with EtOAc (1.0 mL), then the two layers were separated, and the aqueous layer was extracted with EtOAc (1.0 mL $\times$ 3). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, hexane:EtOAc = 10:1 to 3:1) to afford **116** (10.3 mg, 47.6 μmol , 66% yield, 87% ee).

116: pale brown solid; ¹H NMR (500 MHz, CDCl₃) δ 7.10 (s, 1H), 7.00 (s, 1H), 3.47 (sept, J = 6.9 Hz, 1H), 3.22–3.15 (m, 1H), 2.92–2.85 (m, 1H), 2.80–2.74 (m, 1H), 2.22 (s, 3H), 2.21 (dddd, J = 12.6, 8.5, 8.5, 6.2 Hz, 1H), 1.59 (dddd, J = 12.6, 8.6, 6.0, 6.0 Hz, 1H), 1.24 (d, J = 7.4 Hz, 3H), 1.18 (d, J = 6.5 Hz, 3H), 1.16 (d, J = 6.5 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 185.4, 158.2, 149.8, 145.6, 144.7, 138.9, 129.8, 44.9, 34.5, 30.7, 29.8, 25.1, 22.6 (2C), 20.5; FT-IR (ATR) ν 2956, 2868, 1614, 1561, 1516, cm^{-1} ; HRMS (FI) calcd for C₁₅H₂₀O (M⁺): 216.1514, found: 216.1525; m.p. (hexane) 48–53 $^{\circ}\text{C}$; $[\alpha]_D^{19}$ = -4.114 (c 0.25, MeOH).

lit. ^[37] $[\alpha]_D^{20}$ = -5.21 (c 0.15, MeOH)

Chapter 3

Enhancing the Scope of Dienyne Cyclization: Synthetic Attempts toward Cyathin A₃

Introduction

Through the total syntheses of two different natural sesquiterpenoids described in chapter 1 and 2, the synthetic utility of current anionic cyclization method was clearly indicated. These successful results have provided opportunities for further application of this method to the construction of highly complex natural product scaffolds. By considering the substitution patterns of currently accessible seven-membered cyclic motifs and natural products, a series of cyathane diterpenoids were selected as the suitable synthetic target. Cyathane diterpenoid is a family of natural products that consists of over 170 compounds.^[53] They possess a common 7-6-5 fused tricyclic carbon skeleton and two *anti*-oriented quaternary carbon atoms at the C6 and C9 bridgehead positions (Figure 4). Among them, cyathin A₃ (**154**)^[54] possesses a characteristic γ,γ' -dihydroxylated enone substructure on the seven-membered ring, which resembles the 1,4-dioxygenated motif **94** obtained by an *m*CPBA oxidation of cycloheptatriene **86b** (See scheme 38 in chapter 2).

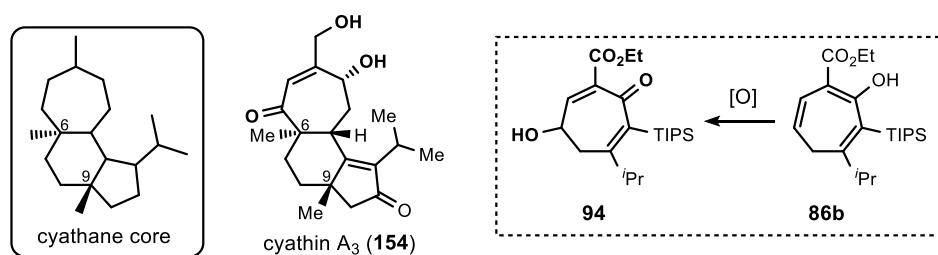
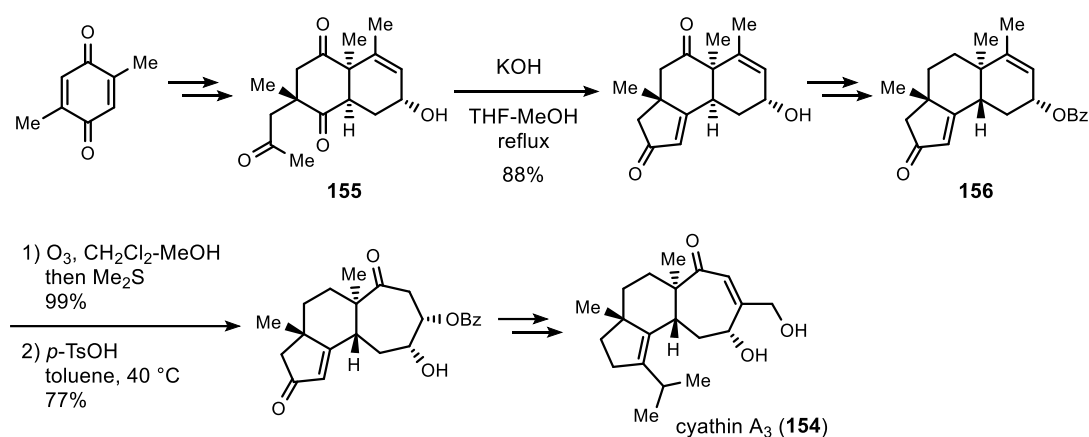


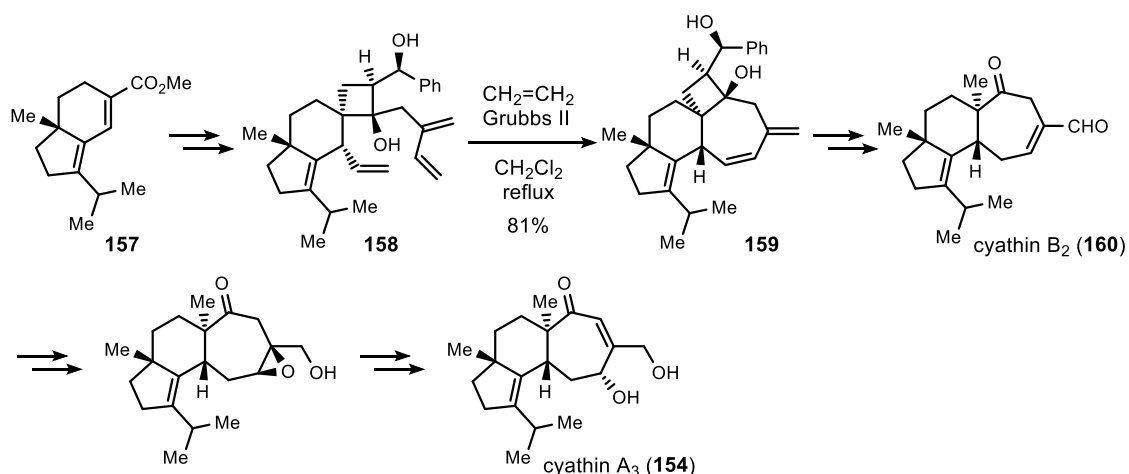
Figure 4. Structure of cyathin A₃ and its functional group similarity to ketoester **94**

There are several preceding synthetic reports of cyathin A₃. In 2007, Ward and coworkers reported the first total synthesis of this compound (Scheme 51).^[55] They constructed the fused 6-5 ring system by an intramolecular aldol condensation reaction of triketone **155**. The seven-membered ring was also constructed by intramolecular aldol reaction of ketoaldehyde that arose from ozonolysis of allyl benzoate **156**. Further manipulation to convert the benzoate moiety to an allylic alcohol completed the total synthesis. In 2009, Cha and coworkers reported another synthetic route to this natural product (Scheme 52).^[56] Starting from a known bicyclic ester **157**,

[57] construction of a spirofused cyclobutane ring followed by ring-closing metathesis of **158** afforded tetracyclic compound **159**, a key intermediate of natural product cyathin B₂ (**160**). After further transformations to convert the enal moiety to allylic 1,3-diols, total synthesis of cyathin A₃ was also achieved. It should be noted that these synthetic routes were also applicable to enantioselective synthesis of other related natural products, while more than 25-long steps were required to obtain the final product **154** from commercial sources.



Scheme 51. Ward's total synthesis of cyathin A₃

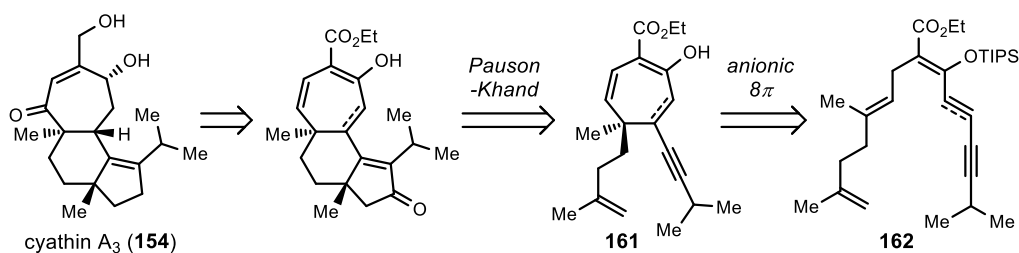


Scheme 52. Cha's total synthesis of cyathin A₃

Results and Discussion

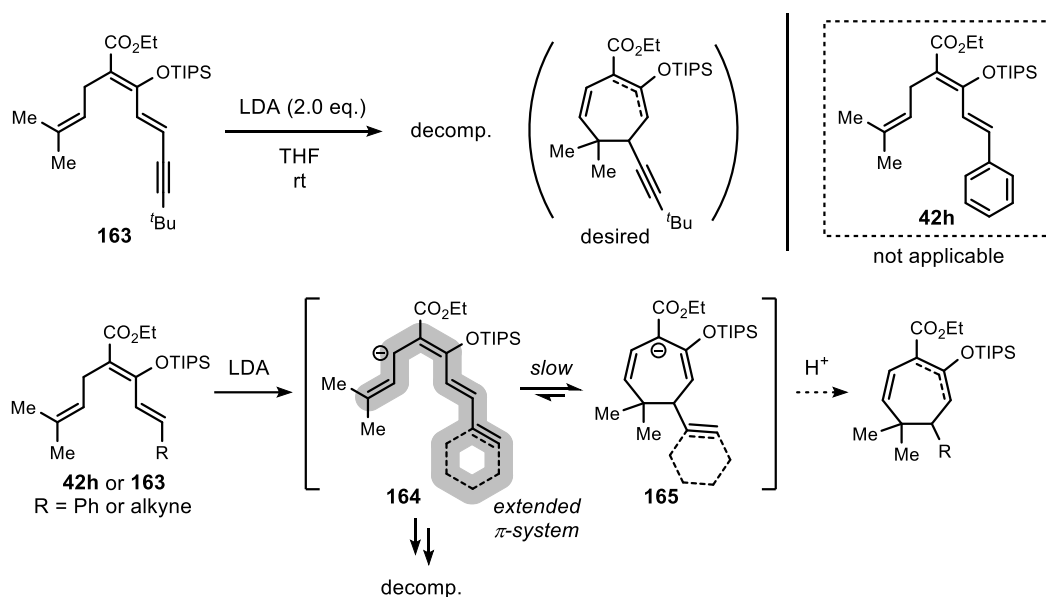
With a view to achieving a short-step synthesis of this natural product, a retrosynthetic analysis was conducted as follows (Scheme 53). The tricyclic skeleton would be accessible by construction of the 6-5 bicyclic skeleton by the Pauson-Khand reaction between the side chains on a seven-

membered ring. To prepare the Pauson-Khand precursor **161** through an anionic 8π -electrocyclization, the substrate **162** possessing a long, branched alkene side chain and a conjugated alkyne moiety was designed. Since the conventional substrates did not have an additional conjugated alkyne moiety, the cyclization reaction seemed a little bit challenging.



