



HOKKAIDO UNIVERSITY

Title	New Synthetic Methods for Nitriles Directed toward Natural Product Synthesis
Author(s)	土門, 大祐
Degree Grantor	北海道大学
Degree Name	博士(理学)
Dissertation Number	甲第13678号
Issue Date	2019-03-25
DOI	https://doi.org/10.14943/doctoral.k13678
Doc URL	https://hdl.handle.net/2115/77052
Type	doctoral thesis
File Information	Daisuke_Domon.pdf



DISSERTATION

New Synthetic Methods for Nitriles

Directed toward Natural Product Synthesis

(天然物合成を志向したニトリル誘導体の新規合成法)

Daisuke Domon

Hokkaido University

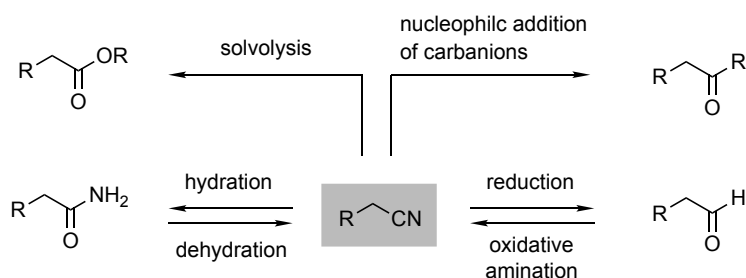
2019

Contents

Introduction	P. 1
Chapter 1 Non-Reductive Decyanation Reactions of Malononitrile Derivatives	P. 6
Chapter 2 The Development of Formal Semi-pinacol Rearrangement Reactions of Cyano Epoxyalcohols	P. 39
Chapter 3 Synthetic Studies on Verrucarin J	P.82
Acknowledgment	P.109

Introduction

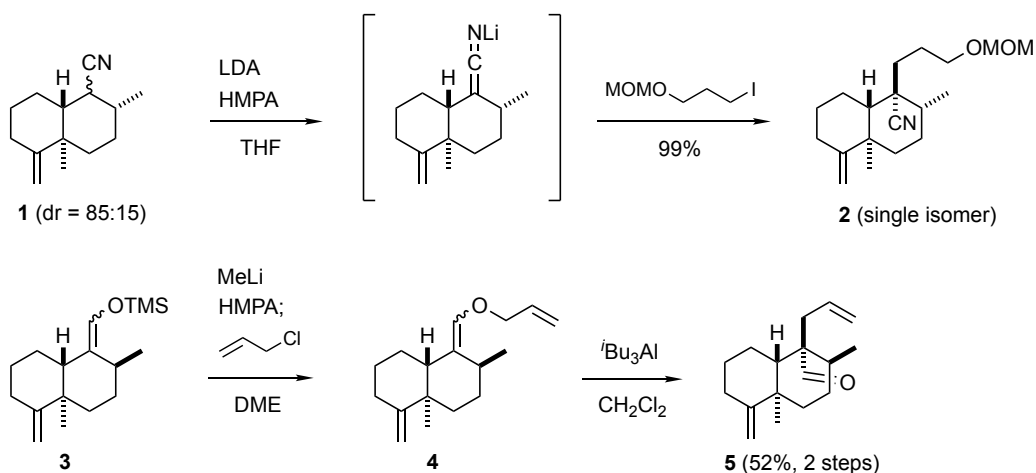
A cyano group is a versatile functional group in synthetic organic chemistry, because it can be considered as an equivalent of carboxyl groups. There are a number of methods for converting a cyano group to a variety of functional groups including carbamoyl, alkoxycarbonyl, formyl, and aminomethyl groups (Scheme 1). For the preparation of nitriles, the dehydration of primary amides and the oxidative amination of aldehydes are frequently used. On the other hand, the synthesis of nitriles through a carbon-carbon bond forming reaction has found widespread use in organic synthesis. For example, the nucleophilic substitution reaction of alkyl halides with a cyanide ion is a useful synthetic method of nitriles via a one carbon homologation.



Scheme 1 Interconversion of nitriles

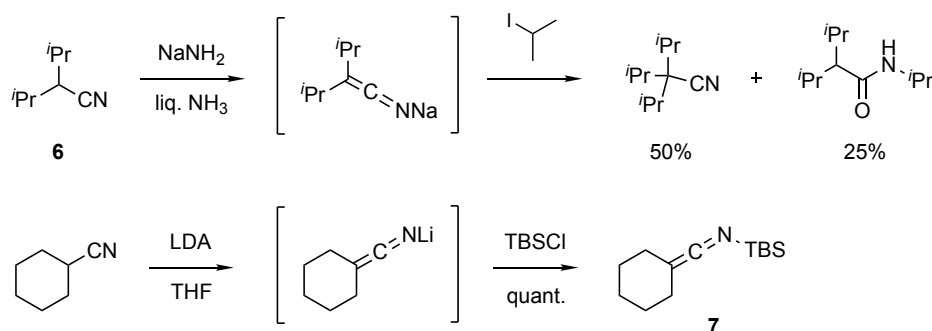
Alkanenitriles having an α -hydrogen atom are sufficiently acidic to give α -cyano carbanions upon treatment with a strong base such as lithium diisopropylamide (LDA). The resulting α -cyano carbanions react with various kinds of carbon electrophiles, resulting in elongation of the carbon chain. While the utility of α -cyano carbanions as a nucleophile are similar with that of ester enolates, there are several advantages in the use of them. The cyano group of nitriles is much less bulky than a carbonyl group, that is advantageous for constructing a sterically demanding quaternary carbon center. For example, in the total syntheses of clerodane diterpenoids reported by Piers and co-workers¹, the alkylation of the α -cyano carbanion generated from nitrile **1** was successfully employed for the construction of the quaternary carbon center

(Scheme 2). In contrast, the alkylation of a lithium enolate, which was generated from enol silyl ether **3**, with allyl iodide inefficiently produced the *C*-alkylated product **5**. Hence, the enolate was reacted with allyl chloride to afford enol ether **4** which was subsequently subjected to a Claisen rearrangement reaction, giving rise to allylated product **5**².



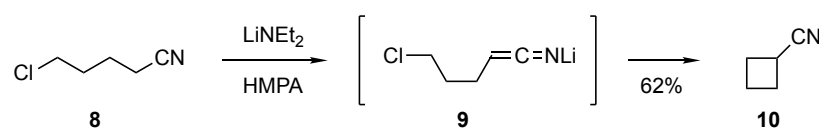
Scheme 2 Comparison of α -cyano carbanion and aldehyde enolate

Even highly hindered nitrile **6** can undergo *C*-alkylation with isopropyl iodide, while a *N*-alkylation product was obtained as a side product (Scheme 3). In the reaction with a silyl chloride, the reaction mainly occurs at the nitrogen atom, affording *N*-silyl ketene imine⁴ **7**.



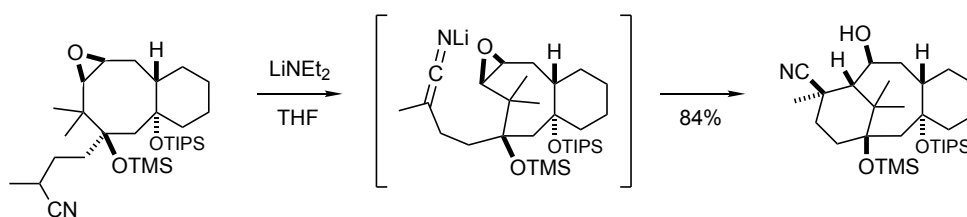
Scheme 3 *N*-alkylation of nitriles with sterically demanding electrophiles

Intramolecular substitution reactions of halo nitriles under basic conditions provide a powerful method for the construction of carbocycles with various ring sizes. For example, cyclobutanecarbonitrile (**10**) was synthesized from chloronitrile **8** by the treatment with LiNEt_2 ⁵ (Scheme 4). It is noteworthy that *N*-alkylation of the α -cyano carbanion **9** is impossible because of the geometric reason.



Scheme 4 Intramolecular cyclization of δ -chloro nitrile

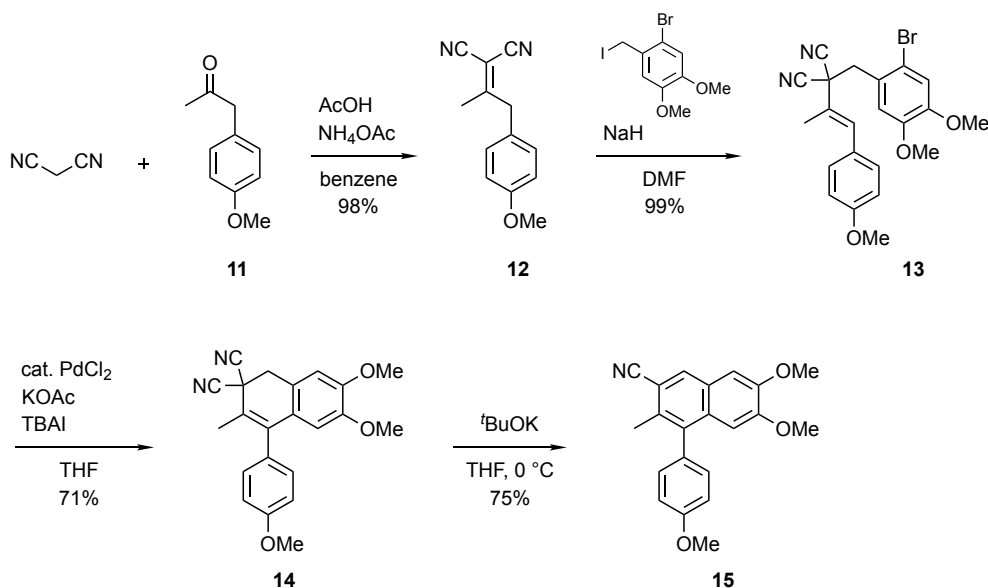
Since the pioneering work by Stork and co-workers⁷, cyclization of epoxy nitriles has become a powerful tool for ring construction. For example, Tanino and co-workers recently reported the successful formation of an eight-membered ring of toxoids by the intramolecular substitution reaction⁸ (Scheme 5). The reaction occurred even at the hindered neopentyl position, accompanied with the formation of a quaternary carbon center.



Scheme 5 Construction of taxane skeleton by epoxynitrile cyclization

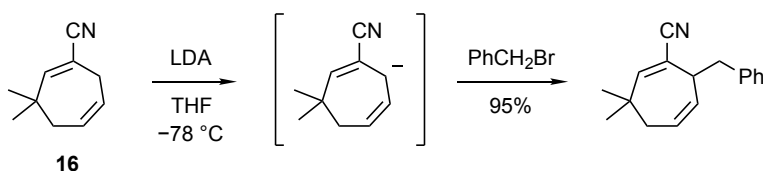
An accumulation of cyano groups makes the negative charge of the α -cyano carbanion more stable. Thus, malononitrile readily generate a stable anionic species under the presence of a mild base, and the anion is utilized for C-C bond forming reactions with electrophiles. As depicted in scheme 6, malononitrile undergoes the Knoevenagel condensation reaction with ketone **11**, and the resulting dinitrile **12** is used for further C-C bond formation. Upon treatment with NaH and a

benzyl iodide, **12** undergoes a deconjugative alkylation reaction, giving rise to dinitrile **13**⁹. Due to the strong inductive effect of two cyano groups, the benzylic proton of dihydronaphthalene **14** is abstracted to generate a benzylic anion species which undergoes β -elimination of a cyano group¹⁰, affording naphthalene **15**.



Scheme 6 Synthesis of the naphthalene derivative

Similar effect of a cyano group, which facilitates the abstraction of a proton at the β -position, was also reported by Tanino and co-workers. For example, treatment of cycloheptadiene **16** with LDA gave a conjugated anionic species at the allylic position which was subsequently trapped by an electrophile (Scheme 7)¹¹.



Scheme 7 Alkylation of cycloheptadienyl anion

Intrigued by these unique properties of nitriles in organic synthesis, the author undertook research to develop novel synthetic methodologies for nitriles. In this dissertation, the author will describe the synthesis of nitrile-containing building blocks and their application to the natural product synthesis. In chapter 1, the unique reactions of geminal dicyano compounds are described. In chapter 2, the formal rearrangement of epoxy cyanoalcohol is described. In chapter 3, the total synthesis of verrucarol is described.

References

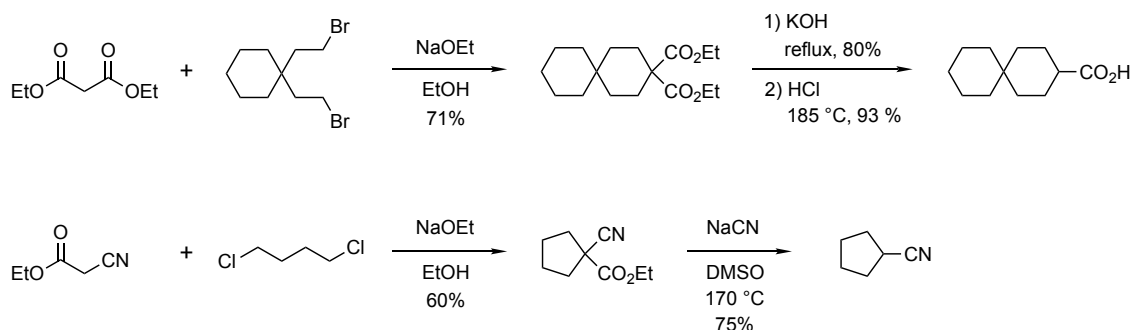
1. Piers, E.; Wai, J. S. M. *J. Chem. Soc. Chem. Commun.* **1987**, 1342.
2. Piers, E.; Fleming, F. F. *J. Chem. Soc. Chem. Commun.* **1989**, 1665.
3. Newman, M. S.; Fukunaga, T.; Miwa, T. *J. Am. Chem. Soc.* **1960**, 82, 873.
4. Watt, D. S. *Synth. Commun.* **1974**, 4, 127.
5. Larcheveque, M.; Mulot, P.; Cuvigny, T. *J. Organomet. Chem.* **1973**, 57, C33.
6. Kim, D.; Kwak, Y. S.; Shin, K. J. *Tetrahedron Lett.* **1994**, 35, 9211.
7. (a) Stork, G.; Cama, L. D.; Coulson, D. R. *J. Am. Chem. Soc.* **1974**, 96, 5268. (b) Stork, G.; Cohen, J. F. *J. Am. Chem. Soc.* **1974**, 96, 5270.
8. Hanada, R.; Mitachi, K.; Tanino, K. *Tetrahedron Lett.* **2014**, 55, 1097.
9. Navaratne, P. V.; Grenning, A. J. *Org. Biomol. Chem.* **2017**, 15, 69.
10. Hauser, C. R.; Brasen, W. R. *J. Am. Chem. Soc.* **1956**, 78, 82.
11. Yamada, T.; Yoshimura, F.; Tanino, K. *Tetrahedron Lett.* **2013**, 54, 522.

Chapter 1.

Non-Reductive Decyanation Reactions of Malononitrile Derivatives

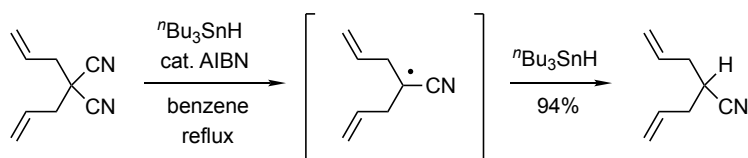
1.1 Introduction

Alkylation reactions of active methylene compounds have found widespread use in organic synthesis, mainly because these reactions proceed under mild conditions using a weak base. The alkylation of malonic ester with alkyl halides and the subsequent decarboxylation affording α -substituted acetic acid derivatives is known as the malonic ester synthesis.¹ For obtaining an α -substituted acetonitrile, a similar procedure starting from ethyl cyanoacetate is available (Scheme 8).²



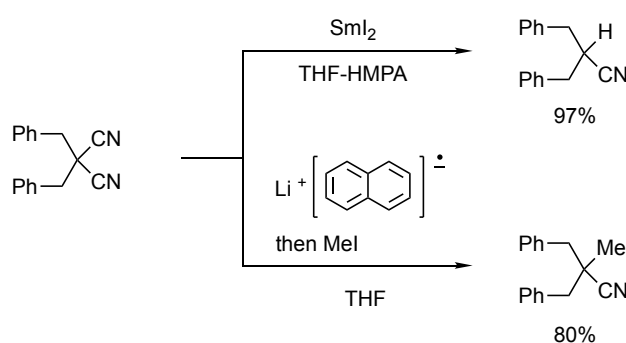
Scheme 8 Decarboxylation of esters

On the other hand, an alkylation reaction of malononitrile followed by a decyanation reaction provides an alternative way to achieve the same purpose. Curran and Seong reported that the mono- and dialkylated malononitriles were reductively decyanated to afford mononitriles upon treatment with tributyltin hydride and a catalytic amount of AIBN (Scheme 9).³



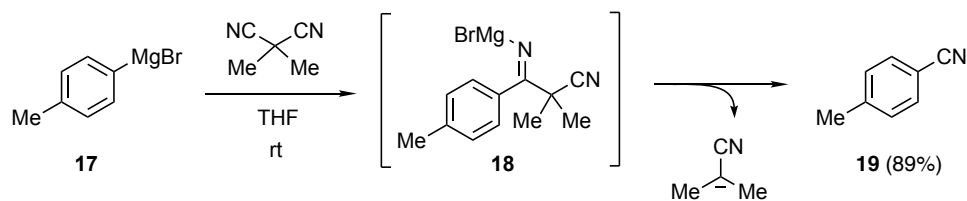
Scheme 9 Reductive decyanation mediated by tributyltin hydride

Kang and co-workers reported an alternative reductive decyanation of malononitriles promoted by samarium(II) iodide/HMPA (Scheme 10). Similarly, lithium naphthalenide has been used as an electron donor for removing a cyano group, as was found by Liu and co-workers⁴. In their work, the α -cyano carbanion intermediate arising from the decyanation can be trapped by an electrophile such as alkyl halides, aldehydes or ketones.



Scheme 10 Reductive decyanation using SmI₂ or lithium naphthalenide

Whereas the aforementioned methods for the cleavage of a cyano group of malononitriles using reductive reagents are reported, there have been few examples of non-reductive decyanation reactions of them. Recently, Reeves and co-workers reported a cyanation of aryl Grignard reagents or aryllithium reagents by the addition reaction with dimethylmalononitrile (Scheme 11).⁶ The proposed reaction mechanism involves the initial formation of anionic intermediate **18** which undergoes decomposition into the desired arenecarbonitrile **19** and an α -carbanion of isobutyronitrile. This result shows promise for achieving a non-reductive decyanation of α,α -disubstituted malononitrile derivatives.

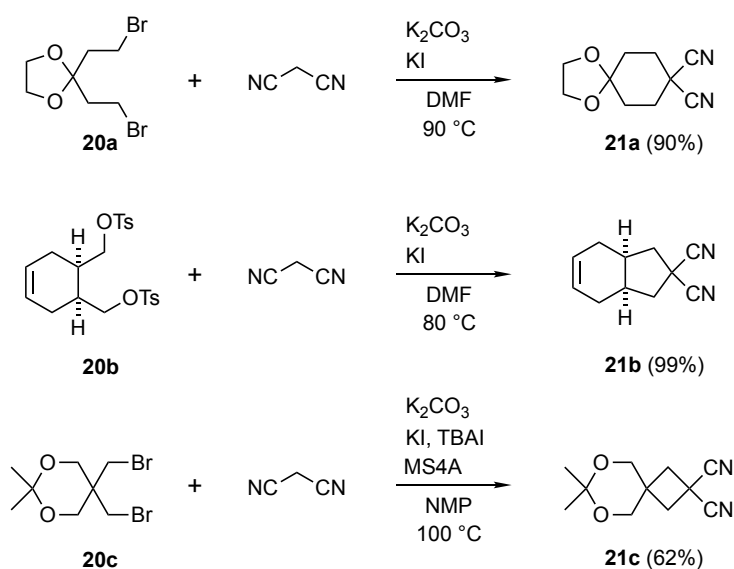


Scheme 11 Decyanation of dimethylmalononitriles induced by Grignard reagents

From the above background, the author undertook research to develop the non-reductive decyanation reactions of α,α -disubstituted malononitrile derivatives with a suitable nucleophile, resulting in the formation of the corresponding α,α -disubstituted acetonitriles.

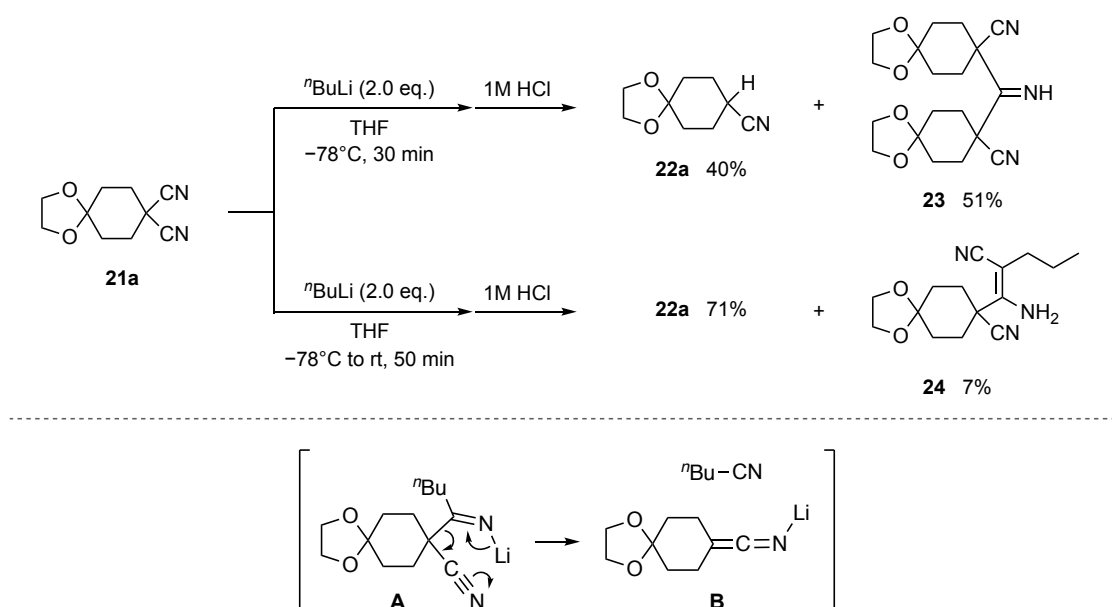
1.2 The Development of Decyanation Reactions of Disubstituted Malononitriles

Initially, six-, five-, and four-membered malononitrile derivatives **21-21c** were synthesized from the corresponding dibromide or ditosylate **20a-20c** and malononitrile (Scheme 12). The combined use of K_2CO_3 and KI in DMF was effective for the synthesis of **21a** and **21b**, while modified reaction conditions⁸ were required for constructing the four-membered ring of **21c**.



Scheme 12 Synthesis of cyclic malononitriles.

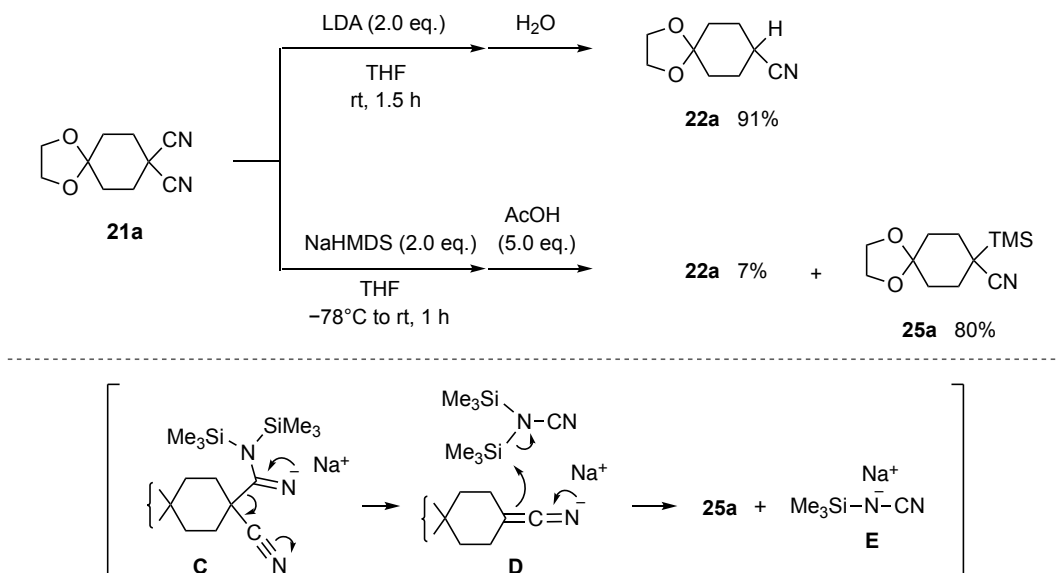
With a view to inducing decyanation via a nucleophilic addition reaction, malononitrile **21a** was treated with *n*-BuLi at $-78\text{ }^{\circ}\text{C}$ to give the desired nitrile **22a** in 40% isolated yield along with 51% of byproduct **23** (Scheme 13). The result suggested that the reaction proceeded through decomposition of the anionic intermediate **A** into the α -cyano anion **B** even at $-78\text{ }^{\circ}\text{C}$ which attacked the remaining substrate **21a** to form **23**. On the other hand, the yield of nitrile **22a** was increased to 71% upon warming the reaction to room temperature before quenching. In this case, a small amount (7%) of byproduct **24** was obtained, which would come from pentanenitrile and malononitrile **21a**.



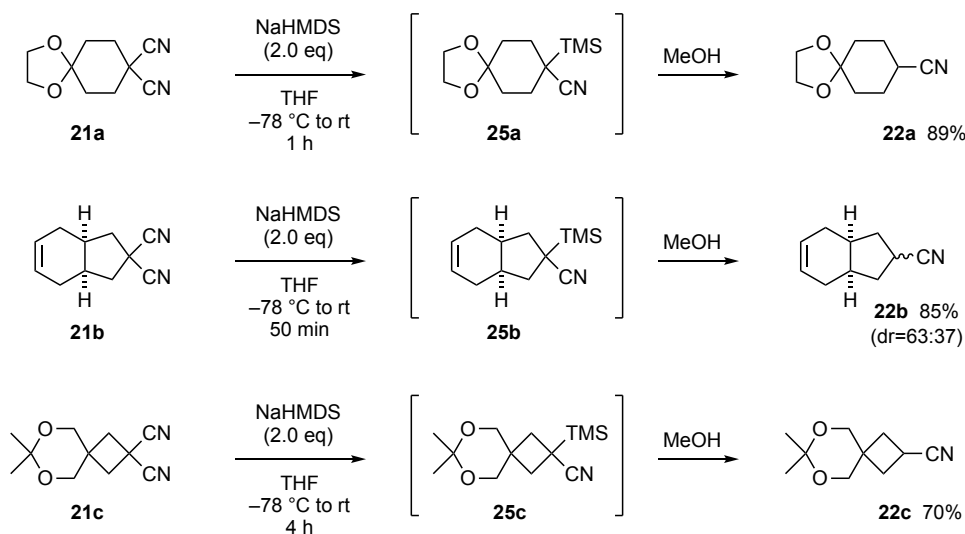
Scheme 13 Nucleophilic decyanation induced by BuLi

Surprisingly, it turned out that sterically demanding amide bases could work as a nucleophile. A smooth decyanation was observed upon treatment of **21a** with LDA to produce **22a** in 91% yield. As for NaHMDS, α -silyl nitrile **25a** was isolated in 80% yield along with 7% of mononitrile **22a** (Scheme 14). The formation of **25a** could be rationalized by intermolecular transfer of a silyl group between α -cyano anion **D** and bis(trimethylsilyl)cyanamide⁹ which are derived from decomposition of anionic intermediate **C**. Since the reactive anion **D** is immediately

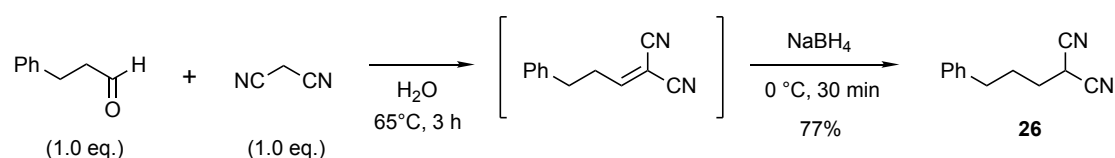
captured by a silyl group to give **25a**, the resulting anion **E** is sufficiently stable which leads to avoid side reactions.



The silyl group of **25a** could be readily removed in one-pot simply by adding methanol to the reaction mixture to give **22a** in 89% yield (Scheme 15). The protocol was also effective for the decyanation reactions of malononitriles **21b** and **21c**, giving rise to the corresponding nitriles **22b** and **22c** in 85% and 70% yields, respectively.

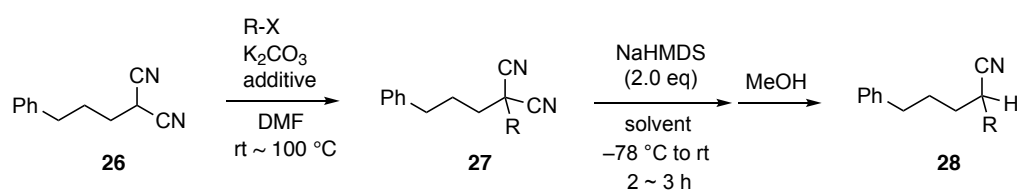


These results led the author to investigate the decyanation reactions of acyclic malononitrile derivatives. Monoalkylated dinitrile **26** was prepared via condensation of 3-phenylpropanal with malononitrile followed by conjugate reduction with NaBH₄ in a one-pot manner (Scheme 16).



Scheme 16 Preparation of monosubstituted malononitrile

Various α,α -disubstituted malononitriles **27** were synthesized from the corresponding alkylating agents under similar conditions for the preparation of **21a** (Table 1). Upon treatment with NaHMDS in THF followed by methanol, malononitriles **27** possessing a methyl group or a (2-benzyloxy)ethyl group at the α -position underwent the decyanation reactions smoothly to afford nitriles **28** in good yields (entries 1 and 2). Surprisingly, the substrate having an allyl group failed to give the desired product, resulting in formation of a complex mixture (entry 3). In the event, the use of a mixture of ether and toluene as the less polar solvent dramatically changed the result, and desired nitrile **28** was obtained in 85% yield (entries 4). An analogue having a prenyl

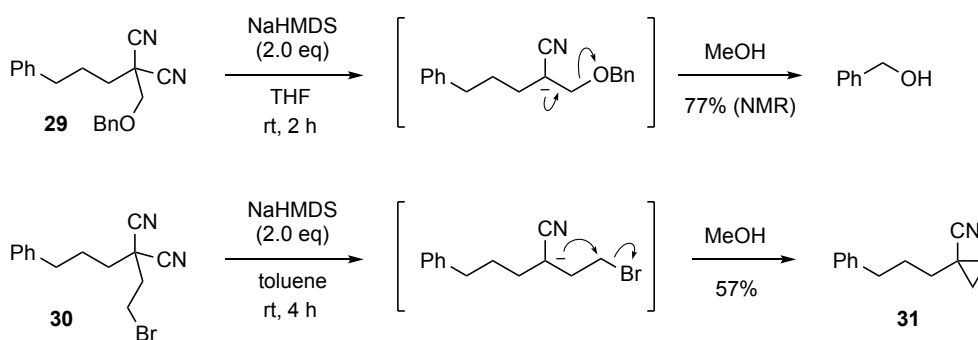


entry	R-X	additive	yield of 27	solvent	yield of 28
1	MeI	-	90%	THF ^a	96%
2	BnOCH ₂ OMs	Nal	83%	THF ^a	95%
3	CH ₂ =CHCH ₂ I	-	98%	THF ^a	0%
4	CH ₂ =CHCH ₂ I	-	98%	ether-toluene ^b	85%
5	CH ₂ =C(CH ₃)CH ₂ Br	Nal	96%	ether-toluene ^b	96%

^aTo a THF solution of the substrate was added a 1.1 M THF solution of NaHMDS

^bTo a ethereal solution of the substrate was added a 0.6 M toluene solution of NaHMDS

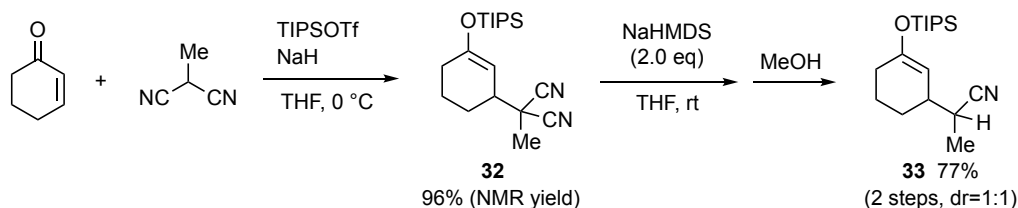
Table 1 Two-step synthesis of acyclic nitriles



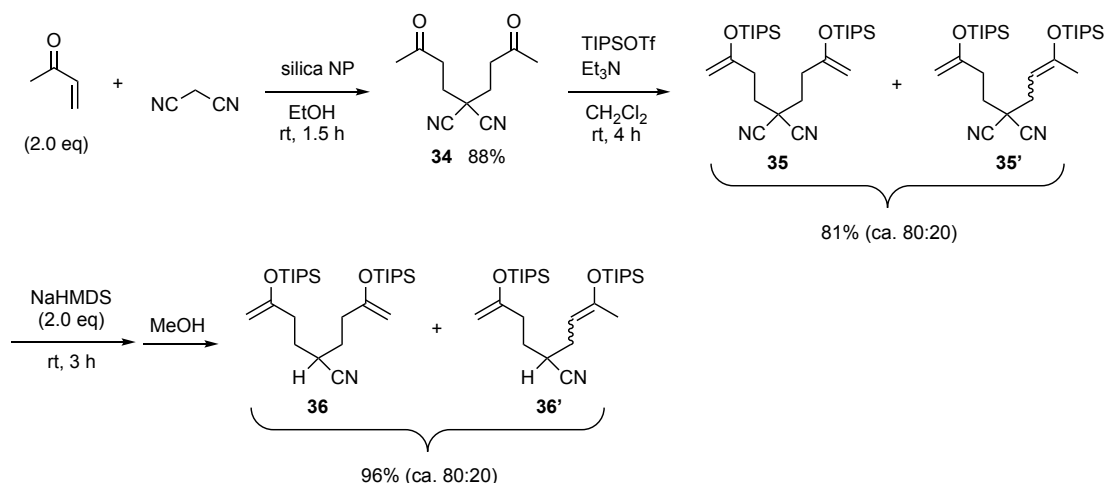
Scheme 17 The reaction of β -alkoxymalononitrile and γ -bromomalononitrile

group was also synthesized in a similar manner (entry 5). Unfortunately, this decyanation reaction could not be applied to β -alkoxy malononitrile **29**, which afforded benzyl alcohol via an elimination reaction (Scheme 10). In the case of γ -bromonitrile **30**, cyanocyclopropane **31** was produced in moderate yield through the intramolecular cyclization of the α -cyano anion intermediate.

Since mononitriles **28** would also be obtainable directly from 5-phenylpentanenitrile through the alkylation reactions with R-X,¹⁰ the present two-step synthesis of **28** via decyanation of malononitriles **27** may show little advancement. On the other hand, it has been recognized that malononitrile can serve as an effective nucleophile in Michael addition to α,β -unsaturated ketones,¹¹ which contrasts with that a simple alkanenitrile generally prefers 1,2-addition rather than 1,4-addition. Indeed, the advancement of the indirect method for obtaining nitriles was demonstrated in Scheme 18. Thus, under the influence of sodium hydride and TIPSOTf, methylmalononitrile reacted with 2-cyclohexen-1-one to afford enol silyl ether **32** in excellent yield¹² which was then converted to mononitrile **33** via decyanation reaction.



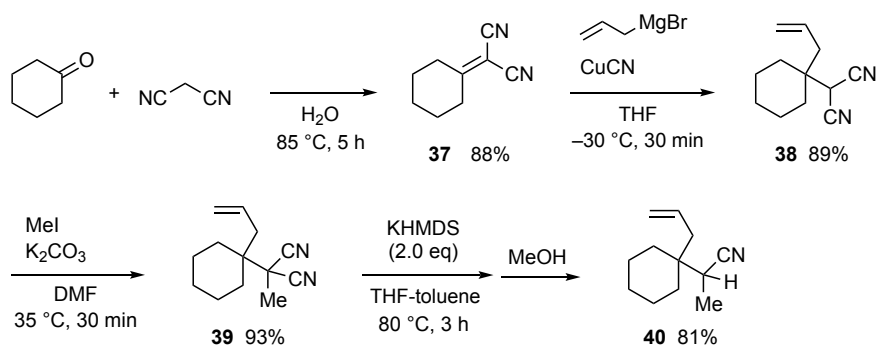
Scheme 18 Synthesis of nitrile through conjugate addition reaction



Scheme 19 Synthesis of nitriles through double Michael addition

A regioisomeric mixture of malononitriles **35** and **35'** was also synthesized from the corresponding diketone **34** which was prepared from malononitrile and methyl vinyl ketone by the double Michael reaction mediated by a silica nano-particle (Scheme 19).¹³ Upon treatment with NaHMDS in THF followed by methanol, malononitriles **35** and **35'** were cleanly transformed into the desired nitriles **36** and **36'**.

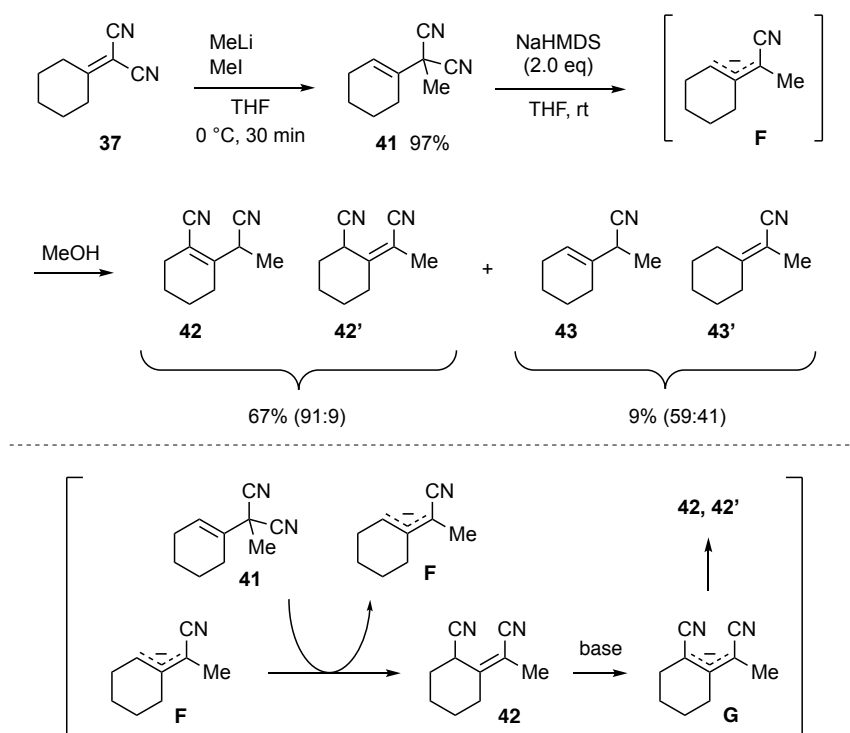
Attention was next turned to the Michael addition reactions of 1,1-dicyanoalkene with nucleophiles, which showed promise for preparing malononitriles with a bulky substituent (Scheme 20). The condensation reaction of cyclohexanone with malononitrile afforded dicyano alkene **37** in high yield.^{14,15} The reaction of **37** with a Grignard reagent in the presence of copper(I) chloride¹⁶ afforded malononitrile **38** in 89% yield which was subjected to the alkylation reaction



Scheme 20 Conversion of 1,1-dicyanoalkene to mononitrile

with methyl iodide. Although NaHMDS failed to induce the decyanation reaction of the sterically demanding malononitrile **39** even under refluxing condition, the use of KHMDS led to formation of the desired nitrile **40** in 81% yield.

