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DISSERTATION

New Method for Constructing Caged Skeleton Directed toward Terpenoid Synthesis

（テルペノイド合成を志向した新規カゴ型骨格構築法）

Kosuke Kato

Hokkaido University

2023

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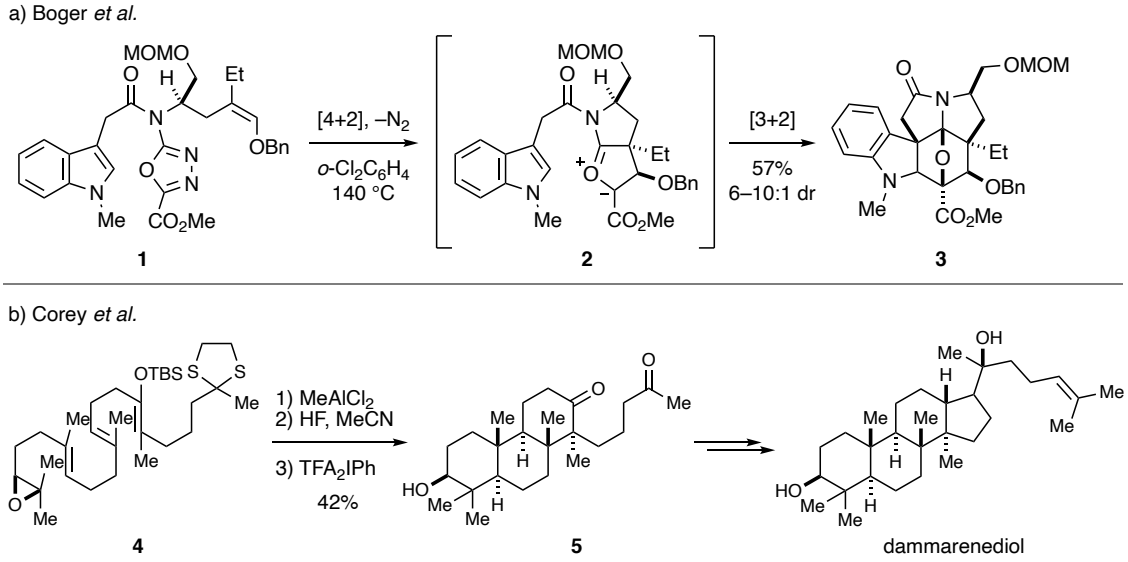
Introduction

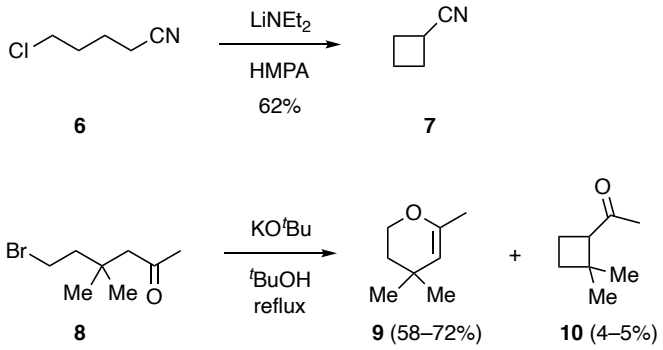
There are a significant number of natural products, pharmaceuticals, and functional organic compounds possessing carbocycles, and the development of an efficient synthetic method for constructing carbocycles is one of the most important issues in synthetic organic chemistry. Since many aromatic compounds having a variety of functional groups with various patterns of substitution are commercially available, synthesis of complex aromatic compounds is usually achieved by introduction of substituents to a simple aromatic compound. On the other hand, alicyclic organic compounds with various ring sizes are usually obtained through construction of the carbocyclic moiety by intramolecular alkylation and addition reactions, ring closing metathesis reaction, cycloaddition reaction, or polyene cyclization, etc. Among them, cycloaddition and polyene cyclization are advantageous for constructing a polycyclic ring system in a single step. For example, Boger's group reported efficient formation of the pentacyclic skeleton of vindoline via cycloaddition cascade. Upon heating in *o*-dichlorobenzene at 140 °C, 1,3,4-oxadiazole **1** underwent an intramolecular Diels-Alder reaction and a retro Diels-Alder reaction to give 1,3-dipole **2** which was converted to pentacyclic compound **3** via an intramolecular [3 + 2] cycloaddition reaction (Scheme 1a).[1] Polyene cyclization reactions are often used in the synthesis of steroids and terpenoids. In the total synthesis of dammarenediol by Corey's group, tricyclic skeleton of diketone **5** was constructed via polyene cyclization of triene **4** (Scheme 1b).[2]



Scheme 1 Cycloaddition and Polyene cyclization for constructing the carbon skeletons

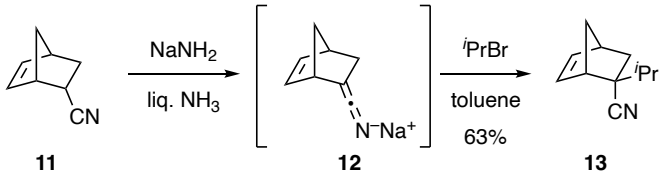
On the other hand, intramolecular reactions of carbon nucleophiles having an electrophilic carbon have been used extensively for building carbon skeletons as a powerful and reliable synthetic method. Intramolecular alkylation reactions of stabilized carbanions have been recognized as one of the most fundamental ones, and various types of carbanions have been employed as a potent nucleophile for the purpose. Among them, nitrile-stabilized carbanions (α-cyano carbanions) have been recognized to exhibit unique properties. In this section, the representative examples of the reactions of α-cyano carbanions which gave carbocycles with various ring-sizes are overviewed.

A cyano group is regarded as a synthetic equivalent of a carboxyl group, and the utilities of α-cyano carbanions are generally similar with those of enolates generated from the corresponding carbonyl compounds. However, there are some differences between the cyclization reactions of them, as is shown in Scheme 2. Upon treatment with $LiNEt_2$, chloronitrile **6** smoothly underwent a cyclization reaction to give four-membered nitrile **7** in 62% yield.[3] On the other hand, four-membered ketone **10** was obtained in only 5% yield from bromoketone **8** under the influence of potassium *tert*-butoxide (KO^{t}Bu). The preferential formation of *O*-alkylated product **9** is explained by the lower strain energy of a six-membered ring.[4]



Scheme 2 Comparison of the reactivity about α-cyanocarbanion and enolate

Because a cyano group is much less bulky than other electron-withdrawing groups such as ester, sulfonyl, or nitro group, α-cyano carbanions are expected to be ideally suited nucleophiles for the formation of quaternary carbon centers. For example, Boehme reported that tertiary nitrile **13** could be synthesized in moderate yield by the alkylation reaction of α-cyano carbanion **12** generated from 5-norbornene-2-carbonitrile **11** with ^{i}PrBr (Scheme 3).[5]

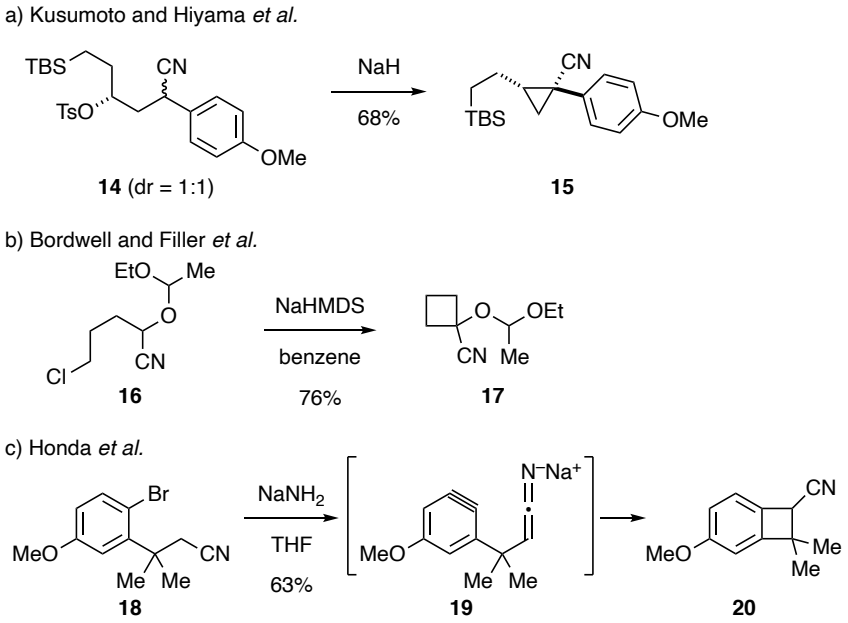


Scheme 3 Installing quaternary center by Alkylation with α-cyano carbanion

The characteristic features of nitrile derivatives make them important substrates of intramolecular alkylation reactions affording carbocycles with various ring sizes.

Some representative examples of small-ring formation are shown in Scheme 4. Three-membered nitrile **15** was synthesized by S_Ni displacement of tosylate **14** under basic conditions.[6] The reaction proceeded through the less congested transition state, giving rise to cyclopropane **15** as a single isomer in which the alkyl group is *cis* to the less hindered cyano group.

Formation of four-membered carbocycles using α-cyano carbanions are classified into two categories. Bordwell and Filler reported an intramolecular S_N2 reaction of chloronitrile **16** mediated by sodium bis(trimethylsilyl)amide (NaHMDS) which gave four-membered nitrile **17** in 76% yield (Scheme 4b).[7] Another type four-membered ring formation is the intramolecular addition of benzynes (Scheme 4c). Thus, bromonitrile **18** was deprotonated with $NaNH_2$ to generate benzyne **19** that underwent cyclization to afford the corresponding benzocyclobutane **20**.[8] This type of cyclization provides useful route to sterically hindered cyclobutanes that are difficult to obtain by other methods.

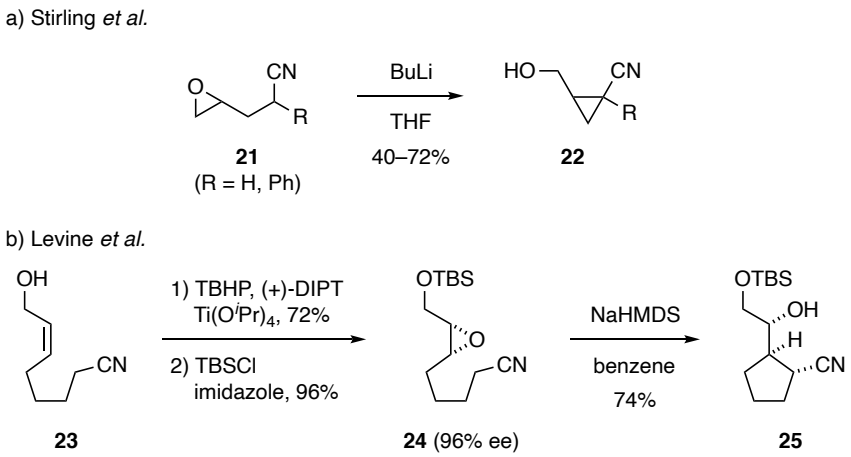


Scheme 4 Formation of Small-Membered Carbon Ring

Since the pioneering work by Stork *et al.*, cyclization reactions of epoxynitriles have provided powerful tools for constructing a small and medium-sized rings. These reactions tend to proceed at the inside carbon atom of the epoxide moiety to give three- to six-membered rings.[9] For example, treatment of γ-epoxynitriles **21** with butyllithium afford cyclopropanes **22** rather than cyclobutene derivatives (Scheme 5a).[10]

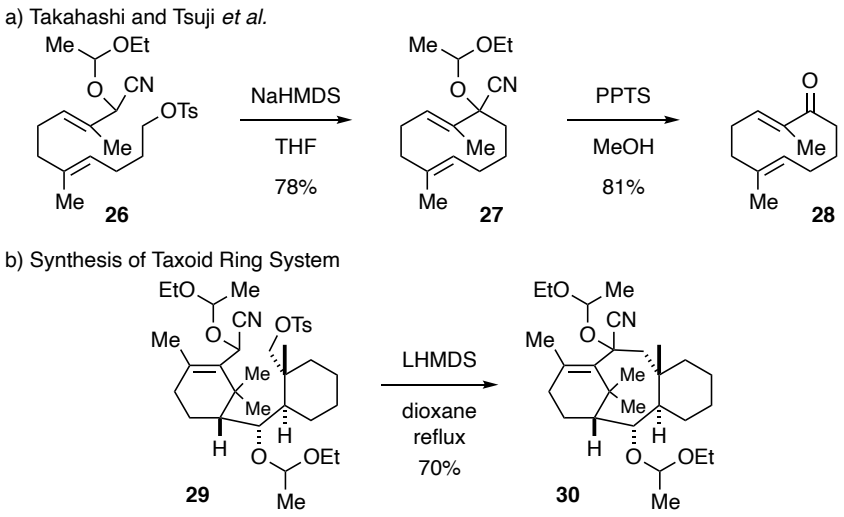
The cyclization of (*E*)- or (*Z*)-epoxynitriles proceeds via S_N2 reaction mechanism leads to stereospecific construction of contiguous two chiral centers. While the configuration of the

resulting α-carbon of the cyano group is generally unpredictable, Levine reported the synthesis of a homochiral *trans*-disubstituted cyclopentane with three chiral centers in a highly stereoselective fashion (Scheme 5b).[11] Optically active cyclization precursor **24** was easily synthesized in 96% ee via Sharpless's asymmetric epoxidation of allylic alcohol **23** followed by protection of the primary hydroxy group. Treatment of nitrile **24** with NaHMDS gave cyclopentane **25** as a single isomer.



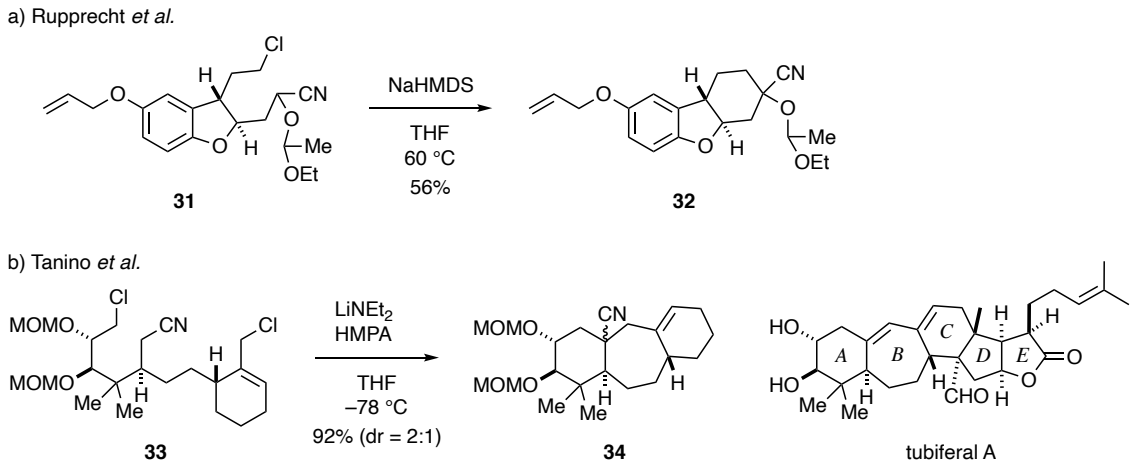
Scheme 5 Cyclizaitons of Epoxynitriles

Intramolecular S_N2 reactions using protected cyanohydrin derivatives are known to be suitable for the formation of medium-sized carbocycles, which is much more difficult than formation of five- or six-membered carbocycles. Takahashi and Tsuji developed a general synthetic method for 2,6-cyclodecadiene system by an intramolecular alkylation reaction of protected cyanohydrin **26** (Scheme 6a).[12] Since the cyclization product **27** can be converted to the corresponding carbonyl compound **28** under acidic hydrolysis conditions, a cyanohydrin is useful as an acyl anion equivalent. This cyclization method was applied to formation of the taxoids ring system, and the cyclization of nitrile **29** formed the highly strained eight-membered ring of **30** in good yield by S_Ni reaction at the neopentyl position (Scheme 6b).[13]



Scheme 6 Medium-sized Ring Construction

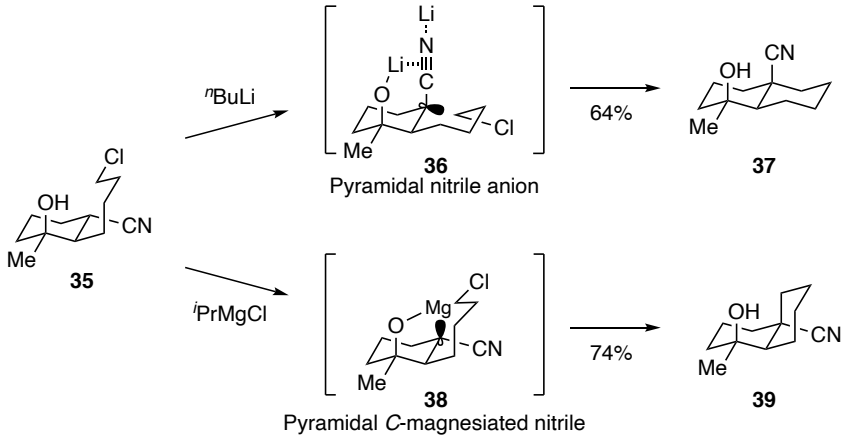
Intramolecular alkylation reactions of nitriles are also applied to the constructing polycyclic skeletons with a fused ring system. Selected examples are shown in Scheme 7. Rupprecht's group reported the synthesis of hexahydro-dibenzofuran **32** by the cyclization reaction of chloronitrile **31** under basic conditions (Scheme 7a).[14] A double alkylation reaction was effectively utilized for constructing a tricyclic skeleton by Tanino's group. Thus, the ABC-ring system of tubiferal A was obtained by the treatment of dichloronitrile **33** with an excess amount of $LiNEt_2$ (Scheme 7b).[15]



Scheme 7 Construction of Fused Tricyclic Skeletons by Intermolecular Alkylation

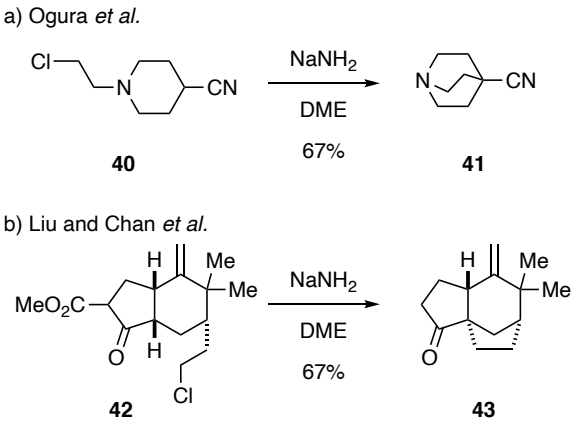
Stereoselective construction of bicyclic ring system has been intensively studied by Fleming's group.[16] As shown in Scheme 8, stereodivergent formation of decalin skeletons from γ-hydroxynitrile **35** was achieved through metal-dependent reaction pathways.[16b] Thus, deprotonation of nitrile **35** with ^{n}BuLi gives *trans*-decalin **37** by the cyclization through the internal-coordinated pyramidal nitrile anion **36**. On the other hand, treatment of the same nitrile **35** with ^{i}PrMgCl

generates *C*-magnesiated nitrile **38** having an axial C–Mg bond which cyclizes to *cis*-decalin **39**.



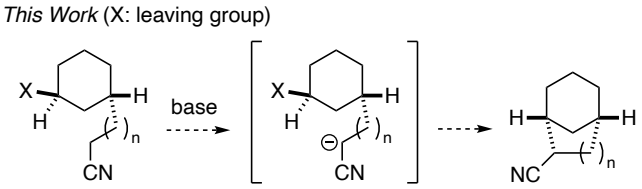
Scheme 8 Stereodivergent Metal-Dependent Cyclization

As described above, formation of a carbocycle fused with another carbocycle by an intramolecular alkylation reaction of nitriles provides powerful tool for obtaining polycyclic compounds. On the other hand, there are limited examples in which this type of reaction is utilized for building a bridged ring system. For example, Ogura *et al.* reported that 4-cyanoquinuclidine **41** was obtained by intramolecular alkylation of chloronitrile **40** (Scheme 9a).[17] In contrast, there are many examples of intramolecular *C*-alkylation of enolates affording a bridged bicyclic system.[18] Lui and Chan achieved the total synthesis of zizane sesquiterpenes through the construction of bicyclo[3.2.1]octane (**43**) by S_Ni reaction of chloroketone **42** (Scheme 9b).[19] It is noteworthy that these cyclization reactions generally occur between a nucleophilic ring carbon and an electrophilic carbon on the side chain, as shown in the scheme below.



Scheme 9 Construction of Bridge-ring system by Intramolecular Alkylation

Intrigued by these backgrounds of the nitrile chemistry, the author decided to develop a synthetic methodology for constructing bridged-ring system by unprecedented S_Ni displacement on the carbocycle (Scheme 10). In this dissertation, the development of a new synthetic method for the caged skeletons using nitrile derivatives and their applications for the natural product synthesis are described. In chapter 1, highly stereoselective construction of bicyclo[3.2.1]octane skeleton by intramolecular alkylation of bromonitriles is described. Then the total synthesis of 2-isocyanoallopupukeanane is described in chapter 2, and synthetic studies on aconitine-type diterpenoid alkaloids is described in chapter 3, respectively.



Scheme 10 S_Ni Displacement on the Carbocycle

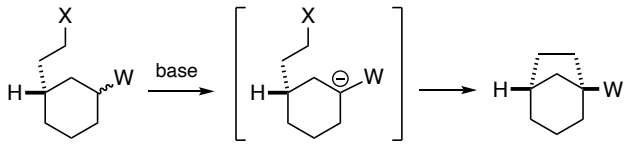
Chapter 1

Highly Stereoselective Construction of Bicyclo[3.2.1]octane Skeleton by Intramolecular Alkylation of Bromonitriles

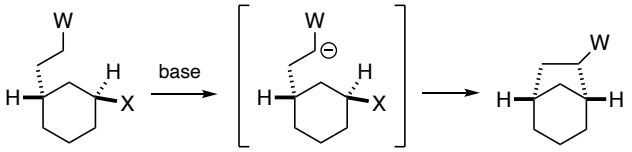
1-1. Introduction

Bicyclo[3.2.1]octane skeletons are widely found as a substructure of natural products, and various methods for constructing the bridged flamework have been developed.[18] Among them, formation of a five-membered ring by an alkylation reaction between a side chain and a ring carbon of the six-membered ring provides straightforward methods, which are classified as two types (Scheme 1.1a,b). Type-1 substrates, which contain a carbanion moiety in the cyclohexane ring and a leaving group X on the side chain, are widely used for the construction of bicyclo[3.2.1]octane skeletons, as shown in the previous section. In contrast, there are only few examples of the type-2 cyclizations in which the nucleophilic site on the side chain undergoes an S_N2 displacement at the ring carbon.[20] The main drawback of the type-2 method is the stereochemical requirement in the preparation of the cyclization precursor, which should have a side chain and leaving group X in an *anti*-relationship to each other. Notably, an intramolecular alkylation reaction of a cyclohexyl halide, in which the leaving group occupies an axial position, is limited by the competing E2 elimination.

a) type-1 cyclization (W: electron withdrawing group, X: leaving group)



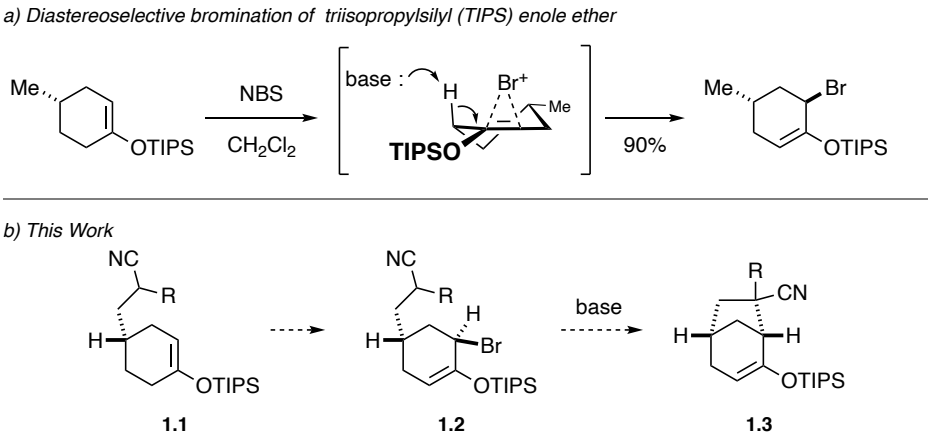
b) type-2 cyclization (W: electron withdrawing group, X: leaving group)



Scheme 1.1 Two Types Approaches for Constructing the Bicyclo[3.2.1]octane Skeletons

In 1990, Magnus and Mugrage reported the stereoselective bromination reaction at allylic position of triisopropylsilyl (TIPS) enol ethers.[21] Treatment of the TIPS enol ether of 4-substituted cyclohexanones with *N*-bromosuccinimide (NBS) gave the bromination products in which the bromide and the C4-substituent were in *anti*-relationship (Scheme 1.2a). The reaction was speculated to occur through an ene reaction-like transition state, leading to the stereoselective introduction of the bromine atom from the opposite face of the C4-substituent.

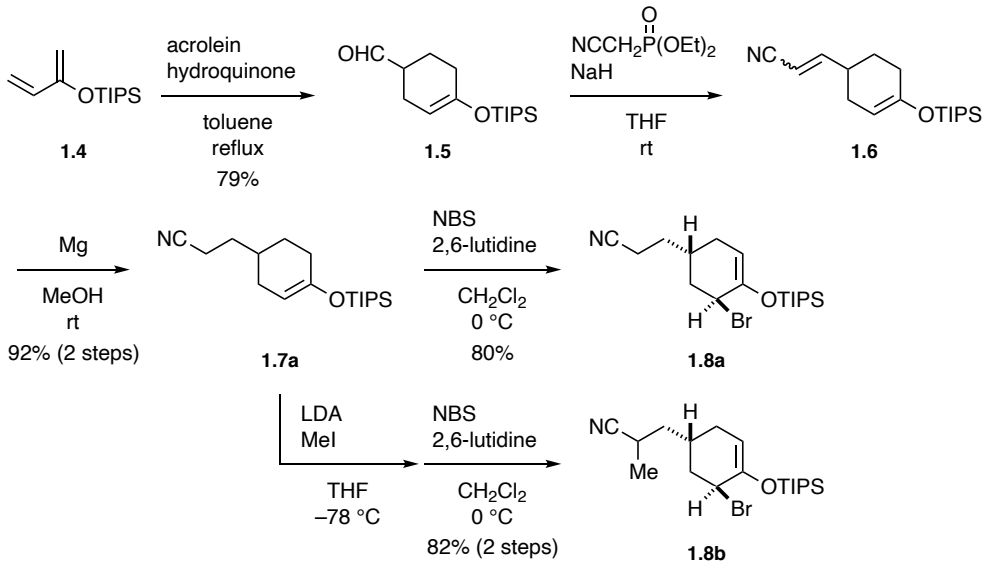
The results inspired the author to design a new type-2 substrate **1.2** that could be prepared diastereoselectively from the corresponding TIPS enol ether **1.1**. It was envisioned that a reactive allylic bromide as the electrophile would be advantageous for inducing the S_Ni displacement rather than the β-elimination reaction.