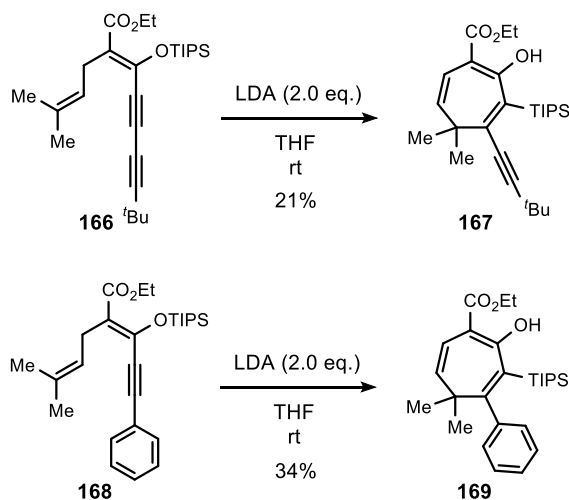
Scheme 53. Retrosynthetic analysis of cyathin A₃

The first cyclization study was performed using trienyne **163** as a model substrate of **162** (Scheme 54). The reaction with 2.0 equiv. of LDA, however, resulted in decomposition of the substrate. It is noteworthy that the behavior of substrate **163** is similar with that of substrate **42h** possessing a phenyl group (See Scheme 20 in chapter 1). These substrates possess an extended π -conjugation system, which would strongly stabilize the intermediate conjugate anion. Therefore, it was proposed that a linear-conjugate anion **164** was too stabilized, which decreased the reaction rate of cyclization and led to decomposition before forming cyclic anion **165**.



Scheme 54. Unsuccessful cyclization of trienyne **163**

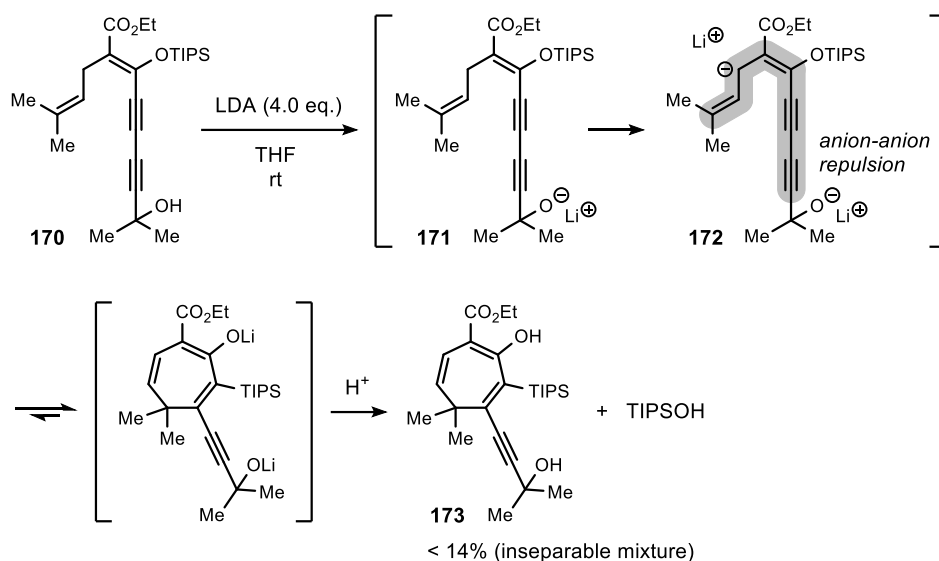
By considering that a terminal phenyl group was tolerated in the cyclization of dienyne-type substrate (See Scheme 35 in chapter 2), the anionic cyclization of dienediynes **166** was tested (Scheme 55). As was expected, the desired cyclic product **167** was obtained, albeit in 21% yield. When a corresponding phenyl-substituted dienyne **168** was subjected to the same reaction conditions, the cyclized product **169** was obtained as well in 34% yield. These results proved that a dienyne-type substrate is more suitable for this type of anionic cyclization, although the product yields were not sufficient.



Scheme 55. Different reactivities in the cyclization of substrates **166** and **168**

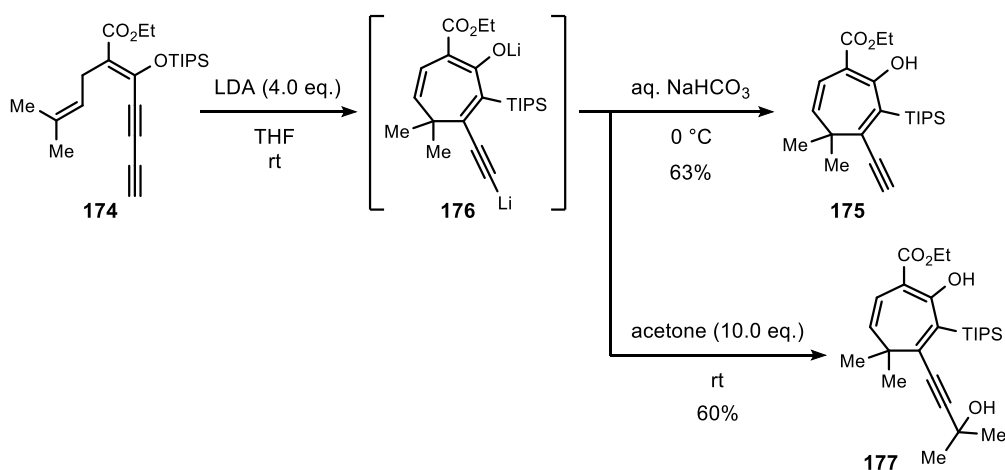
For more efficient cyclization reactions, it requires some modifications on the substrate to decrease the stability of the linear-conjugated anion intermediate. An alkyne-dicobalt complex is known as a protected form of the corresponding alkyne, but it is incompatible with the basic conditions for the anionic cyclization. On the other hand, an additional negative charge to the anionic species, which generates a less stable dianion intermediate, was expected to facilitate the cyclization reaction.

Based on this hypothesis, a dienediynone substrate **170** possessing a tertiary alcohol moiety at the alkyne terminus was designed (Scheme 56). Under strong basic conditions, this substrate would undergo fast deprotonation at the tertiary alcohol moiety to form alkoxide **171**. Then, the second deprotonation would occur at the bis-allylic position to form dianion **172** which might undergo smooth cyclization. Upon treatment with 4.0 equiv. of LDA, substrate **170** underwent cyclization reaction via dianion species **172**; however, the desired product **173** was obtained in < 14% yield as an inseparable mixture with silanol. The result suggests that the tertiary alkoxide has little destabilizing effect on the linear π -conjugation system.



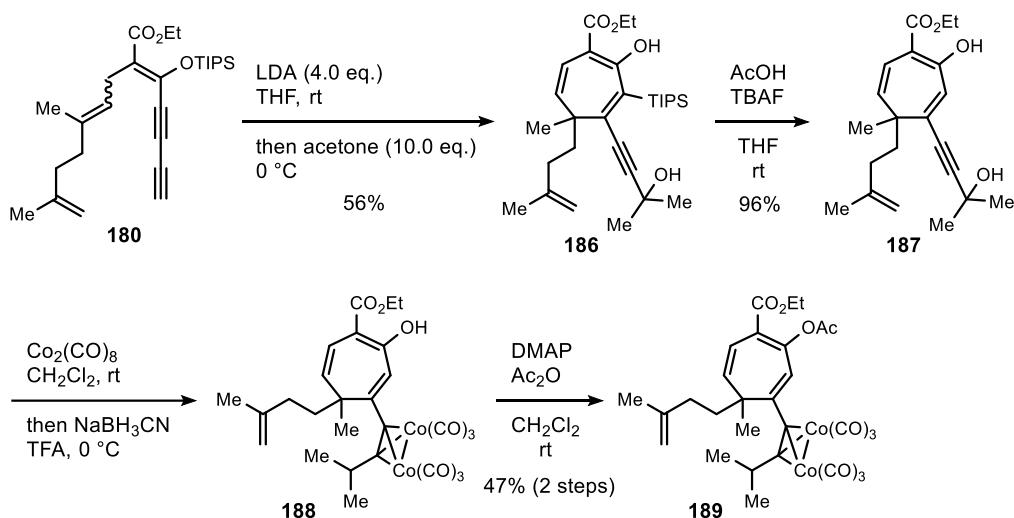
Scheme 56. Anionic cyclization of dienediyne **170** possessing a tertiary alcohol

In pursuit of more effective destabilization by forming a dianion, in situ preparation of a metal acetylide at the alkyne terminus was planned (Scheme 57). Accordingly, a dienediyne substrate **174** possessing a free terminal proton was prepared as the precursor of the dianion. To the author's delight, treatment of **174** with 4.0 equiv. of LDA afforded the desired cyclization product **175** in 63% yield. In addition, the resulting cyclic dianion **176** reacted with acetone at the acetylide moiety, giving rise to tertiary alcohol **177** in 60% yield.