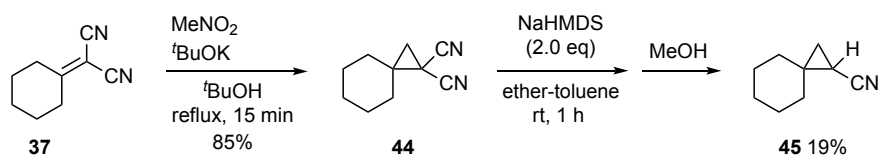
Interestingly, the reaction of β , γ -unsaturated malononitrile **41**, which was prepared by the methylation of **37**¹⁷, mainly afforded dinitrile **42** along with the desired nitrile **43** in 9% yield (Scheme 21). The unusual result can be explained by the transcyanation of the anionic intermediate **F** with the remaining substrate **41** at the γ -position of the cyano group to afford **42**, which is isomerized to **42'** via anionic intermediate **G**.



Scheme 21 Mechanism for transcyanation reaction

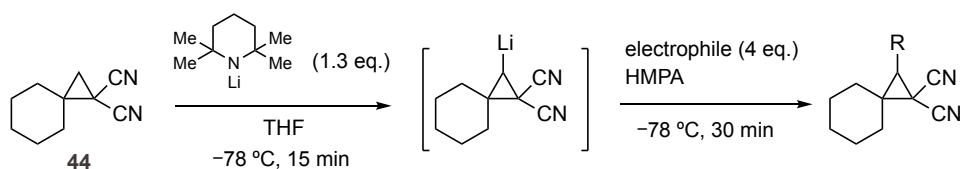
1.3 Alkylation Reaction of Novel Cyclopropylanion Species

In the course of exploring the decyanation of various cyclic malononitrile derivatives, the reaction of three-membered malononitrile **44** gave the desired mononitrile **45** only in poor yield (Scheme 22).



Scheme 22 Unsuccessful decyanation of three-membered malononitrile

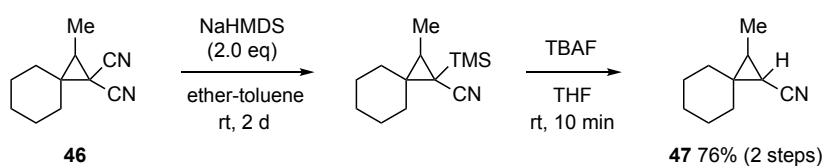
The author found that the exceptional result comes from generation of β -cyano carbanion species via deprotonation on the cyclopropane ring. The use of sterically more hindered LiTMP effected the selective formation of the novel cyclopropyllithium, which could be trapped by alkylating agents. As shown in Table 2, methyl iodide and benzyl bromide smoothly reacted with the anionic intermediate to give the corresponding alkylated products in high yields (entry 1 and 2). The alkylation of cyclopropyllithium with *n*-butyl iodide at -78°C resulted in recovery of **44**, and the reaction at elevated temperature (-50°C) led to decomposition of the anionic species (entry 3). On the other hand, the use of HMPA as an additive facilitated the alkylation reaction, affording the desired product in 69% yield (entry 4), while *i*-propyl iodide failed to induce the alkylation reaction even in the presence of HMPA (entry 5). The hetero atoms such as a silyl group and iodine also could be installed to the cyclopropane ring (entry 6, 7).



entry	electrophile	HMPA (eq.)	R	result
1	Mel	–	Me	93%
2	PhCH ₂ Br	–	PhCH ₂	80%
3	<i>n</i> BuI	–	<i>n</i> Bu	0%
4	<i>n</i> BuI	2	<i>n</i> Bu	69%
5	<i>i</i> PrI	2	<i>i</i> Pr	0%
6	<i>t</i> Pr ₃ SiCl	–	<i>t</i> Pr ₃ Si	100%
7	ICH ₂ CH ₂ I	2	I	83%

Table 2 Alkylation reaction of β -cyano carbanion

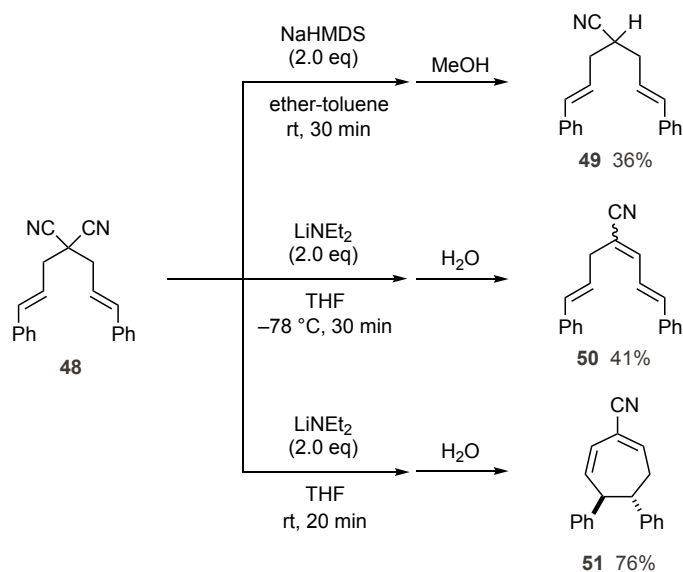
Interestingly, alkylated three-membered malononitrile **46** was found to undergo the decyanation reaction with NaHMDS (Scheme 23), probably because the deprotonation pathway suffered from the increased steric hindrance at the cyclopropane ring. The resulting α -silyl nitrile was subjected to the desilylation with TBAF, and the desired mononitrile **47** was obtained in 76% yield.



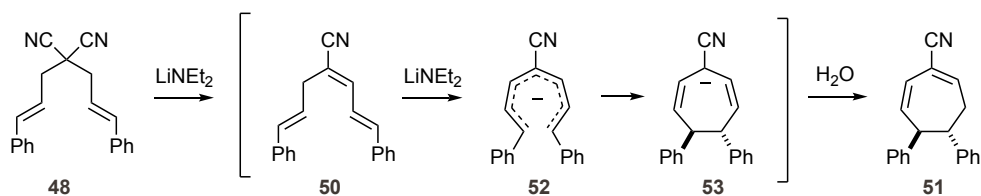
Scheme 23 Decyanation of β -methyl dicyanocyclopropane

1.4 Electrocyclization of Heptatrienyl Anion Species

In accord with earlier studies (Table 1, entry 4 and 5), the nucleophilic decyanation of di-cinnamyl malononitrile **48** occurred in a mixture of ether and toluene, albeit in low yield. On the other hand, treatment of **48** with lithium diethylamide in THF led to different results (Scheme 24).¹⁰ Thus, a dehydrocyanation reaction occurred at $-78\text{ }^{\circ}\text{C}$ to give triene **50** as the major product, while the reaction at elevated temperature led to formation of seven-membered nitrile **51** as a

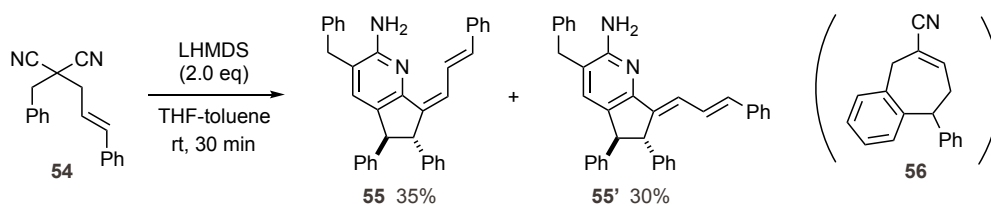


Scheme 24 Dehydrocyanation reaction of dicinnamyl malononitrile



Scheme 25 Proposed mechanism for formation of cycloheptadiene

single diastereomer in good yield. A proposed mechanism for the cyclization reaction is shown in Scheme 25. Since an excess amount of base was used, the relatively acidic allylic proton of **50** would be abstracted to form anionic species **52**. The heptatrienyl anion may undergo the electrocyclization reaction, because the resulting pentadienyl anion is strongly stabilized by the cyano group. It is noteworthy that the trans relationship between the two phenyl groups of **51** is consistent with the conrotatory mechanism of the electrocyclization reaction.



Scheme 26 Dimerization of malononitrile to afford amino pyridine

On the other hand, phenyl cinnamyl malononitrile **54** was found to undergo another type cyclization reaction, resulting in formation of amino pyridines **55** and **55'** (Scheme 26), the structure of which was confirmed by X-ray crystallographic analysis of an imide derivative (Figure 1).

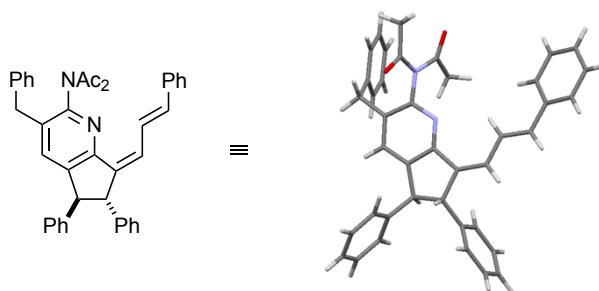
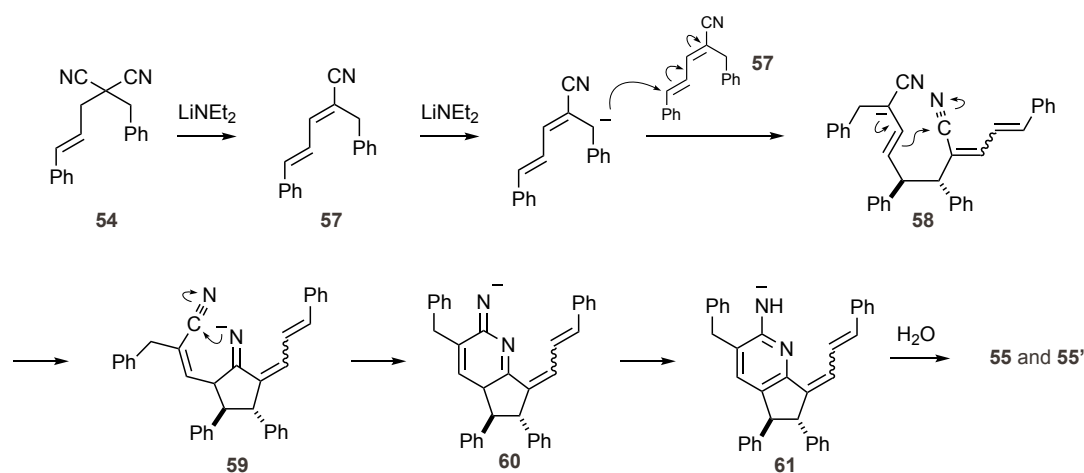


Figure 1 X-ray structure of imide derivative

As shown in Scheme 27, the formation of amino pyridines **55** and **55'** could be initiated by the intermolecular conjugate addition reaction of diene **57** with its anionic form. The resulting dimer **58** would cyclize to form a five-membered imide **59** which undergoes further addition reaction with the cyano group. Finally, the aromatization of pyrimidine intermediate **60** gives aminopyridine **55** and **55'**. Interestingly, **55** was found to show purple fluorescence under sunlight during which isomerization to give a 1:1 mixture of **55** and **55'**.



Scheme 27 Possible mechanism for formation of amino pyridine

1.5 Conclusions

In conclusion, a new method for achieving the decyanation of disubstituted malononitrile derivatives without using reducing agents has been developed. Treatment of malononitriles with NaHMDS followed by methanol afforded the corresponding acetonitrile derivative in high yield. The mild non-reductive reaction condition tolerates functional groups such as benzyl ether (Table 1, entry 2), which shows promise for use in natural product synthesis. On the other hand, dicyano cyclopropane was found to be deprotonated at the β -position of dicyano moiety, which could be trapped by various electrophiles. Furthermore, cycloheptadiene carbonitrile was accessed in a single operation by means of electrocyclization of heptatrienyl anion derived from di-cinnamyl malononitriles.

1.6 References

- 1) Rice, L. M.; Seth, B. S.; Zalucky, T. B. *J. Med. Chem.*, **1972**, *15*, 548.
- 2) Campaigne, E.; Forsch, R. A. *J. Org. Chem.*, **1978**, *43*, 1044.
- 3) Curran, D. P.; Seong, C. M. *Synlett*, **1991**, 107.
- 4) Kang, H.-Y.; Hong, E. S. *Tetrahedron Lett.*, **1995**, *36*, 7661.
- 4) Tsai, T.-Y.; Shia, K.-S.; Liu, H.-J. *Synlett*, **2003**, 97.
- 5) Hattori, K.; Grossman, R. B. *J. Org. Chem.*, **2003**, *68*, 1409.
- 6) Reeves, J.T.; Malapit, C.A.; Buono, F.G. *et al. J Am Chem Soc.*, **2015**, *137*, 9481.
- 7) Mitudera, H.; Otaka, K.; Fujiwara, J. Malononitrile Compound as Pesticides. WO 2005068432 A1, July, 28, 2005.
- 8) Wang, B. Synthesis Method of 3-Oxocyclobutanecarboxylic Acid. CN 103232340, August, 7, 2013.
- 9) Banister, A. J.; Clegg, W.; Gorrell, I. B.; Hauptman, Z. V.; Small, R. W. H. *J. Chem. Soc. Chem. Commun.*, **1987**, 1611.
- 10) Arseniyadis, S.; Kyler, K. S. Watt, D. S. *Org. React.*, **1984**, *31*, 1.
- 11) (a) Freeman, F. *Chem. Rev.*, **1969**, *69*, 591. (b) Black, P. J.; Edwards, M. G.; Williams, J. M. *J. Tetrahedron* **2005**, *61*, 1363. (c) Murahashi, S.; Naota, T.; Taki, H.; Mizuno, M.; Takaya, H.; Komiya, S.; Mizuho, Y.; Oyasato, N.; Hiraoka, M.; Hirano, M.; Fukuoka, A. *J. Am. Chem. Soc.*, **1995**, *117*, 12436. For examples of asymmetric conjugate addition of malononitrile to enones, see; (d) Li, X.; Ma, Y.; Xing, Z.; Tang, N.; Zhu, J.; Deng, J. *Tetrahedron Lett.*, **2014**, *55*, 3868. (e) Li, X.; Cun, L.; Lian, C.; Zhong, L.; Chen, Y.; Liao, J.; Zhu, J.; Deng, J. *Org. Biomol. Chem.*, **2008**, *6*, 349. (f) Russo, A.; Perfetto, A.; Lattanzi, A. *Adv. Synth. Catal.*, **2009**, *351*, 3067. (g) Yang, W.; Jia, Y.; Du, D.-M. *Org. Biomol. Chem.*, **2012**, *10*, 332.
- 12) Iwasawa, N.; Maeyama, K.; Kusama, H. *Org. Lett.*, **2001**, *3*, 3871.
- 13) Banerjee, S.; Santra, S. *Tetrahedron Lett.*, **2009**, *50*, 2037.
- 14) (a) Jones, G. *Org. React.*, **1967**, *15*, 204. (b) Cope, A. C. *J. Am. Chem. Soc.*, **1937**, *59*, 2327.

(c) Ramachary, D. B.; Kishor, M.; Reddy, Y. V. *Eur. J. Org. Chem.*, **2008**, 975.

15) For a review of 1,1-dicyanoalkenes, see; (a) Freeman, F. *Chem. Rev.*, **1980**, 80, 329. (b) Kaur, J.; Chauhan, P.; Chimni, S. S. *Org. Biomol. Chem.*, **2016**, 14, 7832.

16) Holmberg, C. *Liebigs Ann. Chem.*, 1981, 748.

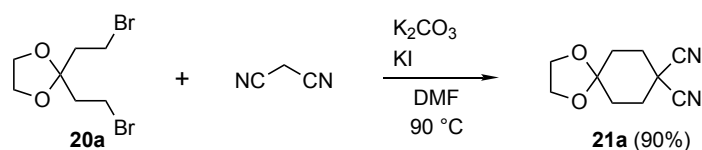
17) (a) Cope, A. C.; Hoyle, K. E. *J. Am. Chem. Soc.*, **1941**, 63, 733. (b) Karlsen, H.; Songe, P. H.; Sunby, L. K.; Hagen, L. C.; Kolsaker, P.; Romming, C. *J. Chem. Soc. Perkin Trans. 1*, **2001**, 497.

1.7 Experimental Section

General Methods

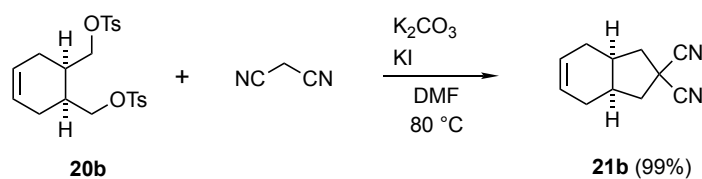
The reactions were performed using flame-dried glasswares under a positive pressure of argon. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Anhydrous 1,2-dichloroethane, toluene, and dichloromethane were purchased from Sigma-Aldrich Co. Ltd or Kanto Chemical Co. Diisopropylamine, triethylamine and hexamethylphosphoric triamide (HMPA) was distilled from CaH_2 under argon and stored in the presence of NaOH (pellets) or MS4A. All other reagents and solvents were used as received from commercial sources without further purification. ^1H NMR spectra were measured using a JEOL ECA-500 (500 MHz) in CDCl_3 (δ_{H} 7.26), C_6D_6 (δ_{H} 7.16), CD_2Cl_2 (δ_{H} 5.30) and $(\text{CD}_3)_2\text{CO}$ (δ_{H} 2.04) with tetramethylsilane as an internal standard. Chemical shifts are reported in parts per million (ppm) from internal tetramethylsilane, and signal are expressed as singlet (s), doublet (d), triplet (t), quartet (q), septet (sept), and multiplet (m). Coupling constants are reported in Hz. ^{13}C NMR spectra were measured using a JEOL ECA-500 (125 MHz) in CDCl_3 (δ_{C} 77.0), CD_2Cl_2 (δ_{C} 53.5) with tetramethylsilane as an internal standard. High-resolution mass spectra (HRMS) were recorded on a JEOL JMS-T100GCV or a JEOL JMS-SX102A at the GC-MS & NMR Laboratory, Faculty of Agriculture, Hokkaido University. Infrared (IR) spectra were recorded on a JASCO FT/IR-4100 spectrophotometer. Melting points were determined with a Mitamura-Riken-Kogyo melting point apparatus and were uncorrected. Analytical thin layer chromatography (TLC) was performed using 0.25 mm E. Merck Silica gel (60F-254) plates. Kanto Chem. Co. Silica Gel 60N (particle size 0.040–0.050 mm) was used for flash column chromatography.

Compound 21a



A mixture of dibromide **20a** (867.6 mg, 3.03 mmol), K₂CO₃ (1.30 g, 9.4 mmol), KI (1.50 g, 9.0 mmol), and malononitrile (300.2 mg, 4.54 mmol) in DMF (6 mL) was heated at 90 °C for 40 min. After cooling to room temperature, the reaction was quenched with H₂O. The mixture was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluted with 15% AcOEt/hexane) to give **21a** (526.5 mg, 2.74 mmol, 90%) as a yellow solid; mp 73.5-75.0 °C; ¹H NMR (500 MHz, CDCl₃) δ 3.95 (s, 4 H), 2.30-2.33 (m, 4 H), 1.84-1.87 (m, 4 H); ¹³C NMR (125 MHz, CDCl₃) δ 115.3, 105.3, 64.6, 32.5, 31.3, 30.9; IR (neat) 2979, 2889, 1448, 1368, 1338, 1289, 1269, 1202, 1102, 1070; HRMS (FI) m/z [M⁺] calcd for [C₁₀H₁₂N₂O₂]⁺ 192.0899, found 192.0918.

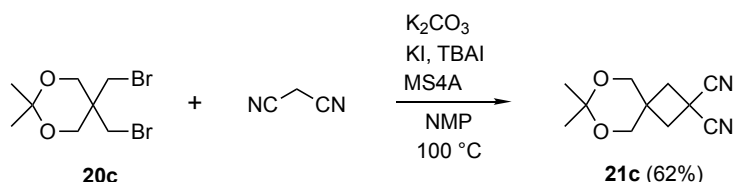
Compound 21b



According to the procedure for the synthesis of **21a**, **21b** was prepared from **20b** (218.3 mg, 0.48 mmol), K₂CO₃ (220.0 mg, 1.59 mmol), KI (255.5 mg, 1.53 mmol) and malononitrile (69.5 mg, 1.05 mmol) in DMF (2 mL) at 80 °C for 3 h. The crude product was purified by silica gel chromatography (eluted with 20% AcOEt/hexane) to give **21b** (82.2 mg, 0.47 mmol, 99%) as a colorless oil; ¹H NMR (500 MHz, CDCl₃) δ 5.71-5.70 (m, 2 H), 2.59 (dd, *J* = 13.2 Hz, 6.3 Hz, 2 H), 2.39-2.45 (m, 2 H), 2.24-2.29 (m, 4 H), 1.90-1.95 (m, 2 H); ¹³C NMR (125 MHz, CDCl₃) δ

124.9, 117.5, 44.9, 35.7, 30.8, 25.5; IR (neat) 3029, 2920, 2842, 2249, 1436; HRMS (FI) m/z [M^+] calcd for $[C_{11}H_{12}N_2]^+$ 172.1000, found 172.1021.

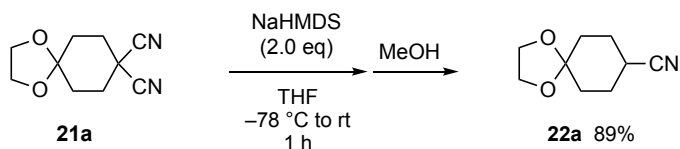
Compound 21c



A mixture of dibromide **20c** (917.9 mg, 3.04 mmol), K_2CO_3 (2.07 g, 15.0 mmol), KI (1.36 g, 8.19 mmol), and malononitrile (533.7 mg, 8.08 mmol), and flame-dried MS4A (1.52 g) in NMP (15 mL) was heated at 100 °C for 3 h. After cooling to room temperature, the reaction was quenched with H_2O . The mixture was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluted with 20% AcOEt/hexane) to give **21c** (384.4 mg, 1.86 mmol, 62%) as a white solid; mp 138.0 °C to 139.0 °C; 1H NMR (500 MHz, $CDCl_3$) δ 3.87 (s, 4 H), 2.74 (s, 4 H), 1.40 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 116.2, 98.3, 67.7, 39.5, 34.1, 23.4, 20.3; IR (neat) 2997, 2944, 2885, 2250; HRMS (FI) m/z [MH^+] calcd for $[C_{11}H_{15}N_2O_2]^+$ 207.1134, found 207.1141.

Typical procedure for the decyanation reaction:

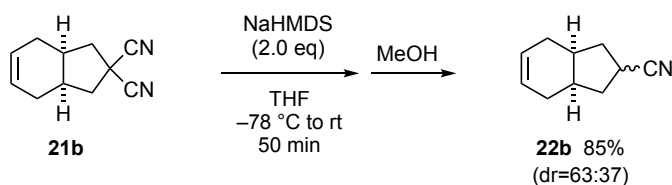
Compound 22a



To a solution of malononitrile **21a** (66.8 mg, 0.35 mmol) in THF (1.7 mL) was added 1.1 M solution of NaHMDS in THF (635 μ L, 0.70 mmol) at -78 °C. The reaction mixture was warmed up to room temperature and allowed to stir for 80 min. The resulting mixture was

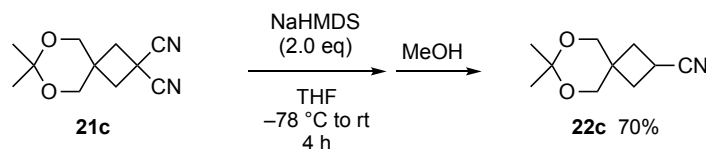
quenched with MeOH (250 μ L) and then a saturated aqueous NaCl aq. The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluted with 20% AcOEt/hexane) to give **22a** (52.2 mg, 0.31 mmol, 89%) as a colorless oil; ¹H NMR (500 MHz, CDCl₃) δ 4.09-3.91 (m, 4 H), 2.62-2.67 (m, 1 H), 1.89-2.01 (m, 4 H), 1.80-1.86 (m, 2 H), 1.58-1.64 (m, 2 H); ¹³C NMR (125 MHz, CDCl₃) δ 121.7, 106.9, 64.3, 64.3, 32.6, 26.8, 26.5; IR (neat) 2954, 2885, 1448, 1373; HRMS (FI) m/z [M⁺] calcd for [C₉H₁₃N₁O₂]⁺ 167.0946, found 167.0963.

Compound 22b



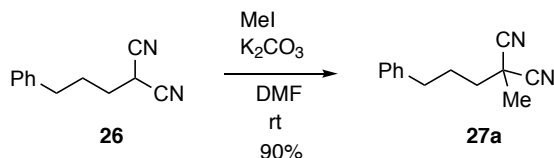
According to the procedure for the synthesis of **22a**, **22b** was prepared from **21b** (54.4 mg, 0.32 mmol) and 1.1 M solution of NaHMDS in THF (575 μ L, 0.63 mmol) in THF (2 mL) at room temperature for 80 min quenched with MeOH (250 μ L). The crude product was purified by silica gel chromatography (eluted with 5% AcOEt/hexane) to give **22b** (39.7 mg, 0.27 mmol, 85%) as a 58:42 mixture of diastereomers. Colorless oil; ¹H NMR (500 MHz, CDCl₃) δ 5.67-5.70 (m, 2 H), 5.61-5.64 (m, 2 H), 2.96-3.02 (m, 1 H), 2.81-2.88 (m, 1 H), 1.73-2.30 (m, 20 H); ¹³C NMR (125 MHz, CDCl₃) δ 125.0, 124.8, 124.8, 36.4, 36.3, 35.9, 35.4, 26.2, 25.8, 24.5, 24.4; IR (neat) 3023, 2911, 2838, 2234, 1456; HRMS (FI) m/z [M⁺] calcd for [C₁₀H₁₃N₁]⁺ 147.1048, found 147.1065.

Compound 22c



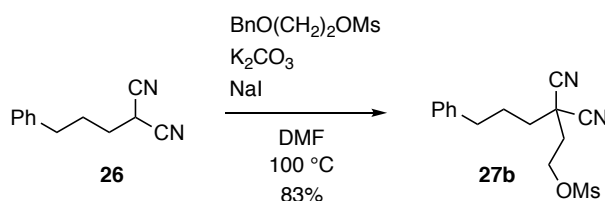
According to the procedure for the synthesis of **22a**, **22c** was prepared from **21c** (63.0 mg, 0.31 mmol) and 1.1 M solution of NaHMDS in THF (555 μ L, 0.61 mmol) in THF (2 mL) at room temperature for 2.5 h quenched with MeOH (250 μ L). The crude product was purified by silica gel chromatography (eluted with 10% AcOEt/hexane) to give **22c** (38.7 mg, 0.21 mmol, 70%) as a colorless crystal; mp 55.8 °C-57.5 °C; ^1H NMR (500 MHz, CDCl_3) δ 3.79 (s, 2 H), 3.73 (s, 2 H), 3.05 (quin, J = 8.0 Hz, 1 H), 2.20-2.34 (m, 4 H), 1.39 (s, 6 H); ^{13}C NMR (125 MHz, CDCl_3) δ 122.3, 97.9, 68.7, 67.3, 35.1, 32.5, 23.6, 16.4; IR (neat) 2993, 2941, 2858, 2237, 1454; HRMS (FI) m/z $[\text{MH}^+]$ calcd for $[\text{C}_{10}\text{H}_{16}\text{N}_2\text{O}_2]^+$ 182.1181, found 182. 1177.

Compound 27a



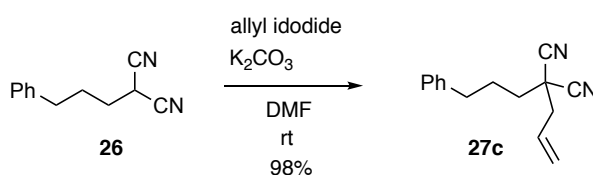
A mixture of malononitrile **26** (113.2 mg, 0.61 mmol), K_2CO_3 (127.2 mg, 0.92 mmol), and iodomethane (58 μ L, 0.92 mmol) in DMF (1.2 mL) was stirred at room temperature for 2 h. The reaction was quenched with H_2O . The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over MgSO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluted with 5% AcOEt/hexane) to give **27a** (109.8 mg, 0.55 mmol, 90%) as a colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 7.17-7.39 (m, 5 H), 2.76 (t, J = 7.5 Hz, 2 H), 1.98-2.31 (m, 2 H); 1.92-1.96 (m, 2 H), 1.78 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 140.0, 128.6, 128.3, 126.4, 116.1, 38.4, 34.6, 31.6, 27.0, 24.6; IR (neat) 3029, 2932, 2866, 2250, 1603; HRMS (FI) m/z $[\text{M}^+]$ calcd for $[\text{C}_{13}\text{H}_{12}\text{N}_2]^+$ 198.1157, found 198.1156.

Compound 27b



According to the procedure for the synthesis of **27a**, **27b** was prepared from malononitrile **26** (113.8 mg, 0.62 mmol), K₂CO₃ (128.6 mg, 0.93 mmol), NaI (138.8 mg, 0.93 mmol) and 2-benzyloxyethyl methanesulfonate (225.1 mg, 0.98 mmol) in DMF (1.2 mL) at 100 °C for 1.5 h. The crude product was purified by silica gel chromatography (eluted with 15% AcOEt/hexane) to give **27b** (163.1 mg, 0.51 mmol, 83%) as a colorless oil; ¹H NMR (500 MHz, CDCl₃) δ 7.38-7.16 (m, 10 H), 4.55 (s, 2 H), 3.76 (t, *J* = 6.3 Hz, 2 H), 2.71 (t, *J* = 6.9, 2 H), 2.22 (t, *J* = 6.3 Hz, 2 H), 1.96-2.07 (m, 4 H); ¹³C NMR (125 MHz, CDCl₃) δ 140.1, 137.2, 128.4, 128.3, 128.2, 127.7, 127.5, 126.2, 115.3, 73.3, 65.5, 37.2, 36.8, 35.2, 34.5, 26.7; IR (neat) 3029, 2973, 2927, 2866, 2169, 1603, 1496; HRMS (FI) *m/z* [*M*⁺] calcd for [C₂₁H₂₂N₂O]⁺ 318.1732, found 318.1742.

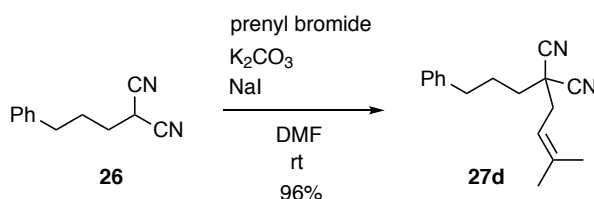
Compound 27c



According to the procedure for the synthesis of **27a**, **27c** was prepared from malononitrile **26** (113.0 mg, 0.61 mmol), K₂CO₃ (127.0 mg, 0.92 mmol), and allyliodide (84 μL, 0.92 mmol) in DMF (1.2 mL) at room temperature for 3 h. The crude product was purified by silica gel chromatography (eluted with 5% AcOEt/hexane) to give **7c** (143.3 mg, 0.64 mmol, 98%) as a colorless oil; ¹H NMR (500 MHz, CDCl₃) δ 7.18-7.33 (m, 5 H), 5.82-5.91 (m, 1 H), 5.41 (d, *J* = 10.3 Hz, 1 H), 5.37 (d, *J* = 17.2, 1 H), 2.74 (t, *J* = 7.5 Hz, 2 H), 2.65 (d, *J* = 7.5 Hz, 2 H), 1.91-2.30 (m, 4 H); ¹³C NMR (125 MHz, CDCl₃) δ 140.1, 128.6, 128.4, 128.3, 126.4, 123.1,

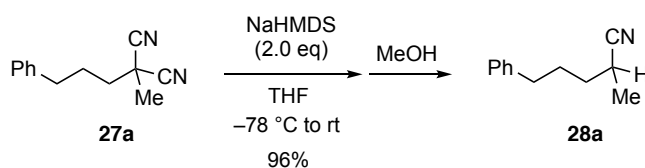
115.1, 41.4, 37.4, 36.3, 34.7, 26.9; IR (neat) 3027, 2931, 2865, 2247, 1644, 1497; HRMS (FI) m/z [M^+] calcd for $[C_{15}H_{16}N_2]^+$ 224.1313, found 224.1316.

Compound 27d



According to the procedure for the synthesis of **27a**, **27d** was prepared from malononitrile **26** (114.0 mg, 0.62 mmol), K_2CO_3 (128.1 mg, 0.93 mmol), NaI (139.0 mg, 0.93 mmol) and prenylbromide (107 μ L, 0.93 mmol) in DMF (1.2 mL) at room temperature for 3 h. The crude product was purified by silica gel chromatography (eluted with 5% AcOEt/hexane) to give **7d** (149.2 mg, 0.59 mmol, 96%) as a yellow oil; 1H NMR (500 MHz, $CDCl_3$) δ 7.18-7.33 (m, 5 H), 5.23-5.26 (m, 1 H), 2.73 (t, $J = 7.5$ Hz, 2 H), 2.63 (d, $J = 7.5$, 2 H), 1.99-2.05 (m, 2 H), 1.89-1.93 (m, 2 H), 1.79 (s, 3 H), 1.69 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.5, 140.2, 128.5, 128.3, 126.3, 115.6, 114.5, 37.7, 36.2, 36.1, 34.7, 27.0, 25.9, 18.3; IR (neat) 3028, 2933, 2862, 2249, 1674, 1604; HRMS (FI) m/z [M^+] calcd for $[C_{17}H_{20}N_2]^+$ 252.1626, found 252.1630.

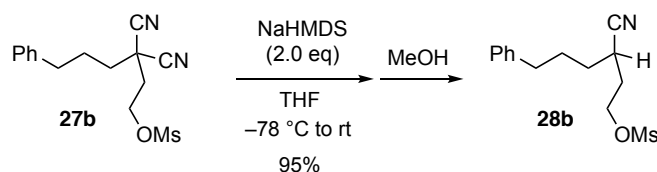
Compound 28a



According to the procedure for the synthesis of **22a**, **28a** was prepared from **27a** (61.5 mg, 0.31 mmol) and 1.1 M solution of NaHMDS in THF (565 μ L, 0.62 mmol) in THF (1.6 mL) at room temperature for 2.5 h quenched with MeOH (250 μ L). The crude product was purified by silica gel chromatography (eluted with 5% AcOEt/hexane) to give **28a** (51.7 mg, 0.30 mmol, 96%) as a colorless oil; 1H NMR (500 MHz, $CDCl_3$) δ 7.17-7.31 (m, 5 H), 2.57-2.67 (m, 3 H),

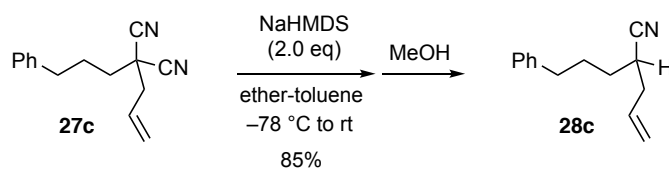
1.83-1.92 (m, 1 H), 1.72-1.81 (m, 1 H), 1.53-1.68 (m, 2 H), 1.30 (d, $J = 7.4$ Hz, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 141.3, 128.4, 128.3, 126.0, 122.9, 35.2, 33.4, 28.6, 25.4, 17.9; IR (neat) 3026, 2979, 1938, 2859, 2238, 1603; HRMS (FI) m/z [M^+] calcd for $[\text{C}_{12}\text{H}_{15}\text{N}_1]^+$ 173.1204, found 173.1210.

Compound 28b



According to the procedure for the synthesis of **22a**, **28b** was prepared from **27b** (105.6 mg, 0.33 mmol) and 1.1 M solution of NaHMDS in THF (605 μL , 0.66 mmol) in THF (1.7 mL) at room temperature for 2.5 h quenched with MeOH (250 μL). The crude product was purified by silica gel chromatography (eluted with 15% AcOEt/hexane) to give **27b** (93.3 mg, 0.32 mmol, 95%) as a yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 7.09-7.30 (m, 10 H), 4.46 (d, $J = 11.5$ Hz, 1 H), 4.41 (d, $J = 11.5$ Hz, 1 H), 3.54 (t, $J = 5.8$ Hz, 2 H), 2.77 (quin, $J = 6.9$ Hz, 1 H), 2.53-2.62 (m, 2 H), 1.76-1.87 (m, 3 H), 1.65-1.74 (m, 1 H), 1.50-1.60 (m, 2 H); ^{13}C NMR (125 MHz, CDCl_3) δ 141.2, 137.8, 128.4, 128.3, 128.3, 127.7, 127.6, 125.9, 121.8, 73.2, 66.8, 35.1, 32.4, 31.4, 28.6, 28.3; IR (neat) 3027, 2929, 2859, 2236, 1603; HRMS (FI) m/z [M^+] calcd for $[\text{C}_{20}\text{H}_{23}\text{N}_1\text{O}]^+$ 293.1780, found 293.1786.