Scheme 1.2 Diastereoselective Bromination and Design of New Type-2 Substrate

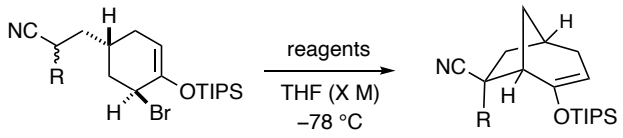
1-2. Substrate Synthesis and Scope of Intramolecular Alkylation

Initially, cyclization precursors **1.8a** and **1.8b** were prepared (Scheme 1.3). The Diels-Alder reaction of silyl enol ether **1.4**[22] with acrolein afforded aldehyde **1.5**. Elongation of the side chain was performed by a Horner-Wadsworth-Emmons reaction, and chemoselective reduction of the conjugated alkene moiety of the resulting nitrile **1.6** with magnesium in methanol[23] gave nitrile intermediate **1.7a**. Upon treatment with NBS in the presence of 2,6-lutidine, silyl enol ether **1.7a** underwent a diastereoselective bromination reaction to afford cyclization precursor **1.8a**. Bromonitrile **1.8b** was also synthesized in 82% yield via alkylation of the nitrile **1.7a** with MeI followed by bromination.



Scheme 1.3 Preparation of the Cyclization Precursors

With the cyclization precursors in hand, the optimal conditions of intramolecular alkylation reactions were investigated (Table 1.1). Upon treatment with 1.2 equiv of LDA at –78 °C in THF (0.2 M), cyclization product **1.9a** was obtained in 70% yield (entry 1), but the use of HMPA as an additive resulted in formation of **1.9a** in lower yield (entry 2). With a view to suppressing a possible competitive intermolecular alkylation reaction, the reaction was performed under diluted conditions (0.05 M), giving rise to **1.9a** in higher yield (entry 3). While bromonitrile **1.8b** underwent incomplete cyclization under the same conditions (entry 5), the use of 1.5 equiv of LDA gave a satisfactory result (entry 6). The use of lithium diethylamide ($LiNEt_2$), which is less bulky than LDA, gave comparable results in the reactions of both **1.8a** and **1.8b** (entries 4 and 7).



1.8a (R = H)
1.8b (R = Me)

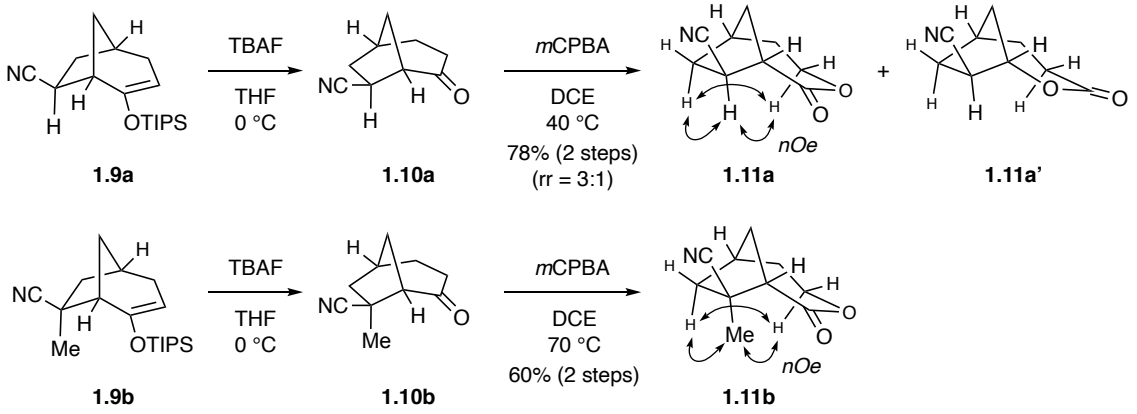
1.9a
1.9b

Entry	Substrate[a]	Reagents (equiv.)	Concentration (M)	yield (%)
1	**1.8a**	LDA (1.2)	0.2	70
2	**1.8a**	LDA (1.2), HMPA (1.0)	0.2	66
3	**1.8a**	LDA (1.2)	0.05	78
4	**1.8a**	$LiNEt_2$ (1.2)	0.05	79
5	**1.8b**	LDA (1.2)	0.05	65[b]
6	**1.8b**	LDA (1.5)	0.05	75
7	**1.8b**	$LiNEt_2$ (1.5)	0.05	75

[a]0.1 mmol scale. [b]Small amount of **1.8b** was recovered (<10%).

Table 1.1 Optimization Studies for Intramolecular Alkylation

Interestingly, the reactions of **1.8a** and **1.8b** proceeded in a stereoselective manner to provide the corresponding products as single diastereomers. The stereochemical configurations of **1.9a** and **1.9b** were determined after transformation into lactone **1.11a** and **1.11b**, respectively (Scheme 1.4). Silyl enol ether **1.9a** was deprotected with tetrabutylammonium fluoride (TBAF), and the resulting ketone **1.10a** was subjected to the Baeyer-Villiger oxidation with *m*-chloroperbenzoic acid (*m*CPBA), generating a 3:1 mixture of seven-membered lactone **1.11a** and its regioisomer **1.11a'**. Lactone **1.11b** was synthesized as a single regioisomer by a similar two-step transformation. The regioselectivity of the Baeyer-Villiger reaction would be reversed because of the inductive effect of the cyano group at the β-position.[24] The NOE NMR experiments of each lactone **1.11a** and **1.11b** indicated that the cyano group of the cyclization products was located on the convex face of the bicyclo[3.2.1]octane skeleton, regardless of the substituent at the α-position.



Scheme 1.4 Determination of Configuration

The preliminary results led the author to explore the substrate scope of the cyclization reaction (Table 1.2). Introduction of various substituents at the α-position of nitrile **1.7a** was achieved by alkylation reactions with LDA and organohalides (R–X), affording nitriles **1.7c-i** in high yields. Upon treatment with NBS in the presence of 2,6-lutidine, nitriles **1.7c-i** were converted into the corresponding bromonitriles, which were subjected to the intramolecular cyclization reaction with $LiNEt_2$.[25] Nitriles with a simple primary or secondary alkyl group afforded the corresponding bicyclo[3.2.1]octane derivatives **1.9c** and **1.9d** as single isomers, respectively. Bicyclic nitriles **1.9e-g** were also obtained as single isomers. An acetal group at the terminal position of the alkyl side chain did not affect the yield or stereoselectivity of the cyclization reaction, resulting in formation of **1.9h** and **1.9i** which were subject to further transformation.

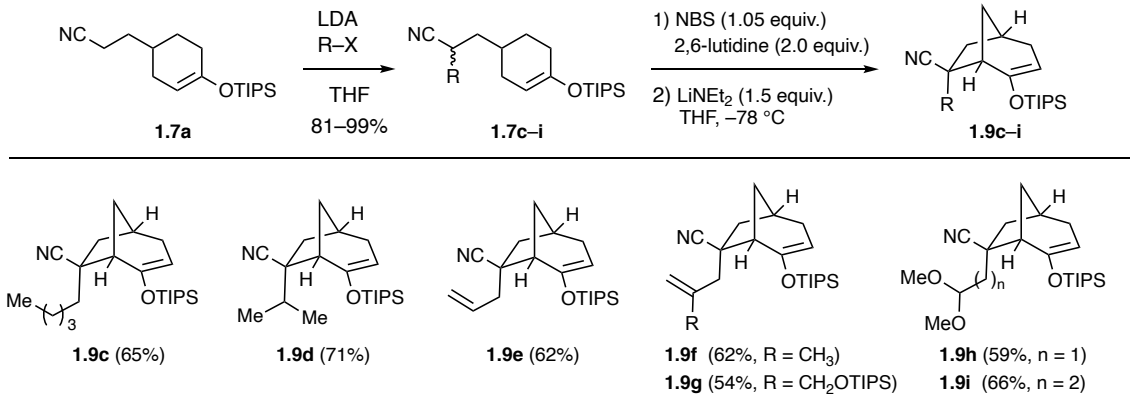
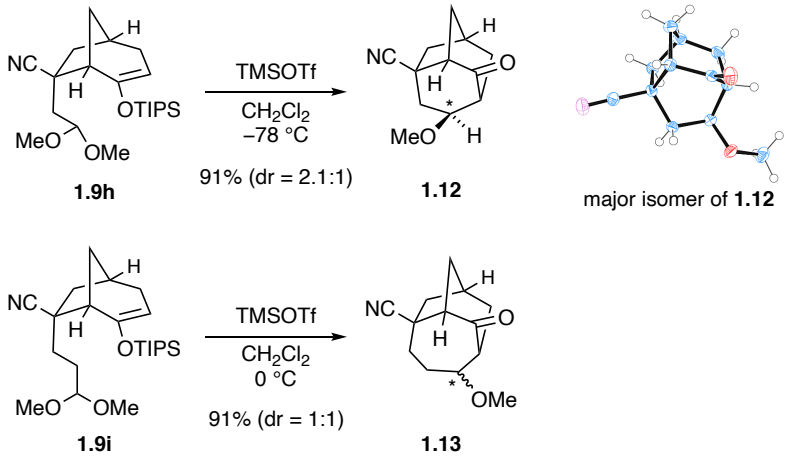


Table 1.2 Substrate Scope of Cyclization Reactions

These obtained bicyclic nitriles were expected to have a stereochemical configuration identical to that of nitriles **1.9a** and **1.9b**, and the author planned to construct tricyclic caged skeletons by further intramolecular cyclization reaction (Scheme 1.5). Thus, acetals **1.9h** and **1.9i** were subjected to intramolecular Mukaiyama aldol reactions[26] with trimethylsilyl trifluoromethanesulfonate

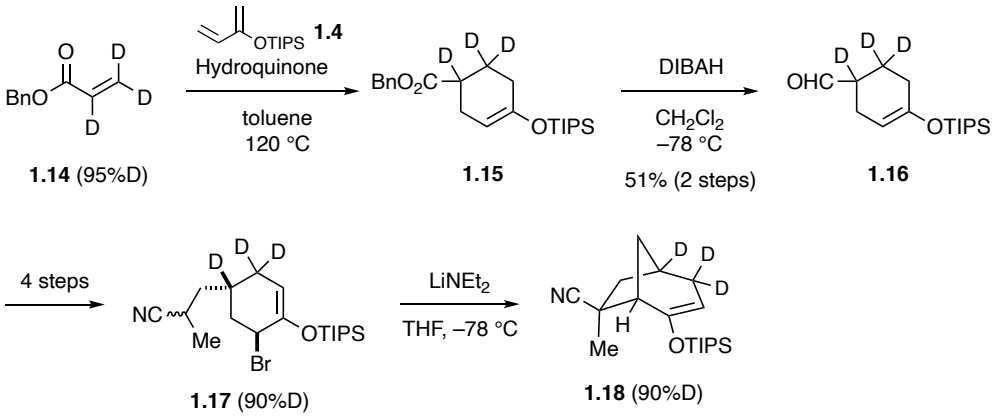
(TMSOTf), providing tricyclic ketones **1.12** and **1.13** in excellent yields, respectively. The structure of the major isomer of **1.12** was confirmed by X-ray crystallographic analysis.



Scheme 1.5 Construction of Caged Skeletons

1-3. Mechanistic Investigation

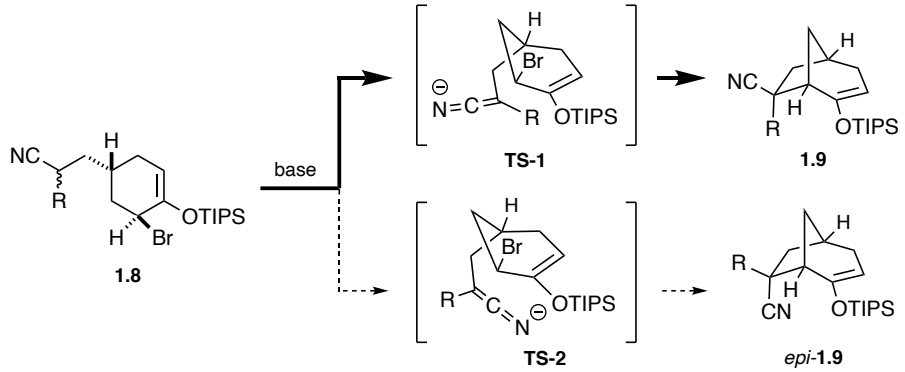
Next, a deuterium labeling experiment was performed to investigate the reaction mechanism of the cyclization (Scheme 1.6). The deuterium-labeled six-membered ring was constructed via the Diels-Alder reaction of the deuterated benzyl acrylate **1.14**[27] with silyl enol ether **1.4**. The resulting ester **1.15** was converted to cyclization precursor **1.17** through reduction with diisobutylaluminum hydride (DIBAH) followed by a similar four-step transformation described in Scheme 1.3. The cyclization reaction of bromonitrile **1.17** under the optimal conditions gave the bicyclic product **1.18** which proved to have two deuterium at the allylic position. This result indicated that the intramolecular alkylation reaction proceeds via S_N2 (not S_N2') displacement pathway.



Scheme 1.6 Deuterium Labeling Experiment

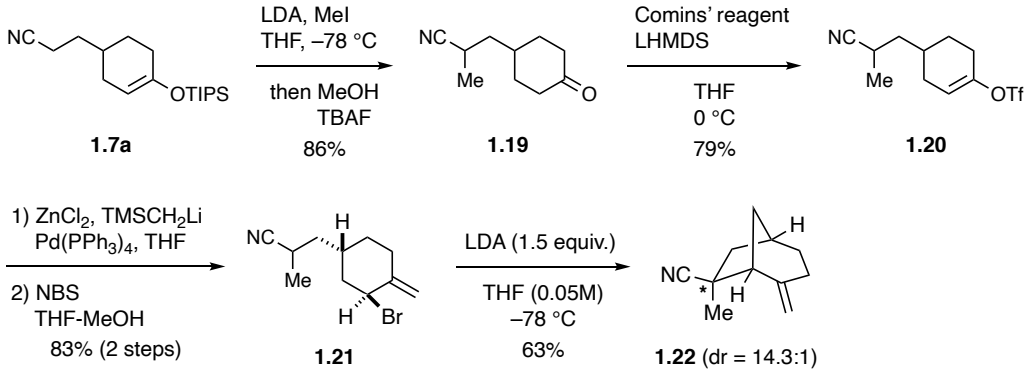
These stereochemical outcomes of the cyclization reactions are rationalized as follows. The stereochemistry of the products cannot be commonly rationalized by considering the relative

bulkiness of the substituents (H < CN < Me), because both **1.9a** and **1.9b** possess a cyano group at the convex face. The common configuration of the nitrile moiety should therefore arise from the Pauli repulsion between the anionic cyano group and the silyl enol ether moiety (Scheme 1.7), making **TS-2** significantly less stable than **TS-1**, regardless of the substituent R.



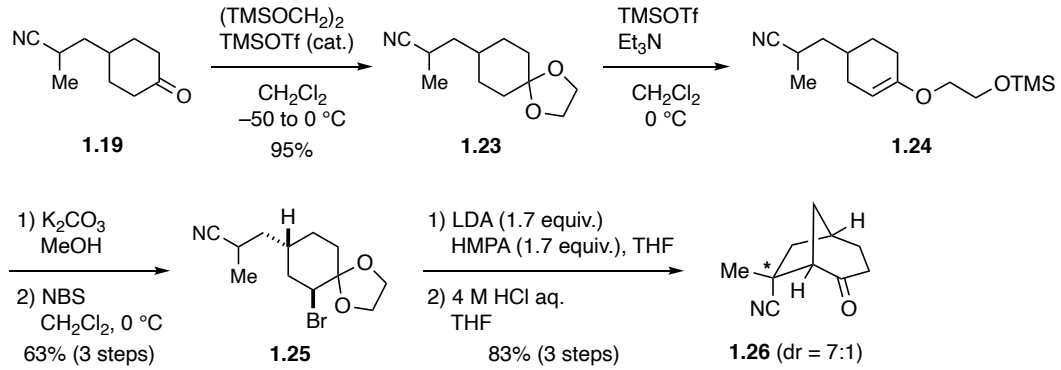
Scheme 1.7 Transition State Models of the Cyclization

Next, the importance of the silyl enol ether moiety in the stereoselective cyclization reactions was verified by comparing with the reactions of analogous substrates. Since the silyl enol ether moiety was supposed to control the direction of the α-cyano carbanion moiety by the Pauli repulsion, bromonitrile **1.21** having an exo alkene moiety instead of a silyl enol ether moiety was prepared (Scheme 1.8). Methylation of nitrile **1.7a** and removal of the silyl group with TBAF in one-pot afforded ketone **1.19**. Upon treatment with lithium bis(trimethylsilyl)amide (LHMDS) and Comins' reagent, ketone **1.19** was converted to enol triflate **1.20**, which was subjected to the Negishi coupling reaction with $TMSCH_2ZnCl$ followed by diastereoselective bromination[28]. The resulting bromonitrile **1.21** was treated with LDA, giving rise to bicyclic compound **1.22** in 63% yield as a 14.3:1 diastereomeric mixture. The cyano group of the major isomer of **1.22** proved to be directed to the convex face of the bicyclic skeleton,[29] suggesting that a similar Pauli repulsion between the exo alkene moiety and the α-cyano carbanion moiety controlled the stereochemistry of the cyclization reaction.



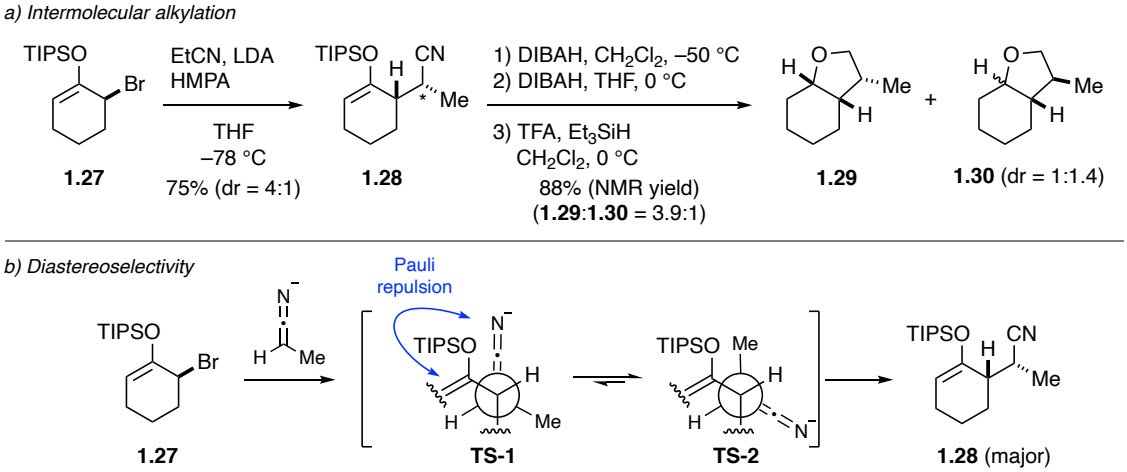
Scheme 1.8 Cyclization Reaction of the Exo Alkene Substrate

These results led the author to investigate the cyclization reaction of bromonitrile **1.25** without a neighboring alkene moiety at the reaction site (Scheme 1.9). Acetalization of ketone **1.19** by the Noyori's protocol[30] afforded ketal **1.23** which was converted to the cyclization precursor **1.25** via three-step sequence comprising enol ether formation,[31] desilylation, and bromination. The cyclization reaction of bromonitrile **1.25** was performed with LDA in the presence of HMPA, and bicyclic ketonitrile **1.26** was obtained as a 7:1 diastereomeric mixture after hydrolysis under acidic conditions. Comparison of the ^{1}H NMR spectra[29] indicated that the cyano group of the major cyclization product **1.26** was located at the concave face of the bicyclo[3.2.1]octane skeleton. The stereochemical outcome contrasting with that of the reactions of bromonitriles **1.8b** and **1.21** clearly indicates the importance of Pauli repulsion to control the direction of the cyano group.



Scheme 1.9 Cyclization Reaction of the Ketal Substrate

Finally, the principle in the stereoselective intermolecular alkylation reaction of bromonitriles was expanded to an intermolecular reaction (Scheme 1.10). Allylic bromide **1.27** prepared from cyclohexanone in two steps was subjected to the S_N2 reaction with a α-cyano carbanion generated from propionitrile. The product **1.28**, which was obtained as a 4:1 diastereomeric mixture, was converted to the known octahydro-2-benzofurans **1.29** and **1.30** via DIBAH reduction (twice) followed by reductive intramolecular etherification using triethylsilane. The ^{1}H NMR spectra were identical to those of **1.29** and **1.30** reported by Engman and Gupta,[32] indicating that the methyl group of the major isomer **1.29** has α-configuration. These results suggested that the intermolecular alkylation reaction of **1.27** proceeded preferentially through **TS-2** rather than **TS-1** which was destabilized by Pauli repulsion.



Scheme 1.10 Intermolecular Alkylation

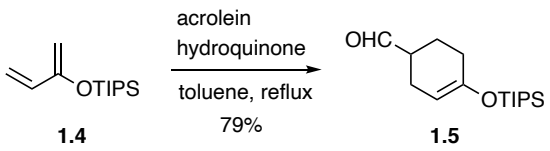
1-4. Conclusion

In summary, the author has developed a new method for constructing a bicylo[3.2.1]octane skeleton by intramolecular alkylation of a nitrile-side-chain-containing cyclohexanone derivative. The cyclization precursors were prepared via stereoselective bromination of the TIPS enol ethers of 4-cyanoethyl substituted cyclohexanones. The cyclization reactions of the bromonitriles were proceeded in a highly stereoselective manner to afford bicyclo[3.2.1]octane derivatives with a cyano group at the convex face. The combined use of this reaction and an intramolecular Mukaiyama aldol reaction showed its potential for constructing caged skeletons.

1-5. Experimental Section

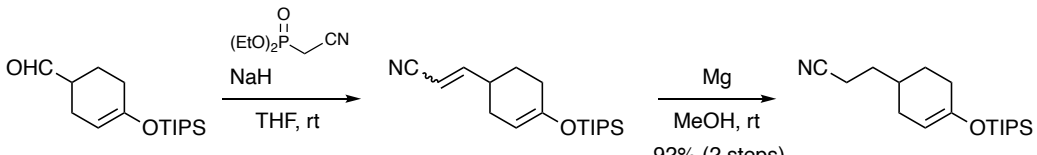
The reactions were performed using flame-dried glasswares under a positive pressure of argon. Oil bath was used when reactions required heating. Dry tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Anhydrous 1,2-dichloroethane (DCE), dichloromethane (CH_2Cl_2), dimethylsulfoxide (DMSO), ethanol (EtOH), methanol (MeOH), and toluene were purchased from Kanto Chemical Co., Inc. Diethylamine (Et_2NH), diisopropylamine (*i*-Pr_2NH), and triethylamine (Et_3N) was distilled from CaH_2 under argon and stored in the presence of NaOH (pellets). Hexamethylphosphoric triamide (HMPA) was distilled from CaH_2 under argon and stored in the presence of molecular sieves 4A. Silyl enol ether **1.4**,[22] allyl bromide **1.S1**,[33] and benzyl acrylate **1.12**[27] were prepared by the known procedures. All other reagents and solvents were used as received from commercial sources without further purification.

^{1}H 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). Chemical shifts are reported in parts per million (ppm), and signals 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 (126 MHz) in $CDCl_3$ (δ_C 77.0), C_6D_6 (δ_C 128.0). High-resolution mass spectra (HRMS) were recorded on a JEOL JMS-T100GCV (GC-TOFMS) at GC-MS & NMR Laboratory, Faculty of Agriculture, Hokkaido University. Infrared (IR) spectra were recorded on a JASCO FT/IR-4100 spectrophotometer. X-ray crystallographic data were recorded with a Rigaku XtaLAB Synergy Diffractometer at the Faculty of Science, Hokkaido University. Melting points (m.p.) were determined using an AS ONE ATM-02 apparatus and uncorrected. Analytical thin layer chromatography (TLC) was performed using 0.25 mm E. Merck Silica gel ($60F_{254}$) plates. Reaction components were visualized by illumination with ultraviolet light (254 nm) and by staining with 8% ethanolic phosphomolybdic acid, ceric ammonium molybdate in 10% sulfuric acid. Flash column chromatography was performed using Silica Gel 60N (neutral, particle size 0.040–0.050 mm, Kanto Chemical Co., Inc.). Purification of acid-sensitive compounds was performed using silica gel pretreated with *N,N*-dimethylaniline as follows: On a silica gel column, *N*,*N*-dimethylaniline (about 10 vol% of the silica gel) is loaded, which is eluted completely with EtOAc. Then, the EtOAc in the silica gel column was replaced with the appropriate solvent before loading the reaction mixture.



1.4 **1.5**

Aldehyde 1.5: To a solution of silyl enol ether **1.4**[22] (17.7 g, 78.1 mmol) in toluene (78 mL) were added freshly distilled acrolein (18.0 mL, 269 mmol) and hydroquinone (430 mg, 3.91 mmol). The reaction mixture was heated in an oil bath to refluxed for 12 h, and then cooled down to room temperature. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (SiO_2, Hexane/EtOAc = 100:0 to 20:1) to afford aldehyde **1.5** (17.4 g, 61.4 mmol, 79%) as a colorless oil: IR (ATR) ν 2943, 2893, 2866, 2711, 1727, 1668, 1463, 1248, 1193, 1070, 1044, 996 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.69 (s, 1H), 4.89 (dd, 1H, J = 4.0, 4.0 Hz), 2.44–2.39 (m, 1H), 2.28–2.25 (m, 2H), 2.16–2.13 (m, 2H), 2.02–1.96 (m, 1H), 1.82–1.75 (m, 1H), 1.17–1.05 (m, 21H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.5, 150.8, 101.0, 45.7, 28.1, 23.3, 22.6, 17.9 (6C), 12.6 (3C); HRMS (FD) *m*/*z*: $[M]^+$ calcd for $C_{16}H_{30}O_2Si$, 282.2015; found, 282.2012.