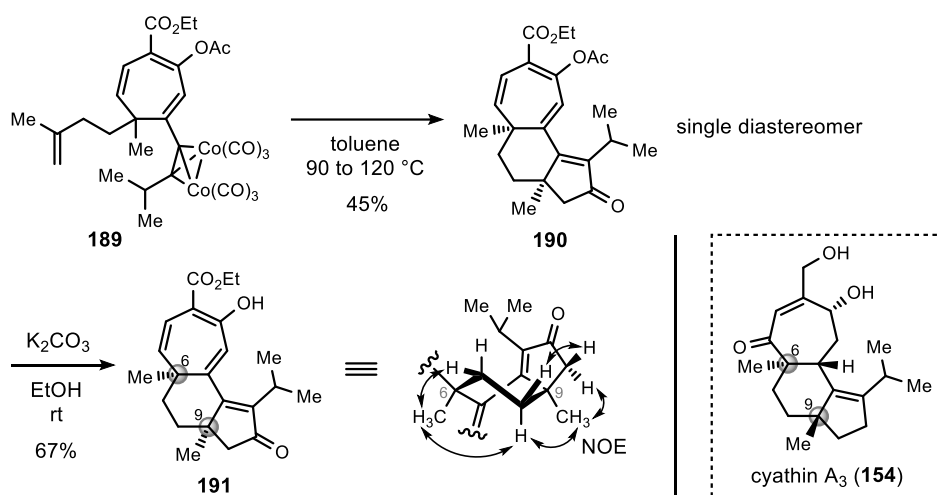
Scheme 57. Anionic cyclization of dienediyne **174** possessing a terminal alkyne

TIPS group decreasing the reaction rate. After removal of the TIPS group by acetic acid and TBAF followed by conversion to the alkyne-dicobalt complex, one-pot deoxygenation was conducted under modified Nicolas' conditions^[59] to obtain product **188** possessing an isopropyl group. Subsequently, the enol moiety on the seven-membered ring was protected as an acetate to afford **189** in 47% yield for 2 steps.

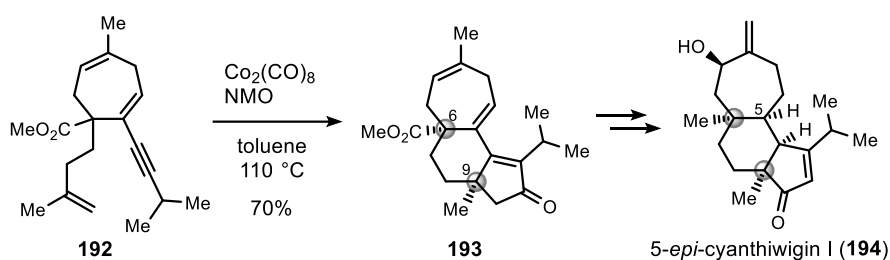


Scheme 60. Anionic cyclization of **180** and synthesis of alkyne-dicobalt complex **189**

With the acetylene-dicobalt complex **189** in hand, construction of the tricyclic skeleton was investigated (Scheme 61). By heating at reflux temperature in toluene, the substrate **189** underwent the Pauson-Khand reaction to afford tricyclic ketone **190** in 45% yield as a single diastereomer. After deprotection of the enol acetate moiety, the stereochemistry of the product **191** was determined by an NOE correlation study. Unfortunately, the C6 and C9 methyl groups were found to be arranged in *syn*-relationship with each other, which was opposite to that of the target compound. Literature study revealed that a similar stereoselectivity was observed in a precedent report made by Yang and coworkers in 2018 (Scheme 62).^[60] In their report, enyne **192** was subjected to an NMO-facilitated Pauson-Khand reaction to afford a tricyclic compound **193** with *syn*-configuration at C6 and C9 carbons, which was utilized in the total synthesis of 5-*epi*-cyanthiwigin I (**194**).



Scheme 61. Construction of a tricyclic skeleton via Pauson-Khand reaction



Scheme 62. Yang's synthetic intermediate of 5-*epi*-cyanthiwigin I

Conclusion

In conclusion, a facile anionic 8π -electrocyclization of a β -ketoester-derived dienediyne was achieved by generating a dianion species from a terminal alkyne substrate. The cyclic compound was further applied to a Pauson-Khand reaction to construct a tricyclic skeleton of cyathane diterpenoids, while the relative stereochemistry of two methyl groups was opposite to that of the natural product.

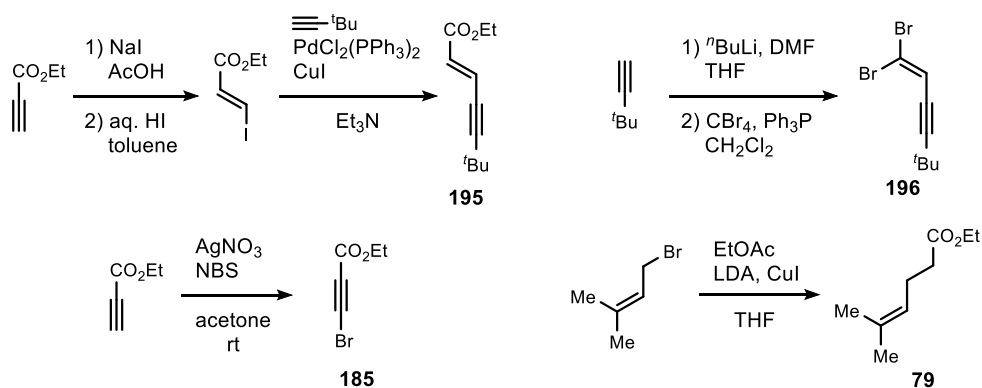
Experimental Section

General Information

All reactions were performed using flame-dried glassware under a positive pressure of argon unless otherwise noted. Reactions at elevated temperatures were performed under heating in an oil bath. THF was distilled from sodium benzophenone ketyl. Other anhydrous solvents were purchased from chemical companies. $i\text{Pr}_2\text{NH}$ was distilled from CaH_2 under argon and stored in the presence of NaOH (pellets). All other reagents were used as received from commercial sources without further purification.

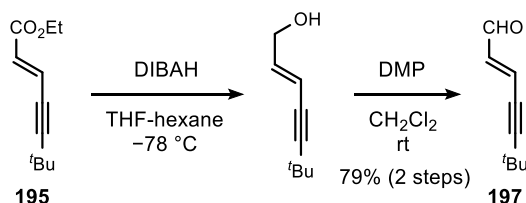
^1H NMR spectra were recorded on JEOL ECA-500 (500 MHz) in CDCl_3 (δ_{H} 7.26). Chemical shifts are reported in parts per million (ppm), and signals are expressed as broad (br), singlet (s), doublet (d), triplet (t), quartet (q), septet (sept), and multiplet (m). Coupling constants are reported in Hz. Analytical TLC was performed using Silica Gel 60 F₂₅₄ (E. Merck). Reaction components were visualized by illumination with UV light (254 nm) and by staining with 8% ethanolic phosphomolybdic acid, ceric ammonium molybdate in 10% sulfuric acid, or basic potassium permanganate aqueous solution. Flash column chromatography was performed on Chromatorex PSQ60B (Fuji Silysia Chemical Ltd.).

Enynyl ester **195**,^[61] dibromoenyne **196**,^[62] bromoester **185**,^[58] and alkenyl ester **79**^[30] were prepared by known procedures.



Experimental and Characterization Details

Enynyl aldehyde **197**

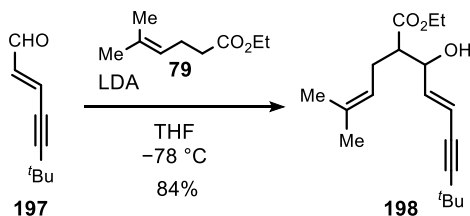


To a solution of **195** (157 mg, 0.869 mmol) in THF (1.8 mL) was added DIBALH (1.03 mol/L in hexane, 2.53 mL, 2.61 mmol) at -78 °C. After stirring for 10 min, the reaction was quenched with saturated aqueous Rochelle salt solution (6.0 mL), and the biphasic mixture was stirred vigorously overnight. Two layers were separated, and the aqueous layer was extracted with EtOAc (5.0 mL $\times$ 3). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure to obtain crude alcohol.

To a solution of above crude alcohol in CH₂Cl₂ (4.3 mL) was added Dess-Martin periodinane (439 mg, 1.03 mmol) at 0 °C. After stirring for 20 min, the reaction was quenched with saturated aqueous NaHCO₃ solution (5.0 mL) and Na₂S₂O₃·5H₂O (438 mg), and the biphasic mixture was stirred vigorously for > 30 min. Two layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (5.0 mL $\times$ 3). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was filtered through a short pad of SiO₂ (hexane + EtOAc) to afford **197** (93.7 mg, 0.688 mmol, 79% yield for 2 steps).

197: yellow oil; ¹H NMR (500 MHz, CDCl₃) δ 9.53 (d, J = 7.9 Hz, 1H), 6.60 (d, J = 15.9 Hz, 1H), 6.37 (q, J = 15.9, 7.9 Hz, 1H), 1.29 (s, 9H)

β -Hydroxyester **198**

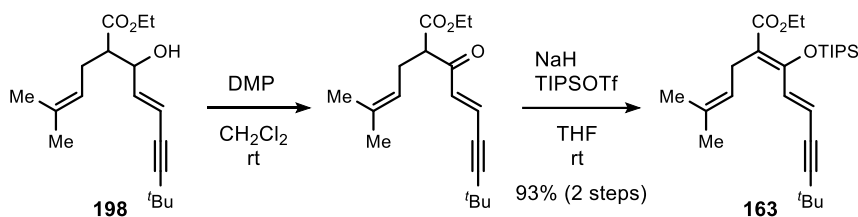


An LDA solution (ca. 1.0 mol/L in THF-hexane) was prepared by the addition of ^{*n*}BuLi (2.64 mol/L in hexane, 758 μ L, 2.00 mmol) to a solution of ^{*i*}Pr₂NH (281 μ L, 2.00 mmol) in THF (1.24 mL) at 0 °C. The mixture was stirred for 20 min at the same temperature before the use. To another reaction vessel charged with **79** (130 mg, 0.832 mmol) in THF (3.4 mL) was added the LDA solution (894 μ L, 0.894 mmol) via a syringe at -78 °C. After stirring for 20 min, **197** (93.7 mg,

0.688 mmol) in THF (0.50 mL) was added via cannula, and the reaction mixture was stirred for another 15 min at the same temperature. The reaction was quenched with saturated aqueous NH_4Cl solution (3.0 mL), and the organic layer was diluted with EtOAc (3.0 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (3.0 mL $\times$ 3). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2 , hexane:EtOAc = 10:1 to 3:1) to afford **198** (dr = 1.3:1, 168 mg, 0.575 mmol, 84% yield).