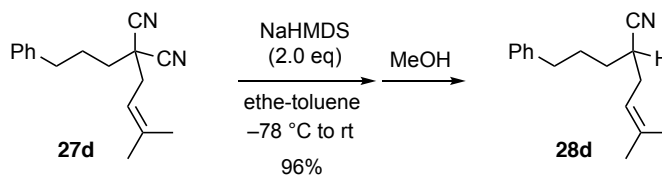
Compound 28c



To a solution of malononitrile **27c** (75.0 mg, 0.33 mmol) in ether (1.7 mL) was added 0.6 M solution of NaHMDS in toluene (1.1 mL, 0.67 mmol) at -78°C . The reaction mixture was

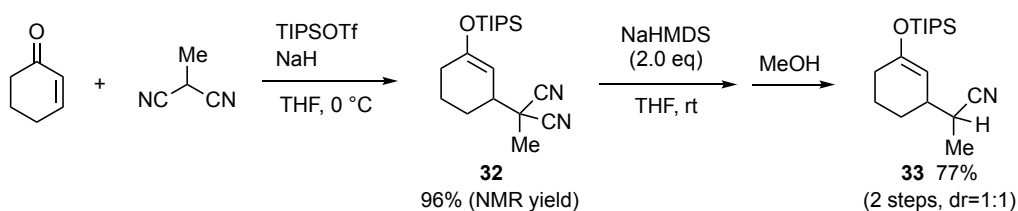
warmed up to room temperature and allowed to stir for 3 h. The resulting mixture was quenched with MeOH (250 μ L) and a saturated aqueous NaCl solution. The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluted with 5% AcOEt/hexane) to give **28c** (57.0 mg, 0.29 mmol, 85%) as a colorless oil; ¹H NMR (500 MHz, CDCl₃) δ 7.17-7.31 (m, 5 H), 5.75-5.83 (m, 1 H), 5.16-5.19 (m, 2 H), 2.66 (t, J = 7.5 Hz, 2 H), 2.59 (quin, J = 8.0 Hz, 1 H), 2.28-2.38 (m, 2 H), 1.84-1.94 (m, 1 H), 1.72-1.81 (m, 1 H), 1.58-1.69 (m, 2 H); ¹³C NMR (125 MHz, CDCl₃) δ 141.2, 133.0, 128.4, 128.3, 126.0, 121.6, 118.8, 36.1, 35.1, 31.3, 31.0, 28.6; IR (neat) 3082, 3027, 2941, 2862, 2238, 1644, 1604, 1497; HRMS (FI) m/z [M^+] calcd for [C₁₄H₁₇N₁]⁺ 199.1361, found 199.1355.

Compound 28d



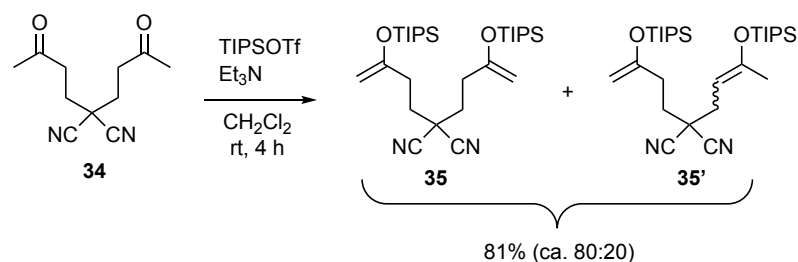
According to the procedure for the synthesis of **9c**, **9d** was prepared from **7d** (78.3 mg, 0.31 mmol) and 0.6 M solution of NaHMDS in toluene (1.0 mL, 0.62 mmol) in ether (1.6 mL) at room temperature for 3 h quenched with MeOH (250 μ L). The crude product was purified by silica gel chromatography (eluted with 2% AcOEt/hexane) to give **9d** (68.0 mg, 0.30 mmol, 96%) as a colorless oil; ¹H NMR (500 MHz, CDCl₃) δ 7.17-7.31 (m, 5 H), 5.13-5.16 (m, 1 H), 2.61-2.70 (m, 2 H), 2.53 (quin, J = 6.3 Hz, 1 H), 2.22-2.34 (m, 2 H), 1.84-1.94 (m, 1 H), 1.72-1.80 (m, 4 H), 1.57-1.67 (m, 5H); ¹³C NMR (125 MHz, CDCl₃) δ 141.3, 135.8, 128.3, 128.3, 125.9, 122.1, 119.0, 35.2, 31.9, 31.0, 30.6, 28.8, 25.7, 17.9; IR (neat) 3028, 2927, 2861, 2236, 1603, 1496; HRMS (FI) m/z [M^+] calcd for [C₁₆H₂₁N₁]⁺ 227.1674, found 227.1686.

Compound 33



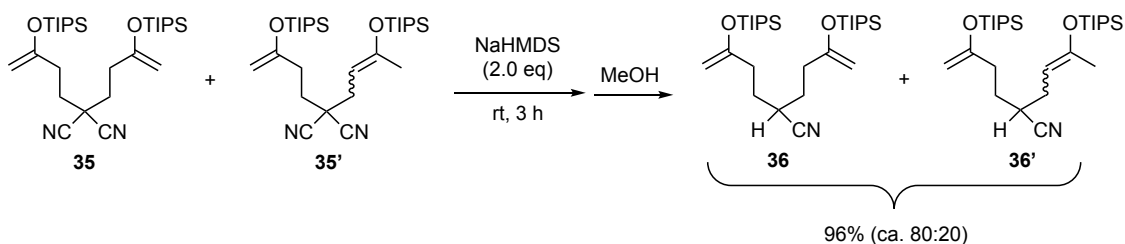
To a suspension of NaH (22.9 mg, 0.52 mmol, 55% w/v dispersion in mineral oil) in THF (0.6 mL) was added a solution of methylmalononitrile (26.2 mg, 0.33 mmol) in THF (0.4 mL) at 0 °C. After 30 min, a solution of 2-cyclohexene-1-one (24 μL , 0.25 mmol) in THF (0.3 mL) and TIPSOTf (74 μL , 0.28 mmol) was added to the reaction mixture. After being stirred for 30 min at 0 °C, the reaction was quenched with pH 7 phosphate buffer. The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over MgSO_4 and concentrated under reduced pressure. The residue was roughly purified by silica gel column chromatography (EtOAc/hexane = 5%). The product was used for next step without further purification. To a solution of malononitrile **32** (80.9 mg) in THF (1.2 mL) was added 1.1 M solution of NaHMDS in THF (460 μL , 0.50 mmol) at -78 °C. The reaction mixture was warmed up to room temperature and allowed to stir for 3 h. The resulting mixture was quenched with MeOH (250 μL) and a saturated aqueous NaCl solution. The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over MgSO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluted with 5% AcOEt/hexane) to give **33** (57.4 mg, 0.19 mmol, 75% for 2 steps) as a 48:52 mixture of diastereomers. Colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 4.86 (s, 1 H), 4.75 (s, 1 H), 2.47-2.57 (m, 2 H), 2.34-2.43 (m, 2 H), 1.99-2.17 (m, 4 H), 1.77-1.88 (m, 4 H), 1.53-1.64 (m, 2 H), 1.24-1.43 (m, 8 H), 1.12-1.22 (m, 6 H), 1.06-1.08 (m, 36 H); ^{13}C NMR (125 MHz, CDCl_3) δ 153.8, 122.3, 122.2, 103.4, 103.0, 38.3, 38.2, 31.5, 31.4, 29.7, 29.6, 26.4, 25.8, 21.5, 21.3, 17.9, 15.4, 15.2, 12.5, 12.5; IR (neat) 2941, 2866, 2364, 1662, 1369; HRMS (FI) m/z [M^+] calcd for $[\text{C}_{18}\text{H}_{22}\text{N}_1\text{O}_1\text{Si}_1]^+$ 307.2331, found 307.2335.

Compound 35 and 35'



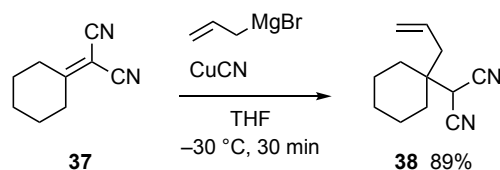
To a mixture of diketone **34** (185.6 mg, 0.90 mmol), Et₃N (1.5 mL, 10.8 mmol) in CH₂Cl₂ (4.5 mL) was added TIPSOTf (1.5 mL, 5.4 mmol) at 0 °C. After stirred for 5.5 h, the reaction was quenched with saturated aqueous NaHCO₃ solution. The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layer was dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluted with 2% AcOEt/hexane) to give **35** and **35'** (378.0 mg, 0.73 mmol, 81%) as inseparable mixture (ca. 60:40). Colorless oil; for **35**: ¹H NMR (500 MHz, CDCl₃) δ 3.96 (m, 4 H), 2.27-2.29 (m, 4 H), 2.01-2.05 (m, 4 H), 0.98-1.11 (m, 6 H), 0.93 (d, *J* = 7.5 Hz, 36 H); ¹³C NMR (125 MHz, CDCl₃) δ 155.8, 115.1, 90.6, 36.8, 35.4, 32.9, 17.9, 12.4; for **35'**: ¹H NMR (500 MHz, CDCl₃) δ 4.32 (t, *J* = Hz, 1 H), 3.95 (s, 1 H), 3.94 (s, 1 H), 2.62 (d, *J* = 7.5 Hz, 2 H), 2.23-2.29 (m, 2 H), 1.96-1.99 (m, 2 H), 1.76 (s, 3 H), 0.98-1.09 (m, 6 H), 0.93 (d, *J* = 7.5 Hz, 36 H); ¹³C NMR (125 MHz, CDCl₃) δ 156.1, 153.3, 115.6, 97.2, 90.4, 38.3, 37.4, 34.6, 33.8, 33.0, 22.7, 17.9, 13.1; IR (neat) 2945, 2867, 2158, 1665, 1632; HRMS (FI) *m/z* [M⁺] calcd for [C₂₉H₅₄N₂O₂Si₂]⁺ 518.3723, found 518.3717.

Compound 36 and 36'



According to the procedure for the synthesis of **22a**, **36** and **36'** were prepared from **35** and **35'** (105.2 mg, 0.20 mmol) and 1.1 M solution of NaHMDS in THF (675 μ L, 0.41 mmol) in THF (1.0 mL) at room temperature for 3 h quenched with MeOH (250 μ L). The crude product was purified by silica gel chromatography (eluted with 5% AcOEt/hexane) to give **36** and **36'** (95.4 mg, 0.19 mmol, 96%) as inseparable mixture (ca. 60:40). Colorless oil; for **36**: ^1H NMR (500 MHz, CDCl_3) δ 4.13 (s, 4 H), 2.67-2.73 (m, 1 H), 2.33-2.39 (m, 2 H), 2.22-2.29 (m, 2 H), 1.86-1.94(m, 4 H), 1.18-1.29 (m, 6 H), 1.14 (d, J = 6.9 Hz, 36 H); for **36'**: ^1H NMR (500 MHz, CDCl_3) δ 4.46 (t, J = 7.5 Hz, 1 H), 4.12 (s, 2 H), 2.61-2.65 (m, 1 H), 2.22-2.48 (m, 4 H), 1.90 (s, 3 H), 1.78-1.94 (m, 2 H), 1.18-1.29 (m, 6 H), 1.14-1.16 (m, 36 H); IR (neat) 2944, 2893, 2867, 1671, 1627, 1464; HRMS (FI) m/z [M^+] calcd for $[\text{C}_{28}\text{H}_{55}\text{N}_1\text{O}_2\text{Si}_2]^+$ 493.3771, found 493.3788

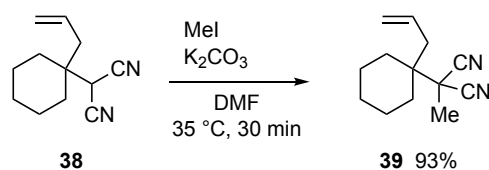
Compound 38



To a suspension of CuCl (81.3 mg, 0.78 mmol) in THF (0.6 mL) was added 1.0 M solution of allylmagnesiumbromide in ether (1.5 mL, 1.5 mmol) in THF (10 mL) at $-78\text{ }^\circ\text{C}$. The mixture was warmed up to $-30\text{ }^\circ\text{C}$. After 30 min, a solution of cyclohexylidenemalononitrile **37** (83.8 mg, 0.57 mmol) in THF (0.5 mL) was added to the reaction mixture at $-78\text{ }^\circ\text{C}$. After being stirred for 30 min, the reaction was quenched with 9:1 v/v mixture of saturated aqueous ammonium chloride and conc. ammonia, and allowed to stir at room temperature until blue solution is formed. The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over MgSO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane = 5%) to give **38** (95.7 mg, 0.51 mmol, 89%) as a colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 5.69-5.78 (m, 1 H), 5.26-5.31 (m, 2 H), 3.70 (s, 1 H), 2.43 (d, J = 7.5 Hz, 2 H), 1.49-1.70 (m, 9 H), 1.30-1.37 (m, 1

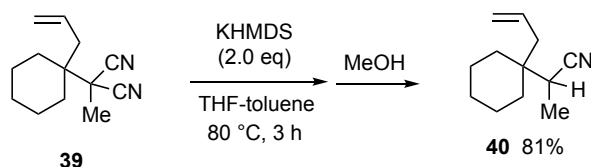
H); ^{13}C NMR (125 MHz, CDCl_3) δ 130.9, 121.1, 111.8, 40.9, 37.2, 32.8, 32.0, 24.9, 21.0; IR (neat) 3078, 2932, 2863, 2227, 1640; HRMS (FI) m/z $[\text{M}^+]$ calcd for $[\text{C}_{12}\text{H}_{16}\text{N}_2]^+$ 188.1313, found 188.1310.

Compound 39



According to the procedure for the synthesis of **27a**, **39** was prepared from malononitrile **16** (44.8 mg, 0.24 mmol), K_2CO_3 (49.0 mg, 0.36 mmol), and iodomethane (73 μL , 1.18 mmol) in DMF (0.5 mL) at 35 $^\circ\text{C}$ for 30 min. The crude product was purified by silica gel chromatography (eluted with 5% AcOEt/hexane) to give **39** (47.2 mg, 0.23 mmol, 98%) as a colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 5.88-5.97 (m, 1 H), 5.25 (d, $J = 17.2$ Hz, 1 H), 5.20 (d, $J = 9.7$ Hz, 1 H), 2.50 (d, $J = 7.5$, 1 H), 1.43-1.84 (m, 12 H), 1.16-1.25 (m, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 132.6, 119.5, 116.2, 42.6, 41.9, 35.7, 31.1, 24.8, 21.2, 19.9; IR (neat) 3079, 3017, 2937, 2862, 2234, 1639; HRMS (FI) m/z $[\text{M}^+]$ calcd for $[\text{C}_{13}\text{H}_{18}\text{N}_2]^+$ 202.1470, found 202.1470.

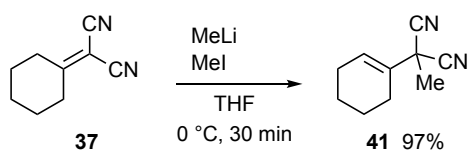
Compound 40



According to the procedure for the synthesis of **22a**, **40** was prepared from **17** (41.3 mg, 0.20 mmol) and 0.5 M solution of KHMDS in toluene (820 μL , 0.41 mmol) in THF (1.6 mL) at 80 $^\circ\text{C}$ for 3 h quenched with MeOH (250 μL). The crude product was purified by silica gel chromatography (eluted with 5% AcOEt/hexane) to give **40** (29.3 mg, 0.17 mmol, 81%) as a colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 5.70-5.79 (m, 1 H), 5.11-5.14 (m, 2 H), 2.70 (q, $J =$

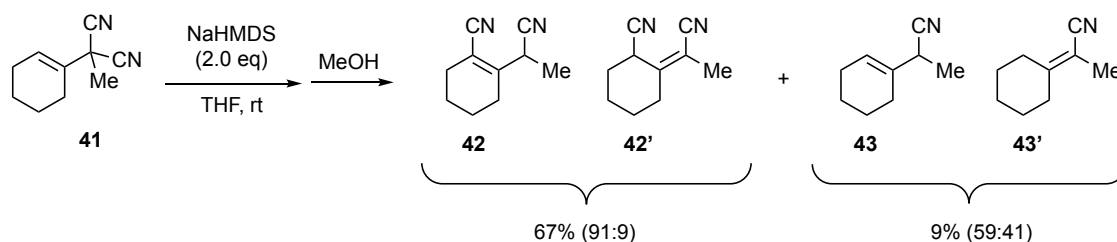
6.9 Hz, 1 H), 2.34 (dd, $J = 7.5$ Hz, 14.4 Hz, 1 H), 2.15 (dd, $J = 7.5$ Hz, 14.4 Hz, 1 H), 1.42-1.57 (m, 9 H), 1.30-1.37 (m, 1 H), 1.24 (d, $J = 6.9$ Hz, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 133.1, 122.3, 118.7, 37.6, 37.0, 33.3, 31.9, 25.6, 21.2, 21.1, 11.8, 21.2, 21.1; IR (neat) 3076, 2930, 2863, 2236, 1638; HRMS (FI) m/z $[\text{M}^+]$ calcd for $[\text{C}_{12}\text{H}_{19}\text{N}_1]^+$ 177.1517, found 177.1524.

Compound 41



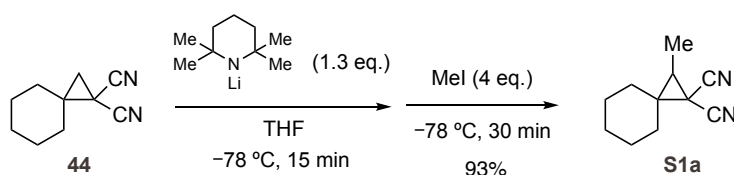
To a solution of cyclohexylidenemalononitrile **37** (81.9 mg, 0.56 mmol) in THF (2.8 mL) was added 1.1 M solution of MeLi in ether (765 μL , 0.84 mmol) at -78 $^\circ\text{C}$. The reaction mixture was warmed up to 0 $^\circ\text{C}$. After 30 min, iodomethane (175 μL , 2.8 mmol) was added to the reaction mixture at -78 $^\circ\text{C}$. The mixture was warmed up to room temperature and allowed stirring for 1 h. The reaction was quenched with saturated aqueous NH_4Cl solution. The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over MgSO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluted with 5% AcOEt/hexane) to give **41** (71.1 mg, 0.44 mmol, 79%) as a colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 6.14 (m, 1 H), 2.08-2.13 (m, 4 H), 1.81 (s, 3 H), 1.66-1.71 (m, 2 H), 1.53-1.58 (m, 2 H); ^{13}C NMR (125 MHz, CDCl_3) δ 129.0, 128.3, 115.3, 37.5, 25.1, 24.6, 24.2, 22.1, 21.1; IR (neat) 3014, 2935, 2863, 2247, 1449; HRMS (FI) m/z $[\text{M}^+]$ calcd for $[\text{C}_{10}\text{H}_{12}\text{N}_2]^+$ 160.1000, found 160.1011.

Compound 42 and 43



According to the procedure for the synthesis of **22a**, **42**, **42'**, **43**, and **43'** were prepared from **19** (32.0 mg, 0.20 mmol) and 0.6 M solution of NaHMDS in toluene (0.67 mL, 0.40 mmol) in ether (1.0 mL) at room temperature for 3 h quenched with MeOH (250 μ L). The crude product was purified by silica gel chromatography (eluted from 5% to 15% AcOEt/hexane) to give **20**, **20'** (21.4 mg, 0.13 mmol, 67%, colorless, oil) as a 91:1 of mixture, and **20**, **20'** (2.4 mg, 0.02 mmol, 9%, colorless, oil) as a 59:41 of mixture; for **20**: ^1H NMR (500 MHz, CDCl_3) δ 4.03 (q, J = 7.5 Hz, 1 H), 2.24-2.43 (m, 4 H), 1.60-1.79 (m, 4 H), 1.49 (d, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 150.5, 119.2, 117.1, 110.3, 31.9, 27.4, 25.5, 21.1, 20.9, 17.9; IR (neat) 2987, 2942, 2864, 2242, 2213, 1640, 1451, 1438; HRMS (FI) m/z [M^+] calcd for $[\text{C}_{10}\text{H}_{12}\text{N}_2]^+$ 160.1000, found 160.1009.

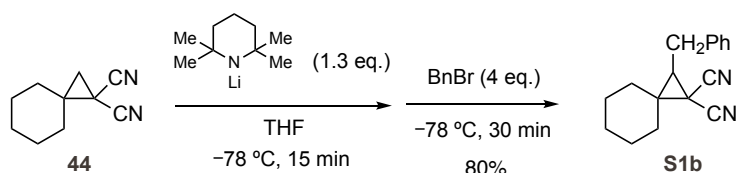
Compound S1a



To a solution of dicyanocyclopropane **44** (14.2 mg, 0.088 mmol) in THF (0.44 mL) was added 0.66 M solution of LiTMP in THF (0.18 mL, 0.12 mmol) at -78 $^\circ\text{C}$. After being stirred for 30 min, methyl iodide (22 μ L, 0.35 mmol) was added at same temperature. After 30 min, the reaction was quenched with saturated aqueous NaCl solution and the mixture was extracted with AcOEt. The combined organic layers were dried over MgSO_4 and concentrated under vacuum. The crude product was purified by silica gel chromatography to give **S1a** (14.4 mg, 0.082 mmol,

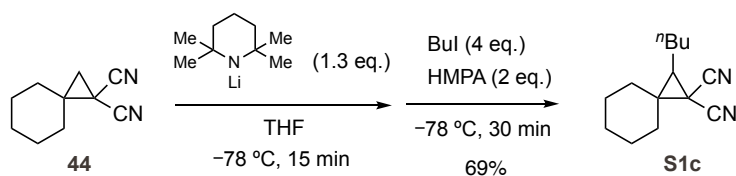
93%) as a colorless crystal. ^1H NMR (500 MHz, CDCl_3) δ : 1.83 (q, $J = 6.3\text{ Hz}$, 1 H), 1.73-1.58 (m, 10 H), 1.34 (t, $J = 6.3\text{ Hz}$, 3 H)

Compound S1b



To a solution of dicyanocyclopropane **44** (17.0 mg, 0.106 mmol) in THF (0.53 mL) was added 0.66 M solution of LiTMP in THF (0.21 mL, 0.14 mmol) at $-78\text{ }^\circ\text{C}$. After being stirred for 30 min, benzyl bromide (51 μL , 0.424 mmol) was added at same temperature. After 30 min, the reaction was quenched with saturated aqueous NaCl solution and the mixture was extracted with AcOEt. The combined organic layers were dried over MgSO_4 and concentrated under vacuum. The crude product was purified by silica gel chromatography to give **S1b** (20.0 mg, 0.079 mmol, 80%) as a yellow oil. ^1H NMR (500 MHz, CDCl_3) δ : 7.38-7.33 (m, 2 H), 7.31-7.22 (m, 3 H), 2.99 (dd, $J = 15.5\text{ Hz}$, 7.4 Hz, 1 H), 2.91 (dd, $J = 15.5\text{ Hz}$, 7.4 Hz, 1 H), 2.03 (t, $J = 7.5\text{ Hz}$, 1 H), 1.84-1.39 (m, 10 H)

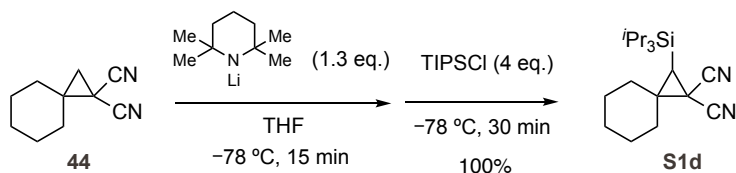
Compound S1c



To a solution of dicyanocyclopropane **44** (15.9 mg, 0.099 mmol) in THF (0.50 mL) was added 0.66 M solution of LiTMP in THF (0.20 mL, 0.132 mmol) at $-78\text{ }^\circ\text{C}$. After being stirred for 30 min, butyl iodide (44 μL , 0.39 mmol) and HMPA (34 μL , 0.19 mmol) were added at same temperature. After 30 min, the reaction was quenched with saturated aqueous NaCl solution and the mixture was extracted with AcOEt. The combined organic layers were dried over MgSO_4 and

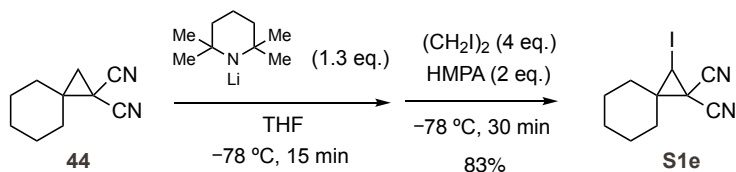
concentrated under vacuum. The crude product was purified by silica gel chromatography to give **S1c** (14.8 mg, 0.068 mmol, 69%) as a yellow oil. ^1H NMR (500 MHz, CDCl_3) δ : 1.80 - 1.36 (m, 17H), 0.94 (t, J = 6.9 Hz, 3H)

Compound S1d



To a solution of dicyanocyclopropane **44** (15.7 mg, 0.099 mmol) in THF (0.50 mL) was added 0.66 M solution of LiTMP in THF (0.20 mL, 0.132 mmol) at $-78\text{ }^\circ\text{C}$. After being stirred for 30 min, TIPSCl (84 μL , 0.39 mmol) was added at same temperature. After 30 min, the reaction was quenched with saturated aqueous NaCl solution and the mixture was extracted with AcOEt. The combined organic layers were dried over MgSO_4 and concentrated under vacuum. The crude product was purified by silica gel chromatography to give **S1d** (32.0 mg, 0.100 mmol, 100%) as a colorless oil. ^1H NMR (500 MHz, CDCl_3) δ : 1.96 (m, 1H), 1.86 - 1.74 (m, 4H), 1.67 - 1.48 (m, 4H), 1.22 - 1.30 (sept, J = 6.9 Hz, 3H), 1.15 (d, J = 6.9 Hz, 9H), 1.10 (d, J = 6.9 Hz, 9H), 0.74 (s, 1H)

Compound S1e



To a solution of dicyanocyclopropane **44** (15.5 mg, 0.097 mmol) in THF (0.48 mL) was added 0.66 M solution of LiTMP in THF (0.195 mL, 0.129 mmol) at $-78\text{ }^\circ\text{C}$. After being stirred for 30 min, 1,2-diiodoethane (109 mg, 0.39 mmol) and HMPA (34 μL , 0.193 mmol) in THF (0.39 mL) were added at same temperature. After 30 min, the reaction was quenched with saturated

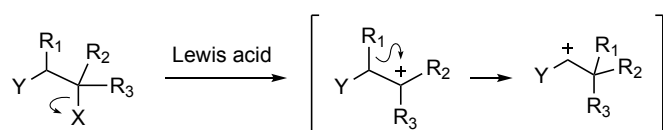
aqueous NaCl solution and the mixture was extracted with AcOEt. The combined organic layers were dried over MgSO₄ and concentrated under vacuum. The crude product was purified by silica gel chromatography to give **S1e** (23.1 mg, 0.081 mmol, 83%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ : 3.40 (s, 1 H), 1.88-1.80 (m, 2 H), 1.77-1.45 (m, 8 H)

Chapter 2.

The Development of Formal Semi-pinacol Rearrangement Reactions of Cyano Epoxyalcohols

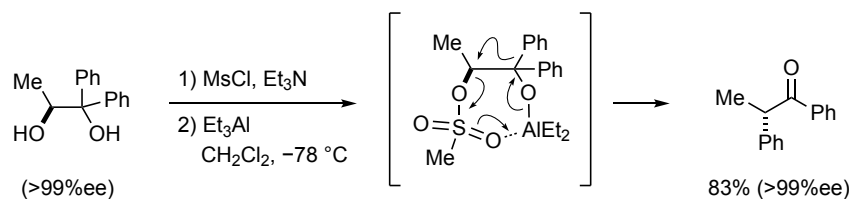
2.1 Introduction

Semi-pinacol rearrangement reactions¹ have found widespread use in organic synthesis especially for the construction of sterically hindered carbon skeleton with quaternary stereogenic centers. This type of reaction is usually conducted under the influence of a Lewis acid or a Brønsted acid, forming carbocation species which undergoes 1,2-shift of a substituent (Scheme 28). The key for the successful semi-pinacol rearrangement depends on, 1) leaving ability of the substituent X, 2) migratory tendency of the substituent R₁, and 3) stabilization of the resulting carbocation by substituent Y.



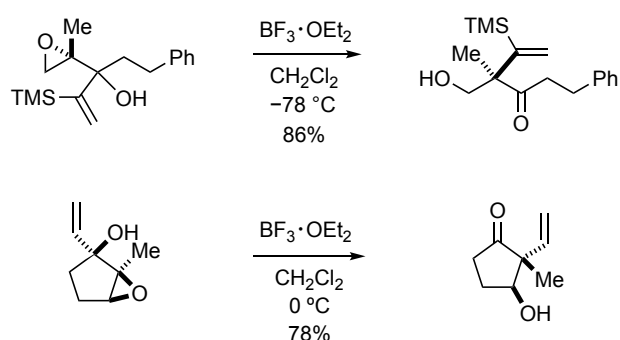
Scheme 28 General description of the 1,2-rearrangement reaction

Suzuki and Tsuchihashi developed the semi-pinacol rearrangement reaction of mono-mesylates of 1,2-diols promoted by an aluminum reagent.² The reaction proceeds in a stereospecific fashion with complete inversion of configuration at the mesylate moiety, indicating that abstraction of the leaving group and migration of the substituent occurs in a synchronous manner (Scheme 29).



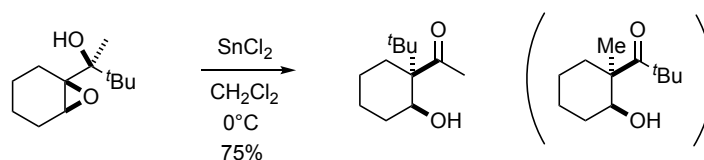
Scheme 29 Semipinacol rearrangement of mesylates

A similar concerted reaction mechanism, which involves no carbocation intermediate, was also suggested for the semi-pinacol rearrangement of epoxy alcohols (Scheme 30). Upon treatment with boron trifluoride etherate, epoxy alcohol was transformed into β -hydroxy ketone having a quaternary stereogenic center at the α -position. Semi-pinacol rearrangement reactions of epoxy alcohols are also applicable to alicyclic systems³, providing a powerful tool for the total synthesis of terpenoids.



Scheme 30 Semipinacol rearrangement of epoxy alcohols

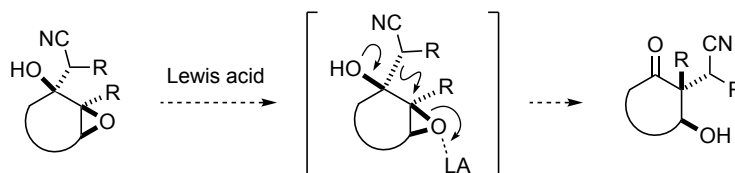
Since sp^2 carbon atoms generally exhibit higher migratory tendency than sp^3 carbon atoms, rearrangement reactions involving selective 1,2-shift of a vinyl or a phenyl group over an alkyl group are easily achieved. In case that two alkyl groups are competing in migration, more electron-rich one, such as *tert*-alkyl, α -silyl alkyl or α -alkoxy alkyl groups, would shift selectively¹ (Scheme 31).



Scheme 31 Migration tendencies of alkyl groups

Although there are few examples of the semi-pinacol rearrangement reaction involving

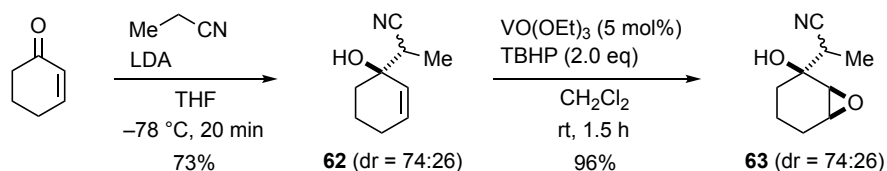
selective migration of an electron poor alkyl group over other alkyl groups, the author was prompted to develop a 1,2-migration reaction of electron poor cyano alkyl groups whose products could be promising building blocks possessing three different functional groups; keto-, hydroxyl- and cyano group (Scheme 32).



Scheme 32 The design for the synthesis of cyano hydroxyketones

2.2 Attempts at Semi-Pinacol Rearrangement

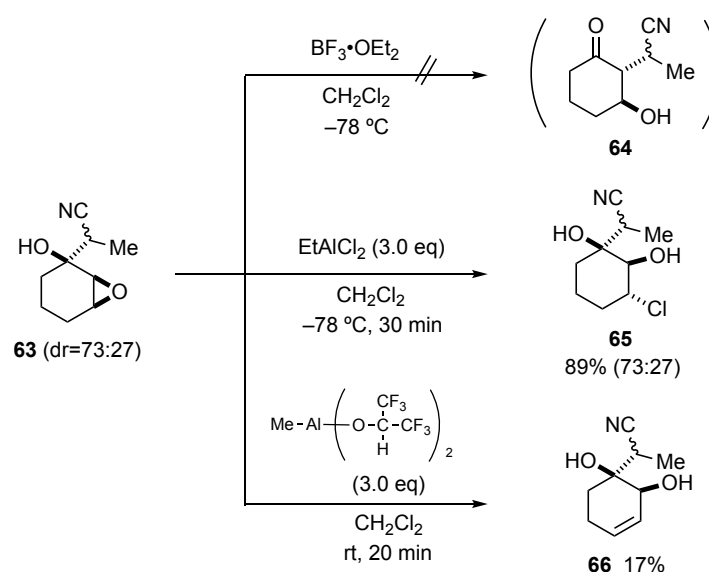
The substrate was readily obtained from 2-cyclohexen-1-one in two steps as depicted in Scheme 33. Cyclohexenone was reacted with an α -cyano anion generated from propionitrile and LDA to afford 1,2-adduct **62** as a 74:26 mixture of diastereomers. Upon treatment with TBHP and a catalytic amount of triethoxyoxovanadium(V), the double bond of **62** was oxidized in a diastereoselective manner, giving rise to epoxide **63**.



Scheme 33 Preparation of cyano epoxyalcohol

Despite a number of experiments, all attempts for achieving the semi-pinacol rearrangement reaction of epoxy alcohol **63** under acidic conditions were fruitless (Scheme 34). Thus, the use of boron trifluoride etherate led to the formation of a complex mixture, and chlorohydrin **65** was obtained in high yield by the reaction with ethylaluminum dichloride through regioselective ring opening of the epoxide. The use of bis(hexafluoroisopropoxy)methyl

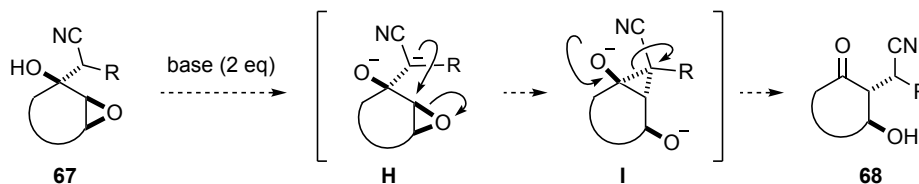
aluminum, the alkoxy group of which was expected to show low nucleophilicity, led to a β -elimination reaction to produce allyl alcohol **66**. These results indicated that the electron withdrawing effect of the cyano group reduced the migratory tendency of the side chain of substrate **63**.



Scheme 34 Attempts at semi-pinacol rearrangement

2.3 Alternative Strategy Employing Basic Conditions

At this point, alternative tactics for achieving the migration of a cyano alkyl group under basic conditions were considered (Scheme 35). Thus, treatment of epoxy alcohol **67** with two equivalents of a base would give an alkoxide which may be further deprotonated at the α -position of the cyano group. The resulting dianion species **H** would undergo an intramolecular S_N2 reaction⁴ to form cyclopropane **I** which would be cleaved by the electron donation from the

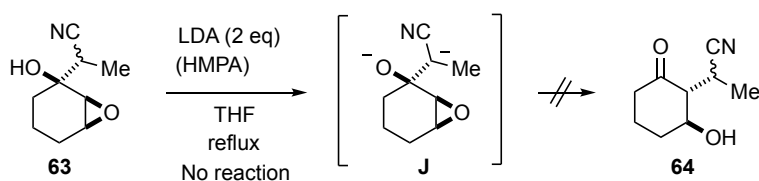


alkoxide moiety. After quenching the reaction with a proton source, β -hydroxy ketone **68**, which

Scheme 35 Formal semi-pinacol rearrangement under basic condition

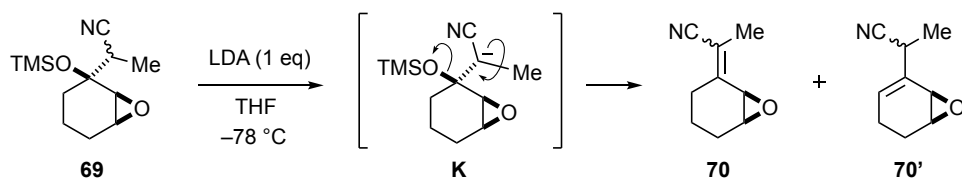
is consistent with the product of semi-pinacol rearrangement, would be obtained.

Treatment of **63** with two equivalents of LDA, however, led to the recovery of **63** even at elevated temperature (Scheme 36). The use of hexamethylphosphoric triamide (HMPA) as an additive also failed to induce the formal semi-pinacol rearrangement, resulting in formation of a complex mixture containing substrate **63** as a major component. These results suggested that the formation of dianion species **J** is disfavored because of the condensed negative charges.



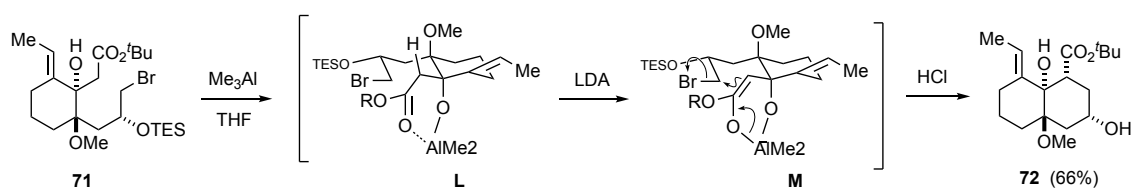
Scheme 36 Initial attempt at formal rearrangement reaction

On the other hand, protection of the hydroxy group of **63** prior to the reaction with LDA led to disappointing results (Scheme 37). Thus, trimethylsilyl ether **69** underwent the β -elimination of the siloxy group giving rise to unsaturated nitrile **70** and **70'**.



Scheme 37 Elimination reaction of β -siloxy nitrile

The difficulties in achieving the desired epoxynitrile cyclization led the author to explore the tentative protection of the hydroxy group as an aluminum alkoxide⁵. A similar method was employed in the total synthesis of ingenol by Kuwajima and Tanino for the intramolecular alkylation of hydroxy ester **71** (Scheme 38). Although the reaction of hydroxy ester **71** with LDA afforded a complex mixture involving cyclic ether, pre-treatment of **71** with trimethylaluminum

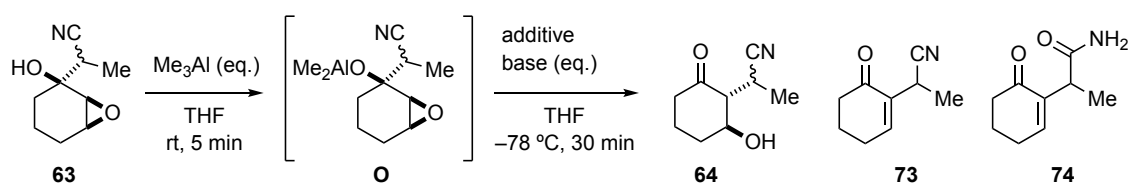


Scheme 38 Intramolecular alkylation by the combined use of AlMe_3 and LDA

effected an intramolecular alkylation reaction, giving rise to bicyclic compound **72** in a highly stereoselective manner. The configuration of product **72** is consistent with the chelated structure of the enolate intermediate **M** which would arise from the aluminum alkoxide **L**.