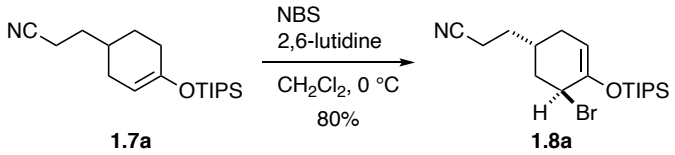


1.5 **1.6** **1.7a**

Nitrile 1.7a: A 55% dispersion of NaH in mineral oil (2.49 g, 56.9 mmol) was washed with hexane twice, and suspended in dry THF (60 mL). Diethyl cyanomethylphosphate (9.70 mL, 61.6 mmol) was added to this suspension at 0 °C. After evolution of hydrogen gas ceased, a solution of aldehyde **1.5** (13.4 g, 47.4 mmol) in dry THF (35 mL) was added at 0 °C. After stirring at room temperature for 1 h, the reaction was quenched with H_2O (100 mL). After the layers were separated, the aqueous layer was extracted with EtOAc (100 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Horner–Wadsworth–Emmons (HWE) reagent was removed by a short pad of silica gel (Hexane/EtOAc = 100:0 to 50:1). The obtained crude nitrile **1.6** was used for the next step without further purification.

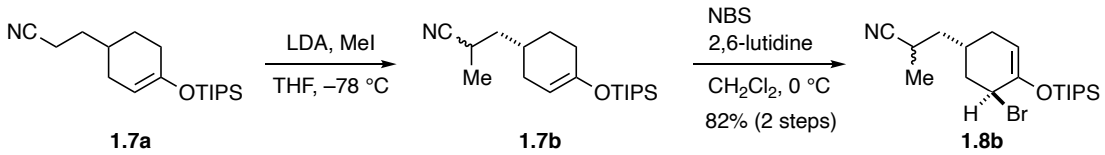
To a solution of the above crude nitrile **1.6** in MeOH (400 mL) was added Mg turnings (not activated, 9.73 g, 400 mmol) at room temperature. After stirring at the same temperature for 1.5 h, the reaction was quenched with saturated aqueous NH_4Cl solution (800 mL). Then, the solvent was removed under reduced pressure, and aqueous layer was extracted with Et_2O (100 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash column chromatography (Hexane/EtOAc = 5:1) afforded nitrile **1.7a** (13.4 g, 43.6 mmol, 92% for 2 steps) as a pale yellow oil: IR (ATR) ν 2925, 2866, 2239, 1669, 1463, 1195, 996, 881 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.82–4.81 (m, 1H), 2.37 (t, 2H, J = 6.9 Hz),

2.20–2.11 (m, 2H), 2.06–2.03 (m, 1H), 1.79–1.60 (m, 5H), 1.38–1.31 (m, 1H), 1.16–1.06 (m, 21H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.6, 119.8, 101.6, 32.4, 31.2, 29.6, 29.2, 28.6, 17.9 (6C), 15.0, 12.6 (3C); HRMS (FD) *m*/*z*: $[M]^+$ calcd for $C_{18}H_{33}NOSi$, 307.2331; found, 307.2341.



1.7a **1.8a**

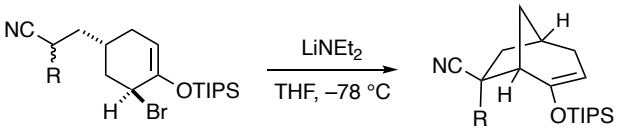
Bromonitrile 1.8a: To a solution of nitrile **1.7a** (128 mg, 0.417 mmol) in CH_2Cl_2 (2 mL) was added 2,6-lutidine (96.0 μL, 0.834 mmol). After the mixture was cooled to 0 °C, *N*-bromosuccinimide (NBS) (not recrystallized (white powder), 79.9 mg, 0.449 mmol) was added to the mixture in one portion. After stirring at 0 °C for 10 min, the reaction was quenched with saturated aqueous $NaHCO_3$ solution (1 mL) and saturated aqueous $Na_2S_2O_3$ solution (1 mL). The mixture was stirred at room temperature for 30 min. After the layers were separated, the aqueous layer was extracted with Et_2O (2 mL × 3). The combined organic layers were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash column chromatography (Hexane/EtOAc = 100:0 to 20:1, using silica gel pretreated with *N*,*N*-dimethylaniline: General Information in page 17) afforded bromonitrile **1.8a** (130 mg, 0.335 mmol, 80%) as a colorless oil: IR (ATR) ν 2943, 2866, 2249, 1655, 1464, 1215, 1186, 997, 881 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.94 (dd, 1H, *J* = 2.3, 5.7 Hz), 4.59 (br s, 1H), 2.39 (t, 2H, *J* = 8.0 Hz), 2.31 (ddd, 1H, *J* = 5.1, 5.1, 17.2 Hz), 2.20–2.15 (m, 2H), 1.90–1.81 (m, 2H), 1.76–1.65 (m, 2H), 1.22–1.07 (m, 21H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.6, 119.5, 104.7, 50.3, 38.9, 31.1, 29.9, 28.5, 18.00 (3C), 17.98 (3C), 14.9, 12.6 (3C); HRMS (FD) *m*/*z*: $[M]^+$ calcd for $C_{18}H_{32}BrNOSi$, 385.1437; found, 385.1444.



1.7a **1.7b** **1.8b**

Bromonitrile 1.8b: To a solution of nitrile **1.7a** (616 mg, 2.00 mmol) in dry THF (10 mL) was added lithium diisopropylamide (LDA) (1.0 M THF solution, 2.10 mL, 2.10 mmol) at –78 °C. After the mixture was stirred for 30 min at the same temperature, MeI (0.19 mL, 3.0 mmol) was added. The reaction mixture was stirred at –78 °C for 20 min, then the reaction was quenched with saturated aqueous $NaHCO_3$ solution (10 mL). After the layers were separated, the aqueous layer was extracted with Et_2O (10 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. The obtained crude nitrile **1.7b** (649 mg, pale yellow oil) was used for the next step without further purification.

To a solution of the above crude nitrile **1.7b** (649 mg) in CH_2Cl_2 (10 mL) was added 2,6-lutidine (0.38 mL, 4.0 mmol). After the mixture was cooled to 0 °C, NBS (378 mg, 2.12 mmol) was added to the mixture in one portion. After stirring at 0 °C for 10 min, the reaction was quenched with saturated aqueous $NaHCO_3$ solution (5 mL) and saturated aqueous $Na_2S_2O_3$ solution (5 mL). The mixture was stirred at room temperature for 30 min. After the layers were separated, the aqueous layer was extracted with Et_2O (10 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash column chromatography (Hexane/EtOAc = 100:0 to 20:1, using silica gel pretreated with *N*,*N*-dimethylaniline: General Information in page 17) afforded bromonitrile **1.8b** (657 mg, 1.64 mmol, 82% for 2 steps) as a yellow oil. The diastereomeric ratio of **1.8b** could not be determined due to overlapping between the signals of each diastereomer: IR (ATR) ν 2943, 2866, 2240, 1655, 1463, 1216, 997, 880, 669 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.94–4.93 (m, 1H), 4.59 (br s, 1H), 2.69 (tq, 1H, *J* = 6.9, 6.9 Hz), 2.33–2.26 (m, 2H), 2.22–2.18 (m, 1H), 1.92–1.80 (m, 2H), 1.76–1.69 (m, 1H), 1.52 (ddd, 1H, *J* = 6.9, 6.9, 13.8 Hz), 1.36 (d, 3H, *J* = 6.9 Hz), 1.22–1.07 (m, 21H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.63, 149.59, 123.0, 122.8, 104.89, 104.86, 50.3 (2C), 39.8, 39.7, 39.1, 38.9, 30.27, 30.25, 27.2, 26.7, 23.2, 23.0, 18.2, 18.1, 18.00 (12C), 12.6 (6C); HRMS (FD) *m*/*z*: $[M]^+$ calcd for $C_{19}H_{34}BrNOSi$, 399.1593; found, 399.1601.

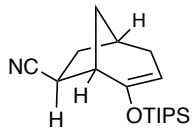


1.8a (R = H)
1.8b (R = Me)

1.9a (R = H)
1.8b (R = Me)

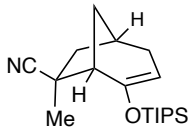
Bicyclo[3.2.1]octanecarbonitriles 1.9a and **1.9b:** To a solution of Et_2NH (115 μL, 1.10 mmol) in dry THF (505 μL) was slowly added *n*-BuLi (2.64 M in Hexane, 380 μL, 1.00 mmol) at –78 °C. Then the mixture was warmed up to 0 °C and stirred for 5 min to prepare lithium diethylamide ($LiNEt_2$) (1.0 M in THF-Hexane).

To a solution of bromonitrile **1.8a** or **1.8b** (1.0 equiv.) in dry THF (0.05 M) was added $LiNEt_2$ (1.0 M in THF-Hexane, 1.5 equiv.) at –78 °C. After stirring for 30 min, the reaction was quenched with saturated $NaHCO_3$ solution (2 mL). After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash column chromatography (using silica gel pretreated with *N*,*N*-dimethylaniline: General Information in page 17) afforded bicyclic product **1.9a** and **1.9b**.



1.9a

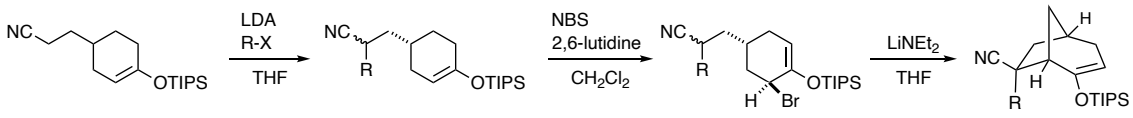
Compound 1.9a: Purification by flash column chromatography (Hexane/EtOAc = 50:1) afforded bicyclic product **1.9a** (33.8 mg, 0.111 mmol, 79%) from bromonitrile **1.8a** (54.1 mg, 0.140 mmol) as a colorless oil: IR (ATR) ν 2944, 2867, 2234, 1659, 1463, 1301, 1257, 1194, 996, 881 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.49 (br s, 1H), 3.10 (dd, 1H, *J* = 3.4, 9.2 Hz), 2.57 (d, 1H, *J* = 3.4 Hz), 2.49 (br d, 1H, *J* = 7.5 Hz), 2.31 (d, 1H, *J* = 16.6 Hz), 2.16 (ddd, 1H, *J* = 3.4, 7.5, 14.3 Hz), 1.94–1.87 (m, 2H), 1.83 (d, 1H, *J* = 11.5 Hz), 1.77 (dd, 1H, *J* = 4.0, 16.6 Hz), 1.19–1.06 (m, 21H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.2, 123.2, 98.3, 46.4, 36.4, 35.2, 33.7, 32.8, 32.7, 17.9 (6C), 12.5 (3C); HRMS (FD) *m*/*z*: $[M]^+$ calcd for $C_{18}H_{31}NOSi$, 305.2175; found, 305.2172.



1.9b

Compound 1.9b: Purification by flash column chromatography (Hexane/EtOAc = 50:1) to afforded bicyclic product **1.9b** (43.6 mg, 0.136 mmol, 75%) from bromonitrile **1.8b** (72.2 mg, 0.181 mmol) as a colorless oil: IR (ATR) ν 2943, 2867, 2230, 1657, 1463, 1251, 1190, 1004, 880 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.61 (br s, 1H), 2.48–2.40 (m, 3H), 2.29 (d, 1H, *J* = 16.6 Hz), 2.15 (ddd, 1H, *J* = 4.0, 4.0, 12.0 Hz), 1.79–1.74 (m, 2H), 1.51 (s, 3H), 1.37 (dd, 1H, *J* = 1.7, 13.2 Hz), 1.20–1.05 (m, 21H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.3, 126.7, 99.5, 50.9, 44.8, 44.2, 34.9, 33.7, 33.1, 22.1, 18.0 (3C), 17.9 (3C), 12.5 (3C); HRMS (FD) *m*/*z*: $[M]^+$ calcd for $C_{19}H_{33}NOSi$, 319.2331; found, 319.2318.

Procedures for Transformation from Nitrile 1.7a to Bicyclo[3.2.1]octanecarbonitriles 1.9

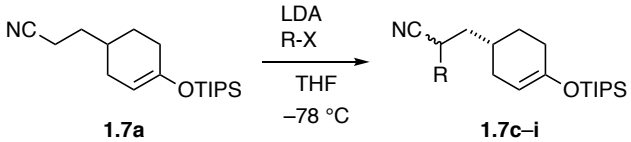


1.7a **1.7c–i** **1.8c–i** **1.9c–i**

Alkylation General Procedure A

Bromination & Intramolecular alkylation General Procedure B

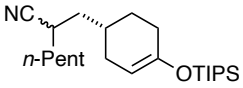
General procedure A for alkylation of nitrile 1.7a



1.7a **1.7c–i**

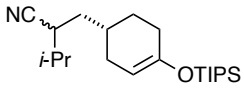
To a solution of nitrile **1.7a** (1.0 equiv.) in dry THF (0.2 M) was added LDA (1M THF solution, 1.05 equiv.) at –78 °C. After the mixture was stirred at the same temperature for 30 min, alkyl halide (1.2 equiv.) was added. In the case of **1.7d** and **1.7h**, HMPA (1.05 equiv.) was further added, and the reaction mixture was warmed up to 0 °C over 1h. After completion of the reaction was monitored by TLC, the reaction was quenched with saturated aqueous $NaHCO_3$ solution. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were dried over

$MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash column chromatography (using silica gel pretreated with *N*,*N*-dimethylaniline: General Information in page 17) afforded an alkylation product **1.7c–i**. Diastereomeric ratios of **1.7c–i** could not be determined due to overlapping between the signals of each diastereomer.



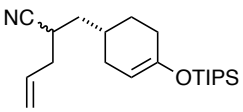
1.7c

Compound 1.7c: According to General Procedure A, the reaction of **1.7a** (159 mg, 0.518 mmol) with LDA (545 μL , 0.545 mmol), and 1-iodopentane (99.0 μL, 0.777 mmol) in dry THF (2.6 mL), followed by purification of the obtained crude product by flash column chromatography (Hexane/EtOAc = 50:1) afforded **1.7c** (158 mg, 0.419 mmol, 81%) as a colorless oil: IR (ATR) ν 2926, 2865, 2237, 1670, 1463, 1366, 1198, 996, 881 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.81 (br s, 1H), 2.62–2.53 (m, 1H), 2.18–2.11 (m, 2H), 2.06–2.02 (m, 1H), 1.82–1.73 (m, 2H), 1.68–1.52 (m, 5H), 1.48–1.38 (m, 2H), 1.35–1.25 (m, 5H), 1.17–1.06 (m, 21H), 0.90 (t, 3H, *J* = 6.9 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.7, 150.4, 122.44, 122.38, 101.8, 101.6, 38.6, 38.2, 32.8, 32.6, 31.3 (2C), 31.2, 30.5, 29.6, 29.5 (2C), 29.4, 29.2, 29.1, 28.2 (2C), 26.8 (2C), 22.4 (2C), 18.0 (12C), 13.9 (2C), 12.6 (6C); HRMS (FD) *m*/*z*: $[M]^+$ calcd for $C_{23}H_{43}NOSi$, 377.3114; found, 377.3106.



1.7d

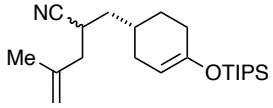
Compound 1.7d: According to General Procedure A, the reaction of **1.7a** (78.2 mg, 0.254 mmol) with LDA (267 μL , 0.267 mmol), HMPA (46.5 μL, 0.267 mmol), and 2-iodopropane (30.5 μL, 0.305 mmol) in dry THF (1.3 mL), followed by purification of the obtained crude product by flash column chromatography (Hexane/EtOAc = 50:1) afforded **1.7d** (82.6 mg, 0.236 mmol, 93%) as a colorless oil: IR (ATR) ν 2942, 2867, 2238, 1670, 1464, 1240, 1199, 997, 881 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.82 (br s, 1H), 2.53–2.46 (m, 1H), 2.19–2.14 (m, 2H), 2.06–2.02 (m, 1H), 1.86–1.72 (m, 3H), 1.69–1.62 (m, 1H), 1.45–1.24 (m, 2H), 1.16–1.04 (m, 28H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.7, 150.4, 121.18, 121.15, 101.9, 101.5, 36.83, 36.75, 36.3, 35.9, 31.4, 31.3, 30.6, 30.5, 30.3, 29.7, 29.4, 29.2, 29.1, 28.1, 21.03. 20.98, 18.6, 18.4, 18.0 (12C), 12.6 (6C); HRMS (FD) *m*/*z*: $[M]^+$ calcd for $C_{21}H_{39}NOSi$, 349.2801; found, 349.2810.



1.7e

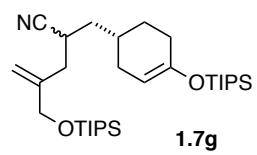
Compound 1.7e: According to General Procedure A, the reaction of **1.7a** (90.3 mg, 0.294 mmol) with LDA (309 μL , 0.309 mmol), and allyl bromide (30.0 μL, 0.353 mmol) in dry THF (1.5 mL), followed by purification of the obtained crude product by flash column chromatography (Hexane/EtOAc = 50:1) afforded **1.7e** (99.8 mg, 0.287 mmol, 98%) as a colorless oil: IR (ATR) ν 2925, 2866, 2238, 1670, 1463, 1366, 1240, 1197, 994, 881 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.86–5.77 (m, 1H), 5.21 (d, 1H, *J* = 17.8 Hz), 5.19 (d, 1H, *J* = 10.3 Hz), 4.81 (br s, 1H), 2.70–2.62 (m, 1H), 2.35 (t, 2H, *J* = 6.3 Hz), 2.19–

2.16 (m, 2H), 2.06 (dd, 1H, J = 2.3, 17.2 Hz), 1.82–1.73 (m, 2H), 1.68–1.63 (m, 2H), 1.51–1.25 (m, 2H), 1.17–1.06 (m, 21H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.6, 150.4, 133.1 (2C), 121.8, 121.7, 118.9, 118.8 101.7, 101.4, 38.0, 37.5, 36.8, 36.6, 31.1 (2C), 30.4, 29.6, 29.4, 29.3, 29.23, 29.17, 29.0, 28.1, 17.93 (12C), 12.6 (6C); HRMS (FD) *m*/*z*: $[M]^+$ calcd for $C_{21}H_{37}NOSi$, 347.2644; found, 347.2640.

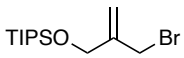


1.7f

Compound 1.7f: According to General Procedure A, the reaction of **1.7a** (90.3 mg, 0.294 mmol) with LDA (309 µL , 0.309 mmol), and 3-bromo-2-methyl-1-propene (38.0 µL, 0.353 mmol) in dry THF (1.5 mL), followed by purification of the obtained crude product by flash column chromatography (Hexane/EtOAc = 50:1) afforded **1.7f** (102 mg, 0.281 mmol, 96%) as a colorless oil: IR (ATR) ν 2942, 2866, 2238, 1670, 1462, 1366, 1197, 996, 881, 861, 682 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.91 (s,1H), 4.84 (s, 1H), 4.81 (br s, 1H), 2.80–2.71 (m, 1H), 2.38 (ddd, 1H, J = 3.5, 8.6, 12.1 Hz), 2.27–2.12 (m, 3H), 2.05–2.02 (m, 1H), 1.84–1.76 (m, 5H), 1.69–1.60 (m, 2H), 1.51–1.29 (m, 2H), 1.16–1.06 (m, 21H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.7, 150.4, 140.5 (2C), 122.1, 122.0, 114.15, 114.12, 101.8, 101.4, 41.0, 40.8, 38.3, 37.9, 31.22, 31.20, 30.6, 29.7, 29.4, 29.2, 29.1, 28.1, 27.9, 27.9, 22.04, 22.02, 18.0 (12C), 12.6 (6C); HRMS (FD) *m*/*z*: $[M]^+$ calcd for $C_{22}H_{39}NOSi$, 361.2801; found, 361.2819.

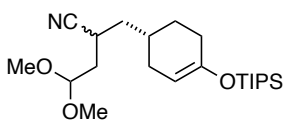


1.7g



1.S1

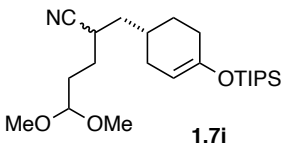
Compound 1.7g: According to General Procedure A, the reaction of **1.7a** (95.2 mg, 0.310 mmol) with LDA (325 µL , 0.325 mmol), and allyl bromide **1.S1**[33] (114 mg, 0.372 mmol) in dry THF (1.6 mL), followed by purification of the obtained crude product by flash column chromatography (Hexane/EtOAc = 100:0 to 50:1) afforded **1.7g** (156 mg, 0.293 mmol, 94%) as a colorless oil: IR (ATR) ν 2942, 2866, 2238, 1670, 1463, 1245, 1199, 1092, 1067, 996, 881, 805, 681 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.19 (s, 1H), 4.99 (s, 1H), 4.81 (br s, 1H), 4.23 (dd, 1H, J = 4.6, 13.8 Hz), 4.19 (dd, 1H, J = 3.5, 13.8 Hz), 2.91–2.82 (m, 1H), 2.37 (d, 2H, J = 7.4 Hz), 2.19–2.15 (m, 2H), 2.05–2.02 (m, 1H), 1.82–1.74 (m, 2H), 1.68–1.62 (m, 1H), 1.53–1.45 (m, 1H), 1.34–1.26 (m, 2H), 1.14–1.05 (m, 42H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.7, 150.4, 143.8 (2C), 122.1, 122.0, 112.93, 112.85, 101.8, 101.5, 66.1, 66.0, 38.6, 38.2, 36.3, 36.2, 31.2 (2C), 30.5, 29.7, 29.4, 29.2, 29.1, 28.40, 28.35, 28.1, 18.0 (24C), 12.6 (6C), 11.9 (6C); HRMS (FD) *m*/*z*: $[M]^+$ calcd for $C_{31}H_{59}NO_2Si_2$, 533.4084; found, 533.4092.



1.7h

Compound 1.7h: According to General Procedure A, the reaction of **1.7a** (63.7 mg, 0.207 mmol) with LDA (218 µL , 0.218 mmol) and HMPA (54.0 µL, 0.311 mmol), and bromoacetaldehyde dimethyl acetal (36.4 µL, 0.311 mmol) in dry THF (1.0 mL), followed by purification of

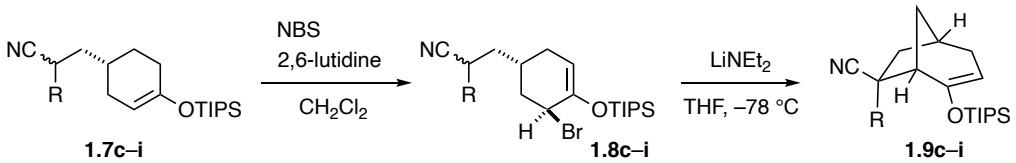
the obtained crude product by flash column chromatography (Hexane/EtOAc = 100:0 to 10:1) afforded **1.7h** (64.4 mg, 0.163 mmol, 81%) as a pale yellow oil: IR (ATR) ν 2942, 2866, 2238, 1670, 1463, 1239, 1195, 1061, 881 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.81 (br s, 1H), 4.57–4.55 (m, 1H), 3.38 (s, 3H), 3.36 (s, 3H), 2.78–2.69 (m, 1H), 2.20–2.12 (m, 2H), 2.05–2.02 (m, 1H), 1.91–1.75 (m, 4H), 1.70–1.64 (m, 2H), 1.50–1.30 (m, 2H), 1.18–1.06 (m, 21H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.6, 150.4, 121.82, 121.75, 102.44
(2C), 101.7, 101.5, 54.13, 54.10, 53.5 (2C), 38.7, 38.2, 35.9, 35.7, 31.1, 30.4, 29.5, 29.4, 29.2, 29.0, 28.1 (2C), 25.3, 25.2, 18.0 (12C), 12.6 (6C); HRMS (FD) *m*/*z*: $[M]^+$ calcd for $C_{22}H_{41}NO_3Si$, 395.2856; found, 395.2848.



1.7i

Compound 1.7i: According to General Procedure A, the reaction of **1.7a** (91.2 mg, 0.297 mmol) with LDA (312 μL, 0.312 mmol), and 3-bromopropionaldehyde dimethyl acetal (48.0 μL, 0.356 mmol) in dry THF (1.5 mL), followed by purification of the obtained crude product by flash column chromatography (Hexane/EtOAc = 100:0 to 10:1) afforded **1.7i** (121 mg, 0.294 mmol, 99%) as a pale yellow oil: IR (ATR) ν 2926, 2866, 2238, 1670, 1462, 1365, 1240, 1196, 1070, 881 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.80 (br s, 1H), 4.37 (t, 1H, *J* = 5.2 Hz), 3.33 (s, 3H), 3.32 (s, 3H), 2.68–2.59 (m, 1H), 2.18–2.12 (m, 2H), 2.05–2.01 (br d, 1H), 1.89–1.70 (m, 4H), 1.68–1.63 (m, 4H), 1.49–1.24 (m, 2H), 1.18–1.06 (m, 21H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.6, 150.4, 122.1, 122.0, 103.8 (2C), 101.7, 101.5, 53.2 (2C), 52.8 (2C), 38.6, 38.2, 31.2 (2C), 30.4, 30.0, 29.52, 29.46, 29.25, 29.16, 29.1 (2C), 28.2 (2C), 27.7, 27.5, 17.9 (12C), 12.6 (6C); HRMS (FD) *m*/*z*: $[M]^+$ calcd for $C_{23}H_{43}NO_3Si$, 409.3012; found, 409.3016.

General Procedure B for Intramolecular alkylation.

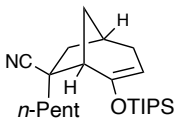


1.7c–i **1.8c–i** **1.9c–i**

To a solution of nitrile **1.7c–i** (1.0 equiv.) in CH_2Cl_2 (0.2 M) was added 2,6-lutidine (2.0 equiv.) followed by NBS (1.0 equiv.) at 0 °C. In the case of **1.7e–g**, NBS was added in five portions at –78 °C, then the mixture was allowed to warm up to 0 °C. After stirring for 10 min at 0 °C, the reaction was quenched with saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$ solution. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. The residue was filtered through a short pad of silica gel (Hexane/EtOAc = 20:1, using silica gel pretreated with *N*,*N*-

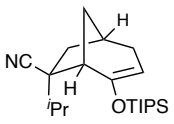
dimethylaniline: General Information in page 17) to remove 2,6-lutidine. The obtained crude bromo nitrile **1.8c–i** was used for the next step without further purification.