198: pale yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 6.01 (dd, J = 6.3, 1.7 Hz, 0.43H), 5.98 (dd, J = 5.7, 1.5 Hz, 0.57H), 5.76 (dd, J = 1.5, 1.3 Hz, 0.57H), 5.73 (dd, J = 1.7, 1.5 Hz, 0.43H), 5.09–5.04 (m, 1H), 4.36 (ddd, J = 5.5, 5.1, 1.5 Hz, 0.43H), 4.24 (ddd, J = 6.7, 6.7, 1.3 Hz, 0.57H), 4.20–4.10 (m, 2H), 2.73 (d, J = 6.7 Hz, 0.57H), 2.62 (d, J = 5.1 Hz, 0.43H), 2.55 (dt, J = 8.7, 5.5 Hz, 0.43H), 2.48 (dt, J = 6.9, 6.7 Hz, 0.57H), 2.44–2.24 (m, 2H), 1.68 (s, 3H), 1.61 (s, 3H), 1.26 (t, J = 6.8 Hz, $0.43 \times 3\text{H}$), 1.25 (t, J = 7.3 Hz, $0.57 \times 3\text{H}$), 1.23 (s, 9H)

Trienyne 163



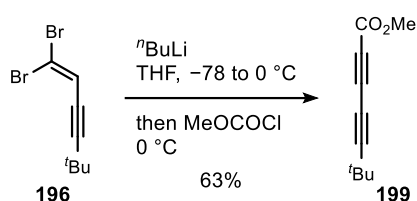
To a solution of **198** (168 mg, 0.575 mmol) in CH_2Cl_2 (2.7 mL) was added Dess-Martin periodinane (276 mg, 0.651 mmol) at 0 °C. The reaction mixture was then warmed up to room temperature and stirred for 40 min. The reaction was quenched with saturated aqueous NaHCO_3 solution (3.0 mL) and $\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$ (534 mg), and the biphasic mixture was stirred vigorously for > 30 min. Two layers were separated, and the aqueous layer was extracted with EtOAc (3.0 mL $\times$ 3). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. Highly polar components were filtered off through a short pad of SiO_2 (hexane:EtOAc = 5:1) to afford β -ketoester along with a small amount of impurities.

NaH (60% dispersion in mineral oil, 42.7 mg, 1.07 mmol) was washed with hexane and suspended with THF (2.7 mL). To this suspension was added above β -ketoester in THF (0.50 mL) via cannula at 0 °C. After stirring for 10 min, TIPSOTf (215 μL , 0.799 mmol) was added. The reaction mixture was then warmed up to room temperature and stirred for 15 min. The reaction was quenched by the careful addition of saturated aqueous NaHCO_3 solution (2.5 mL), and the organic layer was diluted with EtOAc (2.5 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (2.5 mL $\times$ 3). The combined organic layers were dried over MgSO_4 , filtered, and

concentrated under reduced pressure. The residue was purified by flash column chromatography [SiO_2 (neutralized by the elution of *N,N*-dimethylaniline), hexane:EtOAc = 100:1] to afford **163** (238 mg, 0.532 mmol, 93% yield for 2 steps).

163: yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 6.64 (d, J = 15.8 Hz, 1H), 6.03 (d, J = 15.8 Hz, 1H), 5.03 (t, J = 7.2 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 3.02 (d, J = 7.2 Hz, 2H), 1.67 (s, 3H), 1.66 (s, 3H), 1.27–1.16 (m, 6H), 1.26 (s, 9H), 1.09 (d, J = 6.9 Hz, 18H)

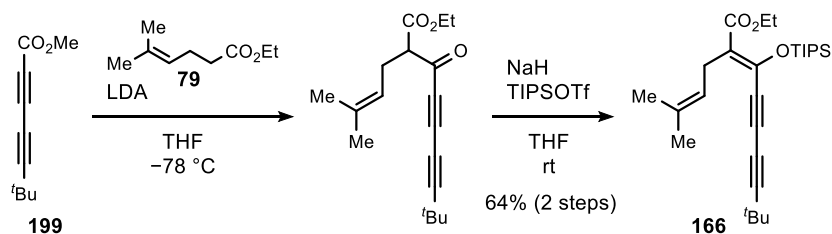
Diyne 199



To a solution of **196** (688 mg, 2.59 mmol) in THF (10 mL) was added $n\text{-BuLi}$ (1.51 mol/L in hexane, 4.23 mL, 6.46 mmol) at $-78\text{ }^\circ\text{C}$, and the mixture was stirred for 10 min. The reaction mixture was then warmed up to $0\text{ }^\circ\text{C}$ and stirred for another 20 min. To this mixture was added MeOCOCl (397 μL , 5.27 mmol), and the reaction mixture was stirred for 10 min at the same temperature. The reaction was quenched with saturated aqueous NaHCO_3 solution (10 mL), and the organic layer was diluted with Et_2O (10 mL). Two layers were separated, and the aqueous layer was extracted with Et_2O (10 mL $\times$ 3). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2 , hexane:EtOAc = 100:1) to afford **199** (268 mg, 1.63 mmol, 63% yield).

199: dark orange oil; ^1H NMR (500 MHz, CDCl_3) δ 3.78 (s, 3H), 1.27 (s, 9H)

Dienediyne 166



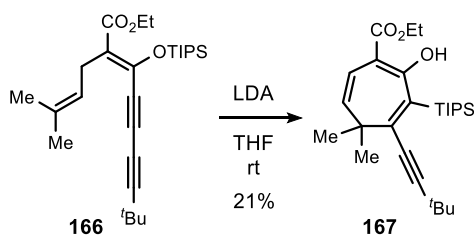
An LDA solution (ca. 1.0 mol/L in THF-hexane) was prepared by the addition of $n\text{-BuLi}$ (2.66 mol/L in hexane, 752 μL , 2.00 mmol) to a solution of $i\text{-Pr}_2\text{NH}$ (281 μL , 2.00 mmol) in THF (1.25 mL) at $0\text{ }^\circ\text{C}$. The mixture was stirred for 20 min at the same temperature before the use. To another reaction vessel charged with **79** (92.2 mg, 0.590 mmol) in THF (2.5 mL) was added the LDA

solution (1.50 mL, 1.50 mmol) via a syringe at $-78\text{ }^{\circ}\text{C}$. After stirring for 10 min, **199** (82.6 mg, 0.503 mmol) in THF (0.50 mL) was added via cannula, and the mixture was stirred for 20 min at the same temperature. The reaction was quenched with saturated aqueous NH_4Cl solution (2.5 mL), and the organic layer was diluted with EtOAc (2.5 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (2.5 mL $\times$ 3). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2 , hexane:EtOAc = 10:1) to afford β -ketoester along with byproducts.

NaH (55% dispersion in paraffin, 43.1 mg, 0.988 mmol) was washed with hexane and suspended with THF (2.0 mL). To this suspension was added above β -ketoester in THF (0.50 mL) via cannula at $0\text{ }^{\circ}\text{C}$. After stirring for 10 min, TIPSOTf (202 μL , 0.750 mmol) was added, and the reaction mixture was stirred for 20 min at the same temperature. The reaction was quenched by the careful addition of saturated aqueous NaHCO_3 solution (2.5 mL), and the organic layer was diluted with EtOAc (2.5 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (2.5 mL $\times$ 3). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2 , hexane:EtOAc = 100:1) to afford **166** as a mixture with **79**. This mixture was further purified by flash column chromatography (SiO_2 , hexane:toluene = 5:1 to 3:1) to afford pure **166** (143 mg, 0.322 mmol, 64% yield for 2 steps).

166: yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 5.08 (t, $J = 7.1\text{ Hz}$, 1H), 4.17 (q, $J = 7.1\text{ Hz}$, 2H), 3.12 (d, $J = 7.1\text{ Hz}$, 2H), 1.68 (s, 6H), 1.32–1.20 (m, 6H), 1.27 (s, 9H), 1.10 (d, $J = 7.4\text{ Hz}$, 18H)

Cycloheptatriene **167**

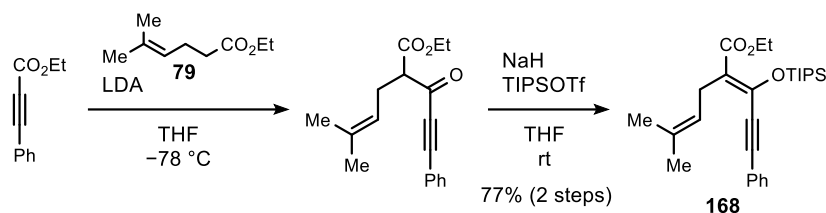


An LDA solution (ca. 1.0 mol/L in THF-hexane) was prepared by the addition of $n\text{BuLi}$ (2.66 mol/L in hexane, 752 μL , 2.00 mmol) to a solution of $i\text{Pr}_2\text{NH}$ (281 μL , 2.00 mmol) in THF (1.25 mL) at $0\text{ }^{\circ}\text{C}$. The mixture was stirred for 20 min at the same temperature before the use. To another reaction vessel charged with **166** (22.1 mg, 49.7 μmol) in THF (0.50 mL) was added the LDA solution (100 μL , 100 μmol) via a syringe at $0\text{ }^{\circ}\text{C}$. The reaction mixture was then warmed up to room temperature and stirred for 20 min. The reaction was quenched with saturated aqueous NaHCO_3 solution (0.50 mL), and the organic layer was diluted with EtOAc (0.50 mL). Two layers

were separated, and the aqueous layer was extracted with EtOAc (0.50 mL $\times$ 3). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, hexane:EtOAc = 100:1) to afford **167** (4.7 mg, 11 μ mol, 21% yield).