Based on this successful cyclization, alcohol **63** was treated with trimethylaluminum in THF at room temperature for 5 min, during which the aluminum alkoxide **O** was formed with the evolution of methane gas (Table 3). After cooling to -78°C , the solution was treated with LDA or lithium diethylamide. While the reaction with LDA resulted in recovery of epoxy alcohol **63** (entry 1), the use of lithium diethylamide led to consumption of the substrate, giving rise to enones **73** and **74** (entry 2). These compounds were supposed to be formed by the aqueous work-up under basic conditions which would induce the dehydration of hydroxyl ketone **64**. Indeed, when the reaction was quenched with a THF solution of acetic acid, the desired ketone **64** was obtained in

Table 3 Optimization of formal semi-pinacol rearrangement



entry	Me_3Al (eq.)	base (eq.)	additive (eq.)	isolated yield
1 ^a	1.5	LDA (3.0 eq.)	-	no reaction
2 ^a	1.5	LiNEt_2 (3.0 eq.)	-	73 (33%) + 74 (32%)
3 ^b	1.5	LiNEt_2 (3.0 eq.)	-	64 (54%, dr = 52:48)
4 ^b	1.5	LiNEt_2 (3.0 eq.)	HMPA (3.0 eq.)	64 (81%, dr = 52:48)
5 ^b	1.5	LiNEt_2 (1.5 eq.)	HMPA (1.5 eq.)	64 (31%, dr = 58:42) + SM (60%)

^a quenched with saturated aqueous NaCl

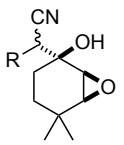
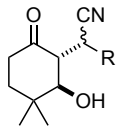
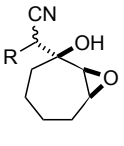
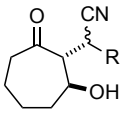
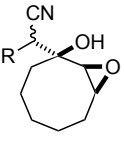
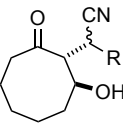
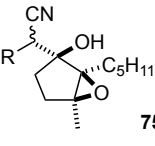
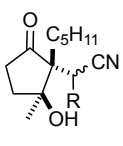
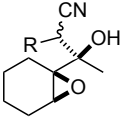
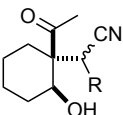
^b quenched with AcOH/THF

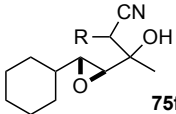
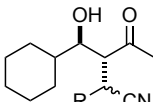
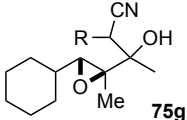
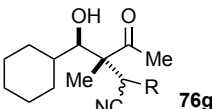
54% yield (entry 3). The yield of ketone **64** was further increased to 89% by the use of HMPA (3 equiv.) as an additive (entry 4), while the use of 1.5 equiv. each of HMPA and lithium diethylamide led to incomplete reaction of epoxy alcohol **63** (entry 5). The desired ketone **64** was obtained as an almost 1:1 mixture of epimers at the cyano group, indicating that the protonation of an anionic species did not occur stereoselectively.

2.4 The Scope of Formal Semi-pinacol Rearrangement

The preliminary results led the author to explore the scope of the formal semi-pinacol rearrangement reaction with the substrates prepared from several enones and 4-phenylbutyronitrile (Table 4). The substrate derived from 4,4-dimethyl-2-cyclohexen-1-one underwent the formal rearrangement reaction to give hydroxy ketone **76a** in 88% yield (entry 1). The substrates having a seven- or an eight-membered ring also afforded the desired hydroxy ketones **76b** and **76c** in high yields, respectively (entries 2 and 3), while elevated temperature was

Table 4 Transformation of various epoxyalcohols into hydroxyketone derivatives

entry	substrate ^a	dr ratio of 75	temp., time	product ^a	yield and dr of 76
1	 75a	81:19	−40 °C, 30 min	 76a	88% dr = 69:31
2	 75b	67:33	−40 °C, 30 min	 76b	82% dr = 85:15
3 ^b	 75c	60:40	−40 °C, 30 min	 76c	87% dr = 88:12
4	 75d	72:28	0 °C, 30 min	 76d	80% dr = 60:40
5	 75e	77:23	0 °C, 30 min	 76e	98% dr = 52:48

entry	substrate ^a	dr ratio of 75	temp., time	product ^a	yield and dr of 76
6 ^c		44:30:14:12	-78 °C, 1 h		94% dr = 52:48
7 ^c		43:39:13:5	0 °C, 10 min		77% dr = 69:31

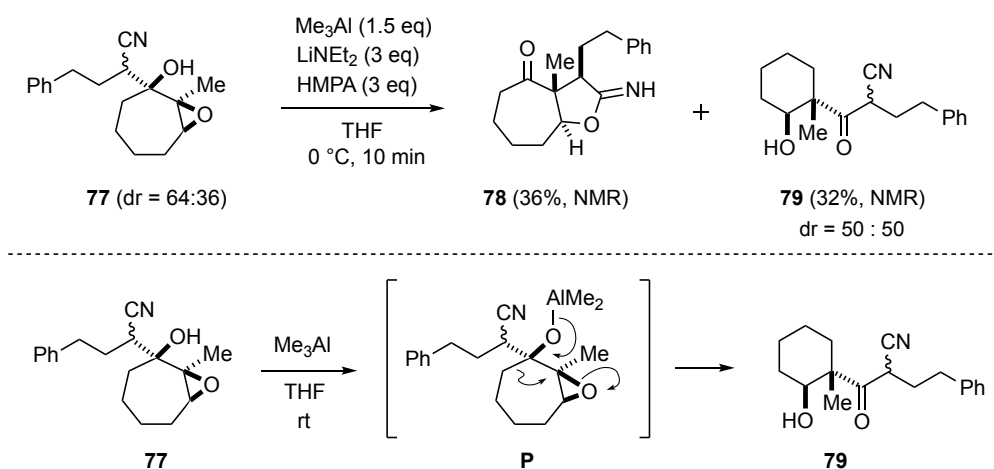
^a R = (CH₂)₂Ph

^b The reaction with Me₃Al was conducted at 55 °C for 1 h.

^c Me₃Al (2 eq.), HMPA (5 eq.) and LiNEt₂ (5 eq.) were used.

required for generating an aluminum alkoxide from eight-membered epoxy alcohol **75c**. It is noteworthy that the present method is quite useful for the stereoselective construction of a quaternary stereogenic center at the α -position of β -hydroxyketones. For example, dihydrojasnone and 1-acetylcyclohexene were converted to hydroxy ketones **76d** and **76e** in good yields, respectively (entries 4 and 5). Acyclic enones were also successfully transformed into the corresponding hydroxy ketones (entries 6 and 7), albeit an excess amount of trimethylaluminum, HMPA, and LiNEt₂ were needed for the complete consumption of the substrates.

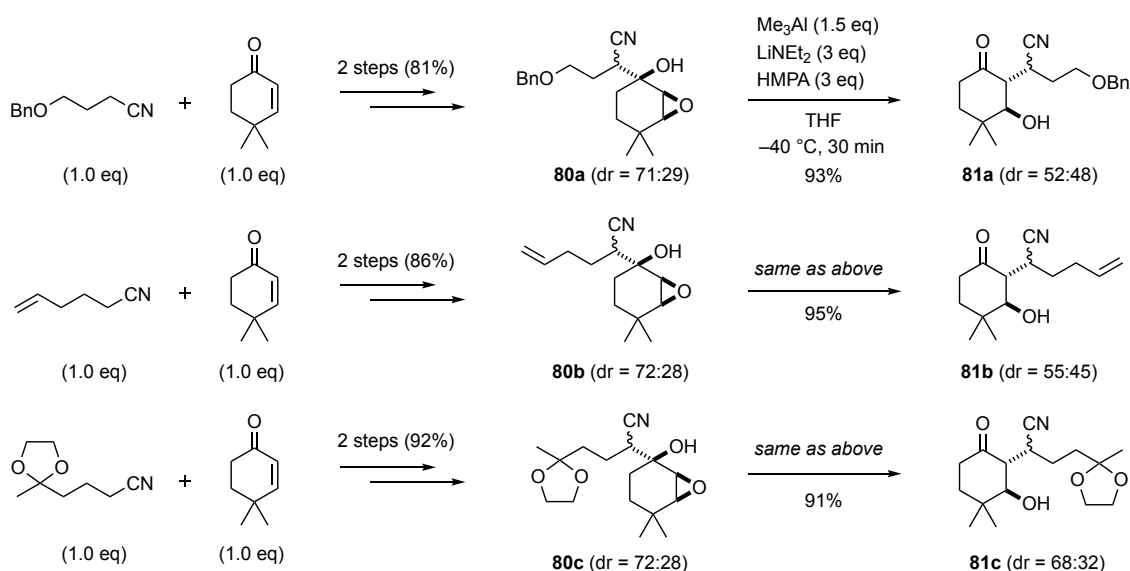
In the case of seven-membered tri-substituted epoxide **77**, the formal rearrangement condition provided a mixture of imino ether **78** resulting from intramolecular cyclization of the rearrangement product and α -cyano ketone **79** (Scheme 39). The result suggests that generation



Scheme 39 Ring-contraction reaction of seven-membered epoxy alcohol

of aluminum alkoxide **P** from substrate **77** suffers from the competitive ring-contraction reaction. Unfortunately, every effort for avoiding the side reaction by choosing a suitable solvent or an additive was fruitless.

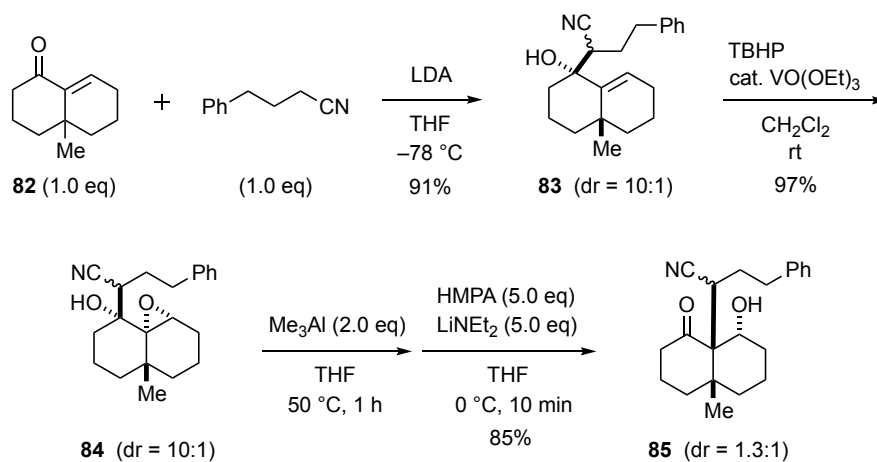
Attention was next turned to the scope of the present method for obtaining various nitriles bearing additional functional groups (Scheme 40). It was found that a terminal olefin moiety, a benzyloxy group, and an ethylene acetal group are tolerated to both preparation of the substrates **80a-c** and the formal semi-pinacol rearrangement reaction, which gave the corresponding products **81a-c** in satisfactory yields.



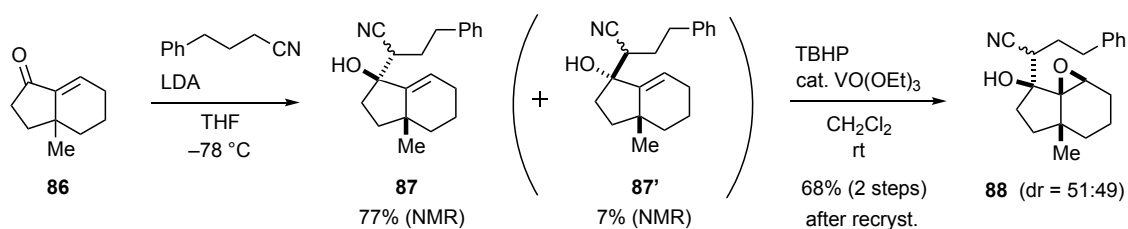
Scheme 40 Synthesis of compounds bearing four different functional groups

It is noteworthy that the formal semi-pinacol rearrangement reaction provides a powerful tool for constructing a quaternary carbon center at the angular position of bicyclic systems. Thus, decalone derivative **82** was converted to epoxyalcohol **84** through the nucleophilic addition/epoxidation sequence (Scheme 41). As was expected from the Koreeda's report⁷, the 1,2-addition reaction of the α -cyano anion of 4-phenylbutyronitrile occurred through an axial attack. The formal rearrangement reaction of **84** proceeded smoothly to afford *cis*-fused decaline

derivative **85** possessing two quaternary carbon centers at the angular positions.



Scheme 41 Formal rearrangement reaction of 6/6-fused epoxyalcohol

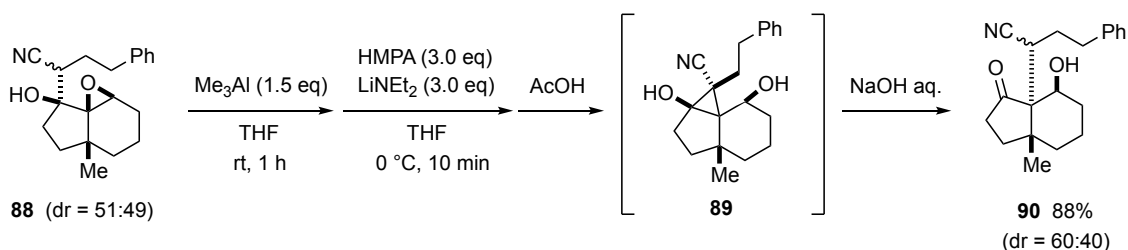


Scheme 42 Preparation of 5/6-fused epoxy alcohol

In the case of hydroindanone **86**, the 1,2-addition reaction mainly occurred from the less hindered α -face to give allyl alcohol **87** along with ca. 7% of minor stereoisomers **87'** and ca. 10% of 1,4-adducts (Scheme 42). Oxidation of the mixture containing allyl alcohols **87** and **87'** (and 1,4-adducts) followed by recrystallization gave pure epoxyalcohol **88** in 68% yield over two steps.

Interestingly, the subjection of epoxyalcohol **88** to the usual rearrangement conditions gave tricyclic nitrile **89** as a single isomer in 82% yield (Scheme 43). The configuration of **89** was confirmed by a X-ray crystallographic analysis (Figure 2), indicating that the cyclopropane ring was retained during the reaction.

Gratifyingly, it was found that the cyclopropane ring of **89** could be cleaved by quenching the reaction with an aqueous solution of sodium hydroxide, affording the desired *trans*-fused hydroindanone **90** in excellent yield.



Scheme 43 The synthesis of 5/6-*trans* fused hydroxyketone

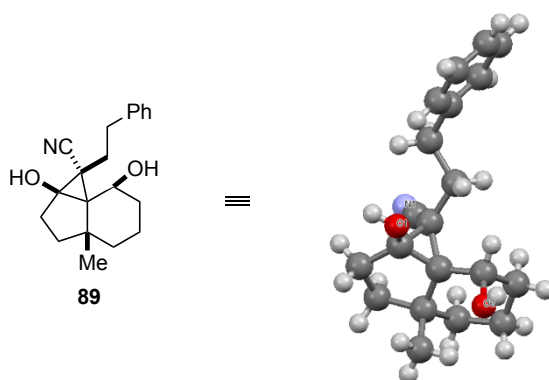
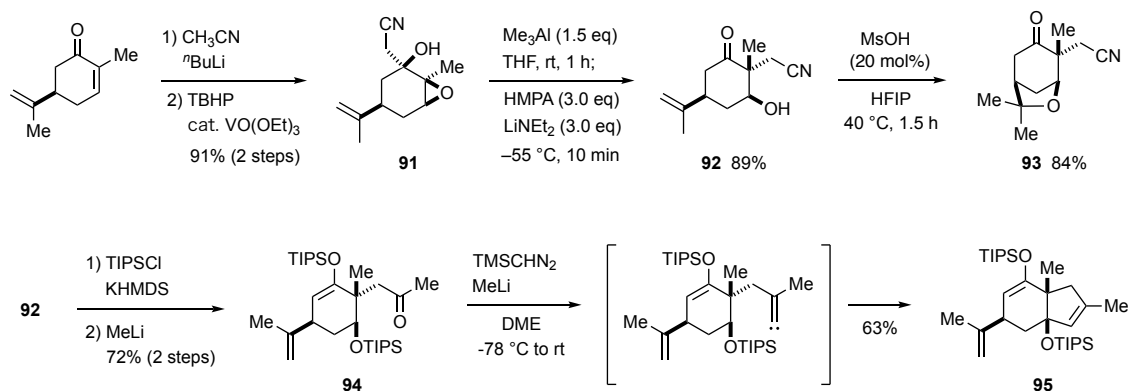


Figure 2 X-ray structure of cyclopropane **89**

With a view to demonstrating the synthetic utility of the present method, further transformation of the product was carried out (Scheme 44). In accord with the results of Scheme 41, epoxyalcohol **91** was synthesized from carvone and acetonitrile in high yield. The formal rearrangement reaction of **91** afforded β -hydroxy ketone **92** in 89% yield as a single isomer. Upon treatment with methanesulfonic acid, **92** underwent the intramolecular etherification⁸ to give cyclic ether **93**. On the other hand, ketone **94** was prepared from **92** through protection of both the hydroxy group and the ketone moiety with TIPS groups followed by the addition reaction with methyl lithium. Treatment of **94** with the lithium salt of TMSCHN_2 afforded bicyclic compound **95** in 63% yield through the C-H insertion⁹ reaction of a carbenoid intermediate. These reactions gave useful information on the stereochemistry of the substituents in **92**, namely, the *cis*

relationship between the hydroxy group and the isopropenyl moiety, and the *trans* relationship between the hydroxy group and the cyanomethyl group.



Scheme 44 Derivatizations of formal rearrangement product

2.5 Conclusions

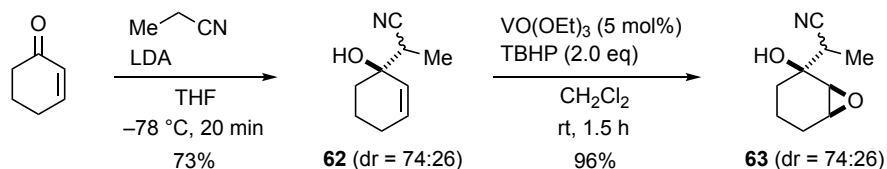
In conclusion, a new method for the synthesis of α -(cyanoalkyl)- β -hydroxyketones was developed on the basis of a formal semi-pinacol rearrangement reaction of epoxy cyanoalcohols. The substrates were prepared from the corresponding α,β -unsaturated ketones and alkanenitriles through a 1,2-addition reaction followed by epoxidation. Treatment of the cyano epoxyalcohol with trimethylaluminum followed by HMPA and lithium diethylamide led to formation of α -(cyanoalkyl)- β -hydroxycycloalkanone in good yield. The present method is especially useful for the stereoselective construction of a quaternary stereogenic center, and the products with three or four different types of functional groups show promise in total synthesis of natural products possessing a complex structure.

2.6 References

- 1) For reviews, see: (a) Coveney, D. J. The Semipinacol and Other Rearrangements. *Comprehensive Organic Synthesis*, Trost, B. M., Fleming, I. Eds.; Pergamon: Oxford, U.K., 1991; Chapter 3.4, pp 777-801 (b) Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.*, **2011**, *111*, 7523. (c) Wang, B.; Tu, Y.-Q.; *Acc. Chem. Rev.* **2011**, *44*, 1207. (d) Snape, T. J. *Chem. Soc. Rev.*, **2007**, *36*, 1823.
- 2) (a) Shimazaki, M.; Hara, H.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1987**, *28*, 5891. (b) Suzuki, K.; Katayama, E.; Tsuchihashi, E. *Tetrahedron Lett.*, **1983**, *24*, 4997. (c) Tsuchihashi, G.; Tomoaka, K.; Suzuki, K. *Tetrahedron Lett.*, **1984**, *25*, 4253. (d) Suzuki, K.; Miyazawa, M.; Shimazaki, M.; Tsuchihashi, G. *Tetrahedron*, **1988**, *44*, 4061.
- 3) Snape, T. J. *Org. Biomol. Chem.*, **2006**, *4*, 4144.
- 4) For examples of intramolecular cyclization of dianion of β -hydroxy nitrile, see: (a) Yang, X.; Fleming, F. F. *Acc. Chem. Res.* **2017**, *50*, 2556. (b) Fleming, F. F.; Gudipati, S. *Eur. J. Org. Chem.* **2008**, 5365. (c) Fleming, F. F.; Vu, V. A.; Shook, B. C.; Rahman, M.; Steward, O. W. *J. Org. Chem.*, **2007**, *72*, 1431.
- 5) Dianionic magnesium salt of β -hydroxynitriles is reported to provide α , β -unsaturated nitriles, see: Fleming, F. F.; Shook, B. C. *Tetrahedron Lett.* **2000**, *41*, 8847.
- 6) Tanino, K.; Onuki, K.; Asano, K.; Miyashita, M.; Nakamura, T.; Takahashi, Y.; Kuwajima, I. *J. Am. Chem. Soc.*, **2003**, *125*, 1498.
- 7) You, Z.; Koreeda, M. *Tetrahedron Lett.* **1993**, *34*, 2745. (c) Koreeda, M.; You, Z. *J. Org. Chem.* **1989**, *54*, 5195.
- 8) This type of oxygen-bridged structure is found in natural products, see: Spivey, A. C.; Weston, M.; Woodhead, S. *Chem. Soc. Rev.*, **2002**, *31*, 43.
- 9) (a) Taber, D. F.; Meagley, R. P. *Tetrahedron Lett.* **1994**, *35*, 7909. b) Yun, S. Y.; Zheng, J.-C.; Lee, D. *J. Am. Chem. Soc.*, **2009**, *131*, 8413.

2.7 Experimental Section

Preparation of β -Hydroxy- γ,δ -Epoxy Nitriles



Compound 62:

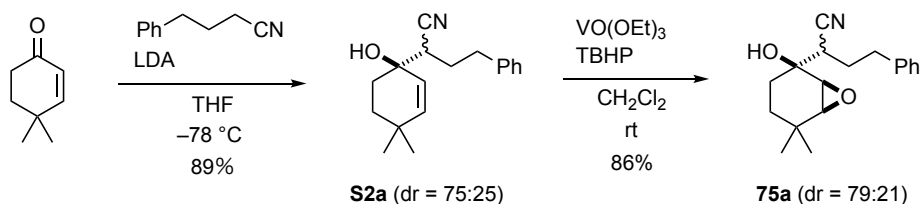
To a solution of *i*Pr₂NH (5.6 mL, 39.6 mmol) in THF (16.8 mL) was added ^{*n*}BuLi (2.65 M in hexane, 13.6 mL, 36.0 mmol) at -78 °C, and the mixture was stirred at 0 °C for 10 min. To the mixture was added propionitrile (2.5 mL, 35.9 mmol) at -78 °C, and the resulting mixture was stirred at this temperature for 1 h. 2-cyclohexene-1-one (3.0 mL, 29.5 mmol) was then added, and the mixture was stirred at -78 °C for 20 min. The reaction was quenched by addition of AcOH (2.0 M in THF, 40 mL, 80 mmol), and then saturated aqueous NaHCO₃ solution. The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluted with 15% AcOEt/hexane) to give **62** (3.31 g, 21.9 mmol, 73%) as a 74:26 mixture of diastereomers. Colorless oil; ¹H NMR (500 MHz, CDCl₃) δ 6.01-6.04 (m, 1 H), 5.69-5.70 (m, 1 H), 2.77 (q, *J* = 7.5 Hz, 0.7 H), 2.71 (q, *J* = 6.9 Hz, 0.3 H), 1.61-2.13 (m, 6H), 1.32 (d, *J* = 7.5 Hz, 2.1 H), 1.31 (d, *J* = 6.9 Hz, 0.9 H); ¹³C NMR (125 MHz, CDCl₃) δ 133.37, 133.31, 128.37, 128.08, 121.23, 121.17, 69.56, 69.37, 37.06, 36.96, 32.58, 32.08, 24.79, 24.77, 18.12, 18.00, 12.54, 12.36; IR (neat) 3343, 3025, 2986, 2939, 2247, 1641, 1458; HRMS (FI) *m/z* [*M*⁺] calcd for [C₉H₁₃NO]⁺ 151.09971, found 151.09970.

Compound 63:

To a solution of allyl alcohol **62** (607.2 mg, 4.02 mmol, dr = 74:26) in CH₂Cl₂ (8.0 mL) was added TBHP (5.5 M in nonane, 1.5 mL, 8.25 mmol) and VO(OEt)₃ (36 μ L, 0.20 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 1.5 h. The reaction was quenched by addition of saturated aqueous Na₂S₂O₃ solution. The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluted with 20%

AcOEt/hexane) to give **63** (644.3 mg, 3.85 mmol, 96%) as a 74:26 mixture of diastereomers. White amorphous solid; ^1H NMR (500 MHz, CDCl_3) δ 3.48-3.49 (m, 0.7 H), 3.45-3.46 (m, 0.3 H), 3.22 (d, $J = 3.5$ Hz, 0.3 H), 3.16 (d, $J = 4.0$ Hz, 0.7 H), 2.82-2.90 (m, 1 H), 2.14-2.17 (m, 1 H), 1.64-1.76 (m, 2 H), 1.35-1.50 (m, 6 H); ^{13}C NMR (125 MHz, CDCl_3) δ 120.51, 120.31, 68.47, 68.30, 56.66, 55.83, 55.51, 55.37, 35.57, 35.14, 32.22, 31.04, 23.44, 13.72, 13.57, 11.80, 11.73 (1C missing); IR (neat) 3476, 2987, 2946, 2241, 1458; HRMS (FI) m/z $[\text{M}^+]$ calcd for $[\text{C}_9\text{H}_{13}\text{NO}_2]^+$ 167.09463, found 167.09545.

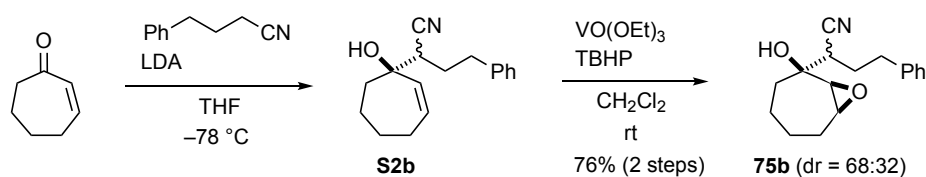
Compound **S2a**:



According to the procedure for the synthesis of **62**, **S2a** was prepared from 4,4-dimethyl-2-cyclohexen-1-one (680 μL , 5.01 mmol), LDA (1.0 M in THF, 5.3 mL, 5.3 mmol) and 4-phenylbutyronitrile (755 μL , 5.01 mmol) in THF (25 mL). The crude product was purified by silica gel chromatography (eluted with 20% AcOEt/hexane) to give **S2a** (1.20 g, 4.45 mmol, 89%) as a 75:25 mixture of diastereomers. Colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 7.22-7.33 (m, 5 H), 5.69-5.72 (m, 1 H), 5.50-5.52 (m, 0.8 H), 5.46 (d, $J = 10.3$ Hz, 0.2 H), 2.98-3.04 (m, 1 H), 2.67-2.74 (m, 1 H), 2.63 (dd, $J = 12.1$ Hz, 4.0 Hz, 0.8 H), 2.57 (dd, $J = 11.5$ Hz, 4.6 Hz, 0.2 H), 1.46-2.08 (m, 7 H), 1.04 (s, 3 H), 0.98 (s, 2.4 H), 0.95 (s, 0.6 H); ^{13}C NMR (125 MHz, CDCl_3) δ 143.71, 143.54, 140.14, 140.04, 128.59, 128.55, 128.40, 126.37, 126.32, 125.99, 125.90, 120.25, 120.17, 69.87, 69.69, 43.09, 43.06, 33.72, 33.61, 32.74, 32.55, 31.98, 31.96, 31.93, 30.13, 29.99, 29.81, 28.77, 28.27, 26.89, 26.60 (1C missing); IR (neat) 3446, 3026, 2955, 2865, 2239, 1455; HRMS (FD) m/z $[\text{M}^+]$ calcd for $[\text{C}_{18}\text{H}_{23}\text{NO}]^+$ 269.17796, found 269.17841.

Compound **75a**:

According to the procedure for the synthesis of **63**, **75a** was prepared from allyl alcohol **S2a** (1.08 g, 4.01 mmol, dr = 75:25), TBHP (5.5 M in nonane, 1.5 mL, 8.25 mmol) and VO(OEt)₃ (35 μ L, 0.20 mmol) in CH₂Cl₂ (8.0 mL) at room temperature for 2 h. The crude product was purified by silica gel chromatography (eluted with 5% AcOEt/hexane) to give **75a** (985.0 mg, 3.45 mmol, 86%) as a 79:21 mixture of diastereomers. White amorphous solid; ¹H NMR (500 MHz, CDCl₃) δ 7.23-7.34 (m, 5 H), 3.20 (d, *J* = 3.5 Hz, 0.2 H), 3.15 (d, *J* = 3.5 Hz, 0.8 H), 2.97-3.07 (m, 3 H), 2.68-2.78 (m, 2 H), 1.93-2.27 (m, 2 H), 1.36-1.67 (m, 2.2 H), 1.13-1.15 (m, 0.8 H), 1.11 (s, 3 H), 1.06 (s, 2.4 H), 1.01 (s, 0.6 H); ¹³C NMR (125 MHz, CDCl₃) δ 139.80, 139.75, 128.59, 128.54, 128.35, 126.41, 126.36, 119.60, 119.55, 68.23, 68.05, 64.17, 63.98, 58.93, 57.38, 41.97, 41.24, 33.44, 33.40, 30.19, 30.05, 28.29, 27.81, 27.77, 27.67, 27.53, 27.50, 27.41, 23.14, 22.85 (2C missing); IR (neat) 3473, 3058, 3028, 2960, 2867, 2224, 1454; HRMS (FD) *m/z* [M⁺] calcd for [C₁₈H₂₃NO₂]⁺ 285.17288, found 285.17183.



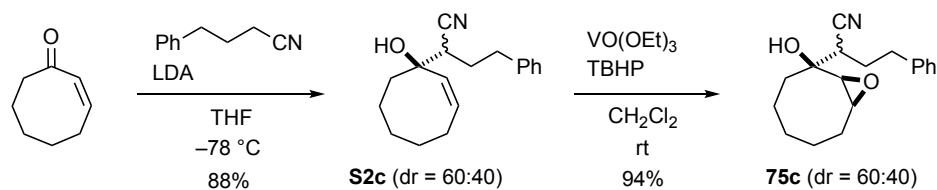
Compound **75b**:

To a solution of ^tPr₂NH (810 μ L, 5.74 mmol) in THF was added ⁿBuLi (2.67 M in hexane, 2.0 mL, 5.34 mmol) at -78 °C and the mixture was stirred at 0 °C for 10 min. To the mixture was added 4-phenylbutyronitrile (755 μ L, 5.01 mmol) at -78 °C, and the resulting mixture was stirred at this temperature for 1 h. 2-Cycloheptene-1-one (590 μ L, 5.02 mmol) was then added, and the mixture was stirred at -78 °C for 20 min. The reaction was quenched by addition of AcOH (2.0 M in THF, 5 mL, 10 mmol), and then saturated aqueous NaHCO₃ solution. The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The residue was roughly purified by silica gel column chromatography. The product was used for next step without further purification. To a solution of allyl alcohol **S2b** in CH₂Cl₂ (10 mL) was added TBHP (5.5 M in nonane, 1.8 mL, 9.9 mmol) and VO(OEt)₃ (44 μ L, 0.25 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 1.5 h. The reaction was quenched by addition of saturated aqueous Na₂S₂O₃ solution. The mixture was separated, and the aqueous layer was extracted with ether. The

combined organic layers were dried over MgSO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluted with 5% AcOEt/hexane) to give **75b** (1.03 g, 3.79 mmol, 76% for 2 steps) as a 68:32 mixture of diastereomers. White amorphous solid.; ^1H NMR (500 MHz, C_6D_6) δ 6.94-7.08 (m, 5 H), 2.83 (d, J = 4.6 Hz, 0.3 H), 2.70-2.79 (m, 1 H), 2.41-2.50 (m, 2 H), 2.25-2.26 (m, 1 H), 2.19 (dd, J = 10.9 Hz, 4.6 Hz, 0.3 H), 2.14 (dd, J = 11.5 Hz, 3.5 Hz, 0.7 H), 2.08 (br, 0.7 H), 1.66-1.82 (m, 3 H), 0.70-1.54 (m, 6 H), 0.70-0.80 (m, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 139.86, 139.82, 128.62, 128.57, 128.38, 126.43, 126.38, 119.99, 119.69, 72.24, 71.80, 59.00, 57.71, 55.80, 55.60, 42.95, 42.37, 36.07, 35.41, 33.40, 33.24, 28.32, 28.10, 28.00, 27.98, 24.03, 23.96, 23.85, 23.66 (1C missing); IR (neat) 3467, 2939, 2864, 2238, 1602, 1497, 1452; HRMS (FD) m/z [M^+] calcd for $[\text{C}_{17}\text{H}_{21}\text{NO}_2]^+$ 271.15723, found 271.15852.

Compound **S2c**:

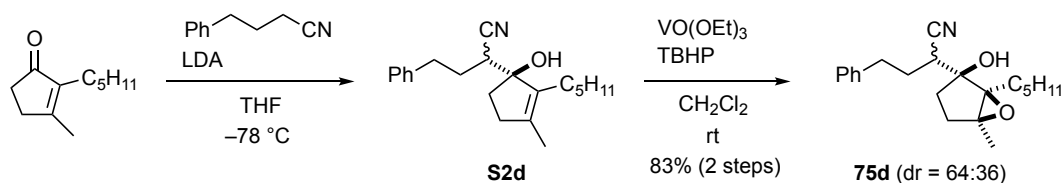
2-Cyclooctene-1-one was synthesized following literature procedures.¹ According to the



procedure for the synthesis of **62**, **S2c** was prepared from 2-cyclooctene-1-one (675.1 mg, 5.43 mmol), LDA (1.0 M in THF, 5.7 mL, 5.7 mmol) and 4-phenylbutyronitrile (820 μL , 5.43 mmol) in THF (20 mL). The crude product was purified by silica gel chromatography (eluted from 1% to 10% AcOEt/hexane) to give **S2c** (1.28 g, 4.75 mmol, 88%) as a 60:40 mixture of diastereomers. Colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 7.19-7.31 (m, 5 H), 5.67-5.74 (m, 1 H), 5.53 (d, J = 12.0 Hz, 0.6 H), 5.47 (d, J = 11.5 Hz, 0.4 H), 2.96-3.04 (m, 1 H), 2.66-2.72 (m, 1 H), 2.52-2.58 (m, 1 H), 2.35-2.45 (m, 1 H), 1.38-2.32 (m, 11 H); ^{13}C NMR (125 MHz, CDCl_3) δ 140.10, 140.02, 132.48, 132.44, 131.55, 131.52, 128.56, 128.40, 126.34, 120.45, 120.32, 75.69, 75.49, 45.12, 45.01, 37.59, 36.76, 33.67, 33.61, 28.65, 26.55, 26.36, 25.02, 24.93, 24.73, 24.40, 22.08, 21.96 (4C missing); IR (neat) 3456, 3065, 3026, 2974, 2928, 2859, 2239, 1652, 1603, 1455; HRMS (FI) m/z [M^+] calcd for $[\text{C}_{18}\text{H}_{23}\text{NO}]^+$ 269.17796, found 269.17879.

Compound **75c**:

According to the procedure for the synthesis of **63**, **75c** was prepared from allyl alcohol **S2c** (1.20 g, 4.46 mmol, dr = 60:40), TBHP (5.5 M in nonane, 1.6 mL, 8.8 mmol) and VO(OEt)₃ (40 μ L, 0.22 mmol) in CH₂Cl₂ (8.9 mL) at room temperature for 1 h. The crude product was purified by silica gel chromatography (eluted from 3% to 10% AcOEt/hexane) to give **75c** (1.19 g, 4.17 mmol, 94%) as a 60:40 mixture of diastereomers. White amorphous solid; ¹H NMR (500 MHz, CD₂Cl₂) δ 7.19-7.30 (m, 5 H), 3.10 (d, *J* = 4.6 Hz, 0.4 H), 2.90-3.02 (m, 2 H), 2.80 (d, *J* = 4.6 Hz, 0.6 H), 2.63-2.72 (m, 1.4 H), 2.52-2.55 (m, 1.0 H), 2.44 (d, *J* = 2.3 Hz, 0.6 H), 1.79-2.19 (m, 7 H), 1.17-1.66 (m, 5 H); ¹³C NMR (125 MHz, CDCl₃) δ 139.90, 139.82, 128.63, 128.59, 128.44, 128.41, 126.43, 126.39, 120.23, 119.91, 72.18, 58.15, 57.25, 56.50, 45.59, 44.84, 38.18, 36.16, 33.52, 33.49, 28.04, 27.91, 25.93, 25.85, 24.20, 24.04, 23.48, 23.35, 19.58, 19.27 (2C missing); IR (neat) 3488, 3026, 2926, 2865, 2238, 1603, 1497, 1455; HRMS (FI) *m/z* [M⁺] calcd for [C₁₈H₂₃NO]⁺ 285.17288, found 285.17305.



Compound **75d**:

To a solution of ^tPr₂NH (810 μ L, 5.74 mmol) in THF was added ⁿBuLi (2.67 M in hexane, 2.0 mL, 5.3 mmol) at -78 °C and the mixture was stirred at 0 °C for 10 min. To the mixture was added 4-phenylbutyronitrile (755 μ L, 5.01 mmol) at -78 °C, and the resulting mixture was stirred at this temperature for 1 h. Dihydrojasnone (925 μ L, 5.01 mmol) was then added, and the mixture was stirred at -78 °C for 30 min. The reaction was quenched by addition of AcOH (2.0 M in THF, 5 mL, 10 mmol), and then saturated aqueous NaHCO₃ solution. The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The residue was roughly purified by silica gel column chromatography. The product was used for next step without further purification.