To a solution of the above crude bromo nitrile **1.8c–i** (1.0 equiv.) in dry THF (0.05 M) was added $LiNEt_2$ (1.0 M in THF-Hexane, 1.5 equiv.) at –78 °C. After stirring for 30 min, the reaction was quenched with saturated $NaHCO_3$ solution. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash column chromatography (using silica gel pretreated with *N*,*N*-dimethylaniline: General Information in page 17) afforded bicyclic product **1.9c–i**.



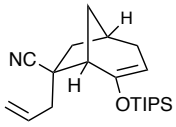
1.9c

Compound 1.9c: According to General Procedure B, the reaction of **1.7c** (56.4 mg, 0.149 mmol) with NBS (26.6 mg, 0.149 mmol) in CH_2Cl_2 (0.75 mL), followed by the reaction of the crude **1.8c** (52.8 mg) with $LiNEt_2$ (174 μL, 0.174 mmol) in dry THF (2.3 mL) afforded a crude product including **1.9c**. Purification of the crude product by flash column chromatography (Hexane/EtOAc = 50:1) afforded **1.9c** (36.2 mg, 96.4 μmol, single diastereomer, 65%) as a colorless oil: IR (ATR) ν 2943, 2866, 2227, 1656, 1463, 1352, 1187, 997, 881 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.58 (br s, 1H), 2.48 (d, 1H, *J* = 3.1 Hz), 2.41–2.37 (m, 2H), 2.28 (d, 1H, *J* = 16.6 Hz), 2.16 (ddd, 1H, *J* = 3.1, 3.1, 11.5 Hz), 1.82–1.65 (m, 4H), 1.51–1.42 (m, 1H), 1.37–1.26 (m, 6H), 1.17–1.05 (m, 21H), 0.88 (t, 3H, *J* = 6.9 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.4, 125.9, 99.5, 50.3, 49.7, 43.7, 35.7, 34.6, 33.8, 32.4, 32.1, 26.6, 22.5, 18.00 (3C), 17.96 (3C), 14.0, 12.5 (3C); HRMS (FD) *m*/*z*: $[M]^+$ calcd for $C_{23}H_{41}NOSi$, 375.2957; found, 375.2940.



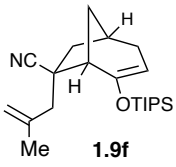
1.9d

Compound 1.9d: According to General Procedure B, the reaction of **1.9d** (51.4 mg, 0.147 mmol) with NBS (26.2 mg, 0.147 mmol) in CH_2Cl_2 (0.74 mL), followed by the reaction of the crude **1.8d** (49.1 mg) with $LiNEt_2$ (173 μL, 0.173 mmol) in dry THF (2.3 mL) afforded a crude product including **1.9d**. Purification of the crude product by flash column chromatography (Hexane/EtOAc = 50:1) afforded **1.9d** (37.1 mg, 0.107 mmol, single diastereomer, 71%) as a colorless oil: IR (ATR) ν 2944, 2867, 2228, 1655, 1464, 1245, 1188, 1015, 986, 881 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.58 (br s, 1H), 2.56 (d, 1H, *J* = 3.5 Hz), 2.42 (br s, 1H), 2.36 (dd, 1H, *J* = 7.5, 13.8 Hz), 2.27 (ddd, 1H, *J* = 2.9, 2.9, 16.7 Hz), 2.20 (ddd, 1H, *J* = 3.5, 3.5, 11.5 Hz), 1.94 (sept, 1H, *J* = 6.3 Hz), 1.78–1.73 (m, 2H), 1.44 (d, 1H, *J* = 13.8 Hz), 1.21 (d, 3H, *J* = 6.3 Hz), 1.19–1.04 (m, 24H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.4, 124.4, 99.4, 57.3, 48.6, 42.7, 34.9, 34.1, 33.0, 32.2, 20.3, 19.7, 18.0 (6C), 12.6 (3C); HRMS (FD) *m*/*z*: $[M]^+$ calcd for $C_{21}H_{37}NOSi$, 347.2644; found, 347.2649.



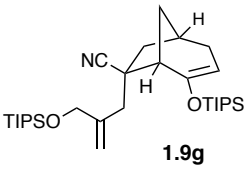
1.9e

Compound 1.9e: According to General Procedure B, the reaction of **1.7e** (70.7 mg, 0.203 mmol) with NBS (36.2 mg, 0.203 mmol) in CH_2Cl_2 (1.0 mL), followed by the reaction of the crude **1.8e** (67.5 mg) with $LiNEt_2$ (304 μL, 0.304 mmol) in dry THF (3.1 mL) afforded a crude product including **1.9e**. Purification of the crude product by flash column chromatography (Hexane/EtOAc = 50:1) afforded **1.9e** (41.5 mg, 0.120 mmol, single diastereomer, 62%) as a colorless oil: IR (ATR) ν 2944, 2867, 2229, 1656, 1463, 1253, 1187, 996, 881 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.02–5.93 (m, 1H), 5.22 (d, 1H, J = 16.0 Hz), 5.17 (d, 1H, J = 10.3 Hz), 4.63 (br s, 1H), 2.63 (dd, 1H, J = 6.3, 14.3 Hz), 2.50 (d, 1H, J = 3.5 Hz), 2.43–2.34 (m, 3H), 2.30 (d, 1H, J = 16.6 Hz), 2.18 (ddd, 1H, J = 3.5, 3.5, 11.5 Hz), 1.81–1.75 (m, 2H), 1.44 (d, 1H, J = 13.8 Hz), 1.19–1.05 (m, 21H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.2, 133.8, 125.2, 118.6, 99.8, 49.94, 49.86, 42.9, 39.8, 34.5, 33.7, 32.5, 17.93 (3C), 17.90 (3C), 12.4 (3C); HRMS (FD) *m/z*: $[M]^+$ calcd for $C_{21}H_{35}NOSi$, 345.2488; found, 345.2475.



1.9f

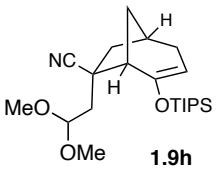
Compound 1.9f: According to General Procedure B, the reaction of **1.7f** (90.3 mg, 0.250 mmol) with NBS (44.4 mg, 0.250 mmol) in CH_2Cl_2 (1.3 mL), followed by the reaction of the crude **1.8f** (74.3 mg) with $LiNEt_2$ (255 μL, 0.255 mmol) in dry THF (3.4 mL) afforded a crude product including **1.9f**. Purification of the crude product by flash column chromatography (Hexane/EtOAc = 50:1) afforded **1.9f** (56.9 mg, 0.158 mmol, single diastereomer, 62%) as a colorless oil: IR (ATR) ν 2944, 2867, 2228, 1656, 1463, 1188, 996, 882 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.93 (s, 1H), 4.89 (s, 1H), 4.61 (br s,1H), 2.65 (d, 1H, J = 14.9 Hz), 2.50 (d, 1H, J = 3.5 Hz), 2.45 (br s, 1H), 2.41–2.38 (m, 2H), 2.30 (d, 1H, J = 16.6 Hz), 2.21 (ddd, 1H, J = 3.5, 3.5, 11.5 Hz), 1.84 (s, 3H), 1.79–1.75 (m, 2H), 1.54 (d, 1H, J = 13.8 Hz), 1.19–1.05 (m, 21H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.3, 141.7, 125.8, 114.2, 99.7, 51.5, 48.7, 43.0, 42.8, 34.2, 33.8, 32.8, 23.7, 18.00 (3C), 17.97 (3C), 12.5 (3C); HRMS (FD) *m/z*: $[M]^+$ calcd for $C_{22}H_{37}NOSi$, 359.2644; found, 359.2660.



1.9g

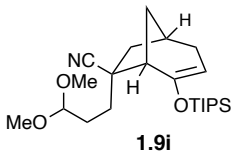
Compound 1.9g: According to General Procedure B, the reaction of **1.7g** (168 mg, 0.314 mmol) with NBS (55.9 mg, 0.314 mmol) in CH_2Cl_2 (1.6 mL), followed by the reaction of the crude **1.8g** (120 mg) with $LiNEt_2$ (300 μL, 0.300 mmol) in dry THF (4 mL) afforded a crude product including **1.9g**. Purification of the crude product by flash column chromatography (Hexane/EtOAc = 50:1) afforded **1.9g** (91.1 mg, 0.171 mmol, single diastereomer, 54%) as a colorless oil: IR (ATR) ν 2943, 2866, 2228, 1656, 1463, 1190, 1091, 996, 881 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.28 (s, 1H), 5.09 (s, 1H), 4.62 (br s, 1H), 4.28 (d, 1H, J = 13.8 Hz), 4.21 (d, 1H, J = 13.8 Hz), 2.62 (d, 1H, J = 14.9 Hz), 2.53 (d, 1H, J = 14.9 Hz), 2.49 (d, 1H, J = 3.4 Hz), 2.45 (br s, 1H), 2.39 (dd, 1H, J = 7.5 Hz, 13.8 Hz), 2.30 (d, 1H, J = 16.6 Hz), 2.20 (ddd, 1H, J = 3.4, 3.4, 11.5 Hz), 1.79–1.75 (m, 2H),

1.63 (d, 1H, J = 13.8 Hz), 1.19–1.05 (m, 42H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.3, 144.7, 125.7, 112.8, 99.8, 66.3, 51.7, 49.0, 42.8, 37.8, 34.2, 33.8, 33.0, 18.0 (12C), 12.5 (3C), 12.0 (3C); HRMS (FD) *m*/*z*: $[M]^+$ calcd for $C_{31}H_{57}NO_2Si_2$, 531.3928; found, 531.3921.



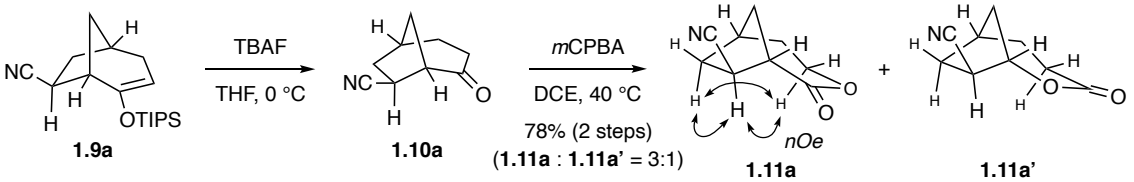
1.9h

Compound 1.9h: According to General Procedure B, the reaction of **1.7h** (64.4 mg, 0.163 mmol) with NBS (29.0 mg, 0.163 mmol) in CH_2Cl_2 (0.82 mL), followed by the reaction of the crude **1.8h** (61.2 mg) with $LiNEt_2$ (195 μL, 0.195 mmol) in dry THF (2.6 mL) afforded a crude product including **1.9h**. Purification of the crude product by flash column chromatography (Hexane/EtOAc = 100:1 to 10:1) afforded **1.9h** (37.6 mg, 95.5 μmol, single diastereomer, 59%) as a pale yellow oil: IR (ATR) ν 2944, 2863, 2839, 2230, 1656, 1463, 1352, 1190, 1066, 942, 880 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.71 (dd, 1H, J = 4.0, 7.5 Hz), 4.61 (br s, 1H), 3.37 (s, 3H), 3.33 (s, 3H), 2.46–2.37 (m, 3H), 2.28 (d, 1H, J = 16.6 Hz), 2.20–2.14 (m, 2H), 2.04 (dd, 1H, J = 7.5, 14.4 Hz), 1.78–1.74 (m, 2H), 1.61 (d, 1H, J = 14.4 Hz), 1.18–1.05 (m, 21H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.0, 125.2, 103.2, 99.9, 53.8, 52.6, 51.1, 46.5, 43.6, 38.1, 34.0, 33.8, 32.8, 18.0 (3C), 17.9 (3C), 12.44 (3C); HRMS (FD) *m*/*z*: $[M]^+$ calcd for $C_{22}H_{39}NO_3Si$, 393.2699; found, 393.2701.



1.9i

Compound 1.9i: According to General Procedure B, the reaction of **1.7i** (103 mg, 0.252 mmol) with NBS (44.9 mg, 0.252 mmol) in CH_2Cl_2 (1.3 mL), followed by the reaction of the crude **1.8i** (93.2 mg) with $LiNEt_2$ (287 μL, 0.287 mmol) in dry THF (3.8 mL) afforded a crude product including **1.9i**. Purification of the crude product by flash column chromatography (Hexane/EtOAc = 20:1) afforded **1.9i** (67.3 mg, 0.165 mmol, single diastereomer, 66%) as a pale yellow oil: IR (ATR) ν 2943, 2867, 2228, 1656, 1463, 1353, 1187, 1057, 881 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.59 (br s, 1H), 4.35 (t, 1H, J = 4.6 Hz), 3.30 (s, 3H), 3.29 (s, 3H), 2.47 (d, 1H, J = 4.0 Hz), 2.42–2.37 (m, 2H), 2.28 (d, 1H, J = 16.6 Hz), 2.16 (ddd, 1H, J = 4.0, 4.0, 11.5 Hz), 2.03–1.96 (m, 1H), 1.89–1.73 (m, 5H), 1.39 (d, 1H, J = 12.6 Hz), 1.18–1.05 (m, 21H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.2, 125.5, 104.0, 99.5, 52.7, 52.3, 49.8, 49.7, 43.4, 34.6, 33.8, 32.5, 30.8, 29.8, 18.0 (3C), 17.9 (3C), 12.5 (3C); HRMS (FD) *m*/*z*: $[M]^+$ calcd for $C_{23}H_{41}NO_3Si$, 407.2856; found, 407.2853.

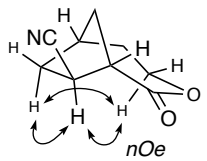


1.9a **1.10a** **1.11a** **1.11a'**

Lactone 1.11a: To a solution of bicyclic product **1.9a** (14.8 mg, 48.4 μmol) in THF (0.25 mL) was added tetra-*n*-butylammonium fluoride (TBAF) (1.0 M in THF, 75.0 μL, 75.0 μmol) at 0 °C. After

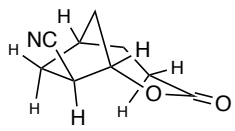
stirring for 10 min, the reaction was quenched with brine (0.5 mL). After the layers were separated, the aqueous layer was extracted with EtOAc (1 mL × 3). The combined organic layers were washed with H_2O, dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. The obtained crude ketone **1.10a** (7.6 mg) was used for the next step without further purification.

To a solution of the above crude ketone **1.10a** (7.6 mg) in DCE (0.25 mL) was added *m*CPBA (29.4 mg, 119 μmol) in one portion. The reaction mixture was warmed up to 40 °C and stirred for 1 h. After cooling to room temperature, 2-methyl-2-butene (51 μL, 0.48 mmol) was added to the mixture, and the mixture was stirred for further 30 min. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (0.5 mL). After the layers were separated, the aqueous layer was extracted with EtOAc (1 mL × 3). The combined organic layers were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash column chromatography (Hexane/EtOAc = 20:1 to 3:2) afforded lactone **1.11a** and **1.11a'** as a regioisomeric mixture (6.2 mg, 38 μmol, **1.11a**:**1.11a'** = 3:1, 78% for 2 steps). Part of the regioisomer could be separated by two times of column chromatography.



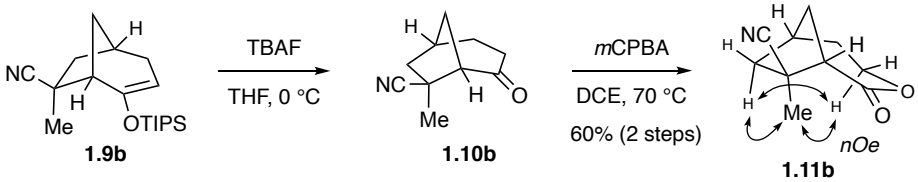
1.11a

Major isomer 1.11a: IR (ATR) ν 2945, 2240, 1715, 1485, 1135, 1060, 896 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.26 (ddd, 1H, *J* = 3.4, 3.4, 13.7 Hz), 4.06 (dd, 1H, *J* = 13.2, 13.7 Hz), 3.60 (d, 1H, *J* = 8.0 Hz), 3.30 (dd, 1H, *J* = 8.0, 8.0 Hz), 2.80 (d, 1H, *J* = 5.8 Hz), 2.29–2.23 (m, 2H), 2.21–2.14 (m, 1H), 2.01–1.96 (m, 2H), 1.78–1.74 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.4, 121.4, 65.9, 51.0, 37.6, 36.2, 35.8, 34.0, 29.4; HRMS (FD) *m*/*z*: $[M]^+$ calcd for $C_9H_{11}NO_2$, 165.0790; found, 165.0788.



1.11a'

Minor isomer 1.11a': IR (ATR) ν 2946, 2865, 2240, 1724, 1446, 1398, 1165, 1031, 875 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.04 (d, 1H, *J* = 6.3 Hz), 3.20 (dd, 1H, *J* = 9.2, 9.2 Hz), 2.85–2.79 (m, 2H), 2.34–2.22 (m, 4H), 1.96 (d, 1H, *J* = 14.9 Hz), 1.76–1.71 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.7, 120.4, 82.8, 40.5, 37.3, 36.1, 35.8, 33.2, 28.0; HRMS (FD) *m*/*z*: $[M]^+$ calcd for $C_9H_{11}NO_2$, 165.0790; found, 165.0797.

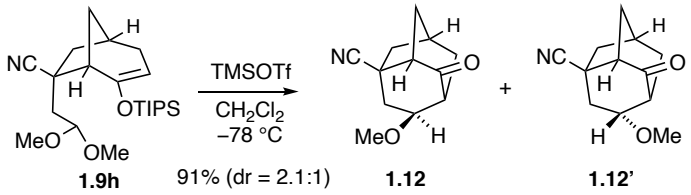


1.9b **1.10b** **1.11b**

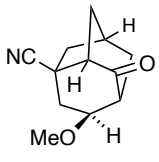
Lactone 1.11b: To a solution of bicyclic product **1.9b** (64.2 mg, 0.201 mmol) in THF (1 mL) was added TBAF (1.0 M in THF, 0.220 mL, 0.220 mmol) at 0 °C. After stirring for 10 min, the reaction was quenched with brine (1 mL). After the layers were separated, the aqueous layer was extracted with EtOAc (1 mL × 3). The combined organic layers were washed with H_2O, dried over $MgSO_4$,

filtrated, and concentrated under reduced pressure. The obtained crude ketone **1.10b** was used for the next step without further purification.

To a solution of the above crude ketone **1.10b** in DCE (1 mL) was added *m*CPBA (74.0 mg, 0.302 mmol) in one portion. The reaction mixture was warmed up to 70 °C and stirred for 7 h. After cooling to room temperature, 2-methyl-2-butene (0.215 mL, 2.01 mmol) was added to the reaction mixture, and the mixture was stirred for further 30 min. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (1 mL). After the layers were separated, the aqueous layer was extracted with EtOAc (1 mL × 3). The combined organic layers were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash column chromatography (Hexane/EtOAc = 20:1 to 3:2) afforded lactone **1.11b** (21.6 mg, 0.121 mmol, 60% for 2 steps) as a white solid. m.p. 70–72 °C (Hexane-EtOAc); IR (ATR) 2940, 2870, 2234, 1717, 1462, 1161, 1041, 904 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.30 (ddd, 1H, *J* = 4.0, 4.0, 13.8 Hz), 4.14 (ddd, 1H, *J* = 2.3, 13.8, 13.8 Hz), 3.57 (d, 1H, *J* = 6.9 Hz), 2.85 (m, 1H), 2.73 (dd, 1H, *J* = 8.6, 14.9 Hz), 2.31 (ddd, 1H, *J* = 6.9, 6.9, 14.3 Hz), 2.07–2.00 (m, 2H), 1.79 (d, 1H, *J* = 14.9 Hz), 1.71–1.68 (m, 1H), 1.62 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.8, 125.4, 65.4, 57.8, 42.3, 40.9, 36.3, 35.6, 34.2, 21.7; HRMS (FD) *m*/*z*: $[M]^+$ calcd for $C_{10}H_{13}NO_2$, 179.0946; found, 179.0946.



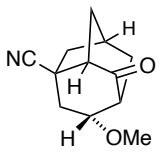
Tricyclic ketone 1.12: To a solution of nitrile **1.9h** (37.6 mg, 95.5 μmol) in CH_2Cl_2 (0.5 mL) was added TMSOTf (26.0 μL, 143 μmol) at –78 °C. After stirring for 2.5 h, the reaction was quenched with saturated aqueous $NaHCO_3$ solution (1 mL). After the layers were separated, the aqueous layer was extracted with EtOAc (1 mL × 3). The combined organic layers were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash column chromatography (Hexane/EtOAc = 20:1 to 1:1) to afforded ketone **1.12** (12.2 mg, 59.4 μmol, 62%) as a white solid and ketone **1.12'** (5.6 mg, 27.3 μmol, 29%) as a colorless oil.



1.12

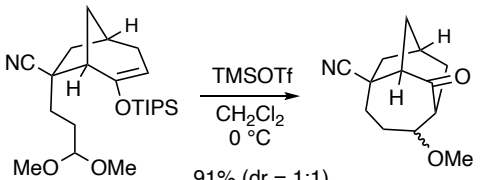
Major isomer 1.12: m.p. 126–129 °C (Hexane-AcOEt); IR (ATR) ν 2947, 2871, 2828, 2235, 1725, 1450, 1362, 1197, 1101, 1086, 977 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.77 (dd, 1H, *J* = 8.0, 8.1 Hz), 3.30 (s, 3H), 3.09 (d, 1H, *J* = 6.3 Hz), 2.68–2.62 (m, 2H), 2.48 (br s, 1H), 2.41–2.33 (m, 2H), 2.11–2.06 (m, 1H), 2.06 (dd, 1H, *J* = 2.3, 12.6 Hz), 1.98 (d, 1H, *J* = 12.6 Hz), 1.80 (d, 1H, *J* = 13.8 Hz), 1.71 (dd, 1H, *J*

= 8.1, 13.8 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.5, 123.5, 82.6, 57.9, 56.5, 50.3, 42.1, 42.0, 37.7, 37.6, 36.5, 35.4; HRMS (FD) *m/z*: $[M]^+$ calcd for $C_{12}H_{15}NO_2$, 205.1103; found, 205.1108.



1.12'

Minor isomer 1.12': IR (ATR) ν 2940, 2872, 2828, 2359, 2341, 2235, 1724, 1439, 1275, 1189, 1098, 983, 835 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.75 (dd, 1H, *J* = 7.5, 7.5 Hz), 3.26 (s, 3H), 2.98 (d, 1H, *J* = 6.3 Hz), 2.89 (dd, 1H, *J* = 7.5, 7.5 Hz), 2.45–2.41 (m, 2H), 2.34–2.28 (m, 2H), 2.21 (d, 1H, *J* = 15.5 Hz), 2.16 (d, 1H, *J* = 13.2 Hz), 2.05 (dd, 1H, *J* = 7.5, 15.5 Hz), 1.98 (d, 1H, *J* = 12.6 Hz), 1.72–1.68 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.8, 123.6, 77.1, 56.9, 56.5, 48.3, 42.5, 41.8, 40.4, 37.1, 35.1, 30.6; HRMS (FD) *m/z*: $[M]^+$ calcd for $C_{12}H_{15}NO_2$, 205.1103; found, 205.1100.



1.9i **1.13+1.13'**

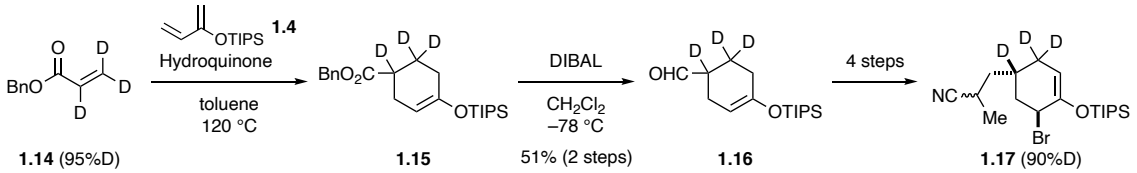
Tricyclic ketone 1.13: To a solution of nitrile **1.9i** (64.8 mg, 0.159 mmol) in CH_2Cl_2 (0.8 mL) was added TMSOTf (43 μL, 0.24 mmol) at –78 °C. Then, the mixture was warmed up to 0 °C and stirred for 30 min. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (1 mL). After the layers were separated, the aqueous layer was extracted with EtOAc (1 mL × 3). The combined organic layers were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash column chromatography (Hexane/EtOAc = 20:1 to 1:1) afforded ketone **1.13** (16.0 mg, 73.0 μmol, 46%) as a white amorphous and ketone **1.13'** (15.8 mg, 72.1 μmol, 45%) as a white amorphous. The stereochemistry in **1.13** and **1.13'** generated in the reaction was not determined.

Less polar isomer 1.13: IR (ATR) ν 2870, 2825, 2360, 2233, 1706, 1456, 1247, 1095, 970, 856 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.28 (s, 3H), 3.22–3.18 (m, 1H), 3.08 (d, 1H, *J* = 5.7 Hz), 3.02 (br d, 1H, *J* = 8.6 Hz), 2.52 (br s, 1H), 2.26–2.22 (m, 3H), 2.07–2.03 (m, 1H), 2.00–1.95 (m, 1H), 1.87–1.78 (m, 3H), 1.76–1.71 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.5, 125.4, 79.9, 59.9, 56.3, 48.2, 39.6, 38.2, 37.3, 34.2, 29.3, 26.4, 26.2; HRMS (FD) *m/z*: $[M]^+$ calcd for $C_{13}H_{17}NO_2$, 219.1259; found, 219.1254.

More polar isomer 1.13': IR (ATR) ν 2934, 2869, 2825, 2231, 1710, 1455, 1246, 1187, 1077, 968, 863 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.36 (s, 3H), 3.33–3.32 (m, 1H), 3.19 (d, 1H, *J* = 5.8 Hz), 3.08 (dd, 1H, *J* = 6.3, 10.3 Hz), 2.52 (d, 1H, *J* = 5.2 Hz), 2.33–2.25 (m, 2H), 2.21 (ddd, 1H, *J* = 1.2,

5.2, 13.8 Hz), 2.14–2.06 (m, 3H), 2.01–1.96 (m, 2H), 1.85 (dd, 1H, *J* = 1.2, 12.6 Hz), 1.47 (d, 1H, *J* = 14.9 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 207.0, 125.8, 78.8, 61.0, 56.5, 47.5, 39.4, 39.1, 37.8, 35.5, 30.4, 29.3, 25.7; HRMS (FD) *m*/*z*: $[M]^+$ calcd for $C_{13}H_{17}NO_2$, 219.1259; found, 219.1262.