167: yellow oil; ¹H NMR (500 MHz, CDCl₃) δ 6.37 (d, J = 10.3 Hz, 1H), 5.22 (d, J = 10.3 Hz, 1H), 4.27 (q, J = 7.2 Hz, 2H), 1.77 (sept, J = 7.2 Hz, 3H), 1.35 (t, J = 7.2 Hz, 3H), 1.25 (s, 9H), 1.12–1.02 (m, 24H)

Dienyne 168



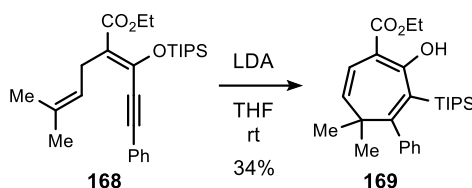
An LDA solution (ca. 1.0 mol/L in THF-hexane) was prepared by the addition of *n*BuLi (2.65 mol/L in hexane, 755 μ L, 2.00 mmol) to a solution of *i*Pr₂NH (281 μ L, 2.00 mmol) in THF (1.25 mL) at 0 $^{\circ}$ C. The mixture was stirred for 20 min at the same temperature before the use. To another reaction vessel charged with **79** (93.6 mg, 0.599 mmol) in THF (2.5 mL) was added the LDA solution (1.20 mL, 1.20 mmol) via a syringe at $-78\text{ }^{\circ}\text{C}$. After stirring for 10 min, ethyl phenylpropiolate (82.2 μ L, 0.500 mmol) was added, and the mixture was stirred for 10 min at the same temperature. Crushed dry ice was added to trap the excessive enolate, and the mixture was stirred under ambient temperature until the evolution of CO₂ gas ceased. The reaction was quenched with saturated aqueous NaHCO₃ solution (2.5 mL), and the organic layer was diluted with EtOAc (2.5 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (2.5 mL $\times$ 3). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, hexane:EtOAc = 10:1) to afford β -ketoester along with byproducts.

NaH (60% dispersion in mineral oil, 40.4 mg, 1.01 mmol) was washed with hexane and suspended with THF (2.0 mL). To this suspension was added above β -ketoester in THF (0.50 mL) via cannula at 0 $^{\circ}$ C. After stirring for 10 min, TIPSOTf (202 μ L, 0.750 mmol) was added. The reaction mixture was then warmed up to room temperature and stirred for 10 min. The reaction was quenched by the careful addition of saturated aqueous NaHCO₃ solution (2.5 mL), and the organic layer was diluted with EtOAc (2.5 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (2.5 mL $\times$ 3). The combined organic layers were dried over MgSO₄, filtered, and

concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, hexane:EtOAc = 100:1) to afford **168** (170 mg, 0.386 mmol, 77% yield for 2 steps).

168: yellow oil; ¹H NMR (500 MHz, CDCl₃) δ 7.45–7.43 (m, 2H), 7.38–7.34 (m, 3H), 5.17 (t, *J* = 7.3 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.22 (d, *J* = 7.3 Hz, 2H), 1.69 (s, 3H), 1.68 (s, 3H), 1.36 (sept, *J* = 7.4 Hz, 3H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.14 (d, *J* = 7.4 Hz, 18H)

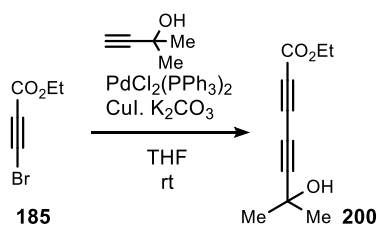
Cycloheptatriene **169**



An LDA solution (ca. 1.0 mol/L in THF-hexane) was prepared by the addition of ^{*n*}BuLi (2.65 mol/L in hexane, 755 μL, 2.00 mmol) to a solution of ^{*i*}Pr₂NH (281 μL, 2.00 mmol) in THF (1.25 mL) at 0 °C. The mixture was stirred for 20 min at the same temperature before the use. To another reaction vessel charged with **168** (43.7 mg, 99.2 μmol) in THF (1.0 mL) was added the LDA solution (200 μL, 200 μmol) via a syringe at 0 °C. The reaction mixture was then warmed up to room temperature and stirred for 20 min. The reaction was quenched with saturated aqueous NaHCO₃ solution (1.0 mL), and the organic layer was diluted with EtOAc (1.0 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (1.0 mL × 3). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, hexane:EtOAc = 100:1) to afford **169** (14.9 mg, 33.8 μmol, 34% yield).

169: yellow oil; ¹H NMR (500 MHz, CDCl₃) δ 7.29–7.23 (m, 2H), 7.21–7.15 (m, 2H), 6.95 (d, *J* = 7.4 Hz, 1H), 6.51 (d, *J* = 10.0 Hz, 1H), 5.28 (d, *J* = 10.0 Hz, 1H), 4.35–4.24 (m, 2H), 1.37 (t, *J* = 7.2 Hz, 3H), 0.95–0.91 (m, 12H), 0.89 (d, *J* = 7.4 Hz, 9H), 0.80 (s, 3H), 0.70 (sept, *J* = 7.4 Hz, 3H)

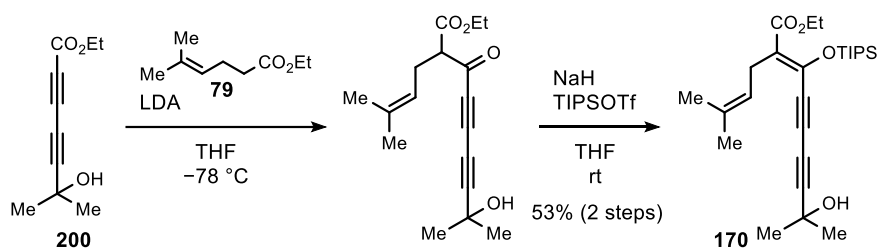
Diyne **200**



To a solution of **185** (177 mg, 1.00 mmol) in THF were added successively $\text{PdCl}_2(\text{PPh}_3)_2$ (14.5 mg, 20.7 μmol), CuI (8.1 mg, 43 μmol), and K_2CO_3 (347 mg, 2.51 mmol) at room temperature, and the resulting mixture was degassed by argon bubbling. To this mixture was added 2-methyl-3-butyne-2-ol (147 μL , 1.50 mmol), and the reaction mixture was stirred for 17 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl solution (5.0 mL), and the organic layer was diluted with EtOAc (5.0 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (5.0 mL $\times$ 3). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2 , hexane: EtOAc = 3:1) to afford **200** (119 mg, 0.659 mmol, 66% yield, containing ca. 9% EtOAc).

200: orange oil; ^1H NMR (500 MHz, CDCl_3) δ 4.25 (q, J = 7.2 Hz, 2H), 2.00 (s, 1H), 1.56 (s, 6H), 1.31 (t, J = 7.2 Hz, 3H)

Dienediynne 170

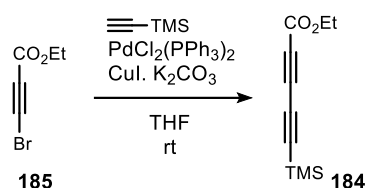


An LDA solution (ca. 1.0 mol/L in THF-hexane) was prepared by the addition of $n\text{BuLi}$ (2.65 mol/L in hexane, 755 μL , 2.00 mmol) to a solution of $i\text{Pr}_2\text{NH}$ (281 μL , 2.00 mmol) in THF (1.25 mL) at 0 °C. The mixture was stirred for 20 min at the same temperature before the use. To another reaction vessel charged with **200** (35.7 mg, 0.198 mmol) and **79** (37.5 mg, 0.240 mmol) in THF (2.0 mL) was added the LDA solution (900 μL , 0.900 mmol) via a syringe at -78 °C. After stirring for 15 min, the reaction was quenched with saturated aqueous NH_4Cl solution (2.0 mL), and the organic layer was diluted with EtOAc (2.0 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (1.0 mL $\times$ 3). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2 , hexane: EtOAc = 5:1 to 2:1) to afford β -ketoester along with byproducts. NaH (60% dispersion in mineral oil, 15.8 mg, 0.395 mmol) was washed with hexane and suspended with THF (1.0 mL). To this suspension was added above β -ketoester in THF (0.50 mL) via cannula at 0 °C. After stirring for 10 min, TIPSOTf (80.6 μL , 0.300 mmol) was added, and the reaction mixture was stirred for 5 min at the same temperature. The reaction was quenched by the careful addition of saturated aqueous NaHCO_3 solution (1.0 mL), and the organic layer was

diluted with EtOAc (1.0 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (1.0 mL $\times$ 3). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, hexane:EtOAc = 20:1 to 5:1) to afford **170** (47.1 mg, 0.105 mmol, 53% yield for 2 steps).

170: yellow oil; ¹H NMR (500 MHz, CDCl₃) δ 5.07 (t, J = 7.3 Hz, 1H), 4.17 (q, J = 7.2 Hz, 2H), 3.11 (d, J = 7.3 Hz, 2H), 1.99 (s, 1H), 1.68 (s, 3H), 1.67 (s, 3H), 1.57 (s, 6H), 1.32–1.23 (m, 3H), 1.26 (t, J = 7.2 Hz, 3H), 1.10 (d, J = 7.4 Hz, 18H)

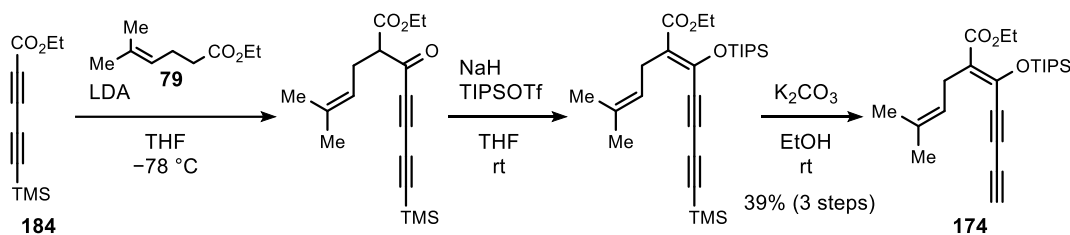
Diyne **184**



To a solution of **185** (1.64 g, 9.27 mmol) in THF were added successively PdCl₂(PPh₃)₂ (65.9 mg, 93.9 μ mol), CuI (35.2 mg, 0.185 mmol), and K₂CO₃ (3.21 g, 23.2 mmol) at room temperature, and the resulting mixture was degassed by argon bubbling. To this mixture was added trimethylsilylacetylene (1.92 mL, 13.9 mmol), and the reaction mixture was stirred for 15 h at room temperature. Additional PdCl₂(PPh₃)₂ (33.3 mg, 47.4 μ mol), CuI (17.0 mg, 89.3 μ mol), and trimethylsilylacetylene (641 μ L, 4.64 mmol) were added successively, and the reaction mixture was stirred for another 4 h at the same temperature. The reaction mixture was filtered through a pad of Celite[®], and the residue was washed with Et₂O. The filtrate was concentrated under reduced pressure and purified by flash column chromatography (SiO₂, hexane:EtOAc = 50:1) to afford **184** (1.03 g, 5.31 mmol, 57% yield).