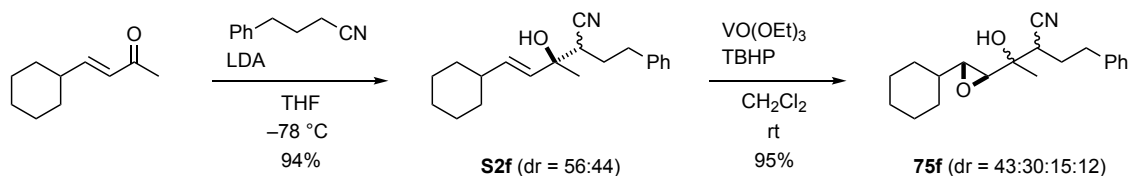
To a solution of allyl alcohol **S2d** in CH₂Cl₂ (10 mL) was added TBHP (5.5 M in nonane, 1.8 mL, 9.9 mmol) and VO(OEt)₃ (44 μL, 0.25 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 2 h. The reaction was quenched by addition of saturated aqueous Na₂S₂O₃ solution. The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluted with 5% AcOEt/hexane) to give **75d** (1.36 g, 4.15 mmol, 83% for 2 steps) as a 64:36 mixture of diastereomers. Amorphous solid with a white color.; ¹H NMR (500 MHz, C₆D₆) δ 6.75-6.94 (m, 5 H), 2.68-2.75 (m, 0.4 H), 2.61-2.67 (m, 1.6 H), 2.37-2.47 (m, 1 H), 2.01-2.09 (m, 0.4 H), 1.31-1.88 (m, 6.6 H), 1.23 (s, 1.2 H), 0.90-1.21 (m, 7 H), 0.88 (s, 1.8 H), 0.82 (t, *J* = 6.9 Hz, 1.2 H), 0.80 (t, *J* = 7.5 Hz, 1.8 H); ¹³C NMR (125 MHz, CDCl₃) δ 140.04, 139.14, 128.71, 128.55, 128.50, 128.35, 126.69, 126.31, 119.95, 119.57, 83.12, 82.63, 72.25, 71.21, 70.02, 69.69, 39.07, 36.54, 33.58, 33.16, 32.92, 32.44, 32.25, 31.39, 31.33, 28.74, 28.23, 25.95, 25.56, 24.58, 24.27, 22.30, 22.16, 15.84, 15.81, 13.96, 13.94 (1C missing); IR (neat) 3407, 3030, 2927, 2859, 2281, 1604, 1455; HRMS (FD) *m/z* [*M*⁺] calcd for [C₂₁H₂₉NO₂]⁺ 327.21983, found 327.22079.

Compound S2e:

3461, 3026, 2927, 2858, 2244, 1603, 1497, 1454; HRMS (FD) m/z $[M]^+$ calcd for $[C_{18}H_{23}NO]^+$ 269.17796, found 269.17861.

Compound 75e:

According to the procedure for the synthesis of **63**, **75e** was prepared from allyl alcohol **@** (1.03 g, 3.82 mmol, dr = 75:25), TBHP (5.5 M in nonane, 1.4 mL, 7.7 mmol) and VO(OEt)₃ (34 μ L, 0.19 mmol) in CH₂Cl₂ (7.7 mL) at room temperature for 3 h. The crude product was purified by silica gel chromatography (eluted from 5% AcOEt/hexane) to give **75e** (924.2 mg, 3.24 mmol, 84%) as a 77:23 mixture of diastereomers. White amorphous solid; ¹H NMR (500 MHz, CDCl₃) δ 7.20-7.33 (m, 5 H), 3.62-3.63 (m, 0.8 H), 3.41-3.42 (m, 0.2 H), 3.01-3.08 (m, 1 H), 2.66-2.73 (m, 1.8 H), 2.58-2.61 (m, 0.2 H), 2.32-2.33 (m, 0.8 H), 2.28-2.29 (m, 0.2 H), 1.67-2.15 (m, 6 H), 1.25-1.52 (m, 6.8 H), 1.08-1.17 (m, 0.2 H) ¹³C NMR (125 MHz, CDCl₃) δ 140.04, 139.91, 128.65, 128.59, 128.33, 126.48, 126.37, 119.52, 72.29, 72.28, 63.23, 62.17, 57.01, 56.42, 39.26, 38.75, 33.44, 33.16, 28.55, 27.98, 24.55, 24.37, 24.19, 24.06, 23.58, 22.20, 20.36, 20.25, 18.81 (3C missing); IR (neat) 3481 3020, 2939, 2859, 2240, 1497, 1454; HRMS (FD) m/z $[M]^+$ calcd for $[C_{18}H_{23}NO_2]^+$ 285.17288, found 285.17364.



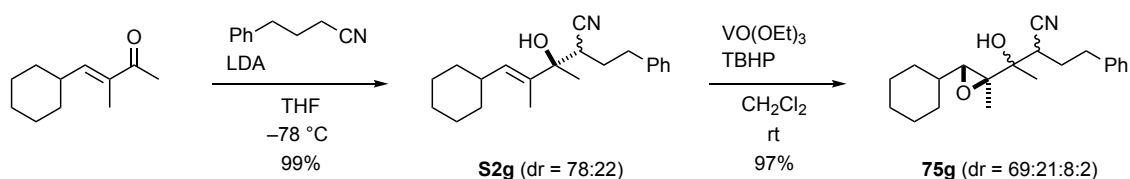
Compound 13:

(*E*)-4-cyclohexylbut-3-en-2-one was synthesized following literature procedures.² According to the procedure for the synthesis of **62**, **S2f** was prepared from (*E*)-4-cyclohexylbut-3-en-2-one (763.4 mg, 5.01 mmol), LDA (1.0 M in THF, 5.3 mL, 5.3 mmol) and 4-phenylbutyronitrile (755 μ L, 5.01 mmol) in THF (20 mL). The crude product was purified by silica gel chromatography (eluted with 5% AcOEt/hexane) to give **S2f** (1.40 g, 4.71 mmol, 94%) as a 56:44 mixture of diastereomers. Colorless oil; ¹H NMR (500 MHz, CDCl₃) δ 7.20-7.33 (m, 5 H), 5.67-5.73 (m, 1 H), 5.47-5.50 (m, 0.6 H), 5.42-5.45 (m, 0.4 H), 2.96-3.02 (m, 1 H), 2.64-2.71 (m, 1 H), 2.57 (dd, J = 12.0 Hz, 4.0 Hz, 0.6 H), 2.51 (dd, J = 11.4 Hz, 4.6 Hz, 0.4 H), 1.66-2.19 (m, 9 H), 1.43 (s, 1.8 H), 1.40 (s, 1.2 H), 1.03-1.33 (m, 5 H); ¹³C NMR (125 MHz, CDCl₃) δ 140.06, 140.03, 137.31,

137.06, 130.10, 129.76, 128.45, 128.30, 126.22, 120.26, 120.18, 72.61, 72.56, 43.40, 43.36, 40.13, 40.10, 33.45, 32.66, 32.64, 28.81, 28.78, 26.38, 25.99, 25.90, 25.76 (6C missing); IR (neat) 3464, 3026, 2924, 2852, 2241, 1604, 1497, 1449; HRMS (FD) m/z $[M^+]$ calcd for $[C_{20}H_{27}NO]^+$ 297.20926, found 297.21025.

Compound 75f:

According to the procedure for the synthesis of **63**, **75f** was prepared from allyl alcohol **62** (1.30 g, 4.37 mmol, dr = 56:44), TBHP (5.5 M in nonane, 1.5 mL, 8.3 mmol) and VO(OEt)₃ (37 μ L, 0.21 mmol) in CH₂Cl₂ (8.3 mL) at room temperature for 2 h. The crude product was purified by silica gel chromatography (eluted from 5% AcOEt/hexane) to give **75f** (1.30 g, 4.15 mmol, 95%) as a 43:30:15:12 mixture of diastereomers. White amorphous solid; ¹H NMR (500 MHz, (CD₃)₂CO) δ 7.17-7.31 (m, 5 H), 4.08, (br, 0.1 H), 4.03 (br, 0.3 H), 4.02 (br, 0.4 H), 3.90 (br, 0.2 H), 2.67-3.00 (m, 5 H), 1.87-2.20 (m, 3 H), 1.60-1.81 (m, 5 H), 1.35 (s, 0.9 H), 1.30 (s, 1.2 H), 1.28 (s, 0.6 H), 1.27 (s, 0.3 H), 1.02-1.26 (m, 5 H); ¹³C NMR (125 MHz, CDCl₃) δ 139.78, 139.68, 128.52, 128.50, 128.30, 128.28, 128.26, 126.34, 126.31, 119.76, 119.64, 119.35, 119.33, 69.64, 69.56, 69.51, 61.11, 61.06, 60.83, 60.07, 59.91, 59.71, 59.26, 58.65, 42.56, 41.33, 40.16, 40.06, 39.22, 39.19, 33.50, 33.46, 33.38, 33.27, 29.51, 29.41, 28.71, 28.68, 28.63, 28.60, 28.38, 28.18, 27.86, 25.95, 25.41, 25.39, 25.33, 25.25, 25.22, 25.16, 24.50, 23.91, 20.77 (11C missing); IR (neat) 3397, 3032, 2980, 2918, 2850, 2238, 1497, 1448; HRMS (FD) m/z $[M^+]$ calcd for $[C_{20}H_{27}NO_2]^+$ 313.20418, found 313.20528.



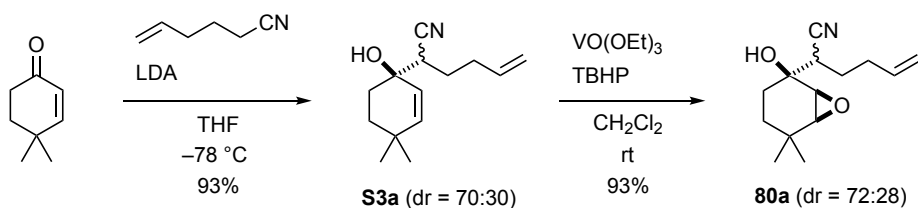
Compound 15:

(*E*)-4-cyclohexyl-3-methylbut-3-en-2-one was synthesized following literature procedures.³ According to the procedure for the synthesis of **62**, **S2g** was prepared from (*E*)-4-cyclohexyl-3-methylbut-3-en-2-one (700.6 mg, 4.21 mmol), LDA (1.0 M in THF, 4.4 mL, 4.4 mmol) and 4-phenylbutyronitrile (635 μ L, 4.21 mmol) in THF (17 mL). The crude product was purified by silica gel chromatography (eluted with 5% AcOEt/hexane) to give **S2g** (1.30 g, 4.17 mmol, 99%)

as a 78:22 mixture of diastereomers. Colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 7.18-7.32 (m, 5 H), 5.44 (d, $J = 9.2$ Hz, 0.2 H), 5.34 (d, $J = 9.2$ Hz, 0.8 H), 2.95-3.00 (m, 1 H), 2.56-2.73 (m, 2 H), 2.10-2.20 (m, 1 H), 1.91-1.99 (m, 0.2 H), 1.81-1.89 (m, 0.8 H), 1.56-1.76 (m, 6 H), 1.51 (s, 2.4 H), 1.47 (s, 0.6 H), 1.43 (s, 2.4 H), 1.39 (m, 0.6 H), 1.01-1.34 (m, 5 H); ^{13}C NMR (125 MHz, CDCl_3) δ 140.13, 139.98, 134.54, 133.63, 133.20, 132.24, 128.49, 128.45, 128.34, 126.30, 126.22, 120.51, 75.37, 75.14, 40.91, 40.30, 36.92, 36.86, 33.46, 33.22, 32.84, 32.74, 32.69, 32.67, 29.27, 28.37, 27.05, 25.87, 25.80, 25.74, 23.90, 12.50, 11.96 (1C missing); IR (neat) 3458, 3026, 2922, 2849, 2242, 1604, 1497, 1448; HRMS (FI) m/z $[\text{M}^+]$ calcd for $[\text{C}_{21}\text{H}_{29}\text{NO}]^+$ 311.22491, found 311.22592.

Compound 75g:

According to the procedure for the synthesis of **63**, **75g** was prepared from allyl alcohol @ (1.23 g, 3.95 mmol, 78:22), TBHP (5.5 M in nonane, 1.4 mL, 7.7 mmol) and $\text{VO}(\text{OEt})_3$ (34 μL , 0.19 mmol) in CH_2Cl_2 (7.6 mL) at room temperature for 2 h. The crude product was purified by silica gel chromatography (eluted from 5% AcOEt /hexane) to give **75g** (1.25 g, 3.82 mmol, 97%) as a 69:21:8:2 mixture of diastereomers. White amorphous solid; ^1H NMR (500 MHz, C_6D_6) δ 6.95-7.11 (m, 5 H), 3.24 (d, $J = 9.1$ Hz, 0.7 H), 2.78-2.90 (m, 1.3 H), 2.47-2.57 (m, 1 H), 2.39-2.45 (m, 0.1 H), 2.24-2.33 (m, 0.8 H), 0.96-2.06 (m, 16 H), 0.93 (s, 0.3 H), 0.90 (s, 2.1 H), 0.78 (s, 0.6 H), 0.62 (s, 0.1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 139.92, 139.88, 139.81, 128.47, 128.45, 128.24, 128.23, 126.33, 126.24, 119.47, 119.33, 72.45, 72.35, 72.29, 64.81, 64.44, 64.07, 64.03, 63.13, 62.53, 39.80, 39.25, 38.58, 37.25, 36.92, 36.38, 36.30, 33.22, 33.12, 30.39, 30.32, 30.29, 28.57, 28.53, 28.44, 28.17, 28.09, 25.90, 25.84, 25.35, 25.32, 25.22, 25.10, 23.95, 22.82, 22.05, 13.58, 13.34, 12.84 (19C missing); IR (neat) 3421, 3032, 2926, 2847, 2260, 1602, 1497; HRMS (FI) m/z $[\text{M}^+]$ calcd for $[\text{C}_{21}\text{H}_{29}\text{NO}_2]^+$ 327.21983, found 327.22145.



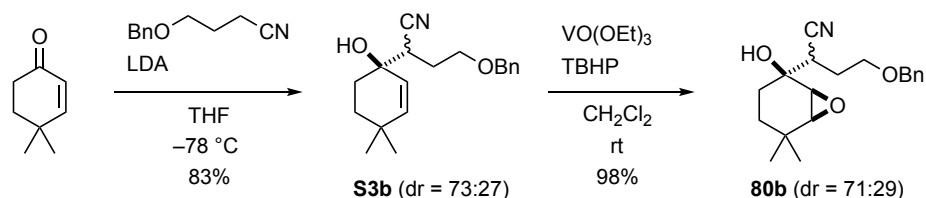
Compound S3a:

According to the procedure for the synthesis of **62**, **S3a** was prepared from 4,4-dimethyl-2-cyclohexen-1-one (410 μL , 3.02 mmol), 5-hexenenitrile (365 μL , 3.02 mmol), and LDA (1.0 M in THF, 3.2 mL, 3.2 mmol) in THF (11 mL). Purification by silica gel chromatography (eluted from 5% AcOEt/hexane) to give **S3a** (614.9 mg, 2.80 mmol, 93%) as a 70:30 mixture of diastereomers; Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 5.71-5.81 (m, 2 H), 5.51-5.55 (m, 1 H), 5.04-5.14 (m, 2 H), 2.68 (dd, J = 11.2 Hz, 4.0 Hz, 0.7 H), 2.64 (dd, J = 8.0 Hz, 4.0 Hz, 0.3 H), 2.39-2.46 (m, 1 H), 2.14-2.21 (m, 1 H), 1.95 (td, J = 12.6 Hz, 4.7 Hz, 0.8 H), 1.50-1.85 (m, 5.2 H), 1.04 (s, 3 H), 1.00 (s, 2.1 H), 0.97 (s, 0.9 H); ^{13}C NMR (125 MHz, CDCl_3) δ 143.09, 142.85, 136.24, 136.16, 126.05, 125.88, 120.15, 120.02, 116.24, 116.06, 69.61, 69.47, 42.88, 42.83, 32.54, 32.37, 31.75, 31.70, 31.45, 31.39, 29.89, 29.82, 29.75, 29.60, 26.76, 26.50, 26.00, 25.40; IR (neat) 3458, 3082, 3012, 2956, 2867, 2240, 1642; HRMS (FD) m/z $[\text{M}^+]$ calcd for $[\text{C}_{14}\text{H}_{21}\text{NO}]^+$ 219.16231, found 219.16181.

Compound 80a:

According to the procedure for the synthesis of **63**, **80a** was prepared from allyl alcohol **S3a** (590.6 mg, 2.69 mmol, dr = 70:30), TBHP (5.5 M in nonane, 980 μL , 5.4 mmol) and $\text{VO}(\text{OEt})_3$ (24 μL , 0.13 mmol) in CH_2Cl_2 (5.4 mL) at room temperature for 2.5 h. The crude product was purified by silica gel chromatography (eluted from 20% AcOEt/hexane) to give **1b** (592.2 mg, 2.52 mmol, 93%) as a 72:28 mixture of diastereomers. Colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 5.74-5.83 (m, 1 H), 5.07-5.16 (m, 2 H), 3.24 (d, J = 3.4 Hz, 0.3 H), 3.18 (d, J = 4.0 Hz, 0.7 H), 3.05 (d, J = 4.0 Hz, 0.7 H), 3.01 (d, J = 3.4 Hz, 0.3 H), 2.74-2.86 (m, 2 H), 2.39-2.49 (m, 1 H), 2.16-2.25 (m, 1 H), 1.36-2.01 (m, 5 H), 1.11-1.16 (m, 4 H), 1.06 (s, 2.1 H), 1.03 (s, 0.9 H); ^{13}C NMR (125 MHz, CDCl_3) δ 135.93, 135.87, 119.35, 119.29, 116.25, 116.07, 68.04, 67.86, 63.61, 63.45, 58.60, 57.18, 41.57, 41.01, 31.11, 29.73, 29.67, 28.02, 27.72, 27.58, 27.20, 27.11, 24.91,

24.63, 22.87, 22.59 (2C missing); IR (neat) 3507, 2961, 2868, 2240, 1644, 1478; HRMS (FI) m/z [M^+] calcd for $[C_{14}H_{21}NO_2]^+$ 235.15723, found 235.15788.



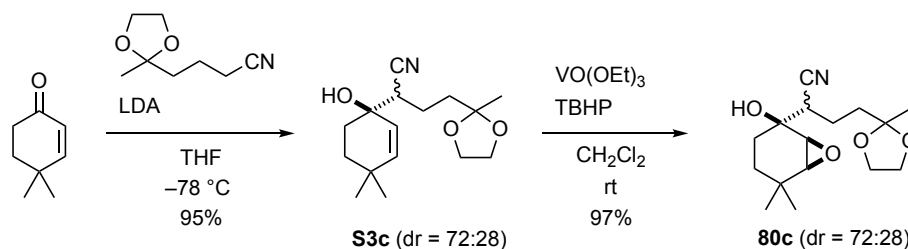
Compound S3b:

4-(Benzyloxy)butanenitrile was synthesized following literature procedures.⁴ According to the procedure for the synthesis of **62**, **S3b** was prepared from 4,4-dimethyl-2-cyclohexen-1-one (403 μL , 2.97 mmol), 4-(benzyloxy)butanenitrile (520.9 mg, 2.97 mmol), and LDA (1.0 M in THF, 3.1 mL, 3.1 mmol) in THF (10 mL). Purification by silica gel chromatography (eluted from 20% AcOEt/hexane) to give **S3b** (747.4 mg, 2.50 mmol, 83%) as a 73:27 mixture of diastereomers; Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.28-7.37 (m, 5 H), 5.69-5.72 (m, 1 H), 5.58 (d, J = 10.3 Hz, 0.3 H), 5.53 (d, J = 9.8 Hz, 0.7 H), 4.52-4.57 (m, 2 H), 3.63-3.76 (m, 2 H), 2.98 (dd, J = 10.3 Hz, 4.0 Hz, 0.7 H), 2.93 (dd, J = 11.5 Hz, 4.0 Hz, 0.3 H), 2.22 (s, 0.7 H), 1.49-2.14 (m, 6.3 H), 1.04 (s, 3 H), 0.99 (s, 2.1 H), 0.96 (s, 0.9 H); ^{13}C NMR (125 MHz, CDCl_3) δ 143.23, 143.06, 137.67, 137.62, 128.32, 127.66, 127.63, 127.61, 126.07, 125.99, 120.04, 119.89, 73.15, 73.12, 69.54, 69.35, 67.28, 67.13, 40.53, 40.48, 32.74, 32.52, 31.91, 31.84, 30.27, 29.98, 29.87, 29.62, 27.40, 27.00, 26.95, 26.62; IR (neat) 3453, 3030, 2956, 2864, 2240, 1653, 1496, 1454; HRMS (FD) m/z [M^+] calcd for $[C_{19}H_{25}NO_2]^+$ 299.18853, found 299.18962.

Compound 80b:

According to the procedure for the synthesis of **63**, **80b** was prepared from allyl alcohol **S3b** (653.1 mg, 2.18 mmol, dr = 73:27), TBHP (5.5 M in nonane, 795 μL , 4.4 mmol) and $\text{VO}(\text{OEt})_3$ (19 μL , 0.11 mmol) in CH_2Cl_2 (4.3 mL) at room temperature for 1 h. The crude product was purified by silica gel chromatography (eluted from 20% AcOEt/hexane) to give **80b** (672.5 mg, 2.13 mmol, 98%) as a 71:29 mixture of diastereomers. Colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 7.29-7.37 (m, 5 H), 4.52-4.58 (m, 2 H), 3.64-3.76 (m, 2 H), 3.27 (d, J = 4.0 Hz, 0.3 H), 3.19 (d, J = 3.5 Hz, 0.7 H), 3.00-3.09 (m, 2 H), 2.88 (br, 0.3 H), 2.83 (br, 0.7 H), 2.23-2.29 (m, 0.7 H), 2.13-2.20 (m, 0.3 H), 1.84-1.97 (m, 1 H), 1.37-1.66 (m, 3.7 H), 1.11-1.16 (m, 3.3 H), 1.05 (s, 2.1

H), 1.02 (s, 0.9 H); ^{13}C NMR (125 MHz, CDCl_3) δ 137.71, 137.66, 128.23, 127.59, 127.55, 127.52, 119.41, 119.35, 73.08, 72.93, 68.01, 67.91, 66.88, 66.86, 63.89, 63.75, 58.61, 57.53, 39.19, 38.74, 29.93, 29.86, 29.77, 28.49, 27.86, 27.73, 27.39, 27.30, 26.58, 26.29, 23.12, 22.86 (2C missing); IR (neat) 3461, 2960, 2869, 2242, 1496, 1474, 1454; HRMS (FD) m/z $[\text{M}^+]$ calcd for $[\text{C}_{19}\text{H}_{25}\text{NO}_3]^+$ 315.18344, found 315.18429.



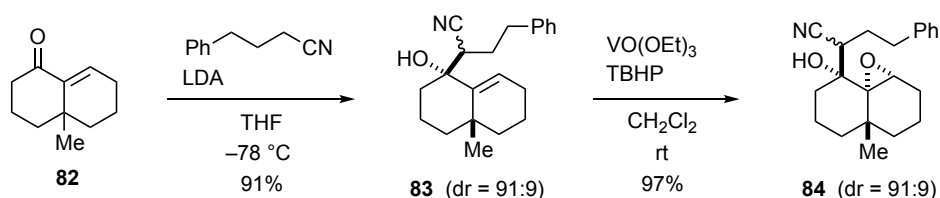
Compound S3c:

4-(2-Methyl-1,3-dioxolan-2-yl)butanenitrile was synthesized following literature procedures.⁵ According to the procedure for the synthesis of **62**, **S3c** was prepared from 4,4-dimethyl-2-cyclohexen-1-one (535 μL , 3.94 mmol), 4-(2-methyl-1,3-dioxolan-2-yl)butanenitrile (612.7 mg, 3.94 mmol), and LDA (1.0 M in THF, 4.1 mL, 4.1 mmol) in THF (15 mL). Purification by silica gel chromatography (eluted from 40% AcOEt/hexane) to give **S3c** (1.06 g, 3.79 mmol, 95%) as a 72:28 mixture of diastereomers; Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 5.71 (d, J = 9.8 Hz, 1 H), 5.52-5.56 (m, 1 H), 3.91-3.98 (m, 4 H), 2.72-2.76 (m, 0.7 H), 2.68-2.71 (m, 0.3 H), 1.48-2.04 (m, 8 H), 1.33 (s, 3 H), 1.04 (s, 3 H), 0.99 (s, 2.1 H), 0.96 (s, 0.9 H); ^{13}C NMR (125 MHz, CDCl_3) δ 143.09, 142.90, 126.14, 125.99, 120.33, 120.22, 109.24, 109.22, 69.68, 69.44, 64.53, 64.39, 43.64, 43.52, 36.65, 36.60, 32.63, 32.48, 31.82, 31.77, 30.05, 29.89, 29.82, 29.63, 26.85, 26.58, 23.73, 23.71, 21.43, 21.02; IR (neat) 3457, 2954, 2869, 2239, 1653; HRMS (FD) m/z $[\text{M}^+]$ calcd for $[\text{C}_{16}\text{H}_{25}\text{NO}_3]^+$ 279.18344, found 279.18377.

Compound 80c:

According to the procedure for the synthesis of **63**, **80c** was prepared from allyl alcohol **S3c** (864.1 mg, 3.09 mmol, dr = 72:28), TBHP (5.5 M in nonane, 1.1 mL, 6.1 mmol) and $\text{VO}(\text{OEt})_3$ (27 μL , 0.15 mmol) in CH_2Cl_2 (6.2 mL) at room temperature for 3 h. The crude product was purified by silica gel chromatography (eluted from 50% AcOEt/hexane) to give **80c** (887.8 mg, 3.01 mmol,

97%) as a 72:28 mixture of diastereomers. Colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 3.93-3.99 (m, 4 H), 3.27 (d, $J = 3.4$ Hz, 0.3 H), 3.19 (m, 0.7 H), 3.06 (d, $J = 4.0$ Hz, 0.7 H), 3.01 (d, $J = 3.4$ Hz, 0.3 H), 2.79-2.89 (m, 2 H), 1.98-2.06 (m, 2 H), 1.35-1.90 (m, 9 H), 1.12 (s, 3 H), 1.06 (s, 2.1 H), 1.03 (s, 0.9 H); ^{13}C NMR (125 MHz, CDCl_3) δ 119.60, 119.54, 108.97, 68.13, 67.94, 64.40, 64.25, 63.65, 63.48, 58.63, 57.19, 42.30, 41.76, 41.16, 40.37, 36.31, 29.80, 29.73, 28.06, 27.82, 27.65, 27.26, 27.18, 23.56, 22.96, 22.66, 20.46, 20.37 (2C missing); IR (neat) 3458, 2989, 2969, 2878, 2238, 1476, 1451; HRMS (FD) m/z $[\text{MH}^+]$ calcd for $[\text{C}_{16}\text{H}_{26}\text{NO}_4]^+$ 296.18618, found 296.18710.

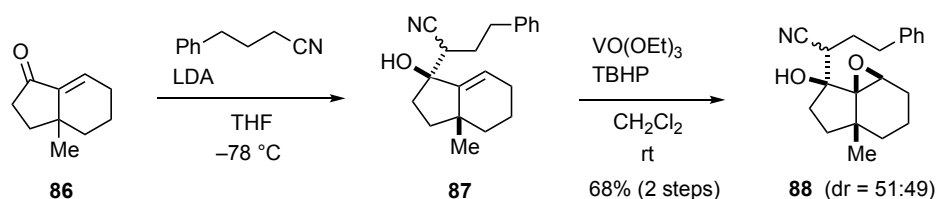


Compound 83:

Enone **82** was synthesized following literature procedures.⁶ According to the procedure for the synthesis of **62**, **83** was prepared from enone **82** (341.1 mg, 2.08 mmol), 4-phenylbutyronitrile (310 μL , 2.08 mmol), and LDA (1.0 M in THF, 2.1 mL, 2.1 mmol) in THF (10 mL) except for the conditions of 1,2-addition (-78°C for 30 min). Purification by silica gel chromatography (eluted by 5% AcOEt/hexane) and recrystallization (from ether/hexane) to give **83** (581.1 mg, 1.88 mmol, 91%) as a 91:9 mixture of diastereomers; Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.18-7.31 (m, 5 H), 6.03 (m, 0.1 H), 5.94 (m, 0.9 H), 2.97-3.09 (m, 1 H), 2.83-2.86 (m, 1 H), 2.62-2.72 (m, 1 H), 2.44-2.46 (m, 0.9 H), 2.23-2.28 (m, 0.1 H), 1.94-2.15 (m, 3 H), 1.02-1.70 (m, 10 H), 0.96 (s, 0.3 H), 0.68 (s, 2.7 H); ^{13}C NMR (125 MHz, CDCl_3) δ 144.29, 141.32, 140.26, 128.48, 128.44, 128.30, 126.22, 126.09, 124.84, 123.27, 120.38, 120.03, 73.73, 73.57, 42.04, 41.82, 41.46, 41.18, 40.57, 40.17, 38.99, 37.05, 34.34, 34.21, 33.53, 33.32, 28.39, 28.26, 26.33, 25.77, 25.54, 24.86, 18.73, 18.29, 17.84, 17.72 (2C missing); IR (neat) 3491, 2963, 2932, 2871, 2240; HRMS (FD) m/z $[\text{M}^+]$ calcd for $[\text{C}_{21}\text{H}_{27}\text{NO}]^+$ 309.20926, found 309.20943.

Compound 84:

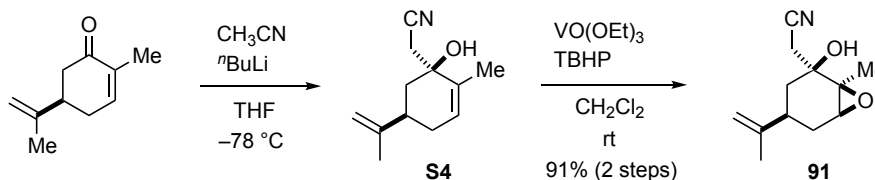
According to the procedure for the synthesis of **63**, **84** was prepared from allyl alcohol **83** (437.5 mg, 1.41 mmol, dr = 91:9), TBHP (5.5 M in nonane, 514 μ L, 2.8 mmol) and VO(OEt)₃ (13 μ L, 0.073 mmol) in CH₂Cl₂ (7.0 mL) at room temperature for 7 h. The crude product was purified by silica gel chromatography (eluted from 5% AcOEt/hexane) and recrystallization (from ether/hexane) to give **84** (445.1 mg, 1.37 mmol, 97%) as a 91:9 mixture of diastereomers. Colorless oil; ¹H NMR (500 MHz, CDCl₃) δ 7.21-7.33 (m, 5 H), 3.69-3.71 (m, 0.1 H), 3.35-3.36 (m, 0.9 H), 3.01-3.12 (m, 1.9 H), 2.91-2.95 (m, 0.1 H), 2.66-2.76 (m, 1 H), 2.44-2.45 (m, 0.1 H), 2.36-2.37 (m, 0.9 H), 2.28-2.32 (m, 1 H), 2.15-2.24 (m, 1 H), 1.86-2.09 (m, 2 H), 1.24-1.71 (m, 9 H), 1.08 (s, 0.3 H), 1.02-1.06 (m, 0.1 H), 0.84-0.89 (m, 0.9 H), 0.75 (s, 2.7 H); ¹³C NMR (125 MHz, CDCl₃) δ 140.01, 139.74, 128.39, 128.35, 128.16, 126.21, 120.21, 119.19, 71.49, 71.22, 66.83, 64.89, 56.97, 56.48, 38.81, 37.31, 37.01, 36.66, 36.39, 36.11, 36.07, 35.26, 33.90, 33.89, 33.70, 33.18, 33.01, 28.76, 28.06, 21.24, 20.68, 20.54, 20.49, 18.70, 18.49, 14.55, 14.52 (1C missing); IR (neat) 3465, 2948, 2925, 2851, 2240, 1603; HRMS (FD) m/z [M⁺] calcd for [C₂₁H₂₇NO₂]⁺ 325.20418, found 325.20477.



Compound **88**:

Enone **86** was synthesized following literature procedures.⁷ To a solution of *i*Pr₂NH (550 μ L, 3.89 mmol) in THF (16.5 mL) was added ^{*n*}BuLi (2.65 M in hexane, 1.31 mL, 3.47 mmol) at -78 °C and the mixture was stirred at 0 °C for 10 min. To the mixture was added 4-phenylbutyronitrile (495 μ L, 3.31 mmol) at -78 °C, and the resulting mixture was stirred at this temperature for 1 h. Enone **86** (497.9 mg, 3.31 mmol) was then added, and the mixture was stirred at -78 °C for 30 min. The reaction was quenched by addition of AcOH (2.0 M in THF, 3.3 mL, 6.6 mmol), and then saturated aqueous NaHCO₃ solution. The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The residue was roughly purified by silica gel column chromatography. The product was used for next step without further purification.

To a solution of allyl alcohol **87** in CH_2Cl_2 (6.6 mL) was added TBHP (5.5 M in nonane, 1.2 mL, 6.6 mmol) and $\text{VO}(\text{OEt})_3$ (29 μL , 0.16 mmol) at 0°C , and the resulting mixture was stirred at room temperature for 2 h. The reaction was quenched by addition of saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution. The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over MgSO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluted with 5% AcOEt /hexane) and recrystallization (from ether/hexane) to give **88** (702.1 mg, 2.25 mmol, 68% for 2 steps) as a 51:49 mixture of diastereomers. Colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 7.17-7.33 (m, 5 H), 3.45 (s, 0.5 H), 2.95-3.03 (m, 1 H), 2.85 (s, 0.5 H), 2.63-2.70 (m, 1.5 H), 2.41 (s, 0.5 H), 1.25-2.29 (m, 12 H), 1.14-1.20 (m, 0.5 H), 1.07 (s, 1.5 H), 1.05 (s, 1.5 H), 0.94-1.00 (m, 0.5 H); ^{13}C NMR (125 MHz, CDCl_3) δ 139.84, 139.45, 128.43, 128.27, 128.19, 128.08, 126.36, 126.07, 119.80, 119.74, 78.38, 77.85, 71.33, 69.96, 60.12, 59.34, 40.11, 38.44, 37.57, 37.54, 37.44, 37.21, 35.62, 35.33, 33.57, 33.35, 32.91, 32.19, 29.17, 28.20, 25.16, 25.00, 22.11, 22.06, 15.02, 14.80; IR (neat) 3523, 3031, 2966, 2933, 2868, 2233, 1604; HRMS (FD) m/z $[\text{M}^+]$ calcd for $[\text{C}_{20}\text{H}_{25}\text{NO}_2]^+$ 311.18853, found 311.18944.



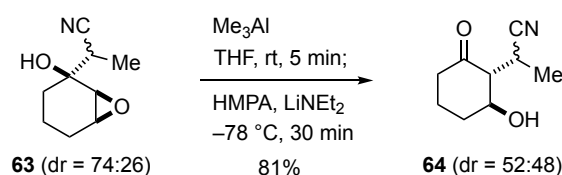
Compound 91:

To a solution of acetonitrile (373 μL , 7.14 mmol) in THF (25 mL) was added $n\text{BuLi}$ (2.65 M in hexane, 2.45 mL, 6.49 mmol) at -78°C and stirred for 1 h. L-carvone (785 μL , 5.01 mmol) was then added, and the mixture was stirred at -78°C for 30 min. The reaction was quenched by addition of 1 M HCl . The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over MgSO_4 and concentrated under reduced pressure. The residue was used for next step without further purification.

To a solution of allyl alcohol **S4** in CH_2Cl_2 (10 mL) was added TBHP (5.5 M in nonane, 1.8 mL, 9.9 mmol) and $\text{VO}(\text{OEt})_3$ (44 μL , 0.25 mmol) at 0°C , and the resulting mixture was stirred at

room temperature for 3 h. The reaction was quenched by addition of saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution. The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over MgSO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluted with 5% AcOEt /hexane) and recrystallization (from ether/hexane) to give **91** (951.0 mg, 4.59 mmol, 91% for 2 steps) as a single diastereomer. White solid.; m.p. 94-94.5 °C; ^1H NMR (500 MHz, CDCl_3) δ 4.75 (s, 1 H), 4.72 (s, 1 H), 3.23 (d, J = 5.2 Hz, 1 H), 2.78 (d, J = 16.6 Hz, 1 H), 2.70 (d, J = 16.6 Hz, 1 H), 2.14-2.21 (m, 1 H), 2.03-2.10 (m, 1 H), 1.97 (br, 1 H), 1.88-1.90 (m, 1 H), 1.78 (dd, J = 15.5 Hz, 11.5 Hz, 1 H), 1.71 (s, 3 H), 1.67 (t, J = 13.2 Hz, 1 H), 1.39 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 146.35, 116.61, 110.00, 72.55, 62.46, 61.84, 38.47, 37.30, 27.60, 25.97, 19.95, 16.07 IR (neat) 3428, 3088, 2980, 2861, 2249, 1645; HRMS (FI) m/z [M^+] calcd for $[\text{C}_{12}\text{H}_{17}\text{NO}_2]^+$ 207.12593, found 207.12696; $[\alpha]_D^{25}$ -46.5 (c 1.1, CHCl_3).

Synthesis of α -(Cyanoalkyl)- β -Hydroxy Ketones

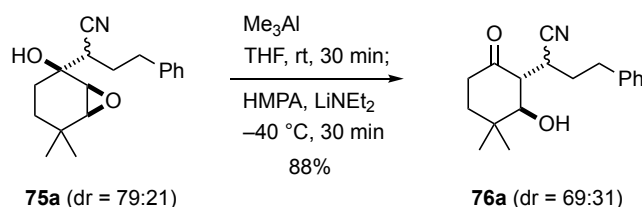


Compound **64**:

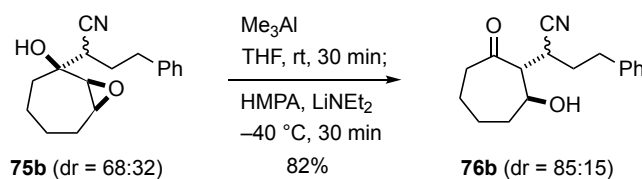
To a solution of epoxy alcohol **63** (35.6 mg, 0.213 mmol, dr = 74:26) in THF (1.1 mL) was added trimethyl aluminum (2.0 M in toluene, 160 μL , 0.320 mmol) at 0 °C and the reaction mixture was warmed up to room temperature. After stirring for 5 min, the reaction mixture was added HMPA (115 μL , 0.654 mmol) and was cooled to -78 °C. LiNEt_2 (1.0 M in THF, 640 μL , 0.640 mmol) which was prepared from $n\text{BuLi}$ (2.65 M in hexane, 380 μL , 1.00 mmol) and diethylamine (115 μL , 1.10 mmol) in THF (505 μL), was added to the reaction mixture. After stirred for 30 min, the reaction was quenched by addition of AcOH (2.0 M in THF, 750 μL , 1.5 mmol) and warmed up to room temperature. The mixture was added saturated aqueous NaCl solution. The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over MgSO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluted with 40% AcOEt /hexane) to give **64** (28.8 mg, 0.172 mmol, 81%) as

a 52:48 mixture of diastereomers. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 3.91-3.96 (m, 0.5 H), 3.80-3.84 (m, 0.5 H), 3.43-3.48 (m, 0.5 H), 3.35 (qd, $J = 7.5$ Hz, 2.3 Hz, 0.5 H), 2.70 (br, 0.5 H), 2.52-2.58 (m, 1.5 H), 2.41-2.45 (m, 1 H), 2.19-2.31 (m, 2 H), 1.98-2.03 (m, 1 H), 1.73-1.85 (m, 1 H), 1.50-1.59 (m, 1 H), 1.43 (d, $J = 7.5$ Hz, 1.5 H), 1.40 (d, $J = 6.9$ Hz, 1.5 H); ^{13}C NMR (125 MHz, CDCl_3) δ 206.12, 205.75, 122.06, 122.00, 72.09, 71.59, 60.54, 60.03, 41.00, 40.38, 34.56, 34.53, 22.24, 21.55, 20.41, 20.23, 16.09, 15.30; IR (neat) 3447, 2948, 2881, 2229, 1710, 1451; HRMS (FD) m/z [M^+] calcd for $[\text{C}_9\text{H}_{13}\text{NO}_2]^+$ 167.09463, found 167.09375.