Mechanistic investigation with deuterated compound

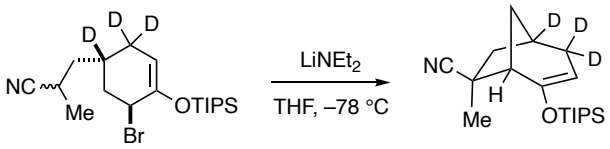


Deuterated Aldehyde 1.17: To a solution of benzyl acrylate **1.14**[27] (95%D, 157 mg, 0.948 mmol) and silyl enol ether **1.4** (322 mg, 1.42 mmol) in toluene (1 mL) was added hydroquinone (5.2 mg, 47 μmol). The reaction mixture was heated in an oil bath to refluxed for 24 h, and then cooled down to room temperature. The solvent was removed under reduced pressure, and the residue was roughly purified by flash column chromatography (SiO_2, Hexane/EtOAc = 50:1). The obtained crude ester **1.15** (249 mg, pale yellow oil) was used for the next step without further purification.

To a solution of the above crude ester (249 mg) in CH_2Cl_2 (3.2 mL) was added diisobutylaluminum hydride (DIBAL) (1.03M in Hexane, 0.687 mL, 0.708 mmol) at –78 °C. After stirring for 40 min at the same temperature, the reaction was quenched with saturated aqueous Rochelle salt solution (5 mL). Then, the mixture was warmed up to room temperature and stirred for 30 min. After the layers were separated, the aqueous layer was extracted with Et_2O (3 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash column chromatography (Hexane/EtOAc = 100:0 to 50:1, using silica gel pretreated with *N*,*N*-dimethylaniline: General Information in page 17) afforded deuterated aldehyde **1.16** (142 mg, 0.497 mmol, 51% for 2 steps, 90%D, trace amount of ester **1.15** was contained) as a colorless oil; IR (ATR) ν 2943, 2866, 1726, 1668, 1464, 1354, 1189, 1071, 881 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.69 (s, 1H), 4.90–4.88 (m, 1H), 2.42–2.39 (m, 0.1H), 2.26 (br s, 2H), 2.13 (br s, 2H), 2.00–1.95 (m, 0.1H), 1.81–1.75 (m, 0.1H), 1.19–1.06 (m, 21H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.6, 150.8, 100.9, 27.9, 23.2, 17.9 (6C), 12.6 (3C) (2C missing); HRMS (FD) *m*/*z*: $[M]^+$ calcd for $C_{16}H_{27}D_3O_2Si$, 285.2203; found, 285.2216.

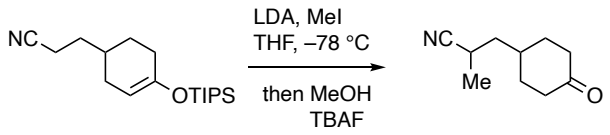
Deuterated Bromonitrile **1.17** was prepared by the same procedure which was used to synthesize **1.8b** from aldehyde **1.5**. The reaction of **1.16** (131 mg, 0.459 mmol) afforded bromonitrile **1.17** (79.9 mg, 0.198 mmol, 43% for 4 steps, 90%D) as colorless oil: IR (ATR) ν 2943, 2866, 2232, 1651, 1462, 1369, 1217, 995, 881 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.93 (s, 1H), 4.59 (br s, 1H), 2.74–2.64 (m, 1H), 2.35–2.28 (m, 0.2H), 2.25–2.17 (m, 1H), 1.91–1.81 (m, 1.1H), 1.74–1.69 (m, 1H), 1.51 (dd, 1H, *J* = 6.5, 14.0 Hz), 1.36 (d, 3H, *J* = 7.0 Hz), 1.23–1.07 (m, 21H); ^{13}C NMR (126 MHz, $CDCl_3$) δ

149.72, 149.67, 123.0, 122.9, 104.7 (2C), 50.3 (2C), 39.7, 39.5, 39.0, 38.8, 23.2, 22.9, 18.3, 18.1, 18.01 (6C), 18.00 (6C), 12.6 (6C) (4C missing); HRMS (FD) *m/z*: $[M]^+$ calcd for $C_{19}H_{31}D_3BrNOSi$, 402.1781; found, 402.1767.



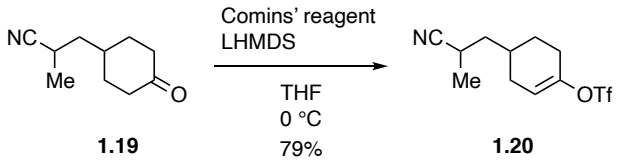
1.17 (90%D) **1.18** (90%D)

Deuterated bicyclic compound **1.18** : According to the cyclization procedure of **1.8b**, the reaction of **1.15** (39.1 mg, 96.9 μmol) with $LiNEt_2$ (145 μL, 145 μmol) afforded a crude product including **1.17**. Purification of the crude product by flash column chromatography (Hexane/EtOAc = 100:0 to 99:1, using silica gel pretreated with *N*,*N*-dimethylaniline: General Information in page 17) afforded **1.18** (20.0 mg, 62.0 μmol, single diastereomer, 64%, 90%D) as a colorless oil: IR (ATR) ν 2943, 2867, 2229, 1654, 1462, 1351, 1192, 996, 882 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.60 (s, 1H), 2.46 (d, 1H, *J* = 13.5 Hz), 2.41 (d, 1H, *J* = 4.0 Hz), 2.27 (d, 0.1H, *J* = 16.6 Hz), 2.13 (dd, 1H, *J* = 4.0, 11.5 Hz), 1.78 (d, 1H, *J* = 11.5 Hz), 1.77–1.73 (m, 0.1H), 1.51 (s, 3H), 1.37 (d, 1H, *J* = 13.5 Hz), 1.20–1.05 (m, 21H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.4, 126.8, 99.4, 51.0, 44.7, 44.2, 34.8, 22.1, 18.0 (3C), 17.9 (3C), 12.5 (3C) (2C missing); HRMS (FD) *m/z*: $[M]^+$ calcd for $C_{19}H_{30}D_3NOSi$, 322.2520; found, 322.2511.

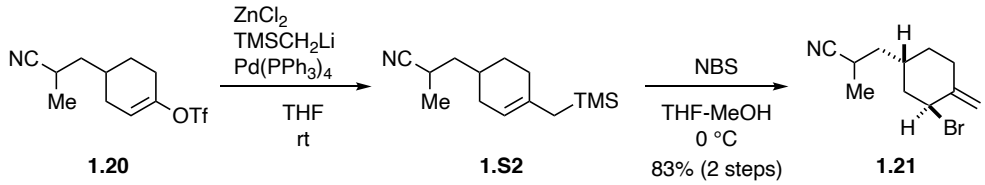


1.7a 86% **1.19**

ketonitrile 1.19: To a solution of nitrile **1.7a** (174.8 mg, 0.568 mmol) in THF (2.8 mL) was added LDA (1.0 M in THF, 0.60 mL, 0.60 mmol) at –78 °C. After being stirred for 30 min at the same temperature, MeI (42.4 μL, 0.68 mmol) was added. The reaction mixture was stirred for 15 min, MeOH (23 μL, 0.57 mmol) was added and warmed up to 0 °C. To the solution was added TBAF (1 M in THF, 0.68 mL, 0.68 mmol) at the same temperature. After stirring for 10 min, the reaction mixture was quenched with brine. After the layers were separated, the aqueous layer was extracted with EtOAc (50 mL × 3). The combined organic layers were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash column chromatography (Hex/EtOAc = 4:1 to 3:2) afforded keto nitrile **1.19** (80.6 mg, 0.49 mmol, 86%) as a colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 2.75 (sext, 1H , *J* = 6.9 Hz), 2.412.37 (m, 4H), 2.162.00 (m, 3H), 1.76 (ddd, 1H, *J* = 5.1 Hz, 10.9 Hz, 14.3 Hz), 1.52–1.40 (m, 3 H), 1.37 (d, 3H, *J* = 6.9 Hz).

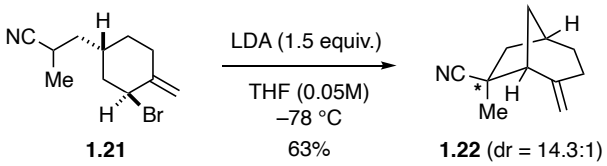


enol triflate 1.20: To a solution of ketonitrile **1.19** (25.2 mg, 0.153 mmol) and Comins reagent (67.6 mg, 0.17 mmol) in THF (0.80 mL) was added LHMDS (1 M in THF, 0.17 mL, 0.17 mmol) at –78 °C. After stirring for 2 h at the same temperature, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution. After the layers were separated, the aqueous layer was extracted with EtOAc (1 ml × 3). The combined organic layers were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash column chromatography (Hexane/EtOAc = 50:1 to 4:1) afforded enol triflate **1.20** (36.0 mg, 0.12 mmol, 79%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74 (d, 1H, *J* = 2.3 Hz), 2.73−2.64 (m, 1H), 2.50−2.40 (m, 1H), 2.39−2.30 (m, 2H), 1.97–1.85 (m, 3H), 1.73–1.66 (m, 1H), 1.51–1.45 (m, 2H), 1.37 (d, 3H, *J* = 7.5 HZ), 1.36 (d, 3H, *J* = 6.9 Hz).



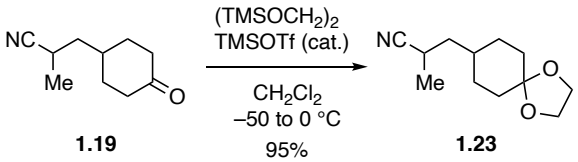
Allyl bromide 1.21: To a solution of $ZnCl_2$ (0.5 M in THF, 0.17 mL, 85 μmol) in THF (total 0.37 mL) was added $TMSCH_2Li$ (1.0 M in pentane, 0.17 mL, 170 μL) at room temperature. The mixture was stirred for 30 min, the solution of enol triflate **1.20** (18.0 mg, 61 μmol) and $Pd(PPh_3)_4$ (10.4 mg, 9.0 μmol) in THF (0.50 mL) was added. After stirring for 1 h at the same temperature, the reaction mixture was quenched with 0.2 M HCl solution. After the layers were separated, the aqueous layer was extracted with Et_2O (1 ml × 3). The combined organic layers were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. The obtained crude allylsilane **1.S2** was used for the next step without further purification.

To a solution of the above crude allylsilane **1.S2** (15.1 mg) in THF (60 μL) and MeOH (480 μL) was added NBS (21.5 mg, 0.12 mmol) at 0 °C. After stirring for 20 min at the same temperature, the reaction mixture was quenched with a saturated aqueous $Na_2S_2O_3$ solution. After the layers were separated, the aqueous layer was extracted with Et_2O (1 ml × 3). The combined organic layers were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash column chromatography (Hexane/EtOAc = 100:0 to 20:1) allyl bromide **1.21** (12.2 mg, 50.4 μmol, 83% for 2 steps) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.01 (s, 1H), 4.96 (br-s, 1H), 4.81 (s, 1H), 2.72−2.63 (m, 2H), 2.31–2.19 (m, 3H), 1.93−1.91 (m, 1H), 1.66–1.57 (m, 2H), 1.44–1.38 (m, 1H), 1.35 (d, 3H, *J* = 6.9 Hz), 1.13−1.00 (m, 1H).



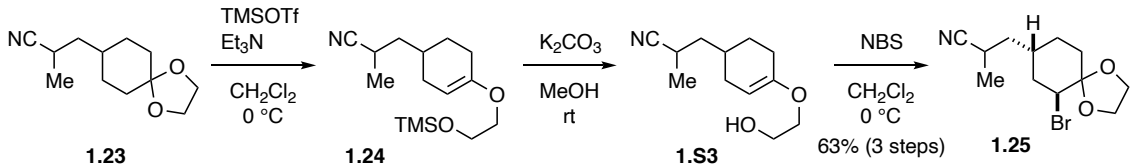
1.21 **1.22** (dr = 14.3:1)

alkene 1.22: To a solution of allyl bromide **1.21** (12.2 mg, 50.4 μmol) in THF (1 mL) was added LDA (1.0 M in THF, 76 μL, 76 μmol) at –78 °C. After stirring for 30 min, the mixture was warmed up to 0 °C and stirred another 10 min. The reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution. After the layers were separated, the aqueous layer was extracted with Et_2O (1 ml × 3). The combined organic layers were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash column chromatography (Hexane/EtOAc = 100:0 to 20:1) afforded alkene **1.22** (5.1 mg, 32 μmol, 14.3:1 diastereomer mixture, 63%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.75 (s, 1H), 4.71 (s, 1H), 2.80 (d, 1H, J = 4.6 Hz), 2.60 (d, 0.07H, J = 4.5 Hz), 2.51 −2.47 (m, 2H), 2.29–2.20 (m, 2H), 2.15–2.08 (m, 1H), 1.58–1.52 (m, 4H), 1.44 (s, 0.21H), 1.37 (s, 3H).



1.19 **1.23**

Ketal 1.23: To a solution of ketone **1.19** (35.4 mg, 0.214 mmol) and 1,2-bis(trimethylsilyloxy)ethane (63.2 μL, 0.257 mmol) in CH_2Cl_2 (1.1 mL) was added TMSOTf (7.7μL, 43 μmol) at –78 °C. The reaction mixture was warmed up to –50 °C over 1 h, and then quenched with pyridine (110 μL) and a saturated aqueous $NaHCO_3$ solution. After the layers were separated, the aqueous layer was extracted with EtOAc (1 ml × 3). The combined organic layers were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash column chromatography (Hexane/EtOAc = 20:1 to 4:1) afforded Ketal **1.23** (42.5 mg, 0.203 mmol, 95%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.97 (ddd, 4H, J = 4.0 Hz, 9.7 Hz, 15.5 Hz), 2.71–2.63 (m, 1H), 1.79 −1.70 (m, 4H), 1.66–1.53 (m, 3H), 1.40−1.34 (m, 2H), 1.33 (d, 3H, J = 6.9 Hz), 1.29−1.17 (m, 2H).



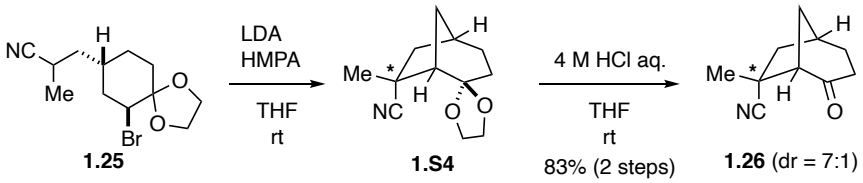
1.23 **1.24** **1.S3** **1.25**

Bromonitrile 1.25: To a solution of Ketal **1.23** (42.5 mg, 0.203 mmol) and Et_3N (85 μL, 0.61 mmol) in CH_2Cl_2 was added TMSOTf (55 μL, 0.31 mmol) at 0 °C. After stirring for 15 min, the reaction

mixture was quenched with a saturated aqueous $NaHCO_3$ solution. After the layers were separated, the aqueous layer was extracted with Et_2O (1 ml × 3). The combined organic layers were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. The obtained crude enol ether **1.24** was used for the next step without further purification.

To a solution of the above crude enol ether **1.24** (84.2 mg) in MeOH (1 mL) was added K_2CO_3 (84.2 mg, 0.61 mmol) at room temperature. After stirring for 15 min, the reaction mixture was quenched with H_2O. After the layers were separated, the aqueous layer was extracted with Et_2O (1 ml × 3). The combined organic layers were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. The obtained crude enol ether **1.S3** was used for the next step without further purification.

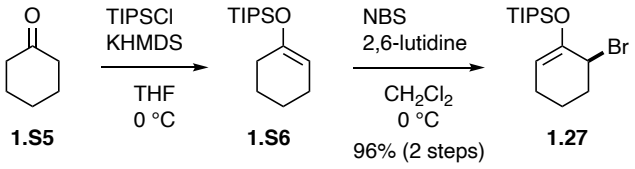
To a solution of the above crude enol ether **1.S3** (55.7 mg) in CH_2Cl_2 (1 mL) was added NBS (38.6 mg, 0.217 mmol) at 0 °C. After stirring for 20 min at the same temperature, the reaction mixture was quenched with a saturated aqueous $Na_2S_2O_3$ and $NaHCO_3$ solution. After the layers were separated, the aqueous layer was extracted with EtOAc (1 ml × 3). The combined organic layers were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash column chromatography (Hexane/EtOAc = 10:1 to 3:2) afforded bromonitrile **1.25** (36.6 mg, 0.127 mmol, 63% for 3 steps) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.14 (br, 1H), 4.06–3.96 (m, 4H), 2.68−2.62 (m, 1H), 2.27 (tt, 1H, *J* = 4.6 Hz, 13.2 Hz), 2.17−2.04 (m, 2H), 1.93–1.86 (m, 1H), 1.80–1.75 (m, 1H), 1.69–1.59 (m, 2H), 1.47−1.41 (m, 1H), 1.34 (d, 3H, *J* = 6.9 Hz).



Bicyclic ketone 1.26: To a solution of bromonitrile **1.25** (13.0 mg, 45 μmol) and HMPA (13.3 μL, 77 μmol) in THF (0.9 mL) was added LDA (1 M in THF, 77 μL, 77 μmol) at –78 °C. After stirring for 30 min at the same temperature, the reaction mixture was warmed up to room temperature and stirred for 14 h. The reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution. After the layers were separated, the aqueous layer was extracted with EtOAc (1 ml × 3). The combined organic layers were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. The obtained crude ketal **1.S4** was used for the next step without further purification.

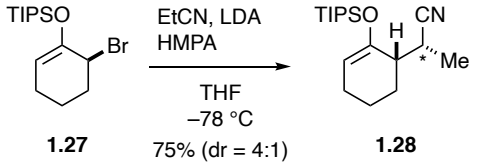
To a solution of the obtained crude ketal **1.S4** (8.6 mg) in THF (0.2 mL) was added aqueous 4 M HCl solution (0.1 mL) at 0 °C. After stirring for 22 h at room temperature, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution. After the layers were separated, the aqueous layer was extracted with EtOAc (1 ml × 3). The combined organic layers were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash column chromatography (Hexane/EtOAc = 1:1) afforded cyclized product **1.26** (6.1 mg, 34 μmol, 83% for 2 steps, 7:1

diastereomer mixture) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.90 (d, 0.13H, J = 4.0 Hz), 2.75–2.69 (m, 1H), 2.68 (d, 1H, J = 4.6 Hz), 2.58 (br-s, 1H), 2.50 (dd, 1H, J = 6.9 Hz, 17.2 Hz), 2.35 (dd, 1H, J = 1.7 Hz, 14.3 Hz), 2.18–2.13 (m, 1H), 2.09 (dd, 1H, J = 6.3 Hz, 13.7 Hz), 1.92–1.87 (m, 1H), 1.83–1.78 (m, 2H), 1.49 (s, 3H), 1.45 (s, 0.43H).



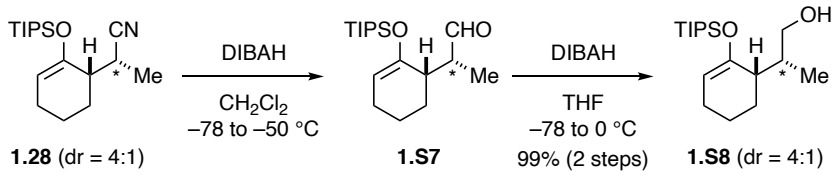
Allyl bromide 1.27: To a solution of cyclohexanone (155 μL, 1.50 mmol) and TIPSCl (368 μL, 1.65 mmol) in THF (5 mL), was added KHMDS (1.0 M in THF, 1.65 mL, 1.65 mmol) at 0 °C. After stirring for 30 min at the same temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution. After the layers were separated, the aqueous layer was extracted with Et_2O (3 ml × 3). The combined organic layers were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. The obtained crude silyl enol ether was used for the next step without further purification.

To a solution of the above crude silyl enol ether (427 mg) and 2,6-lutidine (365 μL, 3.15 mmol) in CH_2Cl_2 (5 mL), was added NBS (280 mg, 1.58 mmol) at 0 °C. After stirring for 10 min, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution and saturated aqueous $Na_2S_2O_3$ solution. After the layers were separated, the aqueous layer was extracted with Et_2O (3 ml × 3). The combined organic layers were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash column chromatography (Hexane/EtOAc = 100:0, using silica gel pretreated with *N*,*N*-dimethylaniline: General Information in page 17) afforded **1.27** (479 mg, 1.44 mmol, 96% for 2 steps) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.99 (t, 1H, J = 3.5 Hz), 4.60 (s, 1H), 2.26–2.15 (m, 3H), 2.08–2.02 (m, 1H), 1.93–1.84 (m, 1H), 1.65–1.60 (m, 1H), 1.21–1.06 (m, 21H)



Nitrile 1.28: To a solution of propionitrile (52.8 μL, 0.747 mmol) and HPMA (130 μL, 0.747 mmol) in THF (1.5 mL) was added LDA (1.0 M in THF, 750 μL, 0.750 mmol) at –78 °C. After the mixture was stirred for 20 min at the same temperature, a solution of allyl bromide **1.27** (165.9 mg, 0.498 mmol) in THF (1.8 mL) was added via cannula.. The reaction mixture was stirred at –78 °C for 15 min, then the reaction was quenched with saturated aqueous $NaHCO_3$ solution (4 mL). After the layers were separated, the aqueous layer was extracted with Et_2O (10 mL × 3). The combined

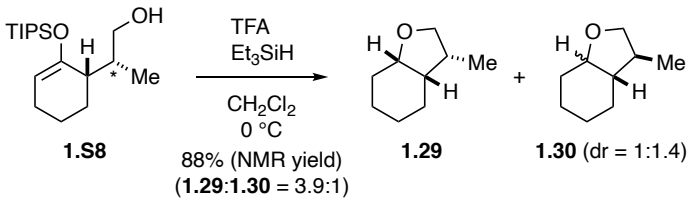
organic layers were washed with brine, dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash column chromatography (Hexane/EtOAc = 100:0 to 99:1, using silica gel pretreated with *N*,*N*-dimethylaniline: General Information in page 17) afforded **1.28** (115 mg, 0.368 mmol, 75%, 4:1 diastereomer mixture) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.95 (br s, 1H), 3.35–3.29 (m, 1H), 2.63 (br s, 0.8H), 2.25 (br s, 0.2H), 2.07–1.89 (m, 3H), 1.77–1.73 (m, 1H), 1.48–1.40 (m, 1H), 1.33 (d, 0.6H, *J* = 7.5 Hz), 1.21–1.05 (m, 24.4H)



1.28 (dr = 4:1) **1.S7** 99% (2 steps) **1.S8** (dr = 4:1)

Alcohol 1.S8: To a solution of nitrile **1.28** (48.2 mg, 0.157 mmol, 4:1 diastereomer mixture) in CH_2Cl_2 (780 μL) was added DIBAH (1.03 M in Hexane, 305 μL, 0.314 mmol) at –78 °C. Then, the reaction mixture was warmed up to –50 °C over 30 min. The reaction mixture was quenched with 10 wt% aqueous tartaric acid solution (1 mL). Then, the mixture was warmed up to room temperature and stirred for 30 min. After the layers were separated, the aqueous layer was extracted with Et_2O (1 ml × 3). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. The obtained crude aldehyde **1.S7** was used for the next step without further purification.

To a solution of the above crude aldehyde **1.S7** (51 mg) in THF (780 μL) was added DIBAH (1.03 M in Hexane, 305 μL, 0.314 mmol) at –78 °C. After stirring for 15 min at the same temperature, the reaction mixture was warmed up to 0 °C. Then, the reaction mixture was stirred for 10 min, the reaction was quenched with saturated aqueous Rochelle salt solution (1 mL). The mixture was stirred for 30 min at room temperature. After the layers were separated, the aqueous layer was extracted with Et_2O (1 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash column chromatography (Hexane/EtOAc = 100:0 to 10:1) afforded **1.S8** (48.6 mg, 0.157 mmol, 99% for 2 steps, 4:1 diastereomer mixture) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.90–4.88 (m, 1H), 3.68 (dd, 0.2H, *J* = 5.2 Hz, 10.3 Hz), 3.60–3.53 (m, 1.6H), 3.44 (dd, 0.2H, *J* = 5.7 Hz, 10.3 Hz), 2.26–2.21 (m, 1H), 2.15–2.09 (m, 1H), 2.00–1.91 (m, 3H), 1.54–1.48 (m, 1H), 1.46–1.38 (m, 1H), 1.21–1.05 (m, 21H), 0.97 (d, 0.6H, *J* = 6.9 Hz), 0.87 (d, 2.4H, *J* = 6.9 Hz).



1.S8 88% (NMR yield) (**1.29**:**1.30** = 3.9:1) **1.29** **1.30** (dr = 1:1.4)

Ether **1.29** and **1.30**: To a solution of alcohol **1.S8** (14.8 mg, 47.3 μmol) in CH_2Cl_2 (500 μL) was added TFA (36.2 μL, 0.473 mmol) at 0 °C. After stirring for 10 min at the same temperature, Et_3SiH (36.7 μL, 0.237 mmol) was further added. Then, the reaction mixture was stirred for 15 min, the reaction was quenched with saturated aqueous $NaHCO_3$ solution. After the layers were separated, the aqueous layer was extracted with Et_2O (0.5 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated, and concentrated under reduced pressure to afford mixture of ethers **1.29** and **1.30**. NMR yields were calculated by using pyrazine as an internal standard. The ^1H NMR spectra of which were identical to those previously reported.[32]

Chapter 2

Total Synthesis of 2-Isocyanoallopupukeanane

2-1. Introduction

The successful results described in chapter 1 encouraged the author to undertake natural product synthesis based on the present method for the stereoselective construction of a caged skeleton. Hence, the author decided to explore the total synthesis of 2-isocyanoallopupukeanane which possess a tricyclic caged skeleton.