184: brown oil; ¹H NMR (500 MHz, CDCl₃) δ 4.24 (q, J = 7.3 Hz, 2H), 1.30 (t, J = 7.3 Hz, 3H), 0.22 (s, 9H)

Dienediynes **174**



An LDA solution (ca. 1.0 mol/L in THF-hexane) was prepared by the addition of ⁿBuLi (2.65 mol/L in hexane, 755 μ L, 2.00 mmol) to a solution of ⁱPr₂NH (281 μ L, 2.00 mmol) in THF (1.25

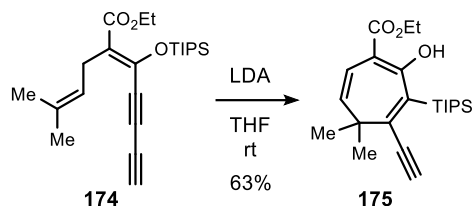
mL) at 0 °C. The mixture was stirred for 20 min at the same temperature before the use. To another reaction vessel charged with **184** (38.2 mg, 0.197 mmol) and **79** (38.2 mg, 0.244 mmol) in THF (2.0 mL) was added the LDA solution (600 μ L, 0.600 mmol) via a syringe at -78 °C. After stirring for 10 min, crushed dry ice was added to trap the excessive enolate, and the mixture was stirred under ambient temperature until the evolution of CO₂ gas ceased. The reaction was quenched with saturated aqueous NaHCO₃ solution (2.0 mL), and the organic layer was diluted with EtOAc (2.0 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (1.0 mL $\times$ 3). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, hexane:EtOAc = 10:1) to afford β -ketoester along with byproducts.

NaH (60% dispersion in mineral oil, 11.0 mg, 0.275 mmol) was washed with hexane and suspended with THF (0.50 mL). To this suspension was added above β -ketoester in THF (0.50 mL) via cannula at 0 °C. After stirring for 10 min, TIPSOTf (56.4 μ L, 0.210 mmol) was added, and the reaction mixture was stirred for 5 min at the same temperature. The reaction mixture was then warmed up to room temperature and stirred for 10 min. The reaction was quenched by the careful addition of saturated aqueous NaHCO₃ solution (1.0 mL), and the organic layer was diluted with EtOAc (1.0 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (1.0 mL $\times$ 3). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, hexane:EtOAc = 100:1) to afford TMS-dienediyne as a mixture with **174**.

To a solution of above dienediyne in EtOH (0.47 mL) was added K₂CO₃ (13.2 mg, 95.5 μ mol) at room temperature. After stirring for 30 min, brine (0.50 mL) was added, and the mixture was extracted with EtOAc (0.50 mL $\times$ 4). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, hexane:EtOAc = 100:1) to afford **174** (30.0 mg, 77.2 μ mol, 39% yield for 3 steps).

174: yellow oil; ¹H NMR (500 MHz, CDCl₃) δ 5.07 (t, J = 7.1 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 3.12 (d, J = 7.1 Hz, 2H), 2.63 (s, 1H), 1.68 (s, 3H), 1.67 (s, 3H), 1.33–1.25 (m, 3H), 1.26 (t, J = 7.2 Hz, 3H), 1.10 (d, J = 7.4 Hz, 18H)

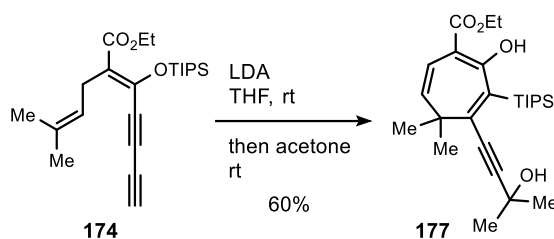
Cycloheptatriene 175



An LDA solution (ca. 1.0 mol/L in THF-hexane) was prepared by the addition of n BuLi (2.65 mol/L in hexane, 755 μ L, 2.00 mmol) to a solution of i Pr₂NH (281 μ L, 2.00 mmol) in THF (1.25 mL) at 0 °C. The mixture was stirred for 20 min at the same temperature before the use. To another reaction vessel charged with **174** (13.0 mg, 33.5 μ mol) in THF (0.35 mL) was added the LDA solution (140 μ L, 140 μ mol) via a syringe at 0 °C. The reaction mixture was then warmed up to room temperature and stirred for 20 min. The reaction was quenched with saturated aqueous NaHCO₃ solution (0.50 mL), and the organic layer was diluted with EtOAc (0.50 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (0.50 mL $\times$ 3). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, hexane:EtOAc = 100:1) to afford **175** (8.2 mg, 21 μ mol, 63% yield).

175: yellow oil; ¹H NMR (500 MHz, CDCl₃) δ 6.39 (d, J = 10.0 Hz, 1H), 5.25 (d, J = 10.0 Hz, 1H), 4.28 (q, J = 7.3 Hz, 2H), 3.27 (s, 1H), 1.75 (sept, J = 7.3 Hz, 3H), 1.35 (t, J = 7.3 Hz, 3H), 1.12–1.04 (m, 24H)

Cycloheptatriene 177

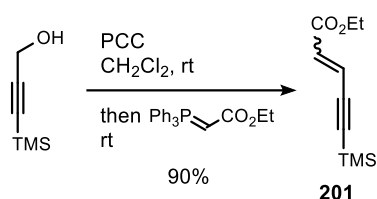


An LDA solution (ca. 1.0 mol/L in THF-hexane) was prepared by the addition of n BuLi (2.65 mol/L in hexane, 755 μ L, 2.00 mmol) to a solution of i Pr₂NH (281 μ L, 2.00 mmol) in THF (1.25 mL) at 0 °C. The mixture was stirred for 20 min at the same temperature before the use. To another reaction vessel charged with **174** (16.4 mg, 42.2 μ mol) in THF (0.42 mL) was added the LDA solution (169 μ L, 169 μ mol) via a syringe at 0 °C. The reaction mixture was then warmed up to room temperature and stirred for 20 min. To this mixture was added acetone (31.0 μ L, 422 μ mol), and the reaction mixture was stirred for another 20 min at the same temperature. The reaction was

quenched with saturated aqueous NH_4Cl solution (0.50 mL), and the organic layer was diluted with EtOAc (0.50 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (0.50 mL $\times$ 3). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2 , hexane:EtOAc = 30:1 to 20:1) to afford **177** (11.4 mg, 25.5 μmol , 60% yield).

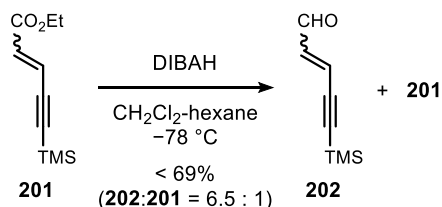
177: yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 6.39 (d, J = 10.0 Hz, 1H), 5.23 (d, J = 10.0 Hz, 1H), 4.27 (q, J = 7.2 Hz, 2H), 1.84 (s, 1H), 1.74 (sept, J = 7.6 Hz, 3H), 1.54 (s, 6H), 1.35 (t, J = 7.2 Hz, 3H), 1.10–1.04 (m, 24H)

Enynyl ester **201**



To a suspension of pyridinium chlorochromate (969 mg, 4.49 mmol) and Celite[®] (972 mg) in CH_2Cl_2 (10 mL) was added dropwise 3-(trimethylsilyl)-2-propyn-1-ol (428 μL , 3.00 mmol) in CH_2Cl_2 at room temperature. After stirring for 3 h, ethyl (triphenylphosphoranylidene)acetate (1.78 g, 5.10 mmol) was added, and the reaction mixture was stirred for 18 h at the same temperature. The reaction mixture was diluted with Et_2O (5.0 mL) and filtered through a short pad of SiO_2 (hexane:EtOAc = 10:1). The filtrate was concentrated under reduced pressure to afford **201** (*E/Z* mixture, 533 mg, 2.71 mmol, 90% yield). The spectral data matched with those reported in literature.^[63]

Enynyl aldehyde **202**

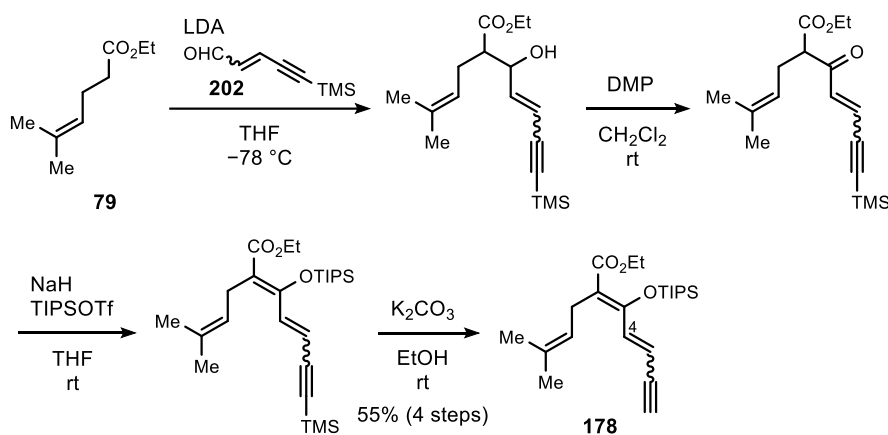


To a solution of **201** (196 mg, 1.00 mmol) in CH_2Cl_2 (5.0 mL) was added DIBAL-H (1.0 mol/L in hexane, 1.20 mL, 1.20 mmol) slowly over 30 sec at $-78\text{ }^\circ\text{C}$. After stirring for another 10 min, the reaction was quenched with saturated aqueous Rochelle salt solution (5.0 mL), and the biphasic mixture was stirred vigorously for 3 h. Two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (5.0 mL $\times$ 3). The combined organic layers were dried over MgSO_4 , filtered,

and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, hexane:EtOAc = 100:1 to 50:1) to afford **202** as a mixture with **201** [**202:201** = 6.5:1 (83% purity for **202**), 105 mg (*E/Z* = 4.8:1, 0.576 mmol, 58% yield for **202**)].