Compound 76a:



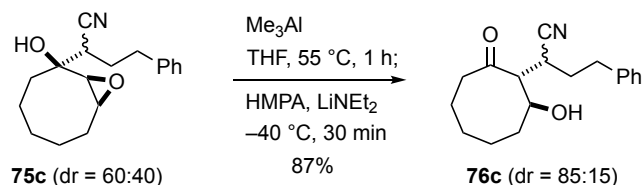
According to the procedure for the synthesis of **64**, **76a** was prepared from epoxy alcohol **75a** (87.2 mg, 0.306 mmol, dr = 79:21), trimethylaluminum (2.0 M in toluene, 230 μL , 0.460 mmol), HMPA (161 μL , 0.917 mmol) and LiNEt_2 (1.0 M in THF, 920 μL , 0.920 mmol) in THF (1.5 mL) except for the reaction conditions of preparation of aluminium alkoxide (room temperature for 30 min) and the conditions of rearrangement reaction (-40°C for 30 min). Purification by silica gel chromatography (eluted with 15% AcOEt /hexane) to give **76a** (76.7 mg, 0.269 mmol, 88%) as a 69:31 mixture of diastereomers. Colorless oil. ^1H NMR (500 MHz, C_6D_6) δ 6.95-7.10 (m, 5 H), 3.34-3.38 (m, 0.3 H), 3.27 (dd, $J = 11.5$ Hz, 5.7 Hz, 0.3 H), 3.15 (dd, $J = 11.5$ Hz, 6.3 Hz, 0.7 H), 3.01-3.07 (m, 0.7 H), 2.74-2.82 (m, 1 H), 2.42-2.49 (m, 1 H), 2.26-2.36 (m, 1 H), 2.03-2.11 (m, 1.7 H), 1.88-1.96 (m, 1.3 H), 1.68-1.77 (m, 1 H), 1.43-1.50 (m, 0.3 H), 1.33-1.40 (m, 0.7 H), 0.94-1.00 (m, 1 H), 0.76-0.88 (m, 1 H), 0.67 (s, 2.1 H), 0.65 (s, 2.1 H), 0.64 (s, 0.9 H), 0.60 (s, 0.9 H); ^{13}C NMR (125 MHz, CDCl_3) δ 205.93, 205.78, 140.30, 140.26, 128.57, 128.53, 128.44, 126.31, 121.02, 120.89, 78.30, 77.63, 54.91, 54.67, 38.05, 37.42, 35.90, 35.73, 34.99, 34.65, 34.11, 34.05, 32.71, 31.30, 28.08, 27.94, 27.82, 17.70, 17.62 (3C missing); IR (neat) 3424, 3029, 2934, 2850, 2251, 1714; HRMS (FI) m/z [M^+] calcd for $[\text{C}_{18}\text{H}_{23}\text{NO}_2]^+$ 285.17288, found 285.17275.



Compound 76b:

According to the procedure for the synthesis of **64**, **76b** was prepared from epoxy alcohol **75b** (57.6 mg, 0.212 mmol, dr = 68:32), trimethylaluminum (2.0 M in toluene, 160 μL , 0.320 mmol), HMPA (112 μL , 0.637 mmol) and LiNEt_2 (1.0 M in THF, 640 μL , 0.640 mmol) in THF (1.1 mL) except for the reaction conditions of preparation of aluminium alkoxide (room temperature for 30 min) and the conditions of rearrangement reaction (-40°C for 30 min). Purification by silica gel chromatography (eluted from 10% to 45% AcOEt /hexane) to give **76b** (47.6 mg, 0.175 mmol, 82%) as an 85:15 mixture of diastereomers. Colorless oil. ^1H NMR (500 MHz, C_6D_6) δ 6.86-7.01 (m, 5 H), 3.39-3.45 (m, 1 H), 2.89 (dt, $J = 10.3$ Hz, 4.6 Hz, 0.9 H), 2.85-2.89 (m, 0.1 H), 2.58-2.67 (m, 1 H), 2.33-2.44 (m, 1 H), 2.13-2.25 (m, 2 H), 1.66-1.98 (m, 2 H), 0.78-1.47 (m, 7 H); ^{13}C NMR (125 MHz, CDCl_3) δ 210.13, 209.48, 139.98, 139.84, 128.56, 128.54, 128.37, 126.37, 126.34, 121.27, 120.65, 70.29, 69.84, 59.74, 59.35, 43.73, 43.27, 38.27, 35.58, 33.61, 33.35, 32.52, 31.44, 31.33, 30.52, 24.47, 23.77, 23.46, 21.87 (1C missing); IR (neat) 3454, 3026, 2927, 2858, 2242, 1704; HRMS (FI) m/z [M^+] calcd for $[\text{C}_{17}\text{H}_{21}\text{NO}_2]^+$ 271.15723, found 271.15844.

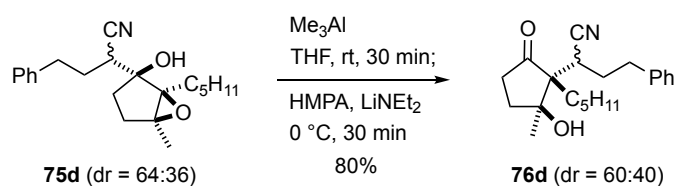
Compound 28:



According to the procedure for the synthesis of **64**, **76c** was prepared from epoxy alcohol **75c** (60.3 mg, 0.211 mmol, dr = 60:40), trimethylaluminum (2.0 M in toluene, 160 μL , 0.320 mmol), HMPA (112 μL , 0.637 mmol), and LiNEt_2 (1.0 M in THF, 635 μL , 0.635 mmol) in THF (1.1 mL) except for the reaction conditions of preparation of aluminium alkoxide (55°C for 1 h) and the conditions of rearrangement reaction (-40°C for 30 min). Purification by silica gel chromatography (eluted from 10% to 15% AcOEt /hexane) to give **76c** (52.7 mg, 0.184 mmol, 87%) as an 85:15 mixture of diastereomers. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.11-7.24 (m, 5 H), 3.90-3.96 (m, 0.9 H), 3.73-3.78 (m, 0.1 H), 3.10-3.20 (m, 1 H), 2.84-2.96 (m, 2 H),

2.59-2.66 (m, 1 H), 2.23-2.44 (m, 2 H), 1.11-2.08 (m, 10 H); ^{13}C NMR (125 MHz, CDCl_3) δ 213.39, 212.86, 139.90, 128.58, 128.53, 128.38, 128.36, 126.39, 126.33, 121.48, 120.31, 73.07, 72.37, 54.96, 45.85, 45.63, 34.93, 34.75, 33.68, 33.43, 32.21, 31.46, 31.31, 31.28, 28.19, 28.00, 22.80, 22.51, 20.20, 20.06 (2C missing); IR (neat) 3458, 3030, 2927, 2859, 2238, 1699; HRMS (FI) m/z $[\text{M}^+]$ calcd for $[\text{C}_{18}\text{H}_{23}\text{NO}_2]^+$ 285.17288, found 285.17160.

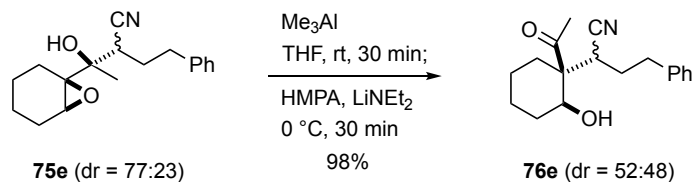
Compound 26:



According to the procedure for the synthesis of **64**, **76d** was prepared from epoxy alcohol **76d** (104.4 mg, 0.319 mmol, dr = 64:36), trimethylaluminum (2.0 M in toluene, 240 μL , 0.480 mmol), HMPA (168 μL , 0.956 mmol) and LiNEt_2 (1.0 M in THF, 960 μL , 0.960 mmol) in THF (1.6 mL) except for the reaction conditions of aluminium alkoxylation (room temperature for 30 min) and the conditions of rearrangement reaction (0 $^\circ\text{C}$ for 30 min). Purification by silica gel chromatography (eluted from 2% to 5% AcOEt /hexane) to give **76d** (50.1 mg, 0.153 mmol, 48%) and **76d'** (33.4 mg, 0.102 mmol, 32%). For **76d** (less polar); Yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 7.20-7.32 (m, 5 H), 2.97-3.02 (m, 1 H), 2.66-2.74 (m, 2 H), 2.45-2.52 (m, 1 H), 2.17-2.30 (m, 2 H), 2.05-2.11 (m, 1 H), 1.96-2.00 (m, 2 H), 1.77-1.84 (m, 1 H), 1.57-1.68 (m, 2 H), 1.34 (s, 3 H), 1.19-1.32 (m, 4 H), 1.00-1.08 (m, 1 H), 0.86 (t, $J = 6.9$ Hz, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 216.66, 139.69, 128.63, 128.51, 126.53, 120.88, 79.76, 58.97, 35.61, 35.09, 33.82, 32.37, 32.06, 29.97, 29.73, 26.17, 23.28, 22.31, 13.96; IR (neat) 3481, 3028, 2957, 2928, 2870, 2248, 1734; HRMS (FI) m/z $[\text{M}^+]$ calcd for $[\text{C}_{21}\text{H}_{29}\text{NO}_2]^+$ 327.21983, found 327.22085.

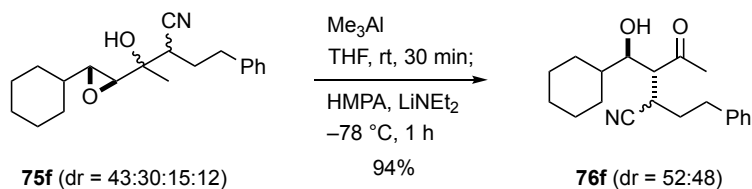
For **76'** (more polar); Yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 7.21-7.33 (m, 5 H), 3.01-3.07 (m, 1 H), 2.80 (dd, $J = 12.1$ Hz, 3.4 Hz, 1 H), 2.66-2.73 (m, 1 H), 2.39-2.47 (m, 1 H), 2.02-2.24 (m, 4 H), 1.89-1.94 (m, 1 H), 1.73-1.79 (m, 2 H), 1.52-1.57 (m, 4 H), 1.02-1.26 (m, 5 H), 0.81-0.90 (m, 4 H); ^{13}C NMR (125 MHz, CDCl_3) δ 214.94, 139.69, 128.67, 128.55, 126.55, 121.18, 79.68, 59.15, 34.95, 34.36, 33.62, 32.24, 30.80, 28.55, 27.94, 26.30, 23.10, 22.25, 13.92; HRMS (FI)

3461, 2954, 2928, 2871, 2249, 1734; HRMS (FI) m/z $[M^+]$ calcd for $[C_{21}H_{29}NO_2]^+$ 327.21983, found 327.22108.



Compound 76e:

According to the procedure for the synthesis of **64**, **76e** was prepared from epoxy alcohol **75e** (63.9 mg, 0.223 mmol, dr = 77:23), trimethylaluminum (2.0 M in toluene, 170 μL , 0.340 mmol), HMPA (120 μL , 0.683 mmol) and LiNEt_2 (1.0 M in THF 680 μL , 0.680 mmol) in THF (1.1 mL) except for the reaction conditions of preparation of aluminium alkoxide (room temperature for 30 min) and the conditions of rearrangement reaction (0 $^\circ\text{C}$ for 30 min). Purification by silica gel chromatography (eluted from 10% to 20% AcOEt /hexane) to give **76e** (62.8 mg, 0.220 mmol, 98%) as a 52:48 mixture of diastereomers. Yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 7.10-7.24 (m, 5 H), 3.73-3.80 (m, 0.5 H), 3.61-3.66 (m, 0.5 H), 3.11 (br, 0.5 H), 3.03-3.06 (m, 0.5 H), 2.91-2.96 (m, 1 H), 2.73 (dd, J = 12.6 Hz, 3.5 Hz, 0.5 H), 2.54-2.63 (m, 1 H), 2.09-2.14 (m, 2 H), 1.94-2.01 (m, 2 H), 1.02-1.85 (m, 9 H); ^{13}C NMR (125 MHz, CDCl_3) δ 213.17, 212.05, 139.39, 139.37, 128.59, 128.41, 128.30, 126.50, 119.52, 74.06, 73.07, 56.62, 56.20, 36.79, 36.48, 33.68, 33.56, 31.91, 31.72, 30.11, 29.83, 29.19, 29.03, 27.29, 23.49, 23.07, 22.10 (5C missing); IR (neat) 3490, 3031, 2929, 2863, 2236, 1699; HRMS (FD) m/z $[M^+]$ calcd for $[C_{18}H_{23}NO_2]^+$ 285.17288, found 285.17381.



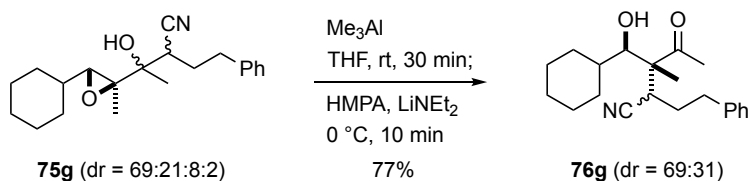
Compound 76f:

According to the procedure for the synthesis of **64**, **76f** was prepared from epoxy alcohol **75f** (101.2 mg, 0.322 mmol, dr = 43:30:15:12), trimethylaluminum (2.0 M in toluene, 325 μL , 0.650 mmol), HMPA (283 μL , 1.61 mmol) and LiNEt_2 (1.0 M in THF 1.60 mL, 1.60 mmol) in THF (1.6 mL)

except for the reaction conditions of preparation of aluminium alkoxide (room temperature for 30 min) and the conditions of rearrangement reaction (-78 °C for 1 h). Purification by silica gel chromatography (eluted from 5% to 10% AcOEt/hexane) to give **76f** (49.5 mg, 0.158 mmol, 49%) and **76f'** (45.6 mg, 0.145 mmol, 45%).

For **76f** (less polar); Colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.09-7.25 (m, 5 H), 3.57-3.61 (m, 1 H), 3.13 (dt, *J* = 10.3 Hz, 3.5 Hz, 1 H), 2.96-3.00 (m, 1 H), 2.87-2.94 (m, 1 H), 2.63-2.69 (m, 1 H), 2.23 (d, *J* = 8.1 Hz, 1 H), 2.14 (s, 3 H), 1.89-1.92 (m, 1 H), 1.76-1.84 (m, 1 H), 1.56-1.72 (m, 5 H), 1.06-1.19 (m, 4 H), 0.87-0.99 (m, 2 H); ¹³C NMR (125 MHz, CDCl₃) δ 210.05, 139.57, 128.71, 128.36, 126.58, 120.18, 76.21, 54.53, 41.95, 33.40, 33.00, 32.13, 31.65, 29.60, 29.01, 26.06, 25.70, 25.53; IR (neat) 3484, 3027, 2925, 2853, 2238, 1705; HRMS (FD) *m/z* [*M*⁺] calcd for [C₂₀H₂₇NO₂]⁺ 313.20418, found 313.20401.

For **76f'** (more polar); Yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 7.15-7.32 (m, 5 H), 3.40-3.46 (m, 1 H), 2.86-3.02 (m, 3 H), 2.68-2.76 (m, 1 H), 2.43-2.52 (m, 1 H), 2.34 (s, 3 H), 1.96-2.04 (m, 1 H), 1.82-1.89 (m, 2 H), 1.70-1.77 (m, 2 H), 1.58-1.66 (m, 2 H), 1.06-1.25 (m, 4 H), 0.86-1.01 (m, 2 H); ¹³C NMR (125 MHz, CDCl₃) δ 211.70, 139.58, 128.69, 128.38, 126.57, 120.34, 74.84, 53.52, 41.79, 33.30, 33.03, 31.13, 30.51, 29.89, 28.51, 26.09, 25.80, 25.59; IR (neat) 3490, 3027, 2925, 2854, 2236, 1703; HRMS (FI) *m/z* [*M*⁺] calcd for [C₂₀H₂₇NO₂]⁺ 313.20418, found 313.20559.

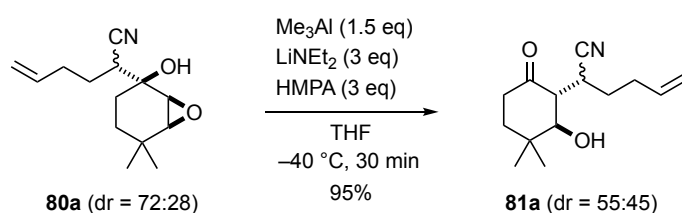


Compound **76g**:

According to the procedure for the synthesis of **64**, **76g** was prepared from epoxy alcohol **75g** (73.0 mg, 0.222 mmol, dr = 69:21:8:2), trimethylaluminum (2.0 M in toluene, 223 μL, 0.446 mmol), HMPA (195 μL, 1.11 mmol) and LiNEt₂ (1.0 M in THF 1.12 mL, 1.12 mmol) in THF (1.1 mL) except for the reaction conditions of preparation of aluminium alkoxide (room temperature for 30 min) and the conditions of rearrangement reaction (0 °C for 10 min). Purification by silica gel chromatography 3 times (eluted from 2% to 10% AcOEt/hexane) to give **76g** (17.6 mg, 0.0537 mmol, 24%) and **76g'** (38.5 mg, 0.117 mmol, 53 %). For **76g** (less polar); Colorless crystal. ¹H

NMR (500 MHz, CDCl₃) δ 7.10-7.25 (m, 5 H), 3.51 (d, J = 8.0 Hz, 1 H), 3.46 (dd, J = 12.6 Hz, 3.5 Hz, 1 H), 2.89-2.94 (m, 1 H), 2.57-2.63 (m, 1 H), 2.44 (d, J = 8.0 Hz, 1 H), 2.06 (s, 3 H), 1.78-1.87 (m, 1 H), 1.40-1.70 (m, 5 H), 0.96-1.32 (m, 10 H); ¹³C NMR (125 MHz, CDCl₃) δ 212.81, 139.66, 128.68, 128.44, 126.59, 120.00, 81.13, 55.62, 39.06, 37.34, 33.97, 32.83, 30.41, 29.85, 26.56, 26.11, 25.84, 15.98 (1C missing); IR (neat) 3475, 2924, 2852, 2244, 1701; HRMS (FI) m/z [M^+] calcd for [C₂₁H₂₉NO₂]⁺ 327.21983, found 327.22070.

For **76g'** (more polar); Colorless crystal. ¹H NMR (500 MHz, CDCl₃) δ 7.20-7.31 (m, 5 H), 3.28-3.33 (m, 2 H), 2.93-3.03 (m, 2 H), 2.65-2.71 (m, 1 H), 2.35 (s, 3 H), 1.96-2.03 (m, 1 H), 1.68-1.75 (m, 3 H), 1.58-1.61 (m, 1 H), 0.98-1.47 (m, 10 H); ¹³C NMR (125 MHz, CDCl₃) δ 215.75, 139.86, 128.61, 128.43, 126.48, 120.44, 79.23, 54.66, 39.64, 37.88, 33.74, 32.78, 30.29, 28.01, 27.26, 26.53, 26.18, 25.80, 16.60; IR (neat) 3504, 3027, 2926, 2853, 2244, 1701; HRMS (FI) m/z [M^+] calcd for [C₂₁H₂₉NO₂]⁺ 327.21983, found 327.22049.

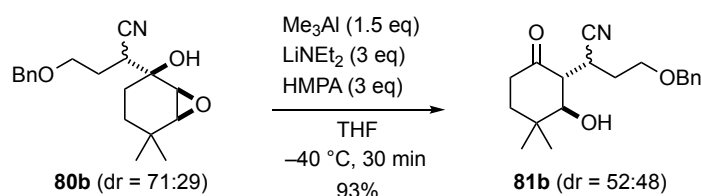


Compound 81a:

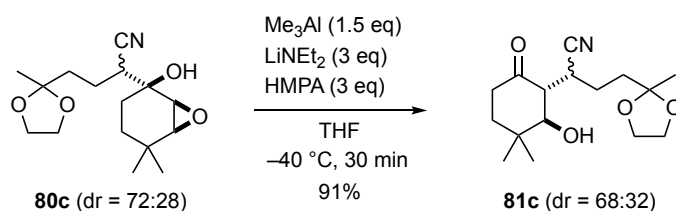
According to the procedure for the synthesis of **64**, **81a** was prepared from epoxy alcohol **80a** (54.3 mg, 0.231 mmol, dr = 72:28), trimethylaluminum (2.0 M in toluene, 173 μ L, 0.346 mmol), HMPA (122 μ L, 0.694 mmol), and LiNEt₂ (1.0 M in THF, 695 μ L, 0.695 mmol) in THF (1.2 mL) except for the reaction conditions of preparation of aluminium alkoxide (room temperature for 30 min) and the conditions of rearrangement reaction (-40 °C for 30 min). Purification by silica gel chromatography (eluted from 2% to 10% AcOEt/hexane) to give **81a** (51.5 mg, 0.219 mmol, 95%) as a 55:45 mixture of diastereomers. Colorless oil. ¹H NMR (500 MHz, C₆D₆) δ 5.49-5.59 (m, 1 H), 4.90-4.99 (m, 2 H), 3.37-3.39 (m, 0.4 H), 3.19 (dd, J = 10.9 Hz, 5.8 Hz, 0.4 H), 3.04 (dd, J = 11.5 Hz, 5.8 Hz, 0.6 H), 2.96-3.00 (m, 0.6 H), 1.86-2.23 (m, 5 H), 1.64-1.73 (m, 1 H), 1.30-1.41 (m, 1 H), 1.04-1.19 (m, 1 H), 0.89-0.94 (m, 1 H), 0.67-0.79 (m, 1 H), 0.61 (s, 1.8 H), 0.60 (s, 1.2 H), 0.53 (s, 1.8 H), 0.49 (s, 1.2 H); ¹³C NMR (125 MHz, CDCl₃) δ 206.25, 206.13, 136.43, 136.40, 121.01, 120.89, 116.26, 116.23, 78.15, 77.46, 54.98, 54.54, 38.11, 37.43, 35.91,

35.71, 35.04, 34.64, 31.88, 31.82, 29.94, 28.74, 27.95, 27.88, 27.83, 27.53, 17.71, 17.64; IR (neat) 3454, 2925, 2871, 2240, 1713, 1641; HRMS (FD) m/z $[M^+]$ calcd for $[C_{14}H_{21}NO_2]^+$ 235.15723, found 235.15771.

Compound 81b:

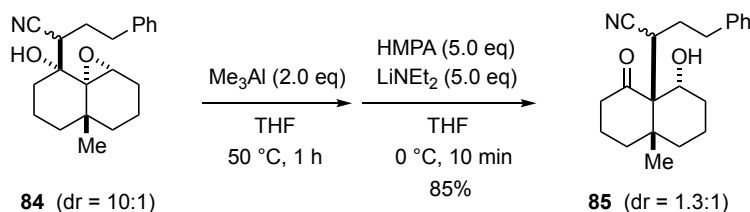


According to the procedure for the synthesis of **64**, **81b** was prepared from epoxy alcohol **80b** (67.6 mg, 0.214 mmol, dr = 71:29), trimethylaluminum (2.0 M in toluene, 160 μ L, 0.320 mmol), HMPA (113 μ L, 0.643 mmol), and LiNEt₂ (1.0 M in THF, 645 μ L, 0.645 mmol) in THF (1.1 mL) except for the reaction conditions of preparation of aluminium alkoxide (room temperature for 30 min) and the conditions of rearrangement reaction (-40 °C for 30 min). Purification by silica gel chromatography (eluted from 5% to 30% AcOEt/hexane) to give **81b** (63.2 mg, 0.200 mmol, 93 %) as a 52:48 mixture of diastereomers. Colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.29-7.37 (m, 5 H), 4.54 (d, J = 12.0 Hz, 1 H), 4.49 (d, J = 12.0 Hz, 1 H), 3.47-3.67 (m, 4 H), 2.71-2.73 (m, 0.5 H), 2.64 (dd, J = 11.5 Hz, 2.3 Hz, 0.5 H), 2.23-2.44 (m, 4 H), 1.97-2.02 (m, 0.5 H), 1.79-1.87 (m, 0.5 H), 1.66-1.72 (m, 1 H), 1.41-1.51 (m, 1 H), 1.09 (s, 1.5 H), 1.08 (s, 1.5 H), 1.06 (s, 1.5 H), 1.03 (s, 1.5 H); ¹³C NMR (125 MHz, CDCl₃) δ 206.25, 137.92, 137.57, 128.44, 128.36, 127.83, 127.82, 127.64, 121.03, 120.71, 77.83, 77.65, 73.27, 73.05, 67.53, 67.44, 54.66, 54.22, 38.07, 37.46, 35.78, 35.69, 35.01, 34.71, 30.57, 29.98, 27.92, 27.84, 25.58, 25.31, 17.64, 17.58 (2C missing); IR (neat) 3446, 2957, 2870, 2237, 1714, 1496; HRMS (FD) m/z $[M^+]$ calcd for $[C_{19}H_{25}NO_3]^+$ 315.18344, found 315.18406.



Compound 81c:

According to the procedure for the synthesis of **64**, **81c** was prepared from epoxy alcohol **80c** (62.6 mg, 0.212 mmol, dr = 72:28), trimethylaluminum (2.0 M in toluene, 160 μ L, 0.320 mmol), HMPA (112 μ L, 0.638 mmol), and LiNEt₂ (1.0 M in THF, 640 μ L, 0.640 mmol) in THF (1.1 mL) except for the reaction conditions of aluminium alkoxylation (room temperature for 1 h) and the conditions of rearrangement reaction (-40 °C for 30 min). Purification by silica gel chromatography twice (eluted from 5% to 30% AcOEt/hexane) to give **81c** (57.3 mg, 0.193 mmol, 91 %) as a 68:32 mixture of diastereomers. Colorless oil. ¹H NMR (500 MHz, CD₂Cl₂) δ 3.86-3.92 (m, 4 H), 3.57 (d, *J* = 11.5 Hz, 0.3 H), 3.46 (d, *J* = 11.5 Hz, 0.7 H), 3.37-3.41 (m, 0.3 H), 3.17-3.22 (m, 0.7 H), 2.60-2.65 (m, 1 H), 2.43 (td, *J* = 14.9 Hz, 6.3 Hz, 1 H), 2.25-2.32 (m, 1 H), 1.98-2.14 (m, 1 H), 1.87-1.94 (m, 1 H), 1.39-1.73 (m, 4 H), 1.27 (m, 3 H), 1.08 (s, 3 H), 1.07 (s, 2.1 H), 1.06 (s, 0.9 H); ¹³C NMR (125 MHz, CD₂Cl₂) δ 206.64, 206.46, 121.56, 121.36, 109.66, 109.58, 78.27, 77.86, 65.04, 65.01, 64.95, 64.92, 55.33, 54.95, 38.50, 37.89, 37.46, 37.37, 36.18, 36.03, 35.36, 35.00, 28.89, 28.47, 28.08, 28.00, 25.12, 24.73, 23.99, 23.96, 17.84, 17.76; IR (neat) 3533, 2960, 2928, 2887, 2234, 1718, 1457; HRMS (FD) *m/z* [M⁺] calcd for [C₁₆H₂₅NO₄]⁺ 295.17836, found 295.17796.



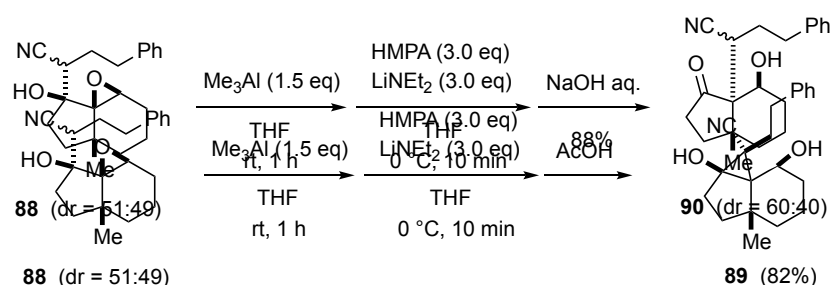
Compound **85**:

According to the procedure for the synthesis of **64**, **85** was prepared from epoxy alcohol **84** (69.8 mg, 0.214 mmol, dr = 91:9), trimethylaluminum (2.0 M in toluene, 215 μ L, 0.430 mmol), HMPA (188 μ L, 1.07 mmol), and LiNEt₂ (1.0 M in THF, 1.07 mL, 1.07 mmol) in THF (1.1 mL) except for the reaction conditions of preparation of aluminium alkoxide (50 °C for 1 h) and the conditions of rearrangement reaction (0 °C for 10 min). Purification by silica gel chromatography twice (eluted from 2% to 16% AcOEt/hexane) to give **85** (59.5 mg, 0.183 mmol, 85 %) as a 63:47 mixture of diastereomers. Colorless oil. ¹H NMR (500 MHz, CD₂Cl₂) δ 7.19-7.34 (m, 5 H), 4.18 (td, *J* = 12.1 Hz, 5.2 Hz, 0.6 H), 3.74 (td, *J* = 11.5 Hz, 5.2 Hz, 0.4 H), 3.43-3.35 (m, 0.4 H), 2.99-3.13 (m, 2.6 H), 2.52-2.77 (m, 2 H), 1.19-2.48 (m, 11 H), 1.17 (s, 1.8 H), 0.95-1.03 (m, 1 H), 0.85

(s, 1.2 H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 214.85, 214.82, 139.72, 139.44, 128.65, 128.64, 128.58, 126.58, 126.55, 121.22, 120.35, 72.34, 69.76, 60.19, 59.02, 43.07, 42.63, 40.39, 39.96, 35.26, 35.07, 34.97, 34.78, 33.83, 33.25, 33.07, 32.41, 31.70, 30.91, 23.82, 23.61, 20.44, 20.32, 19.84, 19.78 (3C missing); IR (neat) 3534, 3028, 2938, 2870, 2239, 1691, 1604; HRMS (FD) m/z $[\text{M}^+]$ calcd for $[\text{C}_{21}\text{H}_{27}\text{NO}_2]^+$ 325.20418, found 325.20493.

Compound 89:

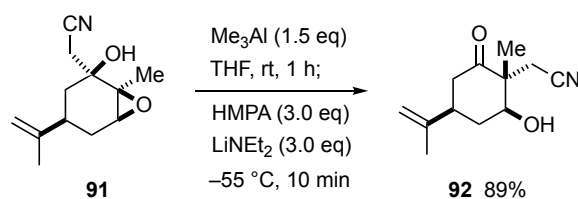
To a solution of epoxy alcohol **88** (68.1 mg, 0.218 mmol, dr = 51:49) in THF (1.1 mL) was added trimethyl aluminum (2.0 M in toluene, 165 μL , 0.330 mmol) at 0 $^\circ\text{C}$ and the reaction mixture was



warmed up to room temperature. After stirring for 1 h, the reaction mixture was added HMPA (115 μL , 0.654 mmol) and was cooled to -78 $^\circ\text{C}$. LiNEt_2 (1.0 M in THF, 655 μL , 0.655 mmol) which was prepared from $n\text{BuLi}$ (2.65 M in hexane, 380 μL , 1.00 mmol) and diethylamine (115 μL , 1.10 mmol) in THF (505 μL), was added to the reaction mixture. After stirred at 0 $^\circ\text{C}$ for 10 min, the reaction was quenched by addition of AcOH (2.0 M in THF, 750 μL , 1.5 mmol) and warmed up to room temperature. The mixture was added saturated aqueous NaCl solution. The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over MgSO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluted with 20% AcOEt/hexane) to give **89** (56.2 mg, 0.180 mmol, 82%) as a single diastereomers. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.27-7.38 (m, 5 H), 4.11 (m, 1 H), 2.95-2.98 (m, 2 H), 1.85-2.17 (m, 7 H), 1.70-1.76 (m, 1 H), 1.46-1.55 (m, 3 H), 1.34 (s, 3 H), 1.25-1.31 (m, 1 H), 0.99 (br, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 140.78, 128.75, 128.64, 126.58, 121.76, 71.99, 68.89, 48.72, 42.69, 35.07, 33.41, 33.02, 31.99, 31.96, 30.10, 26.66, 25.42, 17.25; IR (neat) 3494, 3305, 3024, 2960, 2912, 2222; HRMS (FD) m/z $[\text{M}^+]$ calcd for $[\text{C}_{20}\text{H}_{25}\text{NO}_2]^+$ 311.18853, found 311.18931.

Compound 90:

To a solution of epoxy alcohol **88** (68.0 mg, 0.218 mmol, dr = 51:49) in THF (1.1 mL) was added trimethyl aluminum (2.0 M in toluene, 165 μ L, 0.330 mmol) at 0 °C and the reaction mixture was warmed up to room temperature. After stirring for 1 h, the reaction mixture was added HMPA (115 μ L, 0.654 mmol) and was cooled to -78 °C. LiNEt₂ (1.0 M in THF, 655 μ L, 0.655 mmol) which was prepared from ⁿBuLi (2.65 M in hexane, 380 μ L, 1.00 mmol) and diethylamine (115 μ L, 1.10 mmol) in THF (505 μ L), was added to the reaction mixture. After stirred at 0 °C for 10 min, the reaction was quenched by addition of AcOH (2.0 M in THF, 750 μ L, 1.5 mmol) and warmed up to room temperature. The mixture was added saturated aqueous potassium sodium tartrate solution and then 10% aqueous sodium hydroxide solution. After stirred for 40 min, the aqueous layer was extracted with ether. The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluted from 2% to 16% AcOEt/hexane) to give **90** (59.9 mg, 0.192 mmol, 88%) as a 60:40 mixture of diastereomers. White solid. ¹H NMR (500 MHz, CDCl₃) δ 7.15-7.34 (m, 5 H), 4.37-4.38 (m, 0.6 H), 3.74-3.75 (m, 0.4 H), 2.94-3.04 (m, 2 H), 2.61-2.69 (m, 1 H), 2.30-2.56 (m, 4 H), 1.25-2.04 (m, 9 H), 1.17 (s, 1.2 H), 1.12 (s, 1.8 H); ¹³C NMR (125 MHz, CDCl₃) δ 216.09, 215.05, 138.92, 138.77, 128.80, 128.54, 128.43, 126.84, 126.79, 121.42, 68.19, 66.15, 60.56, 59.90, 41.18, 41.10, 34.60, 32.79, 32.77, 32.66, 32.25, 31.99, 31.74, 30.92, 30.54, 30.47, 30.11, 28.14, 26.91, 26.44, 26.23, 25.82, 17.19, 16.61; IR (neat) 3537, 3408, 3024, 2927, 2870, 2225, 2184, 1729; HRMS (FD) m/z [M⁺] calcd for [C₂₀H₂₅NO₂]⁺ 311.18853, found 311.18889.

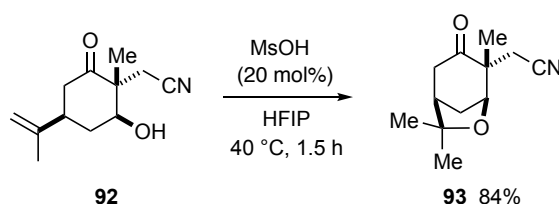


Compound 92:

According to the procedure for the synthesis of **64**, **91** was prepared from epoxy alcohol **91** (214.1 mg, 1.03 mmol), trimethylaluminum (2.0 M in toluene, 775 μ L, 1.55 mmol), HMPA (545 μ L, 3.10 mmol), and LiNEt₂ (1.0 M in THF, 3.1 mL, 3.1 mmol) in THF (5.2 mL) except for the reaction conditions of preparation of aluminium alkoxide (room temperature for 1

h) and the conditions of rearrangement reaction (-50 °C for 10 min). Purification by silica gel chromatography twice (eluted from 2% to 16% AcOEt/hexane) to give **92** (198.5 mg, 0.957 mmol, 89%). Colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 4.83 (s, 1 H), 4.78 (s, 1 H), 3.95 (dt, *J* = 11.5 Hz, 4.6 Hz, 1 H), 2.72 (d, *J* = 16.0 Hz, 1 H), 2.60 (d, *J* = 16.0 Hz, 1 H), 2.52 (t, *J* = 13.8 Hz, 1 H), 2.38-2.42 (m, 1 H), 2.26 (tt, *J* = 3.5 Hz, 13.2 Hz, 1 H), 2.06-2.11 (m, 1 H), 1.85-1.92 (m, 2 H), 1.76 (s, 3 H), 1.26 (s, 3 H); ¹³C NMR (125 MHz, CD₂Cl₂) δ 209.92, 145.65, 118.29, 110.52, 72.10, 53.44, 41.49, 38.67, 34.75, 22.48, 20.18, 16.64; IR (neat) 3430, 2976, 2941, 2866, 2251, 1711; HRMS (FI) *m/z* [*M*⁺] calcd for [C₁₂H₁₇NO₂]⁺ 207.12593, found 207.12685; [*α*]_D²⁵ 260.4 (c 1.1, CHCl₃).

Derivatizations of Formal Rearrangement Product from L-Carvone



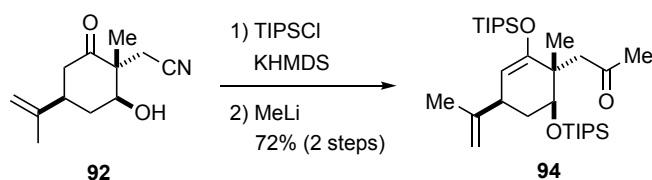
Compound 93:

To a solution of hydroxy ketone **92** (53.8 mg, 0.259 mmol) in HFIP (1.3 mL) was added MsOH (3.5 μL, 0.54 mmol) and the reaction mixture was warmed up to 40 °C. After stirring for 1.5 h, the reaction was quenched by addition of saturated aqueous sodium hydrogen carbonate solution. The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluted with 40% AcOEt/hexane) to give **93** (45.4 mg, 0.219 mmol, 84%). White solid.; m.p. 97-98 °C; ¹H NMR (500 MHz, CDCl₃) δ 4.20 (d, *J* = 5.7 Hz, 1 H), 2.68 (dt, *J* = 18.3 Hz, 2.9 Hz, 1 H), 2.50-2.57 (m, 1 H), 2.45 (dd, *J* = 18.3 Hz, 4 Hz, 1 H), 2.38 (s, 2 H), 2.28-2.33 (m, 1 H), 2.13 (d, *J* = 12.6 Hz, 1 H), 1.34 (s, 3 H), 1.25 (s, 3 H), 1.21 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 211.59, 116.16, 82.70, 80.27, 51.62, 43.19, 41.80, 32.68, 29.30, 25.16,

25.05, 19.96; IR (neat) 2977, 2933, 2247, 1708; HRMS (FI) m/z $[M^+]$ calcd for $[C_{12}H_{17}NO_2]^+$ 207.12593, found 207.12617; $[\alpha]_D^{25} -22$ (c 1.1, $CHCl_3$).