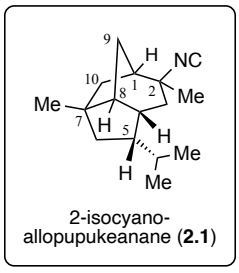
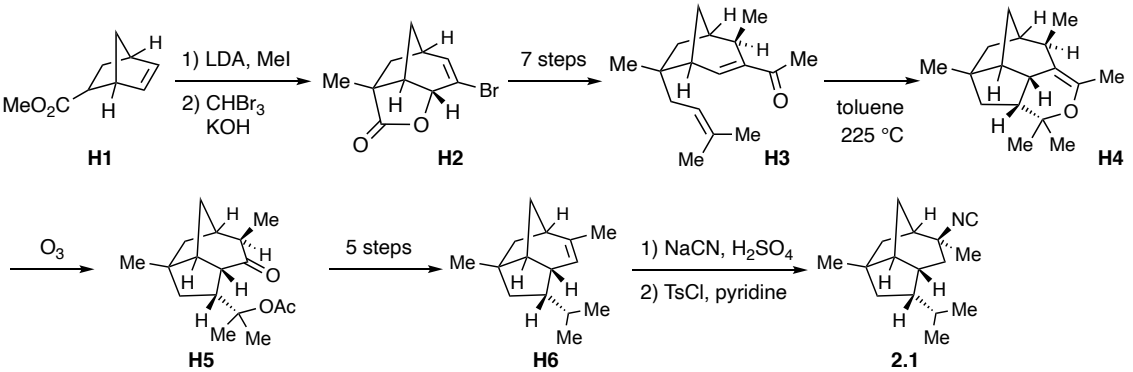


Figure 2.1

2-Isocyanoallopupukeanane (**2.1**) is a marine sesquiterpenoid isolated by Fusetani from *Phyllidiella pustulosa* (Figure 2.1).[34] Structural features of **2.1** are tricyclo[5.2.1.$0^{4,8}$]decane skeleton containing an isocyano group at the C2 position and an isopropyl group at the concave face, and to date, one total synthesis[35] and one synthetic study[36] have been reported.

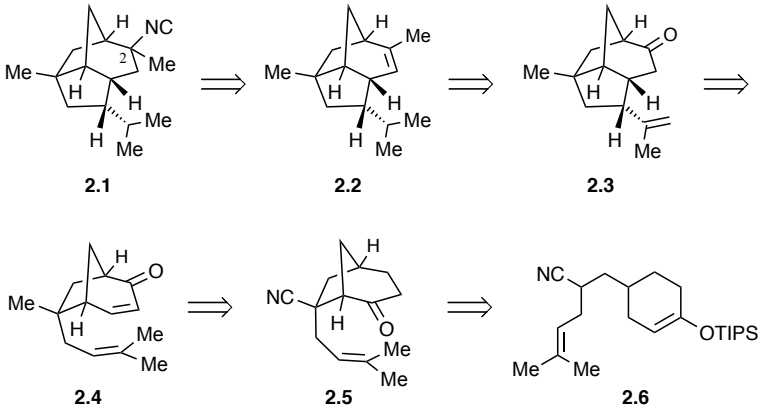
In Scheme 2.1, the overview of the first total synthesis reported by Ho's group is depicted.[35] They started the synthesis from norbornene derivative **H1**, and stereoselective methylation at the α-position of the ester followed by a ring expansion reaction gave lactone **H2**. After seven-step transformation of lactone **H2** into enone **H3**, the C4-C5 bond was formed by an intramolecular hetero-Diels-Alder reaction. The resulting tetracyclic caged compound **H4** was subjected to ozonolysis to give ketone **H5** which was transformed into alkene **H6** through five-step sequence. Finally, isocyano group was introduced via Ritter reaction with HCN followed by dehydration of the resulting formamide, completing the total synthesis of 2-isocyanoallopupukeanane.



Scheme 2.1 First Total Synthesis by Ho's group

On the other hand, the author designed a synthetic plan of 2-isocyanoallopupukeanane based on the diastereoselective intramolecular alkylation reaction. The retrosynthetic analysis is shown in Scheme 2.2. According to the Ho's synthesis, the isocyano group at the C2 position was expected to be introduced through Ritter reaction of alkene **2.2**, and alkene **2.2** could be obtained from ketone **2.3** through functional group interconversion. With a view to constructing the five-membered ring having an isopropyl group at the concave face, the author designed the intramolecular ene reaction of enone **2.4** having an alkene side chain. Enone **2.4** would be obtained from ketonitrile **2.5** via

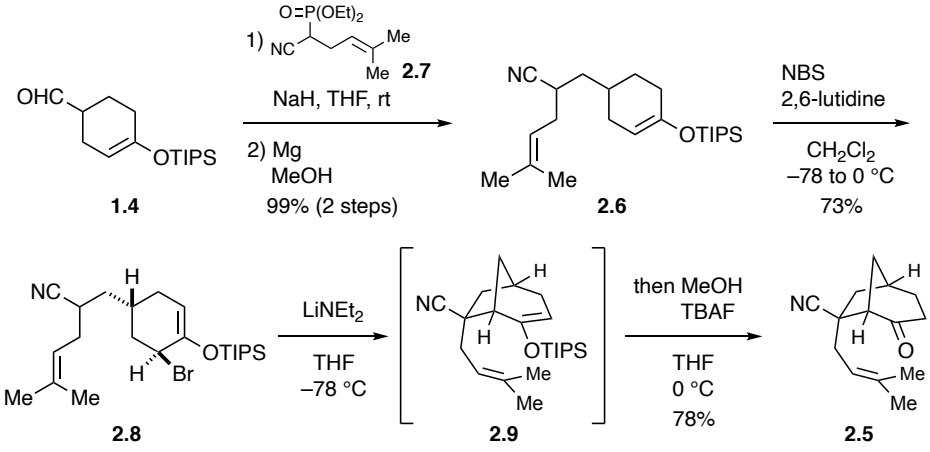
reduction of the cyano group followed by 1,3-transposition of the carbonyl group. The bicylo[3.2.1]octane skeleton of **2.5** would be constructed diastereoselectively by the bromination/cyclization protocol from TIPS enol ether **2.6**.



Scheme 2.2 Retrosynthetic Analysis

2-2. Synthesis of Intramolecular Ene Reaction Precursor

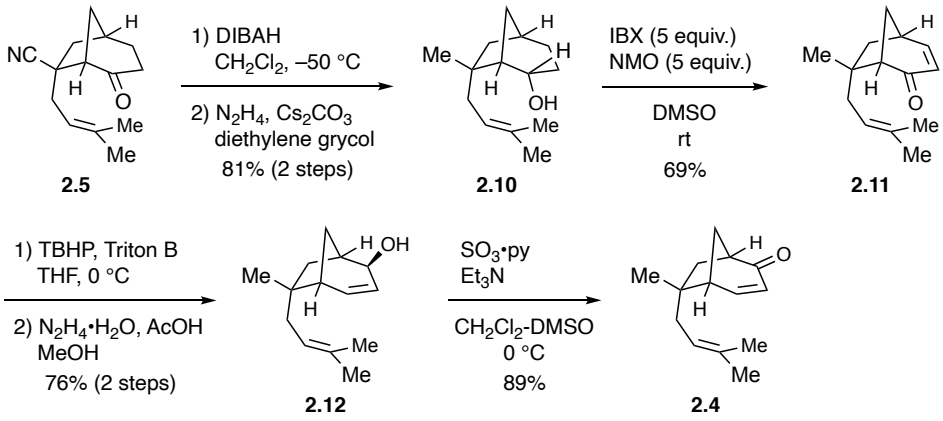
Initially, bicyclic ketonitrile **2.5** was synthesized according to the method developed in chapter 1 (Scheme 2.3). The synthesis started with the Horner-Wadsworth-Emmons reaction of aldehyde **1.4** with the known phosphonate **2.7**,[37] and subsequent chemoselective reduction of conjugated double bond[23] afforded nitrile **2.6** in a quantitative yield. Construction of the bicyclo[3.2.1]octane skeleton was achieved according to the typical protocol described in chapter 1, and bicyclic ketone **2.5** was obtained in 78% yield as a single diastereomer after the one-pot desilylation of the resulting intermediate **2.9** with TBAF.



Scheme 2.3 Constructing the Bicyclo[3.2.1]octane Skeleton

Thereafter, the cyclization precursor of an intramolecular ene reaction was prepared (Scheme 2.4). The cyano group of **2.5** was converted to a methyl group via DIBAH reduction followed by

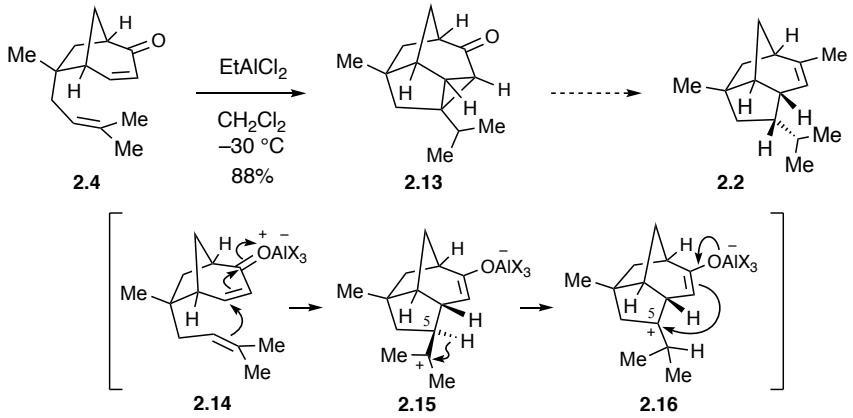
Wolf-Kishner reduction, and the resulting secondary alcohol **2.10** was oxidized to enone **2.11** with IBX.[38] The 1,3-transposition of the carbonyl group[39] was performed by a three-step sequence involving nucleophilic epoxidation with TBHP under basic condition, Wharton reaction, and Parikh-Doering oxidation of the resulting allylic alcohol **2.12**.



Scheme 2.4 Preparation of Intramolecular Ene Reaction precursor

2-3. Total Synthesis of 2-Isocyanoallopupukeanane

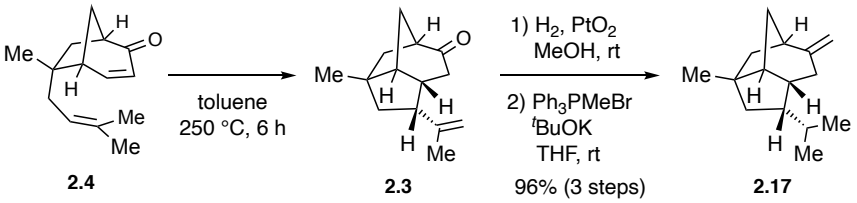
With the key intermediate **2.4** in hand, the author examined the construction of the caged skeleton by an intramolecular ene reaction. Initially, enone **2.4** was treated with $EtAlCl_2$, a Lewis acid which has been widely used as the promotor of ene reactions, but an unexpected tetracyclic compound **2.13** was produced in 88% yield (Scheme 2.5). This result indicated that Lewis acid-activated enone **2.14** would prefer a stepwise conjugate addition reaction with the electron rich alkene moiety rather than a concerted ene reaction. The resulting tertiary cation **2.15** can undergo a 1,2-hydride shift to generate another tertiary cation **2.16** which would be captured by the aluminum enolate moiety to form the cyclopropane ring.[40]



Scheme 2.5 Lewis Acid-Promoted Ene Reaction

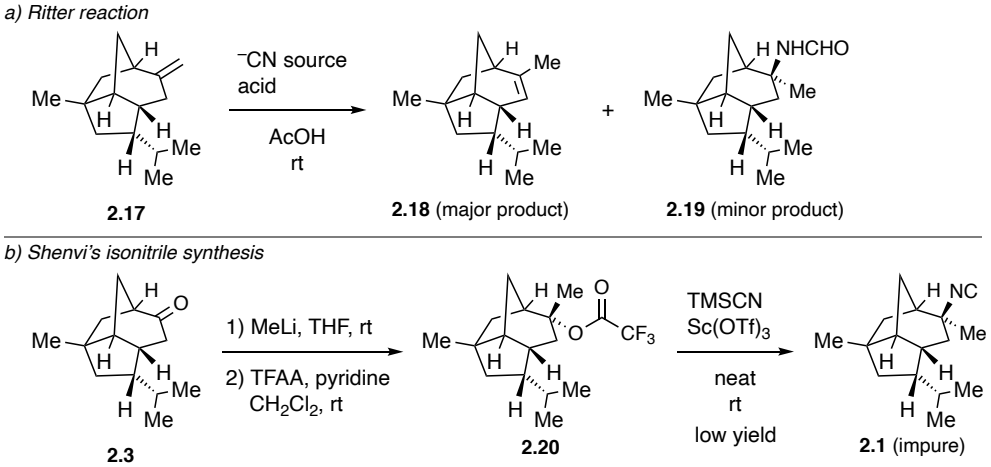
In order to avoid the cationic cyclization pathway, the author examined the ene reaction of

enone **2.4** under thermal conditions[41] (Scheme 2.6). Upon heating of the toluene solution in a sealed tube at 250 °C for 6 h, enone **2.4** underwent the concerted ene reaction, giving rise to the desired tricyclic ketone **2.3** as a single isomer in quantitative yield. The isopropenyl group of **2.3** was reduced to an isopropyl group by catalytic hydrogenation with PtO_2, and the keto group was converted to exo alkene **2.17** by the Wittig reaction.



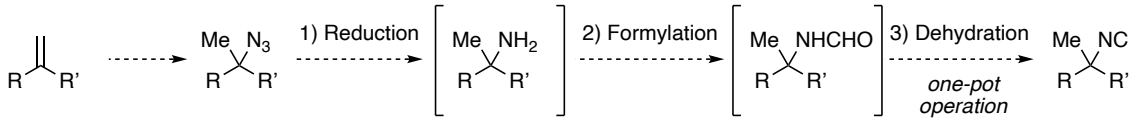
Scheme 2.6 Construction of the Caged Skeleton by Ene reaction

With the caged tricyclic alkene in hand, the stage was set for the introduction of an isocyano group. The efforts directed toward obtaining formamide **2.19** by the Ritter reaction according to Ho's protocol were fruitless, resulting in formation of isomeric alkene **2.18** as a major product (Scheme 2.7a). The combined use of a variety of cyanide sources and acids under various reaction conditions also failed to improve the yield of the desired product. The attempted Shenvi's method[42], in which an isocyano group is introduced by a substitution reaction of the corresponding trifluoroacetate, gave the desired product in low yield as a mixture of inseparable byproduct (Scheme 2.7b).



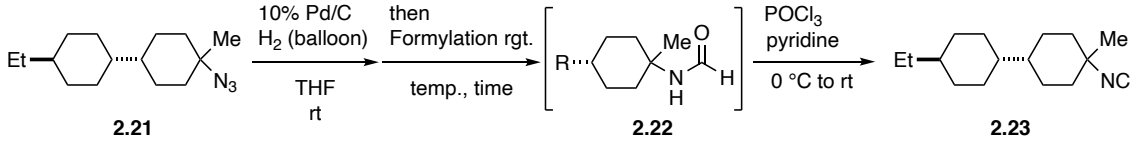
Scheme 2.7 Attempts for Isocyanation at C2-position

Therefore, the author designed a new method for introducing an isocyano group based on the hydroazidation reaction reported by Carreira[43] (Scheme 2.8). Thus, an azide group is introduced as a nitrogen source by hydroazidation of alkene, and the subsequent transformation including the (1) reduction of azide group to amine, (2) formylation of the resulting amine, (3) dehydration of the formamide would afford the desired isonitrile.



Scheme 2.8 Design of a New Method for Introducing an Isocyano group

With a view to conducting the three-step transformation of the azide in one-pot, the reaction conditions were optimized with a model compound (Table 2.1). Catalytic hydrogenation of azide **2.21** with Pd/C in THF solvent and subsequence formylation with various formylation reagents afforded formamide **2.22**, which was subjected to one-pot dehydration with $POCl_3$ and pyridine, affording isonitrile **2.23**. In entry 1, the use of *N*-formylsaccharin as a formylation reagent resulted in formation of a mixture of many products. On the other hand, the desired isonitrile was obtained in good yield by using phenyl formate or 2,2,2-trifluoroethyl formate (entries 2 and 3). Finally, it was found that cyanomethyl formate[44] was a formylation reagent of choice, affording the desired product in quantitative yield (entry 4).



2.21 **2.22** **2.23**

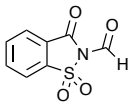
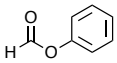
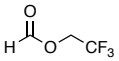
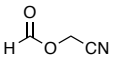
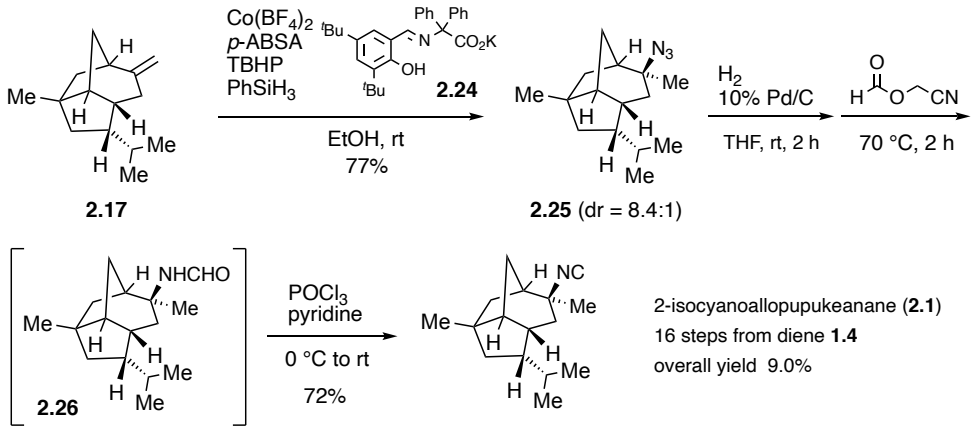
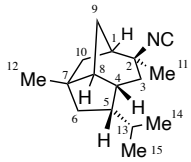
entry	Formylation rgt.	temp.	time	yield
1		rt	20 min	34%
2		70 °C	3 h	90%
4		50 °C	15.5 h	90%
5		70 °C	1.5 h	quant.

Table 2.1 Optimization of the reaction conditions

These results led the author to apply the protocol to the key intermediate of the total synthesis (Scheme 2.9). Treatment of alkene **2.17** with 4-acetoamidebenzenesulfonyl azide (*p*-ABSA), TBHP, phenylsilane, and a cobalt catalyst prepared from $Co(BF_4)_2$ and ligand **2.24** afforded azide **2.25** as a 8.4:1 diastereomeric mixture. The transformation of the azide group into the isocyano group was accomplished by the one-pot protocol, and 2-isocyanoallopupukeanane (**2.1**) was isolated in 72% yield as a single isomer. The spectral data of the artificial compound were identical to those of the natural product **2.1** reported by Fusetani (Table 2.2). Thus, the author achieved the total synthesis of 2-isocyanoallopupukeanane in 9.0% yield from silyl enol ether **1.4** via 16-step transformation.



Scheme 2.9 Total Synthesis of 2-Isocyanoallopupukeanane



2-Isocyanoallopupukeanane (**2.1**)

Carbon No.	^{1}H NMR Chemical shifts in ppm [multipulicity, *J* (Hz)]		
	Natural[a]	Ho's synthesis[b]	This synthesis[c]
1	2.07 (br-dd)	2.06 (t, 5.9)	2.08 (t, 6.3)
2	–	–	–
3a	1.15 (m)	1.15 (m)	1.14-1.19 (m)
b	1.75 (dd)	1.72-1.79 (m)	1.74-1.81 (m)
4	2.16 (dddd)	2.10-2.16 (m)	2.15-2.19 (m)
5	1.51 (m)	1.44-1.59 (m)	1.45-1.60 (m)
6a	1.45 (br-d)	1.44-1.59 (m)	1.45-1.60 (m)
b	1.77 (m)	1.72-1.79 (m)	1.74-1.81 (m)
7	–	–	–
8	1.80 (dd)	1.72-1.79 (m)	1.74-1.81 (m)
9a	1.57 (m)	1.44-1.59 (m)	1.45-1.60 (m)
b	2.21 (dd)	2.19 (d, 13.6)	2.23 (d, 12.6)
10a	1.51 (dd)	1.44-1.59 (m)	1.45-1.60 (m)
b	1.24 (dd)	1.44-1.59 (m)	1.27 (dd, 1.2, 14.3)
11	1.32 (br s)	1.31 (br s)	1.33 (br s)
12	1.05 (s)	1.04 (s)	1.06 (s)
13	1.37 (m)	1.44-1.59 (m)	1.36-1.41 (m)
14	0.78 (d)	0.77 (d, 6.4)	0.80 (d, 6.9)
15	0.84 (d)	0.82 (d, 6.4)	0.86 (d, 6.9)

a) Fusetani, N.; Wolstenholme, H. J.; Matsunaga, S.; Hirota, H. *Tetrahedron Lett.* **1991**, *32*, 7291. 500 MHz ($CDCl_3$)
b) Ho, T.-L.; Kung, L.-R.; Chein, R.-J. *J. Org. Chem.* **2000**, *65*, 5774. 300 MHz ($CDCl_3$)
c)500 MHz ($CDCl_3$, δ_H 7.26)

Carbon No.	^{13}C NMR Chemical shifts in ppm [multipulicity]		
	Natural[a]	Ho's synthesis[b]	This synthesis[c]
1	45.5	45.5	45.5
2	61.3 (t)	61.2	61.2 (t)
3	33.2	33.2	33.2
4	37.5	37.5	37.5
5	53.8	53.8	53.8
6	45.3	45.3	45.3
7	45.4	45.4	45.4
8	52.7	52.7	52.7
9	29.4	29.4	29.4
10	44.4	44.4	44.4
11	29.0	29.0	29.0
12	29.9	29.9	30.0
13	28.3	28.3	28.3
14	21.8	21.8	21.8
15	21.9	21.9	21.9
NC	153.2 (t)	153.2	153.2 (t)

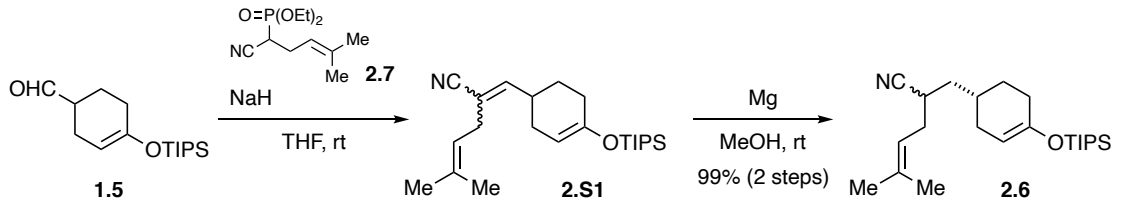
a) Fusetani, N.; Wolstenholme, H. J.; Matsunaga, S.; Hirota, H. *Tetrahedron Lett.* **1991**, *32*, 7291. 126 MHz ($CDCl_3$)
b) Ho, T.-L.; Kung, L.-R.; Chein, R.-J. *J. Org. Chem.* **2000**, *65*, 5774. 74 MHz ($CDCl_3$)
c) 126 MHz ($CDCl_3$, δ_H 7.26)

Table 2.2 Comparison of ^{1}H and ^{13}C NMR spectra between natural and synthetic 2-isocyanoallopupukeanane (**11**) by Fusetani, Ho, and our group.

2-5. Conclusion

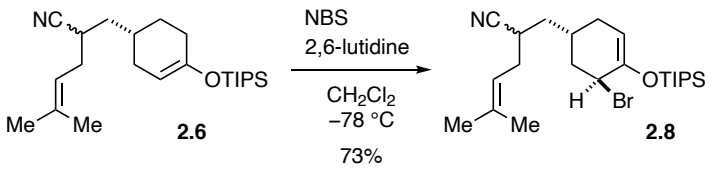
In summary, the author has achieved the total synthesis of 2-isocyanoallopupukeanane. The caged tricyclic skeleton of the natural product was constructed via the diastereoselective intramolecular alkylation reaction, which was developed in Chapter 1. After the intramolecular ene reaction under thermal conditions, introduction of an isocyano group was accomplished by a new protocol including hydroazidation of the alkene and subsequent one-pot transformation of the azide group into an isocyano group.

2-6. Experimental section



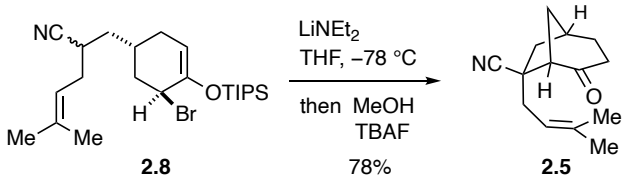
Nitrile 2.6: A 55% dispersion of NaH in mineral oil (445 mg, 10.4 mmol) was washed with Hexane twice, and suspended in dry THF (10 mL). A solution of phosphonate **2.7**[33] (2.87 g, 11.7 mmol) in dry THF (12.5 mL) was added to this suspension at 0 °C. After evolution of hydrogen gas ceased, a solution of aldehyde **1.5** (1.96 g, 6.95 mmol) in dry THF (12.5 mL) was added to the mixture at the same temperature. After stirring at room temperature for 1h, the reaction was quenched with H_2O (30 mL). After the layers were separated, the aqueous layer was extracted with Et_2O (30 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Phosphonate **2.7** was removed by a short pad of silica gel (Hexane/EtOAc = 10:1). The obtained crude nitrile **2.S1** was used for the next step without further purification.

To a solution of the above crude nitrile **2.S1** (2.6 g) in MeOH (70 mL) was added Mg turnings (not activated, 1.71g, 69.5 mmol) in one portion. After stirring for 1 h at the room temperature, the reaction was quenched with saturated aqueous NH_4Cl solution (200 mL). The organic layer was removed under reduced pressure, and then aqueous layer was extracted with Et_2O (100 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash column chromatography (Hexane/EtOAc = 9:1, using silica gel pretreated with *N*,*N*-dimethylaniline: General Information in page 17) afforded nitrile **2.6** (2.59 g, 6.89 mmol, 99% for 2 steps) as a colorless oil: IR (ATR) ν 2924, 2866, 2239, 1670, 1463, 1379, 1239, 1198, 996, 881 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.17 (t, 1H, J = 6.3 Hz), 4.81 (br s, 1H), 2.62–2.56 (m, 1H), 2.34–2.25 (m, 2H), 2.20–2.10 (m, 2H), 2.04 (dd, 1H, J = 2.8, 16.6 Hz), 1.80–1.72 (m, 5H), 1.66–1.61 (m, 5H), 1.49–1.36 (m, 2H), 1.18–1.06 (m, 21H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.7, 150.4, 135.9, 135.8, 122.33, 122.26, 119.1 (2C), 101.9, 101.6, 38.0, 37.6, 31.2 (2C), 31.0 (2C), 30.5 (2C), 29.9, 29.8, 29.6, 29.5, 29.2, 29.1, 28.1 (2C), 25.8 (2C), 18.0 (12C), 12.6 (6C); HRMS (FD) *m*/*z*: $[M]^+$ calcd for $C_{23}H_{41}NOSi$, 375.2957; found, 375.2955.