202: ¹H NMR (500 MHz, CDCl₃) δ 10.16 (d, *J* = 8.3 Hz, 0.17H), 9.56 (d, *J* = 7.9 Hz, 0.83H), 6.63 (d, *J* = 10.9 Hz, 0.17H), 6.58 (d, *J* = 15.9 Hz, 0.83H), 6.47 (dd, *J* = 15.9, 7.9 Hz, 0.83H), 6.29 (dd, *J* = 10.9, 8.3 Hz, 0.17H), 0.24 (s, 0.83 × 9H), 0.21 (s, 0.17 × 9H)

Trienyne 178



An LDA solution (ca. 1.0 mol/L in THF-hexane) was prepared by the addition of ⁿBuLi (2.65 mol/L in hexane, 755 μL, 2.00 mmol) to a solution of ⁱPr₂NH (281 μL, 2.00 mmol) in THF (1.25 mL) at 0 °C. The mixture was stirred for 20 min at the same temperature before the use. To another reaction vessel charged with **79** (31.6 mg, 0.202 mmol) in THF (1.0 mL) was added the LDA solution (240 μL, 240 μmol) via a syringe at −78 °C. After stirring for 15 min, **202** (6.5:1 mixture with **201**, 83% purity, *E/Z* = 4.8:1, 43.9 mg, 0.240 mmol) in THF (0.30 mL) was added via cannula, and the mixture was stirred for 10 min at the same temperature. The reaction was quenched with saturated aqueous NH₄Cl solution (1.0 mL), and the organic layer was diluted with EtOAc (1.0 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (1.0 mL × 3). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, hexane:EtOAc = 20:1 to 5:1) to afford β-hydroxyester.

To a solution of above β-hydroxyester in CH₂Cl₂ (1.0 mL) was added Dess-Martin periodinane (127 mg, 0.300 mmol) at 0 °C. The reaction mixture was then warmed up to room temperature and stirred for 25 min. The reaction was quenched with saturated aqueous NaHCO₃ and Na₂S₂O₃ solution (1.0 mL), and the biphasic mixture was stirred vigorously for > 30 min. The resulting mixture was extracted with EtOAc (1.0 mL × 4). The combined organic layers were dried over

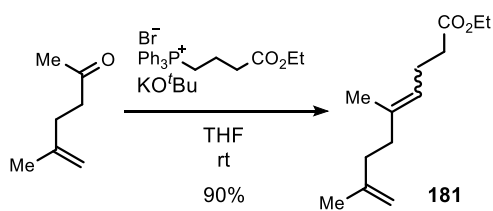
MgSO₄, filtered, and concentrated under reduced pressure. Highly polar components were filtered off through a short pad of SiO₂ (hexane:EtOAc = 10:1) to afford β -ketoester.

NaH (60% dispersion in mineral oil, 16.4 mg, 0.410 mmol) was washed with hexane and suspended with THF (0.50 mL). To this suspension was added above β -ketoester in THF (0.50 mL) via cannula at 0 °C. After stirring for 10 min, TIPSOTf (80.6 μ L, 0.300 mmol) was added. The reaction mixture was then warmed up to room temperature and stirred for 10 min. The reaction was quenched by the careful addition of saturated aqueous NaHCO₃ solution (1.0 mL), and the organic layer was diluted with EtOAc (1.0 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (1.0 mL $\times$ 3). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, hexane:EtOAc = 100:1) to afford TMS-trienyne along with byproducts.

To a solution of above TMS-trienyne in EtOH (1.0 mL) was added K₂CO₃ (27.2 mg, 0.197 mmol) at room temperature. After stirring for 45 min, brine (1.0 mL) was added, and the mixture was extracted with EtOAc (1.0 mL $\times$ 4). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, hexane:EtOAc = 100:1) to afford **178** (4*E*/4*Z* = 9:1, 43.7 mg, 0.112 mmol, 55% yield for 4 steps).

178: yellow oil; ¹H NMR (500 MHz, CDCl₃) δ 6.87 (d, *J* = 15.7 Hz, 1H), 6.04 (dd, *J* = 15.7, 2.5 Hz, 1H), 5.03 (t, *J* = 6.9 Hz, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.16 (d, *J* = 2.5 Hz, 1H), 3.02 (d, *J* = 6.9 Hz, 2H), 1.67 (s, 3H), 1.65 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.23–1.16 (m, 3H), 1.09 (d, *J* = 6.9 Hz, 18H)

Dienyl ester **181**

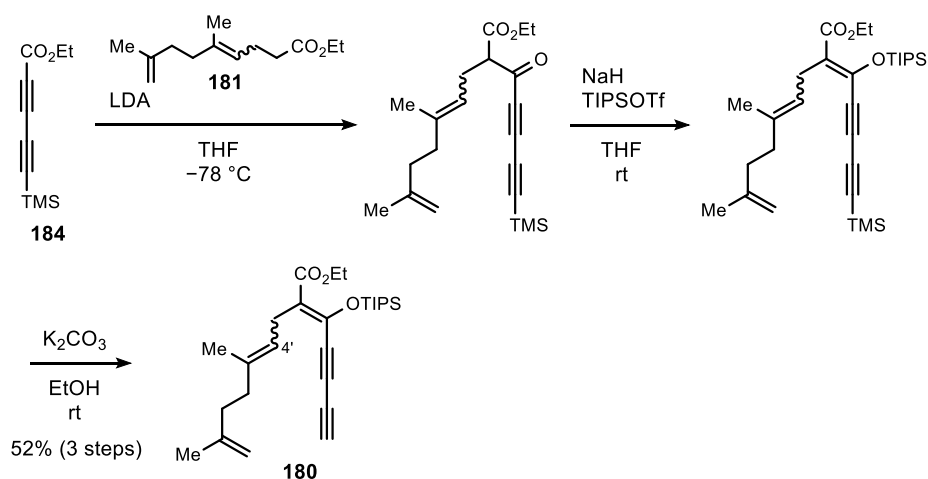


To a suspension of [3-(ethoxycarbonyl)propyl]triphenylphosphonium bromide (2.97 g, 6.50 mmol) in THF (15 mL) was added KOtBu (843 mg, 7.51 mmol) at 0 °C. The reaction mixture was then warmed up to room temperature and stirred for 1.5 h. To this mixture was added 5-methyl-5-hexen-2-one (648 μ L, 5.00 mmol), and the reaction mixture was stirred for 14 h at the same temperature. The reaction was quenched with saturated aqueous NH₄Cl solution (10 mL), and the organic layer was diluted with EtOAc (10 mL). Two layers were separated, and the

aqueous layer was extracted with EtOAc (10 mL $\times$ 3). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, hexane:EtOAc = 30:1) to afford **181** (*E/Z* or *Z/E* = 1.2:1, 943 mg, 4.48 mmol, 90% yield).

181: pale yellow oil; ¹H NMR (500 MHz, CDCl₃) δ 5.13–5.09 (m, 1H), 4.71 (s, 0.55H), 4.69 (s, 1H), 4.66 (s, 0.45H), 4.13 (q, *J* = 7.3 Hz, 0.55 $\times$ 2H), 4.12 (q, *J* = 7.3 Hz, 0.45 $\times$ 2H), 2.32–2.30 (m, 4H), 2.18–2.04 (m, 4H), 1.75 (s, 0.55 $\times$ 3H), 1.71 (s, 0.45 $\times$ 3H), 1.69 (s, 0.55 $\times$ 3H), 1.63 (s, 0.45 $\times$ 3H), 1.25 (t, *J* = 7.3 Hz, 3H)

Trienediynes **180**



To a solution of ^{*i*}Pr₂NH (1.34 mL, 9.54 mmol) in THF (15.9 mL) was added ^{*n*}BuLi (1.51 mol/L in hexane, 6.32 mL, 9.54 mmol) at 0 °C. After stirring for 20 min, the reaction mixture was cooled down to -78 °C, and **181** (802 mg, 3.81 mmol) in THF (1.0 mL) was added via cannula. After stirring for 10 min, **184** (618 mg, 3.18 mmol) in THF (1.0 mL) was added via cannula, and the reaction mixture was stirred for 20 min at the same temperature. Crushed dry ice was added to trap the excessive enolate, and the mixture was stirred under ambient temperature until the evolution of CO₂ gas ceased. The reaction was quenched with saturated aqueous NaHCO₃ solution (20 mL), and the organic layer was diluted with EtOAc (10 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (15 mL $\times$ 3). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, hexane:EtOAc = 10:1) to afford β-ketoester.

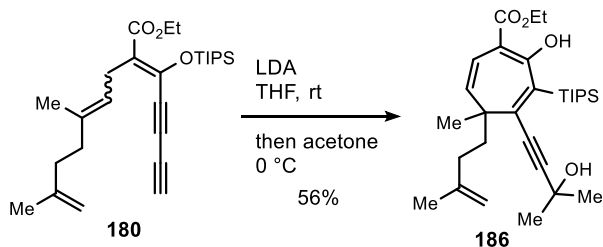
NaH (55% dispersion in paraffin, 250 mg, 5.72 mmol) was washed with hexane and suspended with THF (12 mL). To this suspension was added above β-ketoester in THF (2.0 mL) via cannula at 0 °C. After stirring for 10 min, TIPSOTf (1.14 mL, 4.25 mmol) was added. The reaction mixture

was then warmed up to room temperature and stirred for 10 min. The reaction was quenched by the careful addition of saturated aqueous NaHCO₃ solution (10 mL), and the organic layer was diluted with EtOAc (10 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (10 mL × 3). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, hexane:EtOAc = 100:1) to afford TMS-trienediyne as a mixture with **180**.