Compound 94:

To a solution of hydroxy ketone **92** (165.1 mg, 0.796 mmol) and TIPSCl (445 μ L, 1.99 mmol) in THF (5 mL) was added KHMDS (0.5 M in toluene, 4.46 mL, 2.23 mmol) at -78°C , and the reaction mixture was warmed up to rt. After stirring for 40 min, the reaction was quenched by addition of saturated aqueous sodium hydrogen carbonate solution. The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over



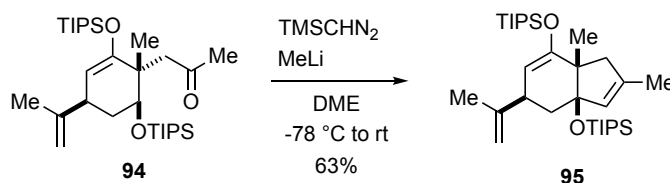
$MgSO_4$ and concentrated under reduced pressure. The residue was roughly purified by silica gel column chromatography pre-treated by *N,N*-dimethylaniline. The product was used for next step without further purification.

To a solution of enol silyl ether in THF (15 mL) was added MeLi (1.13 M in ether, 3.55 mL, 4.01 mmol) at -78°C , and the reaction mixture was warmed up to -35°C . After stirring for 1 h, the reaction was cooled to -78°C and quenched by addition of saturated aqueous sodium hydrogen carbonate solution. The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with 5% AcOEt/hexane) to give **94** (306.6 mg, 0.570 mmol, 72% for 2 steps). Colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 4.75 (s, 1 H), 4.68 (s, 1 H), 4.52 (dd, $J = 12$ Hz, 4.1 Hz, 1 H), 4.48 (s, 1 H), 2.99-3.02 (m, 1 H), 2.80 (d, $J = 17.8$ Hz, 1 H), 2.71 (d, $J = 17.8$ Hz, 1 H), 2.05 (s, 3 H), 1.76-1.80 (m, 1 H), 1.68 (s, 3 H), 1.60 (q, $J = 12$ Hz, 1 H), 1.14-1.22 (m, 3 H), 1.05-1.10 (m, 42 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.75, 153.83, 149.47, 109.53, 103.13, 71.41, 47.01, 44.22, 41.01, 33.88, 30.72, 20.99, 19.76, 18.20, 18.14, 18.10, 12.93, 12.91, 12.82, 12.80, 12.78; IR (neat) 2943, 2866, 2358, 2342,

1722, 1660, 1463; HRMS (FI) m/z $[M^+]$ calcd for $[C_{31}H_{60}O_3Si_2]^+$ 536.40810, found 536.40915; $[\alpha]_D^{25}$ 20.5 (c 1.03, $CHCl_3$).

Compound 95:

To a solution of trimethylsilyl diazomethane (2.0 M in ether, 495 μ L, 0.990 mmol) in DME (4.4 mL) was added MeLi (1.13 M in ether, 800 μ L, 0.904 mmol) at $-78^\circ C$, and the mixture was warmed up to rt. After stirring for 10 min, the reaction was cooled to $-50^\circ C$ and **94** (120.4 mg,



0.224 mmol) in DME (2 mL) was added. The mixture was stirred for 1 h at $-78^\circ C$ and gradually warmed up to rt over 2 h. The reaction mixture was quenched by addition of saturated aqueous sodium hydrogen carbonate solution. The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with hexane) to give **95** (76.2 mg, 0.142 mmol, 63%). Colorless oil. 1H NMR (500 MHz, $CDCl_3$) δ 5.44 (s, 1 H), 4.74 (s, 1 H), 4.69 (s, 1 H), 4.46 (s, 1 H), 2.54-2.57 (m, 2 H), 2.29-2.32 (m, 1 H), 1.88 (dd, $J = 12.6$ Hz, 4.5 Hz, 1 H), 1.69 (s, 3 H), 1.67 (s, 3 H), 1.51 (t, $J = 12$ Hz, 1 H), 1.23 (s, 3 H), 1.16-1.19 (m, 3 H), 1.02-1.08 (m, 39 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.43, 149.78, 144.92, 129.69, 109.45, 103.16, 86.60, 53.26, 45.81, 40.73, 37.30, 20.03, 19.02, 18.41, 18.29, 18.12, 17.83, 17.08, 13.57, 12.85; IR (neat) 2943, 2866, 2025, 1658, 1463; HRMS (FI) m/z $[M^+]$ calcd for $[C_{32}H_{60}O_2Si_2]^+$ 532.41318, found 532.41449; $[\alpha]_D^{25}$ -321.6 (c 1.8, $CHCl_3$)

References

- 1) Lifchits, O.; Mahlau, M.; Reisinger, C. M.; Lee, A.; Farès, C.; Polyak, I.; Gopakumar, G.; Thiel, W.; List, B. *J. Am. Chem. Soc.* **2013**, *135*, 6677.
- 2) Sawada, M.; Kubo, S.; Matsumura, K.; Takemoto, Y.; Kobayashi, H.; Tashiro, E.; Kitahara, T.; Watanabe, H.; Imoto, M. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1385.

- 3) Austin, W. F.; Zhang, Y.; Danheiser, R. L. *Org. Lett.*, **2005**, 7, 3905.
- 4) Nakao, Y.; Yada, A.; Hiyama, T. *J. Am. Chem. Soc.*, **2010**, 132, 10024.
- 5) Bokkman, R. K. Jr. *Tetrahedron*, **1983**, 39, 925.
- 6) Swati, B. A.; Anthony, M.; Paul, H. *J. Org. Chem.* **1982**, 47, 5045.
- 7) Hiyama, T.; Shinoda, M.; Nozaki, H. *J. Am. Chem. Soc.*, **1979**, 101, 1599.

Chapter 3.

Total Synthesis of Verrucarol

3.1 Introduction to Verrucarins Group and Related Natural Products

In 1946, as a result of a search for antibiotics, Brian and McGowan reported¹ the first isolation of verrucarins, initially named glutinosins and assigned as the formula $C_{48}H_{60}O_{16}$ from the cultures of *Metarrhizium glutinosum* S. Pope, which has been identified as *Myrothecium verrucaria* by White and Downing.² Since then, a number of antibiotic materials from *Myrothecium* species have been reported, but all of them were found to be the same substance consisting mainly of verrucarins A (Figure 3). Detailed studies for the chemical structures and properties of the verrucarins have been carried out by Tamm and co-workers. In 1962, they reported³ the isolation of pure crystalline materials which were designated as verrucarins A-G, and roridins A-C. Three years later, additional compounds verrucarins J and roridins D, E, H were isolated from *Myrothecium* species.⁴ They also found that when verrucarins A was subjected to alkaline hydrolysis the common sesquiterpene nucleus verrucarol could be obtained.

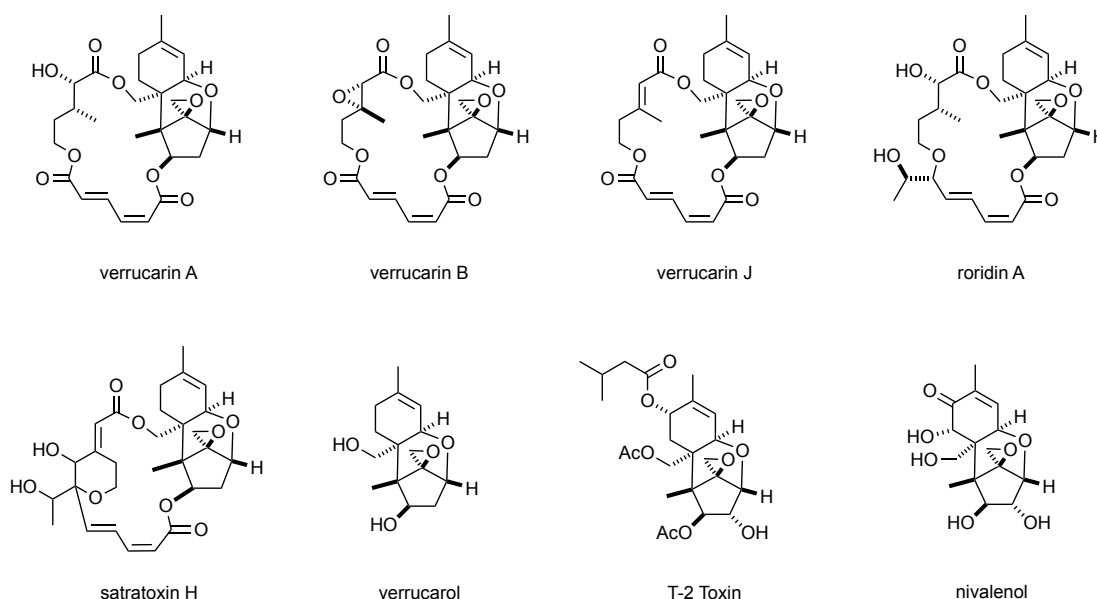


Figure 3 Representative examples of the trichothecene family

Verrucarins and roridins exhibit not only antifungal activity but also mammalian toxicity such as diarrhea, hematuria, vomiting, loss of weight, anorexia, thirst, ataxia, and skin inflammation. In the late 1960's, nonmacrocytic metabolites such as T-2 toxin⁵ and nivalenol⁶ were isolated from *Fusarium* species. Both macrocytic and nonmacrocytic compounds are classified as trichothecenes with more than 200 naturally occurring molecules.

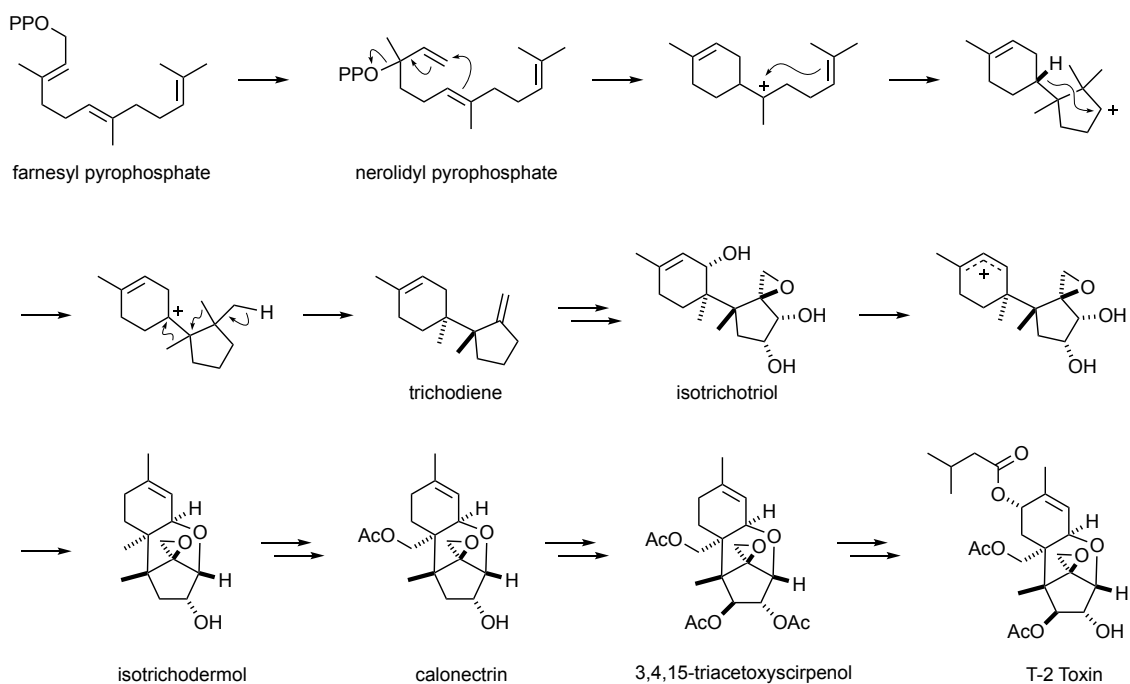
Recently, several incidents related to trichothecenes were reported in Japan, in which people poisoned and some died after consuming a toxic mushroom *Podostroma cornu-damae*, known as *kaen-take* in Japanese (Figure 4). It should be noted that even touching this mushroom causes the redness, swelling up, peeling skin and burning pain in the hands. Nakata and Saikawa reported⁷ that the poisonous constituents of this mushroom are verrucarins J, roridin E, satratoxin H and its derivatives produced by the fungus *Stacybortys atra*.



Figure 4 *Podostroma cornu-damae* (from ref. 8)

3.2 Biogenesis of Trichothecenes

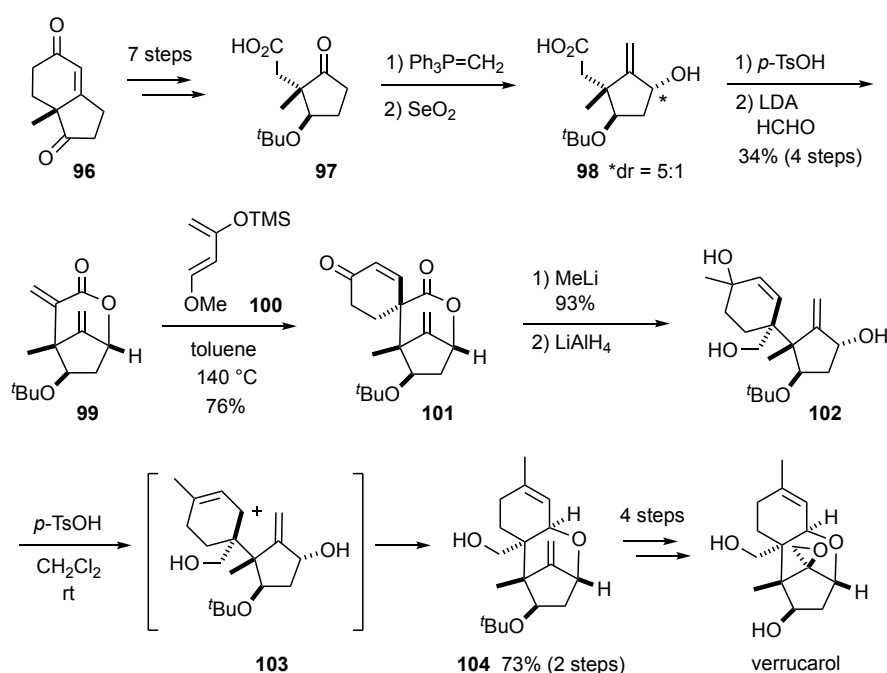
Based on the genetic and precursor feeding experiments in *Fusarium* species, the biogenesis of trichothecenes has been clarified which traced back through the common intermediate trichodiene to farnesyl pyrophosphate⁹. As depicted in Scheme 45, the biosynthetic pathway begins with the isomerization of farnesyl pyrophosphate to nerolidyl pyrophosphate which could undergo cyclization to form the six-membered ring. Resultant tertiary cation is thought to be converted to trichodiene via a sequence of the five-membered ring formation, 1,4-hydride shift, and 1,2-methyl migration. Oxidation of trichodiene then could afford intermediate isotrichotriol, which proceeds a non-enzymatic cyclization via an allylic carbocation to give isotrichodermol. Further oxygenation and acylation processes give the more complex trichothecenes such as calonectrin and T-2 toxin.



Scheme 45 Trichothecene biosynthetic pathway in *Fusarium* species

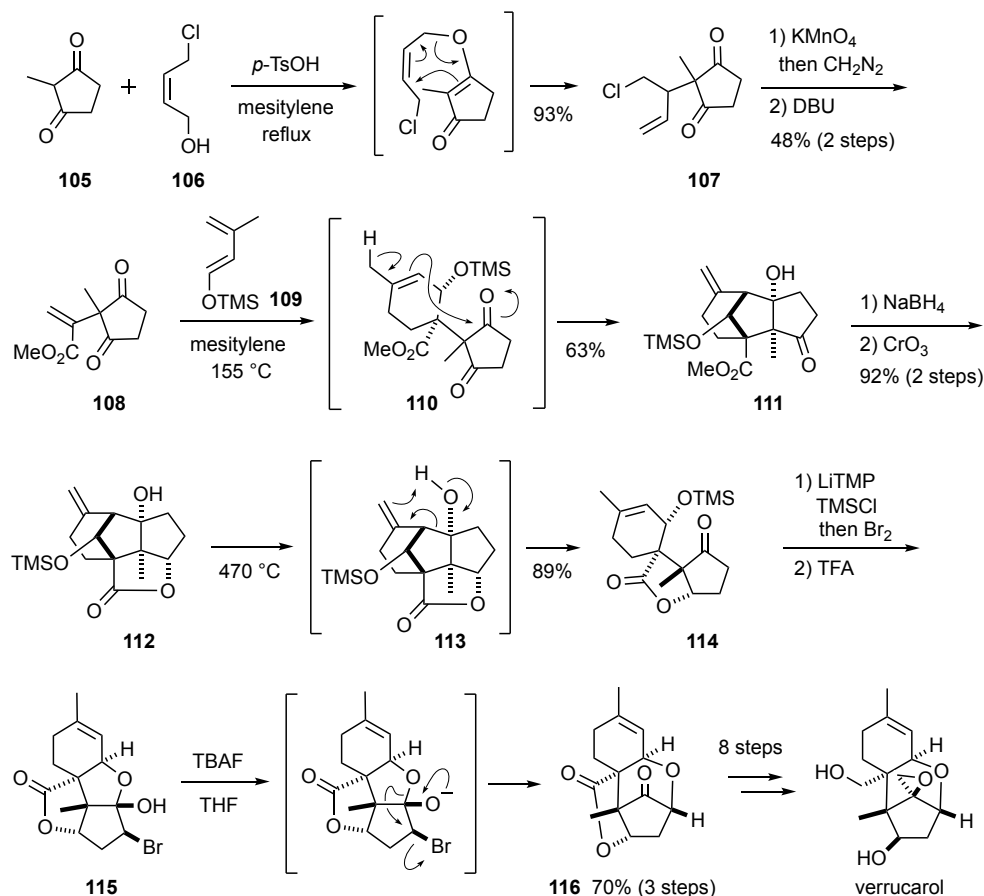
3.3 Schlessinger and Nugent Synthesis of Verrucarol

In 1982, Schlessinger and Nugent reported¹⁰ the first total synthesis of verrucarol (Scheme 46). Their synthesis was initiated with Hajos-Parrish ketone **96** bearing a quaternary carbon center at the angular position, which was converted to keto acid **97** through an oxidative cleavage of the six-membered ring. The Wittig reaction and the subsequent selenium dioxide oxidation afforded allyl alcohol **98** as a 5:1 mixture of diastereomers. Lactonization with *p*-toluenesulfonic acid followed by the aldol condensation with formaldehyde furnished methylenated product **99**. The Diels-Alder reaction with Danishefsky's diene **100** proceeded from the convex face of the bicyclic carbon skeleton, giving rise to the adduct **101** as a sole product. Addition of methyl lithium to enone **101** provided tertiary alcohol, which underwent a reductive ring opening reaction with lithium aluminum hydride, affording triol **102**. Treatment of **102** with a catalytic amount of *p*-toluenesulfonic acid promoted etherification to construct the trichothecene framework via intermediacy of allylic cation **103**. The synthesis was completed through cleavage of the *tert*-butyl ether and epoxidation of the exocyclic olefin, delivering racemic verrucarol.



Scheme 46 Schlessinger synthesis of verrucarol

3.4 Trost and McDougal Synthesis of Verrucarol

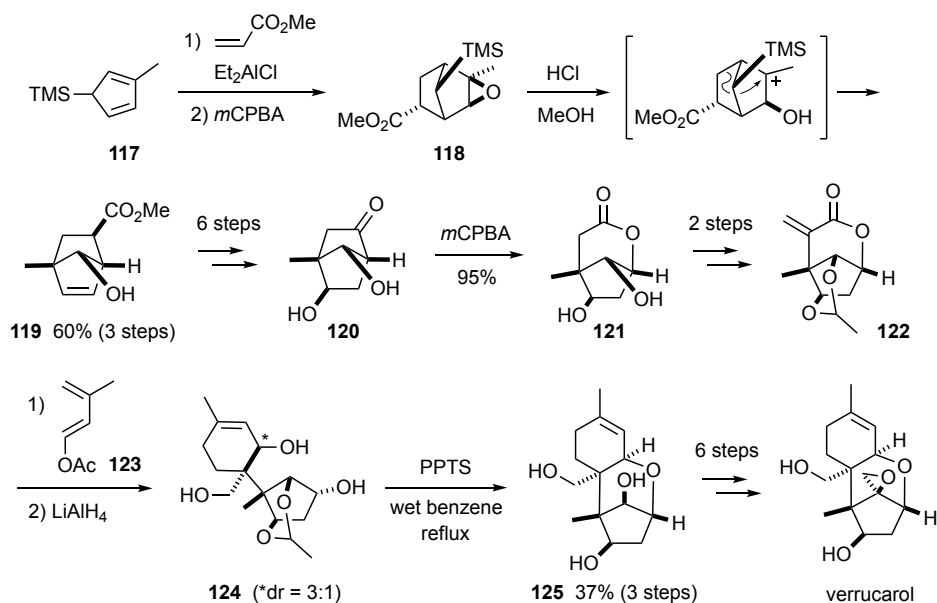


Scheme 47 Trost synthesis of verrucarol

In same 1982, Trost and co-workers reported¹¹ their total synthesis commenced with the Claisen rearrangement of five-membered diketone **105** and allyl alcohol **106** to give homoallyl chloride **107** (Scheme 47). Subsequent oxidative cleavage of the terminal olefin and chloride elimination using DBU afforded the α,β -unsaturated ester **108**. Acrylate **108** and dienol silyl ether **109** underwent a Diels-Alder reaction to produce the adduct **110**, which was further heated to promote an ene reaction resulting in formation of tricyclic compound **111**. Reduction of ketone **111** proceeded stereoselectively, which in turn was lactonized to afford **112** as a single product. The resulting lactone **112**, when heated to 470 °C, underwent a retro-ene reaction to give ketone **114**, which was subsequently converted to bromolactol **115** via α -bromination and silyl

deprotection. Construction of a trichothecene skeleton was achieved by the ring expansion reaction of **115** upon treatment with TBAF providing trichothecane **116**. Finally, the total synthesis was accomplished through inversion of the secondary alcohol and installation of the *exo*-epoxide.

3.5 Roush and D'Ambra Synthesis of Verrucarol



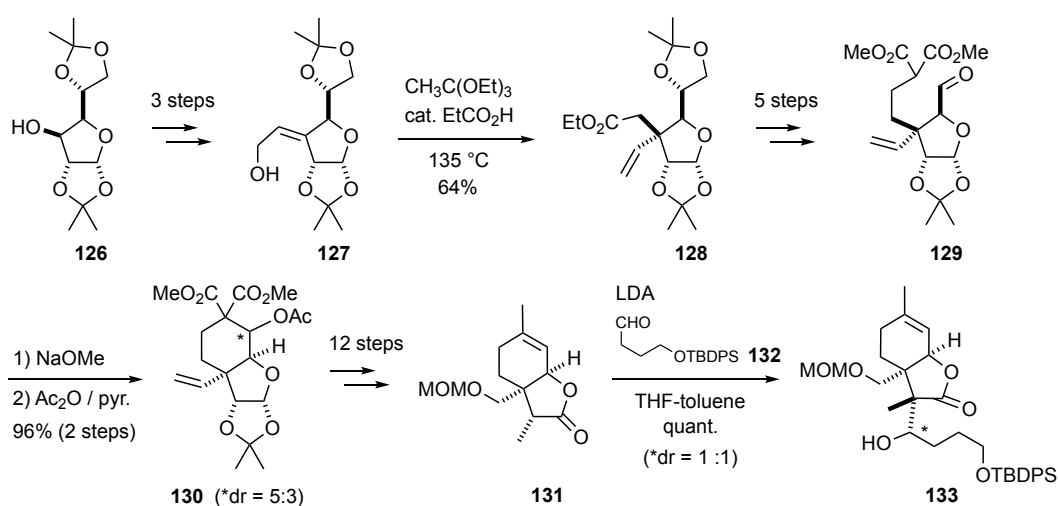
Scheme 48 Roush total synthesis of verrucarol

Roush and D'Ambra completed a total synthesis of verrucarol in 1983¹² (Scheme 48). The synthesis began with the Diels-Alder reaction between cyclopentadiene **117** and methyl acrylate followed by *m*CPBA oxidation to provide epoxide **118**. The treatment of **118** with methanolic HCl induced the silicon directed Wagner-Meerwein rearrangement, giving rise to norbornene **119** containing a bridgehead quaternary carbon center. After conversion to ketone **120**, a Baeyer-Villiger oxidation afforded lactone **121**, and subsequent acetonide formation followed by α -methylenation gave unsaturated lactone **122**. The Diels-Alder reaction of **122** with dienol acetate **123** afforded a 3:1 mixture of diastereomeric cycloadducts, both isomers possessed the

identical configurations at the quaternary spiro center. Without separation, the adducts were reduced by lithium aluminum hydride to give the triol **124**, which was then treated with a catalytic amount of pyridinium *p*-toluenesulfonate to deliver trichothecane **125**. After six steps, the total synthesis was completed furnishing verrucarol.

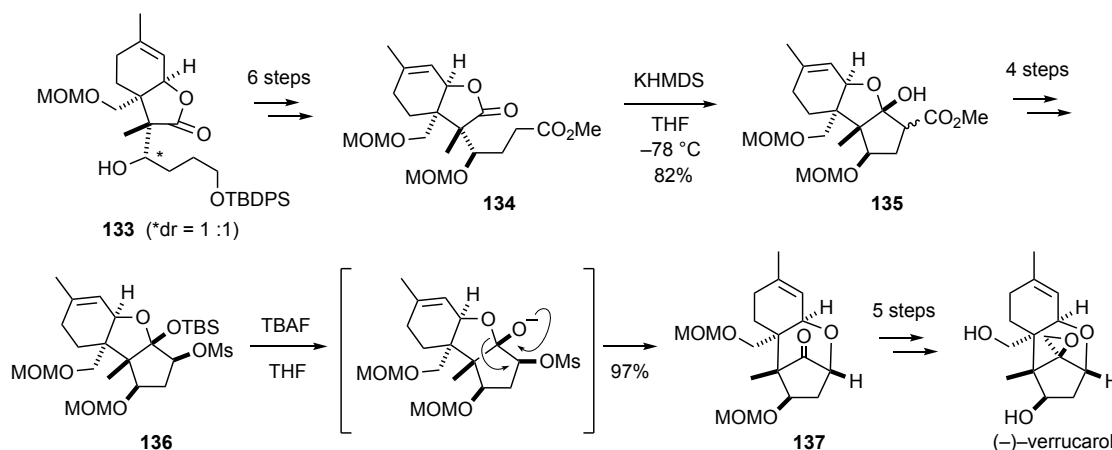
3.6 Tadano and Co-workers Asymmetric Synthesis of Verrucarol

In 1997, the first asymmetric total synthesis of verrucarol was reported by Tadano and co-workers¹³ (Scheme 49). They prepared allyl alcohol **127** in three steps from D-glucose diacetone **126** as chiral pool. When **127** was subjected to a Johnson-Claisen rearrangement, the reaction occurred exclusively from the convex side of the bicyclic skeleton, giving ester **128** as a sole product. Then **128** was converted to malonate **129** in a five-step sequence involving the ester side chain elongation and oxidative cleavage of the vicinal diol. Treatment of **129** with sodium methoxide induced an intramolecular cyclization, and the resultant alcohol was acylated to produce a 5:3 diastereomeric mixture of acetate **130**, which was converted to lactone **131** after additional 12 steps. The aldol reaction between aldehyde **132** and the lithium enolate derived from **131** proceeded on the less hindered face of the bicycle providing the adduct **133**.



Scheme 49 Construction of the vicinal quaternary carbon centers

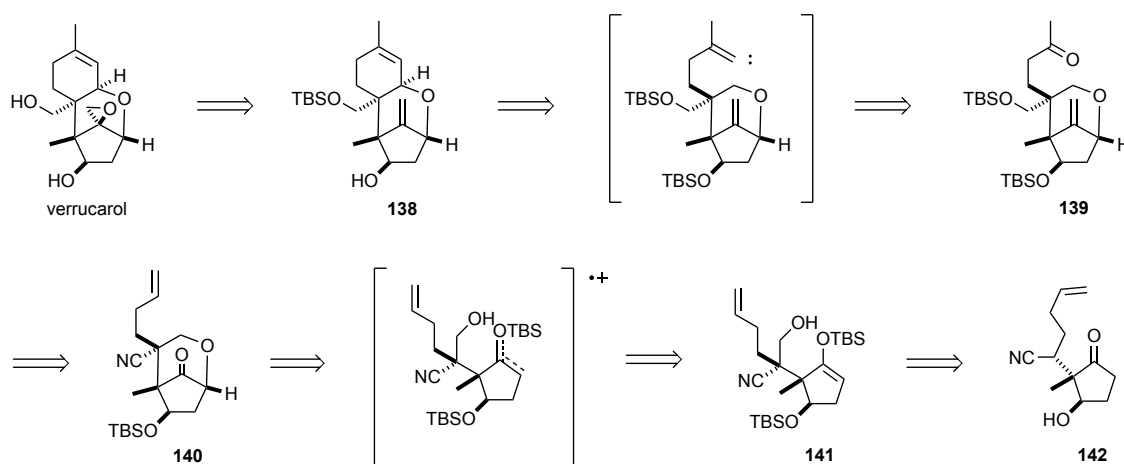
Dieckmann cyclization of ketoester **134** afforded hemiacetal **135** (Scheme 50). Conversion of **135** into mesylate **136** followed by TBAF mediated ring expansion resulted in formation of tricyclic ketone **137**. Finally, the synthesis of (-)-verrucarol was accomplished in 40 steps.



Scheme 50 Completion of Tadano's synthesis

3.7 First Generation Approach toward Verrucarol

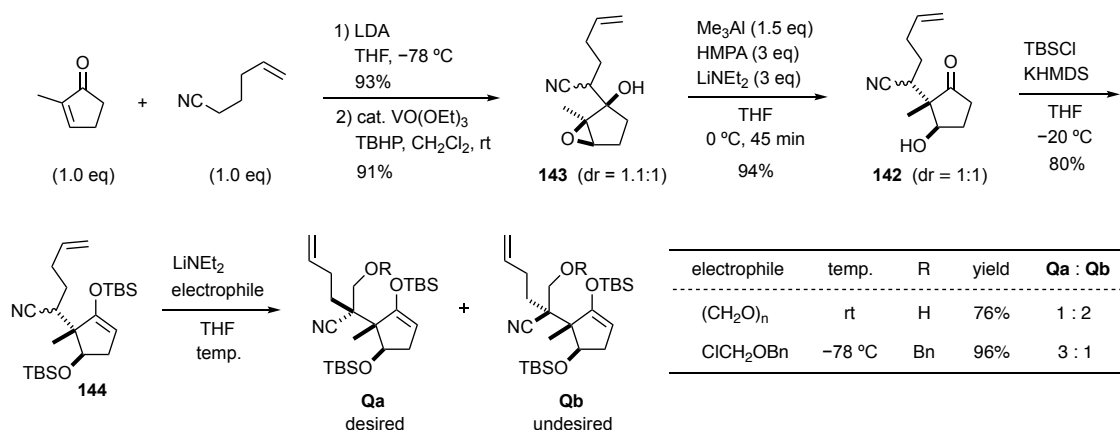
Having developed the formal semi-pinacol rearrangement reaction of cyano epoxyalcohols, the author planned to accomplish the total synthesis of verrucarol based on the original methodology (Scheme 51). In the first retrosynthetic analysis, it was envisioned that the



Scheme 51 Retrosynthesis of verrucarol

exo-epoxide in verrucarol could arise from a regio- and stereoselective epoxidation of alkene **138**, which was designed as the product of a C-H insertion reaction of methyl ketone **139**. Ketone **139** would be obtained via the Wacker oxidation of terminal olefin **140** and oxidative etherification of enol silyl ether **141**. Alcohol **141** would be prepared from cyano hydroxyketone **142** which could be readily accessible by means of the formal rearrangement reaction of the corresponding cyano epoxyalcohol.

In the forward sense, enol silyl ether **144** was prepared by a sequence which commenced with the addition reaction of commercially available 2-methylcyclopentenone and 5-hexenenitrile. The adduct was oxidized to epoxyalcohol **143** which was subjected to the formal rearrangement reaction, giving rise to β -hydroxyketone **142** in high yield (Scheme 52). Protection of both the hydroxy group and the ketone moiety of **142** with TBS groups afforded nitrile **144**. The treatment of **144** with LiNEt_2 and paraformaldehyde provided the adduct **Q** in 76% yield as a 1:2 (desired:undesired) mixture of diastereomers. On the other hand, the use of BOMCl instead of paraformaldehyde afforded the corresponding benzyl ether **Qab** as a 3:1 (desired:undesired) mixture of diastereomers, although the configuration of the products could not be determined at this stage.



Scheme 52 Accessing alcohol **6** via formal semi-pinacol rearrangement

With alcohol **141** in hand, the oxidative etherification reactions were explored (Table 5). Exposure of enol silyl ether **141** to several oxidants, however, resulted in formation of a complex mixture containing cyclic acetals **145** or **146**.

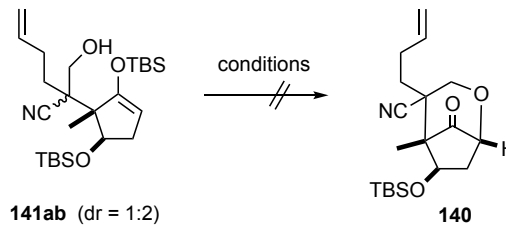
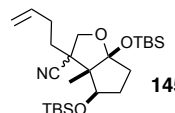
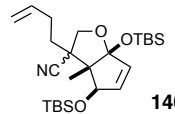
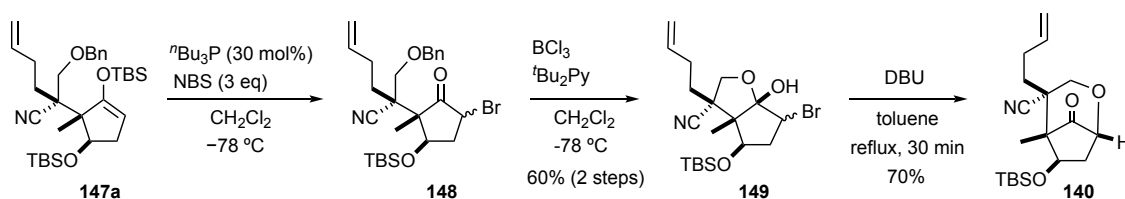
	conditions	result
 141ab (dr = 1:2) 140	CAN, NaHCO ₃ , H ₂ O, THF or CH ₃ CN or acetone	complex mixture
	CAN, H ₂ O, HFIP, rt	 145
	PhI(OCOCF ₃) ₂ , BF ₃ ·OEt ₂ CH ₂ Cl ₂ , rt	 146

Table 5 Attempts at oxidative etherification

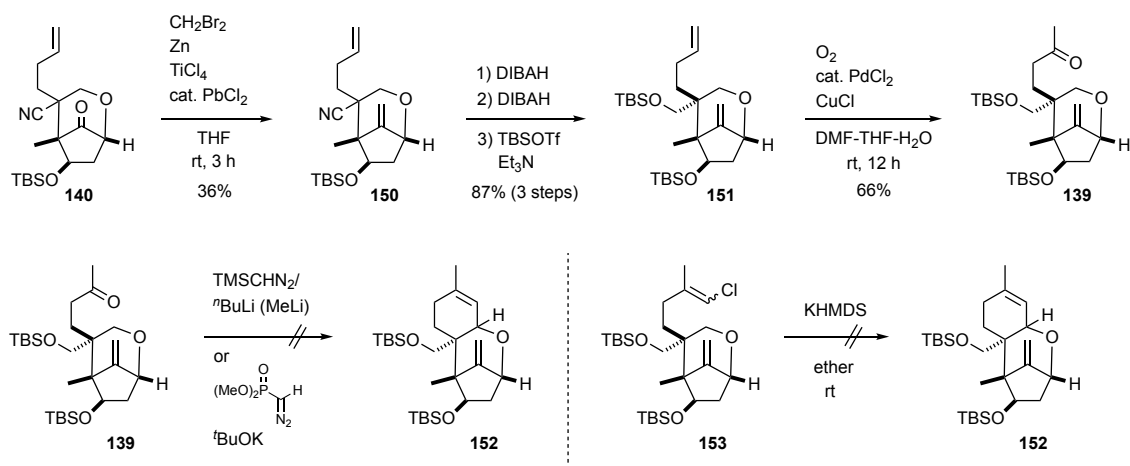
These results led the author to introduce a leaving group at the α -position of the ketone. Thus, enol silyl ether **147a**, the major isomer obtained from **144**, was subjected to the bromination reaction with the Ishihara's protocol, giving rise to bromo ketone **148** (Scheme 53). After removal of the benzyl group with boron trichloride, the resulting lactol **149** was treated with DBU in refluxing toluene, according to the Trost's report. While the bromide was a mixture of diastereomers, the intramolecular S_N2 reaction occurred smoothly to afford cyclic ether **140** in 70% yield, suggesting that the bromide moiety readily epimerizes under the basic conditions.



Scheme 53 Intramolecular etherification reaction of bromo lactol

Having accessed cyclic ether **140**, the author's attention next turned to the construction of the cyclohexene ring. Initial attempts to convert ketone **140** to alkene **150** using a Wittig reaction resulted in formation of a complex mixture (Scheme 54). After several experimentations,

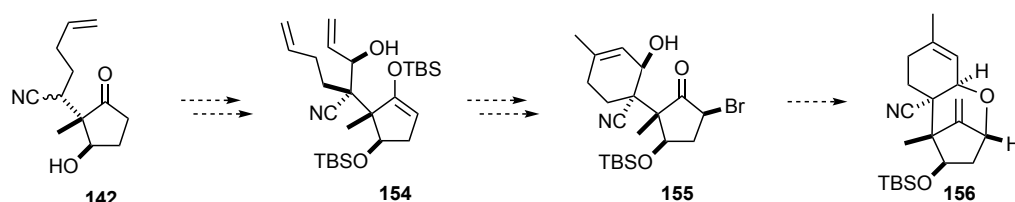
150 was obtained by utilizing the Takai's protocol, albeit in 36% yield. The resulting **150** was moved forward through a reduction/silyl protection/Wacker oxidation sequence to give methyl ketone **139**. Unfortunately, all attempts to construct the cyclohexene ring by a C-H insertion reaction of a carbenoid species generated from ketone **139** or vinyl chloride **153** failed to produce the desired product **152**.