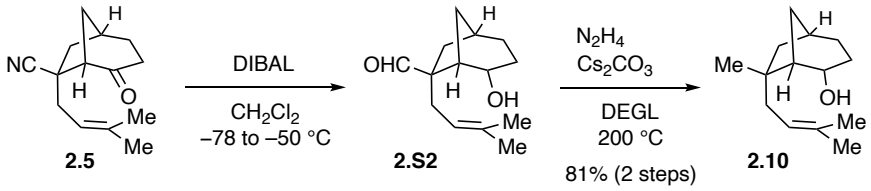
Allyl bromide 2.8: To a solution of nitrile **2.6** (2.84 g, 7.57 mmol) in CH_2Cl_2 (38 mL) was added 2,6-lutidine (1.75 mL, 15.1 mmol). After the mixture was cooled to –78 °C, NBS (1.36 g, 7.57

mmol) was added in five portions. Then, the reaction mixture was warmed up to 0 °C and stirred for further 10 min. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (20 mL) and saturated aqueous $Na_2S_2O_3$ solution (20 mL). The mixture was stirred at room temperature for 30 min. After the layers were separated, the aqueous layer was extracted with Et_2O (50 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash column chromatography (Hexane/EtOAc = 20:1, using silica gel pretreated with *N*,*N*-dimethylaniline: General Information in page 17) afforded bromonitrile **2.8** (2.50 g, 5.50 mmol, 73%) as a pale yellow oil: IR (ATR) ν 2943, 2866, 2238, 1655, 1463, 1382, 1215, 1184, 997, 881, 671 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.19–5.17 (m, 1H), 4.95 –4.93 (m, 1H), 4.59 (s, 1H), 2.60 (quin, 1H, *J* = 7.5 Hz), 2.34–2.29 (m, 4H), 2.22 (d, 1H, *J* =14.3 Hz), 1.94–1.80 (m, 2H), 1.74 (s, 3H), 1.73–1.67 (m, 1H), 1.66 (s, 3H), 1.57–1.50 (m, 1H), 1.19–1.07 (m, 21H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.63, 149.55, 136.15, 136.13, 122.3, 122.0, 118.8 (2C), 105.0, 104.9, 50.3 (2C), 39.13, 39.10, 37.5, 37.4, 30.8 (2C), 30.7, 30.5, 30.2, 29.6, 29.4 (2C), 27.3, 26.8, 25.8 (2C), 18.01 (12C), 12.6 (6C); HRMS (FD) *m*/*z*: $[M]^+$ calcd for $C_{23}H_{40}BrNOSi$, 453.2063; found, 453.2045.



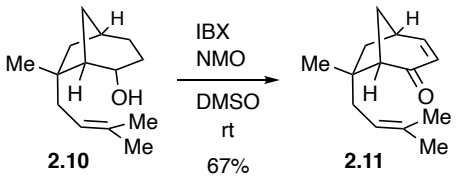
2.8 78% **2.5**

Keto nitrile 2.5: To a solution of bromonitrile **2.8** (2.50 g, 5.50 mmol) in dry THF (100 mL) was slowly added $LiNEt_2$ (1.0 M in THF, 8.25 mL, 8.25 mmol) at –78 °C. After stirring for 30 min at the same temperature, MeOH (334 μL, 8.25 mmol) was added to the mixture. After the reaction mixture was warmed up to 0 °C, TBAF (1 M in THF, 6.1 mL, 6.1 mmol) was further added. After stirring for 10 min, the reaction was quenched with brine (50 mL). After the layers were separated, the aqueous layer was extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash column chromatography (Hexane/EtOAc = 50:1 to 10:1) afforded keto nitrile **2.5** (935 mg, 4.30 mmol, 78%, single diastereomer) as a colorless oil: IR (ATR) ν 2946, 2876, 2231, 1709, 1454, 1378, 1238, 1101, 916, 835 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.21 (t, 1H, *J* = 7.5 Hz), 2.95 (d, 1H, *J* = 4.1 Hz), 2.61 –2.58 (m, 2H), 2.51 (dd, 1H, *J* = 6.9, 18.3 Hz), 2.43–2.40 (m, 1H), 2.31 (d, 2H, *J* = 7.5 Hz), 2.28 (ddd, 1H, *J* = 10.3, 10.3, 18.3 Hz), 1.87 (d, 1H, *J* = 12.6 Hz), 1.82–1.78 (m, 2H), 1.74 (s, 3H), 1.73 (d, 1H, *J* = 12.6 Hz), 1.63 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.1, 136.8, 124.3, 117.7, 59.4, 46.4, 39.8, 36.6, 35.8, 33.2, 32.6, 30.6, 25.8, 18.1; HRMS (FD) *m*/*z*: $[M]^+$ calcd for $C_{14}H_{19}NO$, 217.1467; found, 217.1470.



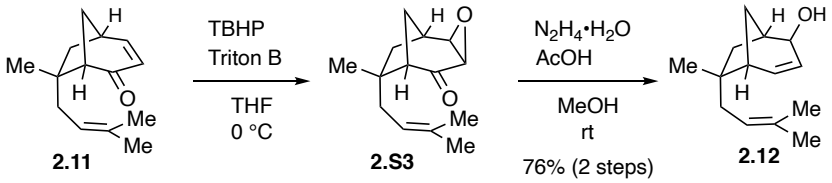
Alcohol 2.10: To a solution of keto nitrile **1.5** (1.63 g, 7.50 mmol) in CH_2Cl_2 (38 mL) was slowly added DIBAL (1.03 M in Hexane, 21.8 mL, 22.5 mmol) at –78 °C. The reaction mixture was warmed up to –50 °C over 40 min, and the reaction was quenched with 10% aqueous tartaric acid solution (40 mL). Then, the mixture was warmed up to room temperature and stirred for 1 h. After the layers were separated, the aqueous layer was extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. The obtained crude aldehyde **2.S2** was used for the next step without further purification.

To a solution of the above crude aldehyde **2.S2** (1.71 g) in diethylene glycol (DEGL) (38 mL) was added Cs_2CO_3 (14.7 g, 45.1 mmol) and anhydrous N_2H_4 (4.80 mL, 151 mmol). The reaction mixture was stirred for 30 min at 100 °C, for 2 h at 180 °C, and for 1 h at 200 °C. The reaction was quenched with 1 M HCl solution (60 mL) at room temperature. After the layers were separated, the aqueous layer was extracted with Et_2O (50 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash column chromatography (Hexane/EtOAc = 50:1 to 10:1) afforded alcohol **2.10** (1.26 g, 6.08 mmol, 81% for 2 steps) as a colorless oil: IR (ATR) ν 3359, 2922, 2865, 1468, 1374, 1292, 1079, 998, 841, 766, 724 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.26 (t, 1H, J = 6.9 Hz), 3.80–3.70 (m, 1H), 2.42 (d, 2H, J = 6.9 Hz), 2.15 (br d, 1H, J = 2.9 Hz), 2.04 (dddd, 1H, J = 2.3, 6.3, 6.3, 13.8 Hz), 1.95–1.84 (m, 1H), 1.81 (br s, 1H), 1.78–1.70 (m, 5H), 1.63 (s, 3H), 1.54 (dd, 1H, J = 7.5, 13.2 Hz), 1.48–1.40 (m, 2H), 1.34 (d, 1H, J = 13.2 Hz), 1.15 (d, 1H, J = 13.8 Hz), 0.99 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 132.8, 122.9, 75.1, 51.2, 44.2, 42.6, 37.3, 35.6, 34.1, 31.6, 30.5, 29.0, 26.0, 18.1; HRMS (FD) m/z: $[M]^+$ calcd for $C_{14}H_{24}O$, 208.1827; found, 208.1824.



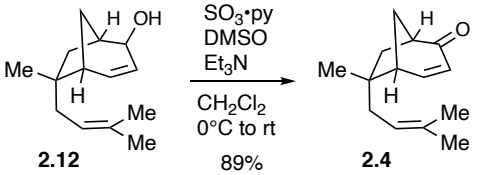
Enone 2.11: To a solution of 2-iodoxybenzoic acid (IBX) (4.32 g, 15.5 mmol) in DMSO (9 mL) was added 4-methylmorpholine *N*-oxide (NMO) (1.83 g, 15.5 mmol) and stirred until the mixture was turned to pale yellow solution (about 10 min). To this solution was added a solution of alcohol **2.10** (643 mg, 3.09 mmol) in DMSO (6 mL). After stirring for 66 h at room temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ solution (30 mL). After the layers were separated, the aqueous layer was extracted with Et_2O (30 mL × 3). The combined organic layers were washed with

brine, dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash column chromatography (Hexane/EtOAc = 100:1 to 50:1) afforded enone **2.11** (425 mg, 2.08 mmol, 67%) as a colorless oil: IR (ATR) ν 2954, 2870, 1675, 1448, 1376, 1247, 1156, 1085, 849 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.29 (ddd, 1H, *J* = 1.8, 7.5, 9.7 Hz), 5.79 (dd, 1H, *J* = 1.8, 9.7 Hz), 5.14 (t, 1H, *J* = 6.3 Hz), 2.81–2.80 (m, 1H), 2.58 (d, 1H, *J* = 3.5 Hz), 2.08–2.00 (m, 3H), 1.91 (dd, 1H, *J* = 7.5, 14.3 Hz), 1.68 (s, 3H), 1.67 (d, 2H, *J* = 6.3 Hz), 1.52 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.7, 157.6, 133.2, 127.4, 121.3, 62.9, 43.0, 41.3, 39.4, 39.1, 37.9, 28.7, 25.9, 17.9; HRMS (FD) *m*/*z*: $[M]^+$ calcd for $C_{14}H_{20}O$, 204.1514; found, 204.1520.

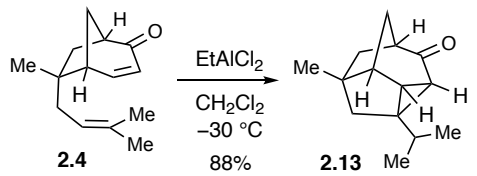


Allyl alcohol 2.12: To a solution of enone **2.11** (281 mg, 1.38 mmol) in THF (13.8 mL) were added *tert*-butyl hydroperoxide (TBHP) (5.5 M in nonane, 1.35 mL, 7.43 mmol) and benzyltrimethylammonium hydroxide (Triton B) (40% in MeOH, 1.35 mL, 2.97 mmol) at 0 °C. After stirring for 2 h at the same temperature, the reaction was quenched with saturated aqueous $Na_2S_2O_3$ solution (20 mL). After the layers were separated, the aqueous layer was extracted with Et_2O (30 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. The residue was purified with a short pad of silica gel (Hexane/EtOAc = 20:1). The obtained crude epoxide **2.S3** was used for the next step without further purification.

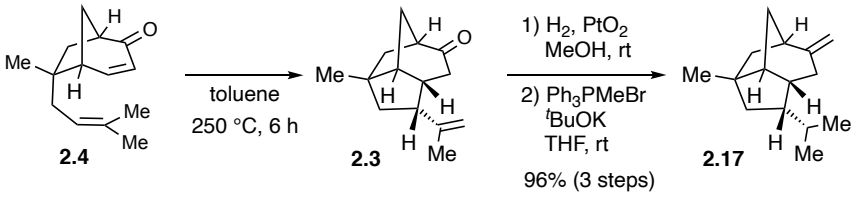
To a solution of the above crude epoxide **2.S3** (430 mg) in MeOH (13.8 mL) were added N_2H_4•H_2O (0.340 mL, 6.99 mmol) and AcOH (0.400 mL, 6.99 mmol) at 0 °C. Then the mixture was warmed up to room temperature and stirred for 14 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (20 mL), and MeOH was removed under reduced pressure. The aqueous mixture was extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash column chromatography (Hexane/EtOAc = 50:1 to 5:1) afforded allyl alcohol **2.12** (217 mg, 1.05 mmol, 76% for 2 steps) as a yellow oil: IR (ATR) ν 3342, 3026, 2957, 2924, 2863, 1447, 1375, 1263, 1097, 974, 854 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.08 (dd, 1H, *J* = 8.0, 8.6 Hz), 5.58 (ddd, 1H, *J* = 1.7, 5.5, 8.6 Hz), 5.11 (t, 1H, *J* = 6.9 Hz), 3.73 (br s, 1H), 2.34 (br s, 1H), 2.05–1.98 (m, 3H), 1.73–1.70 (m, 5H), 1.65–1.57 (m, 5H), 1.06 (d, 1H, *J* = 13.7 Hz), 1.00 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.5, 132.3, 126.0, 122.3, 72.6, 47.5, 44.8, 41.0, 40.4, 38.8, 29.1, 27.4, 26.0, 17.9; HRMS (FD) *m*/*z*: $[M]^+$ calcd for $C_{14}H_{22}O$, 206.1671; found, 206.1667.



Enone 2.4: To a solution of allyl alcohol **2.12** (113 mg, 0.547 mmol) in CH_2Cl_2 (4 mL) and DMSO (2 mL) was added Et_3N (0.382 mL, 2.74 mmol). After the mixture was cooled to 0 °C, SO_3•pyridine (257 mg, 1.64 mmol) was added. The reaction mixture was stirred for 30 min at the same temperature, then stirred for additional 30 min at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (10 mL). After the layers were separated, the aqueous layer was extracted with Et_2O (5 mL × 3). The combined organic layers were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash column chromatography (Hexane/EtOAc = 100:0 to 20:1) afforded enone **2.4** (99.2 mg, 0.486 mmol, 89%) as a colorless oil: IR (ATR) ν 2958, 2933, 2896, 1681, 1448, 1377, 1246, 1153, 1079, 1040, 833 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.23 (ddd, 1H, *J* = 1.8 Hz, 6.9, 9.8 Hz), 5.92 (dd, 1H, *J* = 1.8, 9.8 Hz), 5.12 (t, 1H, *J* = 6.6 Hz), 2.88 (dd, 1H, *J* = 5.7, 7.5 Hz), 2.47 (dd, 1H, *J* = 4.6, 6.9 Hz), 2.08−1.99 (m, 3H), 1.97 (d, 1H, *J* = 11.5 Hz), 1.92 (dd, 1H, *J* = 7.5, 13.8 Hz), 1.71 (s, 3H), 1.56 (s, 3H), 1.42 (d, 1H, *J* = 13.8 Hz), 1.17 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.8, 156.6, 133.4, 127.8, 121.3, 50.9, 48.0, 47.2, 39.6, 38.8, 38.7, 28.1, 26.0, 18.0; HRMS (FD) *m*/*z*: $[M]^+$ calcd for $C_{14}H_{20}O$, 204.1514; found, 204.1522.



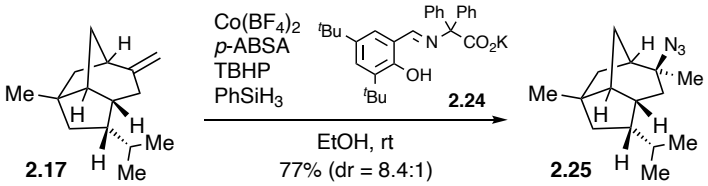
Tetracyclic Compound 2.13: To a solution of enone **2.4** (54.7 mg, 0.268 mmol) in CH_2Cl_2 (2.5 mL) was added $EtAlCl_2$ (1.05 M in Hexane, 0.765 mL, 0.804 mmol) at –30 °C. After stirring for 40 min at the same temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ solution (5 mL). After the layers were separated, the aqueous layer was extracted with Et_2O (2 mL × 3). The combined organic layers were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash column chromatography (Hexane/EtOAc = 50:1 to 25:1) afforded cyclopropane **2.13** (47.9 mg, 0.236 mmol, 88%) as a colorless oil: IR (ATR) ν 2948, 2865, 1682, 1457, 1365, 1251, 1144, 1088, 1036, 882 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.61 (br s, 1H), 2.48 (dd, 1H, *J* = 5.2, 5.2 Hz), 2.08–1.98 (m, 3H), 1.92 (d, 1H, *J* = 13.2 Hz), 1.76 (ddd, 1H, *J* = 4.0, 4.0, 11.5 Hz), 1.54 (dd, 1H, *J* = 5.2, 12.6 Hz), 1.46–1.36 (m, 3H), 1.22 (s, 3H), 0.95 (d, 3H, *J* = 6.9 Hz), 0.87 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 213.2, 51.4, 50.5, 49.5, 46.8, 46.4, 46.0, 40.8, 38.1, 34.4, 33.6, 29.3, 19.8, 19.7; HRMS (FD) *m*/*z*: $[M]^+$ calcd for $C_{14}H_{20}O$, 204.1514; found, 204.1515.



Alkene 2.17: A solution of enone **2.4** (81.8 mg, 0.400 mmol) in toluene (8 mL) in a sealed tube was heated in an oil bath at 250 °C for 6 h. After the solution was cooled to room temperature, the solvent was removed under reduced pressure. The obtained crude ketone **2.3** (90.2 mg, colorless oil) was used for the next step without further purification.

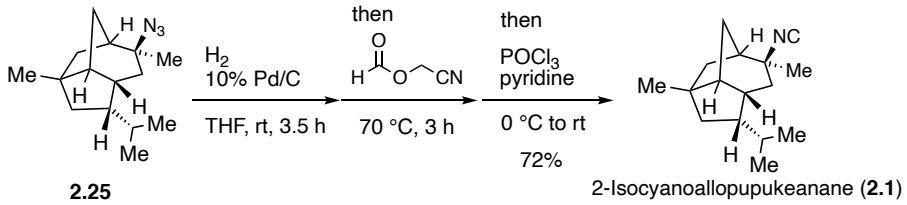
A mixture of the above crude ketone **2.3** (90.2 mg) and PtO_2 (10.6 mg) in THF (0.5 mL) and MeOH (1.5 mL) was stirred under H_2 atmosphere (balloon) at room temperature for 2h. The reaction mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure. The obtained crude ketone was used for the next step without further purification.

To a suspension of Ph_3PMeBr (365 mg, 1.02 mmol) in dry THF (1 mL) were added potassium *tert*-butoxide (96.5 mg, 0.860 mmol) followed by a solution of the above crude ketone (89.5 mg) in dry THF (1.5 mL) at 0 °C. The reaction mixture was warmed up to room temperature and stirred for 2 h. The reaction was quenched by H_2O (5 mL). After the layers were separated, the aqueous layer was extracted with CH_2Cl_2 (2 mL × 3). The combined organic layers were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash column chromatography (Hexane/EtOAc = 100:0) afforded alkene **2.17** (79.1 mg, 0.384 mmol, 96% for 3 steps) as a colorless oil: IR (ATR) ν 2939, 2864, 1638, 1469, 1449, 1384, 1365, 1313, 1166, 961, 876 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.58 (s, 1H), 4.57 (s, 1H), 2.74 (br s, 1H), 2.25–2.22 (m, 1H), 2.19 (d, 1H, J = 9.2 Hz), 2.12 (d, 1H, J = 15.5 Hz), 1.96 (dd, 1H, J = 5.8, 5.8 Hz), 1.76–1.69 (m, 2H), 1.52–1.47 (m, 3H), 1.44–1.40 (m, 2H), 1.32 (dd, 1H, J = 12.0, 12.0 Hz), 1.08 (s, 3H), 0.89 (d, 3H, J = 6.3 Hz), 0.85 (d, 3H, J = 6.3 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.7, 106.2, 52.6, 52.43, 52.37, 47.4, 46.2, 43.8, 41.0, 31.6, 30.3, 29.1, 27.2, 22.2, 22.0; HRMS (FD) *m*/*z*: $[M]^+$ calcd for $C_{15}H_{24}$, 204.1878 found, 204.1873.



Azide 2.25: To a solution of $Co(BF_4)_2$•$6H_2O$ (25.8 mg, 75.7 μmol) in EtOH (2.5 mL) was added ligand **2.24**[40] (38.1 mg, 79.1 μml). After stirring 30 min, a solution of alkene **2.17** (79.1 mg, 0.387 mmol) in EtOH (1.5 mL), followed by 4-acetamidobenzenesulfonyl azide (283 mg, 1.18 mmol) were added to the homogenous orange solution. After the mixture was degassed with argon for 20 min,

TBHP (5.5 M in nonane, 42.0 μL, 0.231 mmol) was added. The reaction mixture was stirred until the color changed to dark orange (10 min), then phenylsilane (95.0 μL, 0.780 mmol) was added dropwise. After stirring at room temperature for 30 min, the reaction was quenched with H_2O (2 mL). Saturated aqueous $NaHCO_3$ solution (2 mL) and brine (2 mL) were added to the mixture, then the reaction mixture was extracted with Et_2O (4 mL × 3). The combined organic layers were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash column chromatography (Hexane/EtOAc = 100:0) afforded azide **2.25** (73.8 mg, 0.298 mmol, 77%, 8.4:1 inseparable diastereomer mixture) as a colorless oil: IR (ATR) 2949, 2926, 2866, 2098, 1454, 1377, 1251, 1121, 1072, 926, 824 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 2.24 (d, 1H, J = 12.6 Hz), 1.99–1.94 (m, 1H), 1.84 (dd, 1H, J = 6.3, 6.3 Hz), 1.64–1.60 (m, 1H), 1.58 (dd, 1H, J = 4.6, 4.6 Hz), 1.48 (dd, 1H, J = 7.4, 14.3 Hz), 1.35–1.19 (m, 5H), 1.14 (s, 0.35H, minor isomer), 1.07 (d, 1H, J = 12.6 Hz), 1.02 (s, 3H), 0.93 (s, 3H), 0.89 (dd, 1H, J = 8.6, 15.5 Hz), 0.78–0.76 (m, 6H); ^{13}C NMR of major isomer (126 MHz, C_6D_6) δ 65.4, 54.1, 53.1, 45.62, 45.57, 45.52, 45.47, 38.2, 30.6, 30.2, 28.8, 28.4, 25.8, 22.1, 22.0; HRMS (FD) m/z: $[M]^+$ calcd for $C_{15}H_{25}N_3$, 247.2045 found, 247.2049.



2.25 2-Isocyanoallopupukeanane (**2.1**)

2-isocyanoallopupukeanane (2.1): A solution of azide **2.25** (44.1 mg, 0.178 mmol, dr = 8.4:1) and 10% palladium on charcoal (10.7 mg) in dry THF (1.2 mL) was stirred under H_2 atmosphere (balloon) for 3.5 h. Then, cyanomethyl formate (38.0 μL, 0.534 mmol) was added to the reaction mixture under argon atmosphere. The reaction mixture was warmed up to 70 °C and stirred for 3 h. Then, pyridine (216 μL, 2.67 mmol) and $POCl_3$ (81.0 μL, 0.890 mmol) were added to the reaction mixture at 0 °C. After being stirring at the same temperature for 30 min, the reaction mixture was warmed up to room temperature and further stirred for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (1.5 mL). After the layers were separated, the aqueous layer was extracted with Et_2O (2 mL × 3). The combined organic layers were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash column chromatography (Hexane/EtOAc = 100:0 to 50:1), followed by recrystallization from EtOH/H_2O (2:1) afforded 2-isocyanoallopupukeanane (29.5 mg, 0.127 mmol, 72%) as a white solid: m.p. 82–85 °C (Hexane); IR (ATR) 2952, 2925, 2912, 2867, 2132, 1465, 1385, 1237, 1165, 1128, 1078, 826 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.23 (d, 1H, J = 12.6 Hz), 2.19–2.15 (m, 1H), 2.08 (dd, 1H, J = 6.3, 6.3 Hz), 1.81–1.74 (m, 3H), 1.60–1.45 (m, 4H), 1.41–1.36 (m, 1H), 1.33 (br s, 3H), 1.27 (dd, 1H, J = 1.2, 14.3 Hz), 1.19–1.14 (m, 1H), 1.06 (s, 3H), 0.86 (d, 3H, J = 6.9 Hz), 0.80 (d, 3H, J = 6.9 Hz); ^{13}C

NMR (126 MHz, $CDCl_3$) δ 153.2 (t, J = 4.8 Hz), 61.2 (t, J = 4.8 Hz), 53.8, 52.7, 45.5, 45.4, 45.3, 44.4, 37.5, 33.2, 29.9, 29.4, 29.0, 28.3, 21.9, 21.8; HRMS (FD) m/z: $[M]^+$ calcd for $C_{16}H_{25}N$, 231.1983 found, 231.1987.

Chapter 3

Synthetic Studies on Aconitine-type Diterpenoid Alkaloids

3-1. Introduction

In chapter 2, the efficiency of the intramolecular alkylation reaction of bromonitriles was shown through the total synthesis of a natural product having a caged skeleton. The results motivated the author to undertake synthetic studies on natural products with highly complex structure, namely, aconitine-type C_{19}-diterpenoid alkaloids.

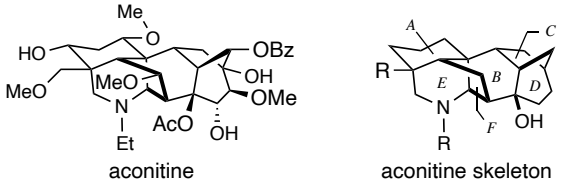
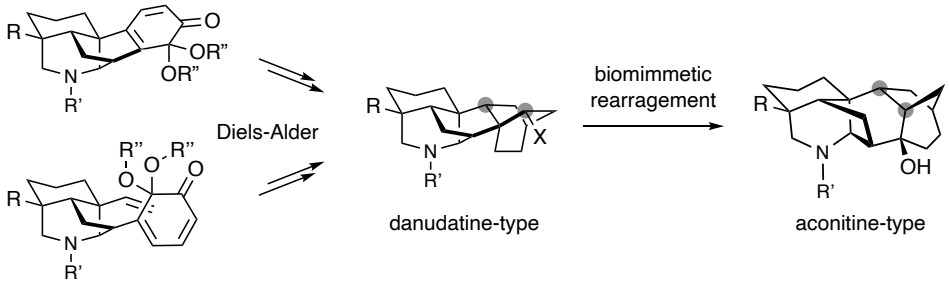


Figure 3.1 Aconitine-type C_{19}-Diterpenoid Alkaloids

Aconitine-type C_{19}-diterpenoid alkaloids (aconitine alkaloids) are usually isolated from *Aconitum* and *Delphinium* genera, and many of them are known to exhibit a variety of biological activities.[45] As a typical example, aconitine is well-known as the most potent phytotoxin which activates voltage-gated Na^+ channels and induces depolarization.[46] Structural features of the aconitine alkaloids are the hexacyclic skeleton containing two bicyclo[3.2.1]octanes and one 2-azabicyclo[3.3.1]nonane substructures, which are called aconitine skeleton. The complexity of the structure and diverse biological activities have stimulated the interest of organic chemists, and to date, total synthesis of aconitine alkaloids have been reported by Wiesner,[47a,b] Sarpong,[47c] Fukuyama and Yokoshima,[47d] Inoue,[47e] and Riesman[47f] laboratories.