To a solution of above TMS-trienediyne in EtOH (8.2 mL) was added K₂CO₃ (229 mg, 1.66 mmol) at room temperature. After stirring for 1 h, the reaction mixture was diluted with Et₂O (10 mL) and brine (10 mL). Two layers were separated, and the aqueous layer was extracted with Et₂O (5.0 mL × 3). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, hexane:EtOAc = 100:1) to afford **180** (4'E/4'Z or 4'Z/4'E = 1.2:1, 730 mg, 1.65 mmol, 52% yield for 3 steps).

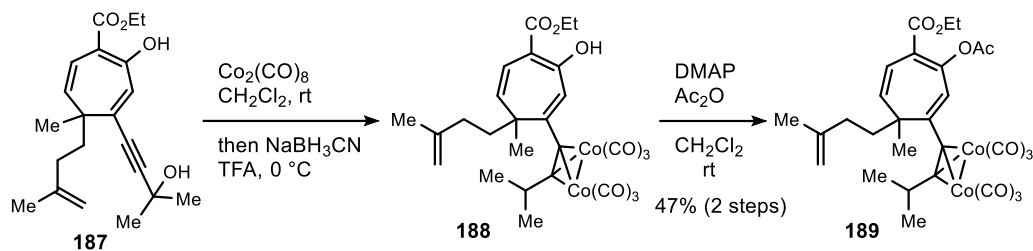
180: yellow oil; ¹H NMR (500 MHz, CDCl₃) δ 5.12–5.07 (m, 1H), 4.72 (s, 1H), 4.68 (s, 0.55H), 4.66 (s, 0.45H), 4.18 (q, *J* = 7.0 Hz, 0.55 × 2H), 4.18 (q, *J* = 7.2 Hz, 0.45 × 2H), 3.14 (d, *J* = 6.9 Hz, 2H), 2.63 (s, 0.45H), 2.63 (s, 0.55H), 2.24–2.06 (m, 4H), 1.76 (s, 0.55 × 3H), 1.71 (s, 0.45 × 3H), 1.69 (s, 0.55 × 3H), 1.68 (s, 0.45 × 3H), 1.31–1.24 (m, 6H), 1.10 (d, *J* = 7.4 Hz, 18H)

Cycloheptatriene **186**



An LDA solution (ca. 1.0 mol/L in THF-hexane) was prepared by the addition of ⁿBuLi (2.66 mol/L in hexane, 2.48 mL, 6.59 mmol) to a solution of ⁱPr₂NH (926 μL, 6.59 mmol) in THF (4.11 mL) at 0 °C. The mixture was stirred for 20 min at the same temperature before the use. To another reaction vessel charged with **180** (730 mg, 1.65 mmol) in THF (16.5 mL) was transferred the full volume of the LDA solution via a syringe at 0 °C. The reaction mixture was then warmed up to room temperature and stirred for 20 min. After cooling down to 0 °C, acetone (1.21 mL, 16.5 mmol) was added, and the reaction mixture was stirred for 10 min at the same temperature. The reaction was quenched with saturated aqueous NaHCO₃ solution (20 mL), and the organic layer was diluted with EtOAc (10 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (10 mL × 3). The combined organic layers were dried over MgSO₄, filtered, and

Alkyne-dicobalt complex **189**

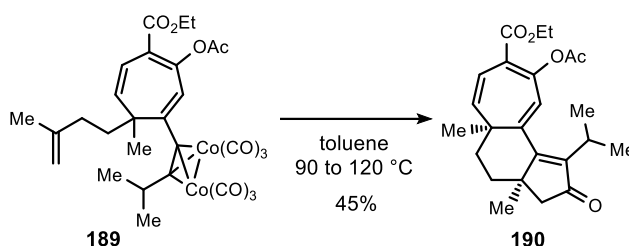


To a solution of **187** (34.1 mg, 99.0 μmol) in CH_2Cl_2 (1.0 mL) was added $\text{Co}_2(\text{CO})_8$ (66.0 mg, 0.193 mmol) at room temperature. After stirring for 2 h, the reaction mixture was cooled down to $0\text{ }^\circ\text{C}$, and NaBH_3CN (50.5 mg, 0.804 mmol) was added. To this mixture was added dropwise trifluoroacetic acid (76.5 μL , 1.00 mmol) over 1 min under vigorous stirring. After stirring for another 15 min at the same temperature, the reaction was quenched with saturated aqueous NaHCO_3 solution (1.0 mL), and the organic layer was diluted with Et_2O (1.0 mL). Two layers were separated, and the aqueous layer was extracted with Et_2O (1.0 mL $\times$ 3). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. Highly polar components were filtered off through a short pad of SiO_2 (hexane: EtOAc = 30:1) to afford **188** along with byproducts.

To a solution of **188** in CH_2Cl_2 were added successively *N,N*-dimethylaminopyridine (24.0 mg, 0.196 mmol) and Ac_2O (14.2 μL , 0.150 mmol) at $0\text{ }^\circ\text{C}$. The reaction mixture was then warmed up to room temperature and stirred for 10 min. The reaction was quenched with saturated aqueous NaHCO_3 solution (1.0 mL). Two layers were separated, and the aqueous layer was extracted with EtOAc (1.0 mL $\times$ 3). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2 , hexane: EtOAc = 50:1 to 20:1) to afford **189** (30.8 mg, 46.9 μmol , 47% yield for 2 steps).

189: dark brown oil; ^1H NMR (500 MHz, CDCl_3) δ 6.75 (d, J = 10.3 Hz, 1H), 6.61 (s, 1H), 5.19 (d, J = 10.3 Hz, 1H), 4.64 (s, 1H), 4.62 (s, 1H), 4.25 (q, J = 7.0 Hz, 2H), 3.29 (sept, J = 6.5 Hz, 1H), 2.24 (s, 3H), 2.00–1.93 (m, 1H), 1.90–1.84 (m, 1H), 1.64 (s, 3H), 1.57–1.39 (m, 2H), 1.48 (s, 3H), 1.32 (t, J = 7.0 Hz, 3H), 1.31 (d, J = 6.5 Hz, 3H), 1.22 (d, J = 6.5 Hz, 3H)

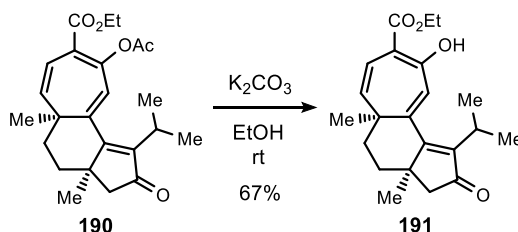
Tricyclic ketone 190



In a sealed tube, **189** (30.8 mg, 46.9 μmol) was dissolved in toluene (0.47 mL) and stirred at 90 °C for 20 h. The reaction mixture was then warmed up to 120 °C and stirred for another 3 h. The resulting mixture was filtered through a pad of Celite[®], and the residue was washed with Et₂O. The filtrate was concentrated under reduced pressure and purified by flash column chromatography (SiO₂, hexane:EtOAc = 10:1 to 3:1) to afford **190** (8.4 mg, 21 μmol , 45% yield).

190: brown oil; ¹H NMR (500 MHz, CDCl₃) δ 6.69 (d, J = 10.3 Hz, 1H), 5.94 (s, 1H), 5.14 (d, J = 10.3 Hz, 1H), 4.32–4.25 (m, 2H), 2.52 (sept, J = 7.1 Hz, 1H), 2.45 (d, J = 17.8 Hz, 1H), 2.33 (d, J = 17.8 Hz, 1H), 2.27 (s, 3H), 1.93–1.89 (m, 2H), 1.79–1.77 (m, 1H), 1.65–1.60 (m, 1H), 1.35 (t, J = 7.2 Hz, 3H), 1.26 (s, 3H), 1.13 (d, J = 7.1 Hz, 3H), 1.01 (d, J = 7.1 Hz, 3H), 0.99 (s, 3H)

Tricyclic ketone 191



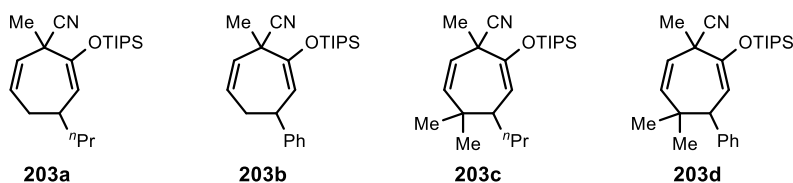
A solution of **190** (4.0 mg, 10 μmol) and K₂CO₃ (4.2 mg, 30 μmol) in EtOH (0.20 mL) was stirred for 21 h at room temperature. The reaction mixture was then diluted with Et₂O (0.50 mL), and saturated aqueous NH₄Cl solution (0.50 mL) was added. Two layers were separated, and the aqueous layer was extracted with Et₂O (0.50 mL $\times$ 3). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, hexane:EtOAc = 20:1) to afford **191** (2.4 mg, 6.7 μmol , 67% yield).

191: yellow solid; ¹H NMR (500 MHz, CDCl₃) δ 6.51 (d, J = 10.3 Hz, 1H), 6.08 (s, 1H), 5.04 (d, J = 10.3 Hz, 1H), 4.41–4.27 (m, 2H), 2.58 (sept, J = 6.9 Hz, 1H), 2.45 (d, J = 17.8 Hz, 1H), 2.34 (d, J = 17.8 Hz, 1H), 1.94–1.84 (m, 2H), 1.65 (ddd, J = 13.5, 3.1, 3.1 Hz, 1H), 1.59–1.53 (m, 1H), 1.38 (t, J = 7.2 Hz, 3H), 1.26 (s, 3H), 1.16 (d, J = 6.9 Hz, 3H), 1.03 (d, J = 6.9 Hz, 3H), 0.98 (s, 3H)

References and Notes

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