Scheme 54 Attempts for C-H insertion reaction

3.8 Second Generation Approach Toward Verrucarol

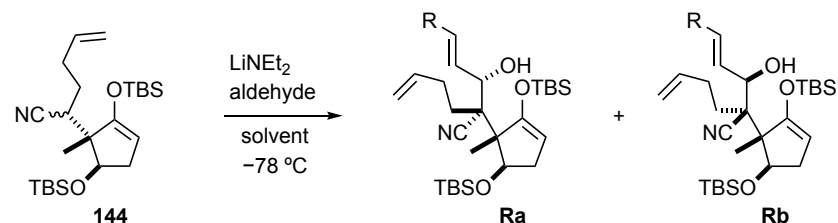
These results led the author to design an alternative pathway to access the cyclohexene by using a ring-closing metathesis of diene **154** (Scheme 55).



Scheme 55 Alternative pathway to construct the six-membered ring

To implement this strategy, diene **R** was prepared from **144** by the 1,2-addition reaction with an α,β -unsaturated aldehyde (Table 6). The sequential treatment of nitrile **144** with LiNEt_3 and acrolein in THF afforded the desired isomer **Ra** (40%) along with its diastereomer **Rb** (18%) (entry 1). Although the reaction in ether or toluene led to decreased yield of **Ra** (entries 2 and 3),

the use of other aldehydes was found to give the desired isomer in higher yields (entries 4 and 5). Consequently, adduct **157a**, which was obtained in 64% isolated yield along with its diastereomer **157b** (19%), was employed as the key intermediate of the total synthesis.



entry	aldehyde	R	solvent	Ra (desired)	Rb (undesired)
1	acrolein	H	THF	40%	18%
2	acrolein	H	ether	21%	23%
3	acrolein	H	toluene	21%	15%
4	crotonaldehyde	Me	THF	64%	19%
5	cinnamaldehyde	Ph	THF	56%	29%

Table 6 nitrile-aldol reaction with various unsaturated aldehydes

The stereochemistry of **157a** was determined by the X-ray crystallographic analysis of compound **158a**, which was obtained through a three-step sequence (Figure 6). Similarly, the configuration of diastereomer **157b** was confirmed after the conversion to compound **158b**.

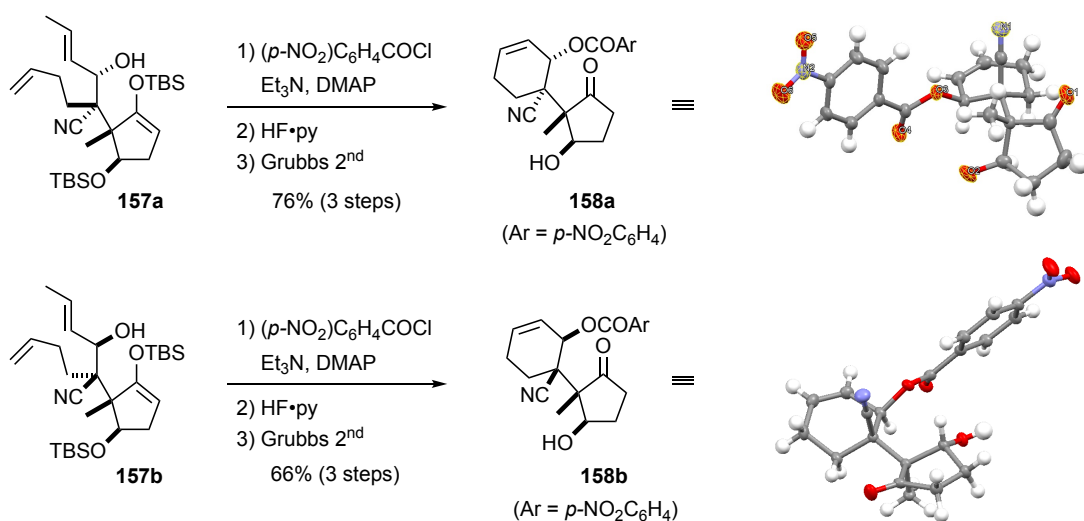
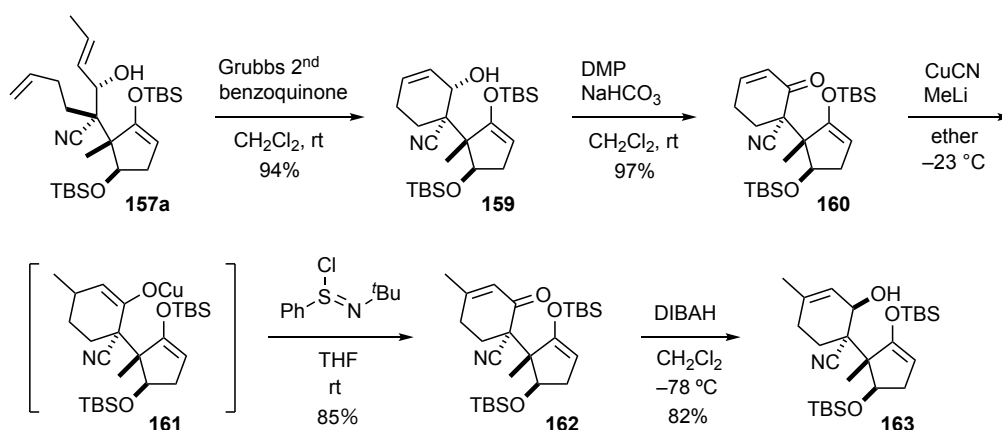


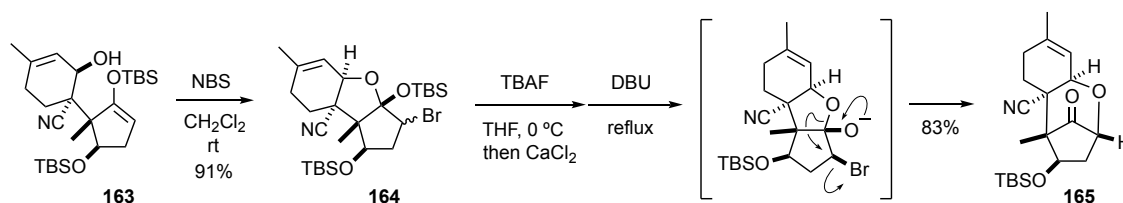
Figure 6 X-ray structure of **158a** and **158b**

With diene **157a** in hand, the efforts now turned to construction of the tricyclic skeleton (Scheme 56). Diene **157a** was subjected to a ring-closing metathesis to afford allyl alcohol **159** which was oxidized with Dess-Martin periodinane, giving rise to cyclohexenone **160**. Conversion of **160** to β -methyl enone **162** was accomplished by utilizing the Matsuo's protocol. Thus, the conjugate addition reaction with a higher order cuprate afforded copper enolate **161** which was oxidized with *N*-*tert*-butylbenzenesulfinimidoyl chloride in a one-pot manner. Gratifyingly, reduction of enone **162** with DIBAH afforded allyl alcohol **163** as a single diastereomer, suggesting that the hydride attack occurred from the opposite face of the bulky cyclopentene moiety. The sterically compact nature of a cyano group is effective for achieving such a high stereoselectivity.



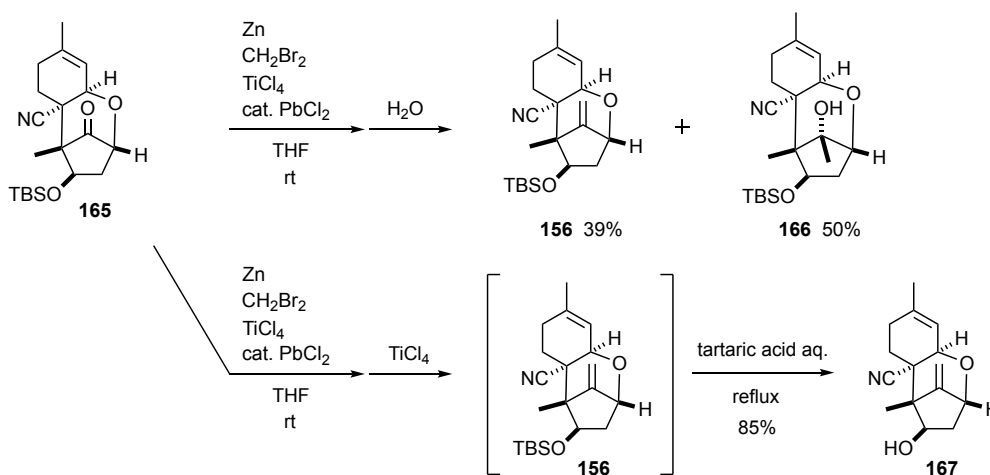
Scheme 56 Preparation of allyl alcohol 163

Upon exposure to NBS, enol silyl ether **163** was converted to a diastereomeric mixture of bromo lactol **164** (Scheme 57). Construction of the trichothecene skeleton was accomplished by a sequential treatment of **164** with TBAF, calcium chloride, and DBU. Calcium chloride was used for removing an excess amount of fluoride ion as a precipitate of CaF_2 , and the resulting lactol intermediate underwent the rearrangement reaction under basic conditions, affording tricyclic ketone **165** in 83% yield.



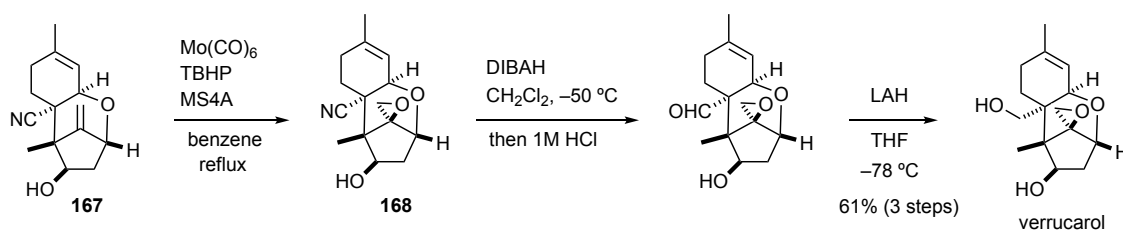
Scheme 57 Construction of trichothecene skeleton

Having ketone **165** in hand, the stage was set for the installation of the *exo*-epoxide moiety (Scheme 58). Thus, ketone **165** was subjected to the Takai olefination reaction, resulting in formation of the desired *exo*-alkene **156** in 39% yield along with 50% of tertiary alcohol **166**. It was expected that alcohol **166** arose from protonation of an organotitanium intermediate which may produce additional alkene **156** under certain activation conditions. Indeed, addition of TiCl_4 to the reaction mixture, after monitoring the consumption of substrate **165** by TLC, led to the increased formation of desired *exo*-methylene **156**. With a view to effecting the removal of the silyl group in one pot, the reaction mixture was refluxed with an aqueous tartaric acid solution, and the desired alcohol **167** was obtained in 85% isolated yield.



Scheme 58 Takai olefination of ketone 165

The attempts to achieve site-selective epoxidation of diene **167** by the combined use of TBHP and vanadium catalysts resulted in formation of a complex mixture containing the corresponding di-epoxide. On the other hand, hexacarbonyl molybdenum was found to effect the epoxidation more cleanly, while ca. 15% of di-epoxide was also produced (Scheme 59). Finally, reduction of nitrile **168** over two steps afforded verrucarol in 61% yield from homoallyl alcohol **167**. The spectral data of the final product were consistent with that of reported natural product.



Scheme 59 Completion of total synthesis of verrucarol

3.9 Conclusions

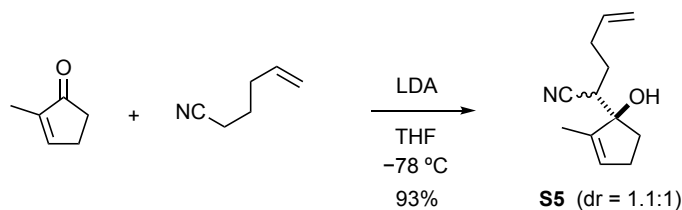
In conclusion, a 15-step (10.4% overall yield) synthesis of verrucarol from commercially available 2-methylcyclopentenone and 5-hexenenitrile has been accomplished. The synthesis is based on the formal semi-pinacol rearrangement reaction of cyano epoxyalcohol for constructing the two contiguous stereogenic centers, with one being quaternary. The formation of the tricyclic trichothecene ring was achieved through a ring-closing metathesis reaction and a ring-expansion reaction of bromo lactol under basic conditions.

3.10 References

- 1) Brian, P. W.; McGowan, J. C. *Nature* **1946**, *157*, 334.
- 2) White, W. L.; Downing, M. H. *Mycologia*, **1947**, *39*, 546.
- 3) Härrä, E.; Loeffler, W.; Sigg, H. P.; Stähelin, H.; Tamm, C. *Helv. Chim. Acta* **1962**, *45*, 839.
- 4) Böhner, B.; Fetz, E.; Härrä, E.; Sigg, H. P.; Tamm, C. *Helv. Chim. Acta* **1965**, *48*, 1079.
- 5) Bamberg, J. R.; Riggs, N. V.; Strong, F. M. *Tetrahedron*, **1968**, *24*, 3329.

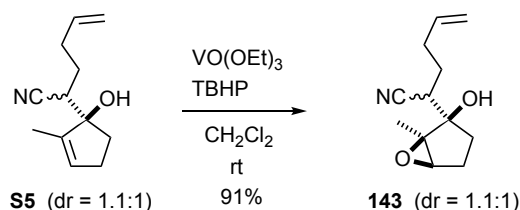
- 6) Tatsuno, T.; Saito, M.; Enomoto, M.; Tsunoda, H. *Chem. Pharm. Bull.* **1968**, *16*, 2519.
- 7) Saikawa, Y.; Okamoto, H.; Inui, T.; Makabe, M.; Okuno, T.; Suda, T.; Hashimoto, K.; Nakata, M. *Tetrahedron* **2001**, *57*, 8277.
- 8) Choe, S.; In, S.; Jeon, Y.; Choi, H.; Kim, S. *Forensic Sci. Int.*, **2018**, *291*, 234.
- 9) Kimura, M.; Tokai, T.; Takahashi-Ando, N.; Ohsato, S.; Fujimura, M. *Biosci. Biotechnol. Biochem.*, **2007**, *71*, 2105.
- 10) Schlessinger, R. H.; Nugent, R. A. *J. Am. Chem. Soc.* **1982**, *104*, 1116.
- 11) Trost, B. M.; McDougal, P. G. *J. Am. Chem. Soc.* **1982**, *104*, 6110.
- 12) Roush, W. R.; D'Ambra, T. E. *J. Am. Chem. Soc.* **1983**, *105*, 1058.
- 13) Ishihara, J.; Nonaka, R.; Terasawa, Y.; Shiraki, R.; Yabu, K.; Kataoka, H.; Ochiai, Y.; Tadano, K. *J. Org. Chem.* **1998**, *63*, 2679.
- 14) Takai, K.; Kakiuchi, T.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 2668.
- 15) Matsuo, J.; Aizawa, Y. *Chem. Commun.* **2005**, 2399.
- 16) Roush, W. R.; Blizzard, T. A. *J. Org. Chem.* **1984**, *49*, 1772.

3.11 Experimental Section



Compound **S5**:

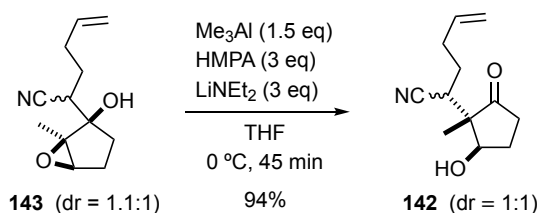
To a solution of $i\text{Pr}_2\text{NH}$ (6.42 mL, 45.8 mmol) in THF (110 mL) was added $n\text{BuLi}$ (2.65 M in hexane, 14.2 mL, 37.9 mmol) at $-78\text{ }^{\circ}\text{C}$, and the mixture was stirred at $0\text{ }^{\circ}\text{C}$ for 10 min. To the mixture was added 5-hexenenitrile (3.60 g, 37.8 mmol) at $-78\text{ }^{\circ}\text{C}$, and the resulting mixture was stirred at this temperature for 30 min. 2-methylcyclopentenone (3.32 g, 34.6 mmol) was then added, and the mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min. The reaction was quenched by addition of AcOH (5.0 M in THF, 14 mL, 70 mmol), and then saturated aqueous NaHCO_3 . The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over MgSO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give **S5** (6.14 g, 32.12 mmol, 93%) as a 1.1:1 mixture of diastereomers. Yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 5.84-5.64 (m, 2H), 5.16-5.05 (m, 2 H), 2.87 (dd, $J = 12.1\text{ Hz}$, 4.1 Hz, 0.55 H), 2.83 (dd, $J = 12.6\text{ Hz}$, 3.4 Hz, 0.45 H), 2.48-2.16 (m, 8 H), 1.79 (s, 1.65 H), 1.66 (s, 1.35 H).



Compound **143**

To a solution of allyl alcohol **S5** (6.14 g, 32.12 mmol, dr = 1.1:1) in CH_2Cl_2 (64 mL) was added TBHP (5.5 M in nonane, 12 mL, 64.2 mmol) and $\text{VO}(\text{OEt})_3$ (285 μL , 1.6 mmol) at $0\text{ }^{\circ}\text{C}$, and the resulting mixture was stirred at room temperature for 1.5 h. The reaction was quenched by addition of saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution. The mixture was separated, and the

aqueous layer was extracted with ether. The combined organic layers were dried over MgSO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give **143** (6.06 g, 29.3 mmol, 91%) as a 1.1:1 mixture of diastereomers. Yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 5.83-5.75 (m, 0.55 H), 5.79-5.71 (m, 0.45 H), 5.18 (d, $J = 17.2$, 0.45 H), 5.14 (d, $J = 17.2$ Hz, 0.55 H), 5.11 (d, $J = 9.8$ Hz, 0.45 H), 5.08 (d, $J = 10.3$ Hz, 0.55 H), 3.55 (m, 0.55 H), 3.48 (m, 0.45 H), 2.88 (dd, $J = 12.6$ Hz, 2.3 Hz, 0.45 H), 2.76 (m, 0.55 H), 2.51-2.37 (m, 1 H), 2.24-1.95 (m, 5.1 H), 1.74-1.66 (m, 0.55 H), 1.72-1.47 (m, 1.8 H), 1.50 (s, 1.65 H), 1.37 (m, 1.35



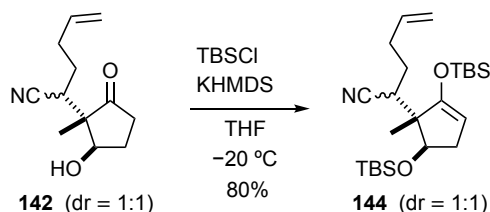
H), 1.34-1.23 (m, 0.55 H)

Compound 142

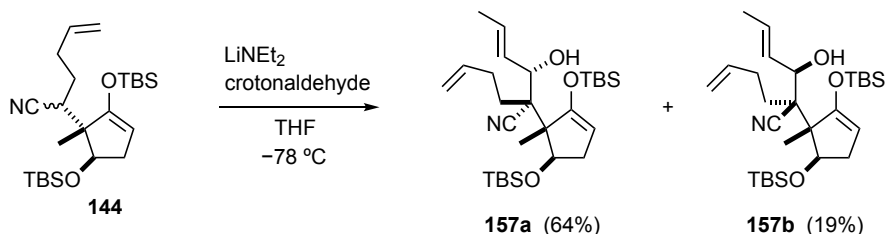
To a solution of epoxy alcohol **143** (6.06 g, 29.3 mmol, dr = 1.1:1) in THF (150 mL) was added trimethyl aluminum (2.0 M in toluene, 22.5 mL, 45.0 mmol) at 0 °C and the reaction mixture was warmed up to room temperature. After stirring for 1 h, the reaction mixture was added HMPA (15.4 mL, 90.0 mmol) and was cooled to -78 °C. LiNEt_2 (1.0 M in THF, 90.0 mL, 90.0 mmol) which was prepared from $n\text{BuLi}$ (2.65 M in hexane, 34.0 mL, 90.0 mmol) and diethylamine (10.0 mL, 98.9 mmol) in THF (60 mL), was added, and the resulting mixture was stirred at 0 °C for 40 min. The reaction was quenched by addition of AcOH (5.0 M in THF, 46 mL, 180 mmol) and warmed up to room temperature. The mixture was added saturated aqueous NaHCO_3 solution. The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over MgSO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give **142** (5.72 g, 27.6 mmol, 94%) as a 1:1 mixture of diastereomers. Yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 5.78-5.66 (m, 1 H), 5.12 (d, $J = 17.2$ Hz, 1 H), 5.07 (d, $J = 9.8$ Hz, 1 H), 4.55-4.47 (m, 1 H), 2.85-2.78 (m, 1 H), 2.56 (d, $J = 8.6$ Hz,

0.5 H), 2.53 (d, $J = 8.0$ Hz, 0.5 H), 2.46-1.70 (m, 7H), 1.19 (s, 1.5 H), 1.08 (s, 1.5 H)

Compound 144



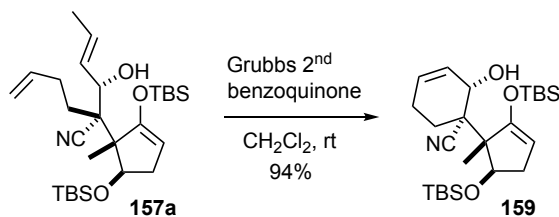
To a solution of hydroxyl ketone **142** (5.55 g, 26.80 mmol) and TBSCl (10.3 g, 68.73 mmol) in THF (140 mL), KHMDS (0.5 M solution in toluene, 140 mL, 68.73 mmol) was added at -78 °C and stirred for 30 min. Then the mixture was warmed to -20 °C and stirred for 1 h. The mixture was quenched with saturated aqueous NaHCO_3 solution, extracted with Et_2O . The combined organic layers were dried over MgSO_4 and filtered. The filtrate was concentrated under vacuum, and the residue was purified by silica gel column chromatography (Hexane) pre-eluted with N,N -dimethyl aniline to give **144** (9.42 g, 21.63 mmol, 81%) as a 1:1 mixture of diastereomers. Yellow oil.; ^1H NMR (500 MHz, CDCl_3) δ 5.74 (m, 1H), 5.19 (dd, $J = 17.2$ Hz,



1.8 Hz, 1 H), 5.02 (t, $J = 9.2$ Hz, 1 H), 4.42-4.41 (m, 1 H), 4.29-4.23 (m, 1 H), 2.61-2.56 (m, 1 H), 2.49-2.37 (m, 2 H), 2.16-2.06 (m, 2 H), 1.71-1.65 (m, 2 H), 1.12 (s, 1.5 H), 1.06 (s, 1.5 H), 0.94 (s, 4.5 H), 0.91 (s, 4.5 H), 0.90 (s, 4.5 H), 0.88 (s, 4.5 H), 0.20 (s, 1.5 H), 0.17 (s, 1.5 H), 0.16 (s, 1.5 H), 0.16 (s, 1.5 H), 0.12 (s, 1.5 H), 0.07 (s, 1.5 H), 0.06 (s, 1.5 H), 0.05 (s, 1.5 H)

Compound 157a and 157b

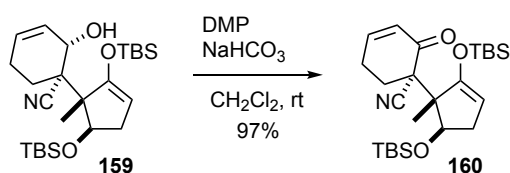




Compound 159

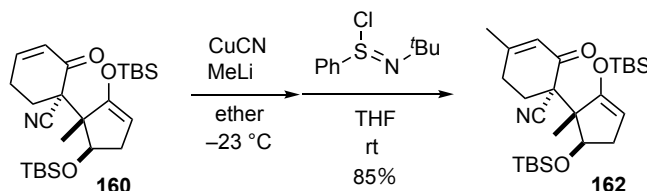
To a solution of diene **157a** (845.1 mg, 1.67 mmol) in CH₂Cl₂ (600 mL) were added Grubbs 2nd catalyst (70.8 mg, 0.083 mmol) and benzoquinone (9.0 mg, 0.083 mmol) at room temperature. After stirring for 2 h, DMSO (296 μL, 4.17 mmol) was added. After stirring for 13 h in air, the mixture was concentrated under vacuum, and the residue was purified by silica gel

column chromatography (AcOEt/ hexane= 5%) gave **159** (731.4 mg, 1.58 mmol, 94%) as a yellow oil. ; ^1H NMR (500 MHz, CDCl_3) δ 5.83 (m, 1 H), 5.56 (d, $J = 9.7$ Hz, 1 H), 4.56 (m, 1 H), 4.50 (m, 1 H), 4.40 (t, $J = 5.8$ Hz, 1 H) 2.63 (ddd, $J = 14.3$ Hz, 7.5 Hz, 2.3 Hz, 1 H), 2.48-2.38 (m, 1 H), 2.15-2.38 (m, 2 H), 2.00 (dd, $J = 13.2$ Hz, 5.2 Hz, 1 H), 1.29 (s, 3 H), 0.97 (s, 9 H), 0.90 (s, 9 H), 0.22 (s, 3 H), 0.20 (s, 3 H), 0.10 (s, 6 H)



Compound 160

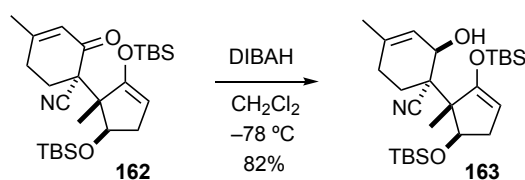
To a solution of alcohol **159** (693.8 mg, 1.49 mmol) in CH_2Cl_2 (7.5 mL) were added NaHCO_3 (1.27 g, 15.1 mmol) and Dess-Martin periodinane (1.57 g, 3.71 mmol) at 0 °C. After stirring for 40 min at room temperature, the reaction was quenched with saturated aqueous NaHCO_3 solution and then saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution and then extracted with Et_2O . The combined organic layers were dried over MgSO_4 and filtered. The filtrate was concentrated under vacuum and the residue was purified by silica gel column chromatography (AcOEt/ hexane=10%) to give **160** (669.5 mg, 1.45 mmol, 97%) as a pale yellow oil. ; ^1H NMR (500 MHz, CDCl_3) δ 7.00 (m, 1 H), 6.03 (dd, $J = 10.3$ Hz, 1.8 Hz, 1H), 4.61 (dd, $J = 7.4$ Hz, 5.2 Hz, 1 H), 4.47 (t, $J = 2.3$ Hz, 1 H), 2.72-2.66 (m, 1H), 2.59 (ddd, $J = 14.9$ Hz, 7.5 Hz, 2.9 Hz, 1 H), 1.32 (s, 3 H), 0.90 (s, 18 H), 0.16 (s, 3 H), 0.13 (s, 3 H), 0.07 (s, 3 H), 0.02 (s, 3 H)



Compound 162

To a suspension of CuCN (163.1 mg, 1.82 mmol) in ether (6.0 mL) was added MeLi (1.12 M in ethereal solution, 3.05 mL, 3.42 mmol) at -78 °C. The mixture was warmed up to 0 °C

and stirred for 10 min. Then the mixture was cooled to -78 °C, and enone **160** (525.8 mg, 1.13 mmol) in ether (5.0 mL) was slowly added. After stirred for 30 min at -23 °C, the mixture was cooled to -78 °C followed by addition of *N*-tert-butylbenzenesulfinimidoyl chloride (1.44 g, 5.69 mmol) in THF (1.0 mL). The mixture was allowed to warm up to room temperature and stirred for 1 h. The reaction mixture was quenched with 10% aqueous NH₃/NH₄Cl solution, extracted with Et₂O. The combined organic layers were dried over MgSO₄ and filtered. The filtrate was concentrated under vacuum and the residue was roughly purified by silica gel chromatography (AcOEt/Hexane=0.5% to 3%) to give enone **162** (462.6 mg, 0.97 mmol, 85%) as a pale yellow oil.

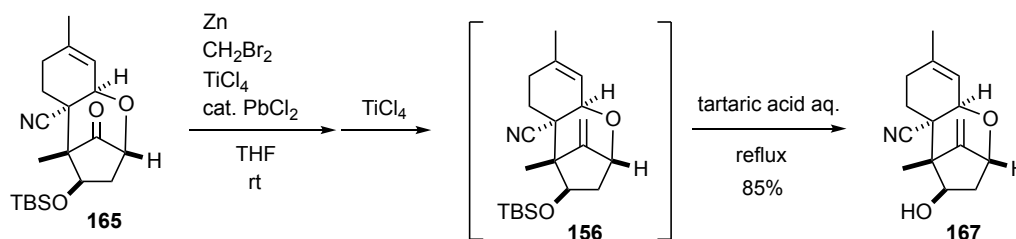


Compound 163

To a solution of the enone **162** in CH₂Cl₂ (4.6 mL) was added DIBAH (1.03 M solution in hexane, 1.80 mL, 1.85 mmol) at -78 °C. After string for 30 min, the reaction mixture was quenched with saturated aqueous potassium sodium tartrate solution. The mixture was allowed to warm up to room temperature and diluted with AcOEt and water, and mixture was separated. The aqueous layer was extracted with Et₂O, and the combined organic layers were dried over MgSO₄ and filtered. The filtrate was concentrated under vacuum and the residue was purified by silica gel column chromatography (AcOEt/ hexane=0.5% to 3%) to give alcohol **163** (363.4 mg, 0.76 mmol, 82%) as a yellow oil; ¹H NMR (500 MHz, CDCl₃) δ 5.62 (m, 1 H), 4.56 (t, *J* = 7.5 Hz, 1 H), 4.50 (br, 1 H), 4.40 (br, 1 H), 2.56-2.48 (m, 1 H), 2.36-2.28 (m, 1 H), 2.25-2.20 (m, 1 H), 1.75 (s, 3 H), 1.30 (s, 3 H), 0.99 (s, 9 H), 0.91 (s, 9 H), 0.21 (s, 3 H), 0.15 (s, 3 H), 0.12 (s, 3 H), 0.00 (s, 6 H)

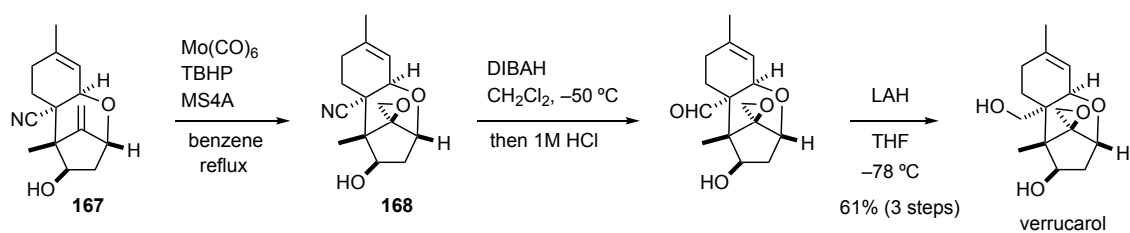
To a solution of lactol **164** (574.3 mg, 1.03 mmol) in THF (5.1 mL) was added TBAF (1.0 M in THF solution, 1.55 mL, 1.55 mmol) at 0 °C. After stirring for 10 min, CaCl₂ (193.5 mg, 1.55 mmol) was added and the mixture was warmed up to room temperature and stirred for 30 min followed by addition of DBU (462 µL, 3.01 mmol). The mixture was warmed up to 75 °C for 30 min. The reaction mixture was cooled to room temperature, and quenched with saturated aqueous NaCl solution, extracted with ether. The combined organic layers were dried over MgSO₄ and filtered. After concentration of the filtrate, the residue was purified by recrystallization from ether/hexane to give **165** (308.0 mg, 0.85 mmol, 83%) as a white solid; ¹H NMR (500 MHz,

CDCl₃) δ 5.44 (m, 1 H), 4.61 (dd, J = 8.1 Hz, 3.5 Hz, 1 H), 4.36 (m, 1 H), 3.97 (d, J = 5.7 Hz, 1 H), 2.79 (dd, J = 16 Hz, 8 Hz, 1 H), 2.31-2.24 (m, 1 H), 2.10 (dd, J = 18.9 Hz, 5.2 Hz, 1 H), 1.93 (dd, J = 13.2 Hz, 5.15 Hz, 1 H), 1.87-1.82 (m, 1 H), 1.75 (s, 3 H), 1.63 (dt, J = 13.2 Hz, 5.8 Hz, 1 H), 1.15 (s, 3 H), 0.87 (s, 9 H), 0.12 (s, 3 H), 0.11 (s, 3 H)



Compound 167

To a suspension of zinc powder (2.51 g, 38.33 mmol), PbCl₂ (55.9 mg, 0.19 mmol) in THF (43 mL) was added CH₂Br₂ (1.5 mL, 21.27 mmol) at room temperature. After stirring for 10 min, the mixture cooled to 0 °C followed by addition of TiCl₄ (470 μ L, 4.25 mmol) and the mixture was warmed up to room temperature. After stirring for 1 h, ketone **165** (308.0 mg, 0.851 mmol) in THF (1.7 mL) was added at room temperature. After stirring for 2.5 h, TiCl₄ (470 μ L, 4.25 mmol) was added and stirred for 1.5 h. The reaction mixture was cooled to 0 °C, then quenched with saturated tartaric acid. The mixture was warmed up to 75 °C. After stirred for 1 h, the mixture cooled to room temperature and saturated aqueous potassium sodium tartrate solution was added. The aqueous layer was extracted by ether, the combined organic layers were dried over MgSO₄ and filtered. The filtrate was concentrated under vacuum and the residue was purified by recrystallization from ether/hexane to give alkene **167** (177.5 mg, 85%) as a white powder; ¹HNMR δ : 5.43 (m, 1 H), 5.23 (s, 1 H), 4.86 (s, 1 H), 4.53 (m, 1 H), 4.43 (d, J = 5.2 Hz, 1 H), 4.09 (d, J = 4.6 Hz, 1 H), 2.64 (dd, J = 15.5 Hz, 7.5 Hz, 1 H), 2.28 (m, 1 H), 2.10 (dd, J = 18.3 Hz, 5.2 Hz, 1 H), 2.00 (br, 1 H), 1.86 (dt, J = 12.6 Hz, 5.2 Hz, 1 H), 1.78-1.69 (m, 5 H), 1.27 (s, 3 H)



verrucarol

To a mixture of freshly activated powdered MS4A (203.6 mg), alkene **167** (71.5 mg, 0.291 mmol) in $(\text{CH}_2\text{Cl})_2$ (4.2 mL) were added Mo(CO)_6 (38.7 mg, 0.15 mmol), Na_2HPO_4 (5.2 mg, 0.03 mmol). The resulting mixture was warmed up to $80\text{ }^\circ\text{C}$ stirring for 1 h, during which the TBHP (5.5 M in nonane, 200 μL , 0.8 mmol) was added in four portions in every 15 minutes. The reaction mixture was cooled to $0\text{ }^\circ\text{C}$ and quenched with saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution. The aqueous layer was extracted with AcOEt. The combined organic layers were dried over MgSO_4 and filtered. The filtrate was concentrated under vacuum and the residue was roughly purified by silica gel column chromatography (AcOEt/ hexane=30%) gave epoxide **168** which was used for the next step without further purification.

To a solution of **168** in CH_2Cl_2 (3.7 mL) was added DIBALH (1.0 M in toluene, 960 μL , 0.96 mmol) at $-78\text{ }^\circ\text{C}$. The mixture was allowed to warm up to $-30\text{ }^\circ\text{C}$. After stirring for 30 min, the reaction mixture was cooled to $-78\text{ }^\circ\text{C}$ and quenched with 1 M HCl (2.0 mL). The resulting mixture was warmed up to $40\text{ }^\circ\text{C}$. After stirring for 4 h, the mixture was cooled to room temperature. The aqueous layer was extracted with chloroform. The combined organic layers were washed with saturated aqueous NaHCO_3 solution and dried over MgSO_4 and filtered. The filtrate was concentrated under vacuum. The crude aldehyde was used for the next step without further purification.

To a solution of aldehyde in THF (3.3 mL) was added LiAlH_4 (27.3 mg, 0.697 mmol) at $-78\text{ }^\circ\text{C}$. After stirred for 25 min, the reaction mixture was quenched with saturated aqueous potassium sodium tartrate. The resulting mixture was warmed up to $35\text{ }^\circ\text{C}$, and the mixture was separated. The aqueous layer was extracted with chloroform, and the combined organic layers

were dried over MgSO_4 and filtered. The filtrate was concentrated under vacuum. The residue was purified by recrystallization from CH_2Cl_2 to give verrucarol (47.4 mg, 0.178 mmol, 61%, over 3 steps) as a colorless crystal; ^1H NMR (500MHz, CDCl_3) δ 5.42 (m, 1H), 4.63 (t, J = 6.9 Hz, 1 H), 3.80 (d, J = 5.2 Hz, 1 H), 3.74 (d, J = 11.5 Hz, 1 H), 3.61 (d, J = 5.2 Hz, 1 H), 3.5 (d, J = 12.0 Hz, 1 H), 3.1 (d, J = 4.0 Hz, 1 H), 2.8 (d, J = 4.0 Hz), 2.6 (dd, J = 7.5 Hz, 15.5 Hz, 1 H), 2.06-1.87 (m, 5 H), 1.73 (br, 1 H), 1.71 (s, 3 H), 1.67 (br, 1 H), 0.93 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 140.99, 118.65, 78.60, 74.42, 66.49, 65.71, 62.37, 66.49, 65.72, 62.38, 48.90, 47.63, 43.81, 39.81, 28.16, 23.27, 20.91, 7.25

Acknowledgment

All the studies in this thesis were carried out under the supervision of Professor Dr. Keiji TANINO, Department of Chemistry, Faculty of Science, Hokkaido University. The author would like to express deeply sincere appreciation to Professor Tanino for his guidance and constant encouragement throughout the course of this work, in the preparation of this thesis, and or helpful discussions.

The author expresses his sincere thanks to Associate Professor Dr. Takahiro SUZUKI, Associate Professor Fumihiko YOSHIMURA for practical advice and fruitful discussion.

The author expresses his sincerely thanks to Professor Dr. Masaya SAWAMURA, Department of Chemistry, Faculty of Science, Hokkaido University, Professor Dr. Takeshi OHKUMA, Division of Chemical Process Engineering, Faculty of Engineering and Professor Dr. Tamaki NAKANO, Division of Biotechnology and Macromolecular Chemistry, Hokkaido University for serving my dissertation committee.

The author would like to express special thanks to Dr. Masaru IWAKURA for his helpful guidance, discussions and encouragement.

The author wishes to thank all the members of the laboratory, especially to Ryusei ITOH, Mirai HATAKE and Taku OKADA for your helpful advice and encouragement.

Finally, the author would like to thank sincerely his family, Ikuko and Yuki for their encouragement and understanding.