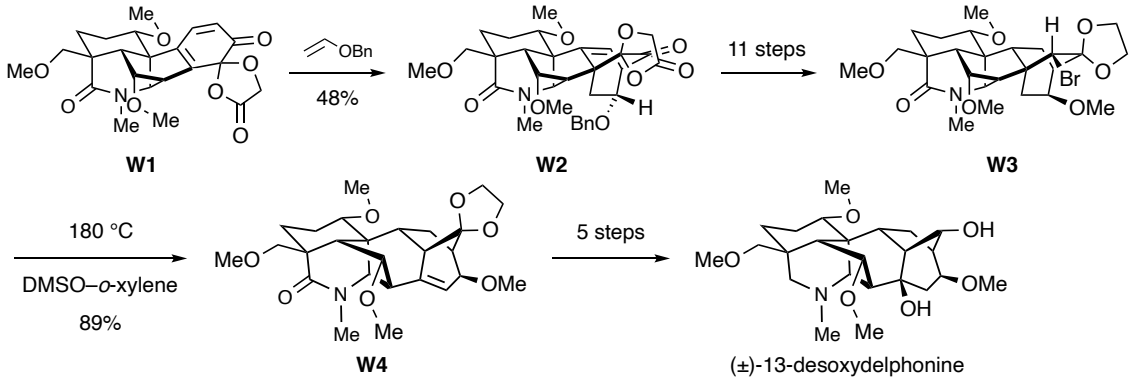
Aconitine alkaloids are known to be biosynthesized via skeletal rearrangements of denudatine flameworks containing a bicyclo[2.2.2]octane CD-ring system,[48] and the biomimetic cationic rearrangements have been established as a promising synthetic method for constructing the aconitine skeleton (Scheme 3.1).[47a–e] Thus, bicyclo[2.2.2]octane moiety of the denudatine-type skeleton is assembled by a Diels-Alder reaction, and then it is subjected to a rearrangement reaction to afford the aconitine-type flamework.



Scheme 3.1 Aconitine Skeleton Formation by Biomimetic Rearrangement

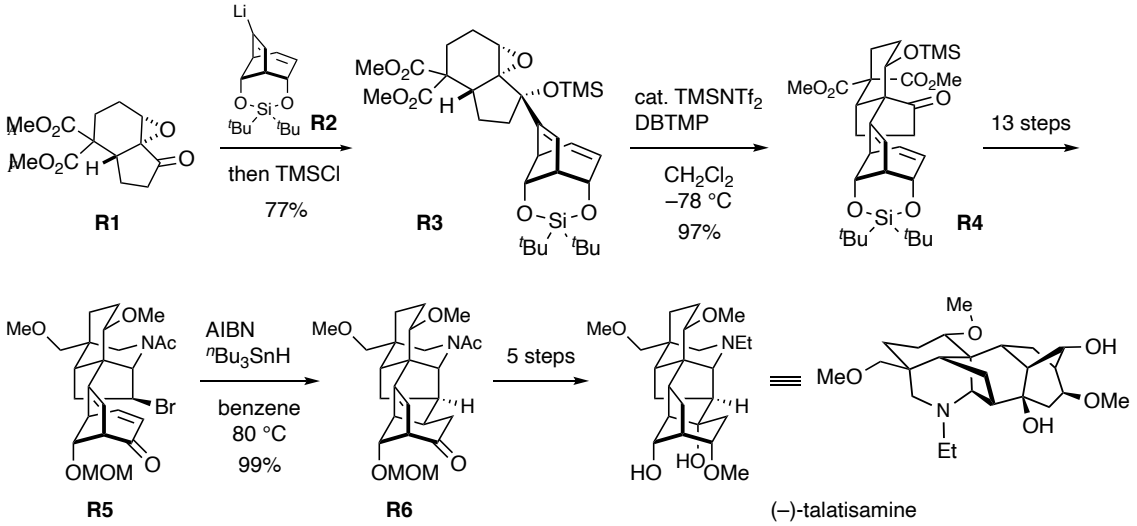
As an example, the overview of the total synthesis of 13-desoxydelphonine by Wiesner's group[47b] is shown in Scheme 3.2. The Diels-Alder reaction of masked-*o*-benzoquinone **W1** with

benzyl vinyl ether afforded bicyclo[2.2.2]octane **W2**, which was converted to bromide **W3** via eleven-step transformation. The skeletal rearrangement of bromide **W3** was conducted under thermal condition, resulting in construction of the aconitine skeleton in 89% yield. After subsequent five-step transformation, total synthesis of 13-desoxydelphonine was accomplished.



Scheme 3.2 Total Synthesis of 13-desoxydelphonine by Wiesner

On the other hand, Reisman's group achieved the total synthesis of aconitine alkaloids based on different type approach (Scheme 3.3).[47f] Thus, the AF-ring fragment **R1** and the CD-ring fragment **R2** were subjected to an addition reaction followed by semi-pinacol rearrangement. Thereafter, thirteen-step transformation of **R4** provided bromide **R5** which underwent a radical cyclization reaction mediated by AIBN and $^{n}Bu_3SnH$ in quantitative yield. Total synthesis of talatisamine was then accomplished after five-step transformation.



Scheme 3.3 Convergent Total Synthesis of Talatisamine by Riesman

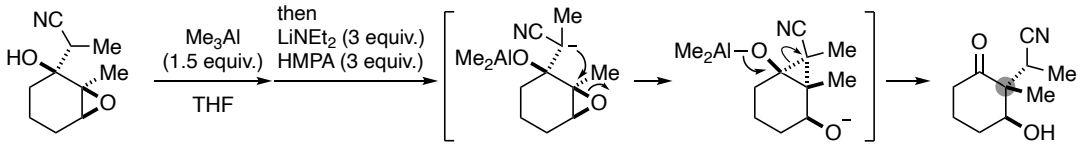
As described above, the synthetic methodology for forming the aconitine skeleton is limited even after half a century since the Wiesner's pioneering work. Therefore, the author decided to

develop a new method for constructing the hexacyclic core skeleton using nitrile derivatives to achieve the total synthesis of aconitine alkaloids.

3-2. Retrosynthetic Analysis

In this study, the author aimed to construct the aconitine skeleton by a convergent synthetic approach via fragment coupling. The main issue in this approach is how to construct the highly hindered B ring moiety. While Riesman *et al.* circumvented the problem through cationic semi-pinacol rearrangement and radical cyclization, the author decided to apply a novel method for C–C bond formation using an α-cyano carbanion as shown below.

Dr. Domon, in his dissertation, reported the formal semi-pinacol rearrangement of epoxy cyanoalcohol (Scheme 3.4a). Treatment of the cyano epoxyalcohol with Me_3Al followed by HMPA and $LiNEt_2$ proceeded cyclopropane formation and subsequent ring-opening, affording α-(cyanoalkyl)-β-hydroxycycloalkanone containing quaternal carbon center in a stereoselective manner.



Scheme 3.4 Formal Semi-Pinacol Rearrangement

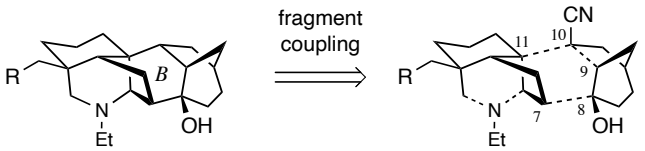
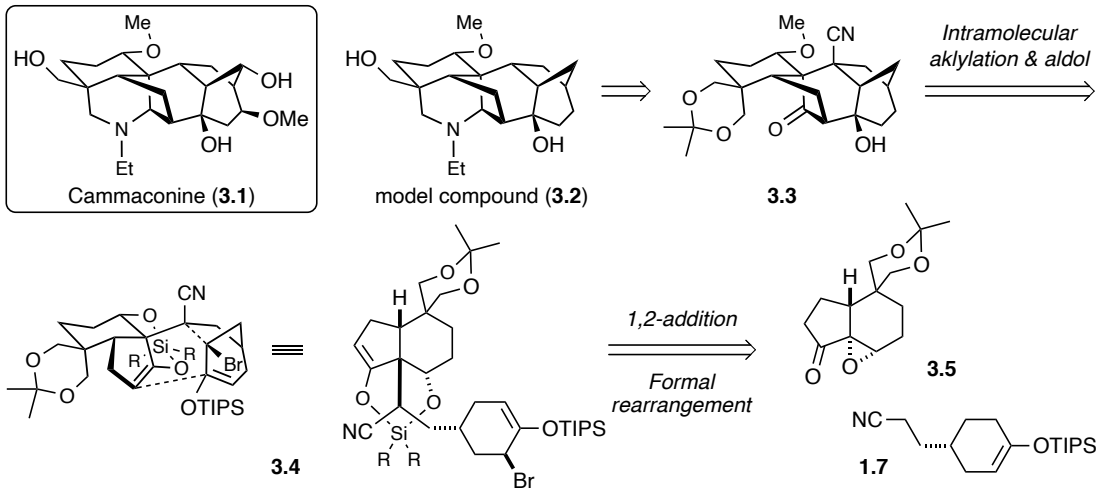


Figure 3.2 Conceptual Synthetic Strategy

This report led the author to apply a synthetic strategy in which the hexacyclic aconitine skeleton is divided into two fragments (Figure 3.2). Thus, connection of the two fragments at the C10–C11 bond would be achieved by the 1,2-addition/formal semi-pinacol rearrangement, and the C ring would be formed by the intramolecular alkylation reaction described in chapter 1.

Cammaconine (**3.1**) was set as the synthetic target, and the author designed the model compound **3.2** which lacks the hydroxy groups on the D-ring. The retrosynthetic analysis of **3.2** is depicted in Scheme 3.5. Formation of the heterocycle moiety of **3.2** would be performed at the late stage of the synthesis, and the pentacyclic skeleton of ketone **3.3** could be constructed via an intramolecular alkylation reaction of bromonitrile **3.4** followed by an intramolecular aldol reaction. The cyclization precursor **3.4** would be synthesized by the fragment coupling between epoxyketone

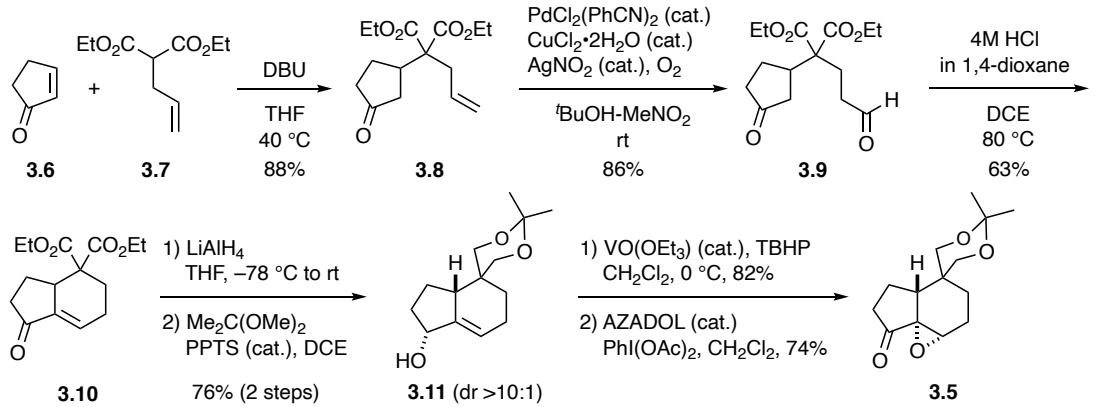
3.5 and nitrile **1.7** by the 1,2-addition/formal rearrangement protocol.



Scheme 3.5 Retrosynthetic analysis

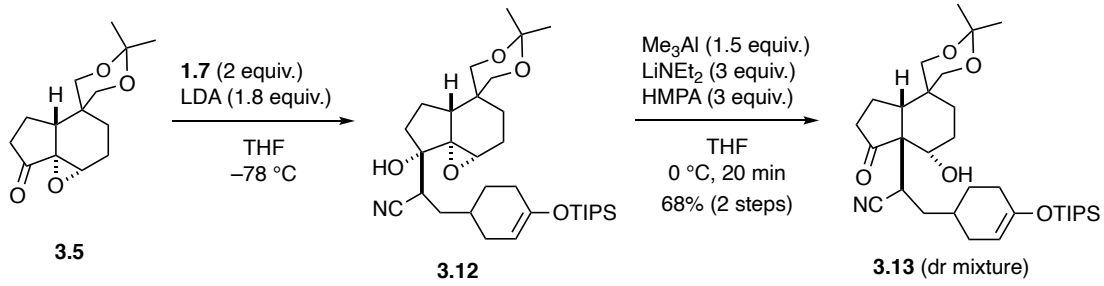
3-3. Fragment Coupling and Attempts for Intramolecular Alkylation

Synthesis of the left-hand fragment was started with the Michael addition reaction of cyclopentenone with diethyl allylmalonate **3.7** under basic conditions[50] (Scheme 3.6). The resulting alkene **3.8** was subjected to the aldehyde-selective Wacker-type oxidation reaction reported by Grubbs and Stoltz,[51] affording aldehyde **3.9** in 86% yield. Intramolecular aldol condensation was performed under acidic conditions, and the resulting enone **3.10** was converted to allylic alcohol **3.11** via stereoselective reduction with $LiAlH_4$ followed by protection of the 1,3-diol. Upon treatment with vanadium(V) oxytriethoxide ($VO(OEt)_3$) catalyst and TBHP, allylic alcohol **3.11** underwent a diastereoselective epoxidation, and the remaining secondary alcohol was oxidized with AZADOL[52] to give the desired epoxyketone **3.5** as a single diastereomer.



Scheme 3.6 Preparation of racemic epoxyketone

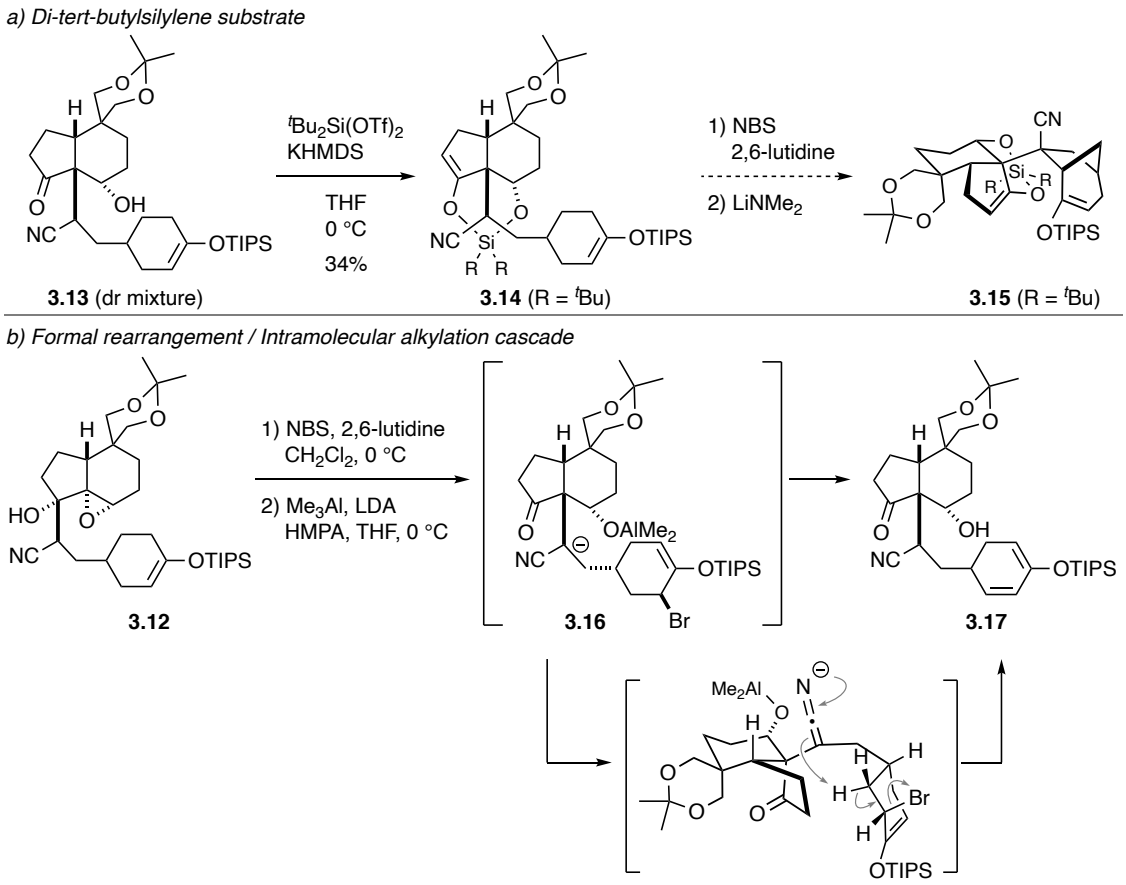
Then the left-hand fragment was subjected to the 1,2-addition/formal semi-pinacol rearrangement sequence (Scheme 3.7). Treatment of epoxyketone **3.5** with the α-cyano carbanion generated from nitrile **1.7** afforded cyano epoxyalcohol **3.12**. The addition reaction proceeded from the opposite face of the epoxide to provide the product having the nitrile side chain and epoxide in an *anti*-relationship. Upon treatment with 1.5 equiv of Me_3Al followed by 3 equiv of HMPA and 3 equiv of $LiNEt_2$, cyano epoxyalcohol **3.12** underwent a formal semi-pinacol rearrangement to give the desired *cis*-hydrindanone **3.13** as a mixture of epimers at the nitrile moiety in 68% yield for 2 steps.



3.5 **3.12** **3.13** (dr mixture)

Scheme 3.7 Fragment Coupling by Formal Semi-Pinacol Rearrangement

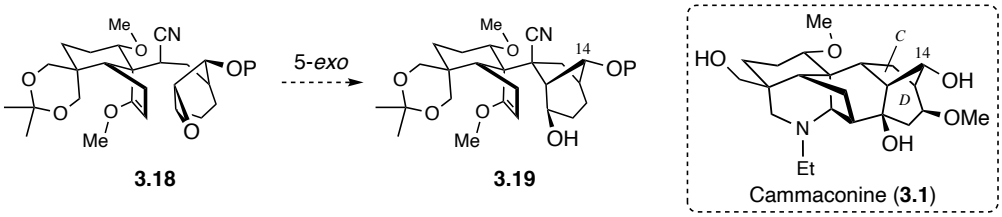
With the key intermediate in hand, the intramolecular alkylation reaction was explored (Scheme 3.8). At first, β-hydroxyketone **3.13** was converted to cyclic silyl ether **3.14** by the treatment with di-*tert*-butylsilyl bis(trifluoromethanesulfonate) and LHMDS (Scheme 3.8a). After bromination with NBS, the resulting bromonitrile **3.4** was subjected to the intramolecular alkylation reaction with $LiNMe_2$. However, the cyclization product **3.15** could not be obtained, probably because of the steric repulsion between the cyclohexene moiety and the bulky silylene protecting group. With a view to avoiding the use of a protecting group, intermediate **3.12** was brominated with NBS before the formal rearrangement reaction under basic conditions (Scheme 3.8b). It was expected that the anionic intermediate **3.16** produced by the ring-opening of the cyclopropane intermediate may undergo the cyclization with the bromide moiety, but the reaction merely afforded diene **3.17** as a major product. This result indicated that the α-cyano carbanion **3.16** preferred to abstract the axial proton, leading to β-elimination.



Scheme 3.8 Attempts for Constructing the Bicyclo[3.2.1]octane Ring System

3-4. CD-ring Construction by 5-exo cyclization

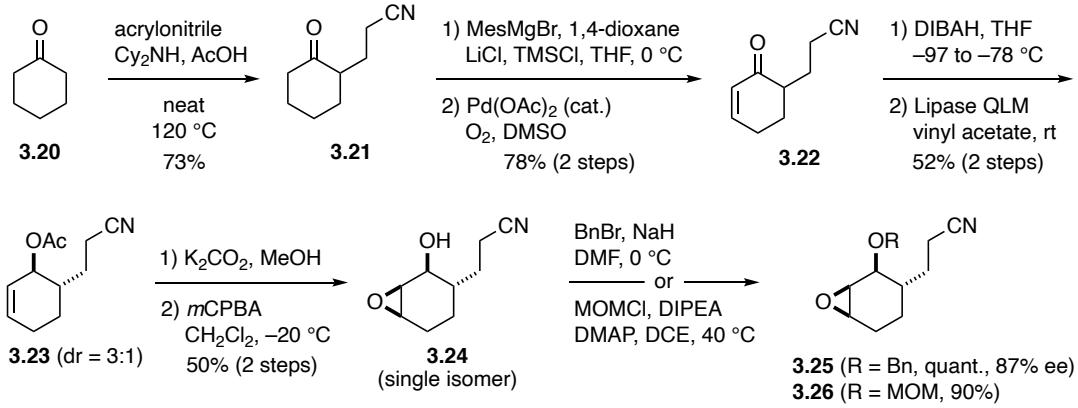
These results led the author to prepare epoxynitrile **3.18** as a cyclization precursor with the expectation of suppressing the undesired β-elimination pathway. The intramolecular S_N2 reaction requires the use of a substrate in which the epoxide and the nitrile moiety are in *anti*-relationship. To achieve the stereoselective formation of the β-epoxide, introduction of a β-hydroxy group, which corresponds to the C14 oxygen of cammaconine, was also planned.



3.18 **3.19**

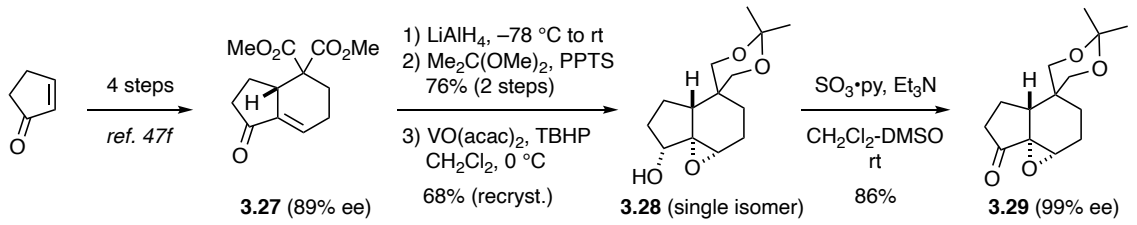
Figure 3.3 Redesign of the 5-exo cyclization precursor

Based on the new synthetic strategy, the corresponding nitrile fragment was prepared in an optically active form (Scheme 3.9). The synthesis of the fragment started with introduction of a cyanoethyl side chain at the C2-position of cyclohexanone by the known procedure.[53] Oxidation of ketone **3.21** was achieved by conversion to silyl enol ether with MesMgBr and TMSCl[54] followed by Saegusa-Ito oxidation. The resulting enone **3.22** was reduced with DIBAH to afford allylic alcohol, which was subjected to kinetic resolution[55] with lipase QLM in vinyl acetate, providing optically active allylic acetate **3.23** as a 3:1 diastereomeric mixture. The diastereomers could be separated by column chromatography of epoxyalcohol **3.24** which was obtained through removal of the acetate and diastereoselective epoxidation with *m*CPBA. Finally, the secondary alcohol was protected with BnBr or MOMCl to give nitriles **3.25** (quant.) and **3.26** (90% yield), respectively. The enantiomeric excess of benzyl ether **3.25** (87% ee) was determined by chiral HPLC analysis.



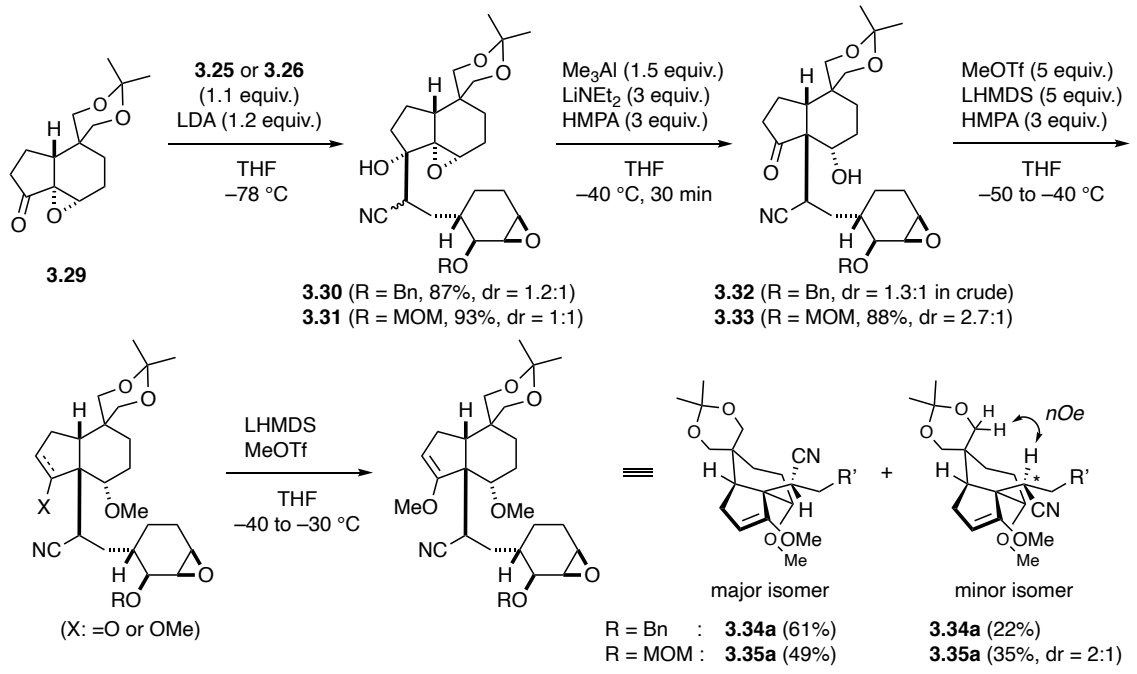
Scheme 3.9 Preparation of the Optically Active Nitrile Fragment

Epoxyketone fragment was also synthesized in an enantioselective manner (Scheme 3.10). The enantiomerically enriched (89% ee) enone **3.27** was prepared by the four-step protocol reported by Riesman.[47f] Conversion of enone **3.27** to allylic alcohol **3.28** was conducted via a three-step sequence similar with that described in Scheme 3.6. At this time, optical purity was increased by recrystallization, and the resulting alcohol was subjected to Parikh-Doering oxidation to afford the optically active left-hand fragment **3.29**. The enantiomeric excess of **3.29** (99% ee) was confirmed by chiral HPLC analysis.



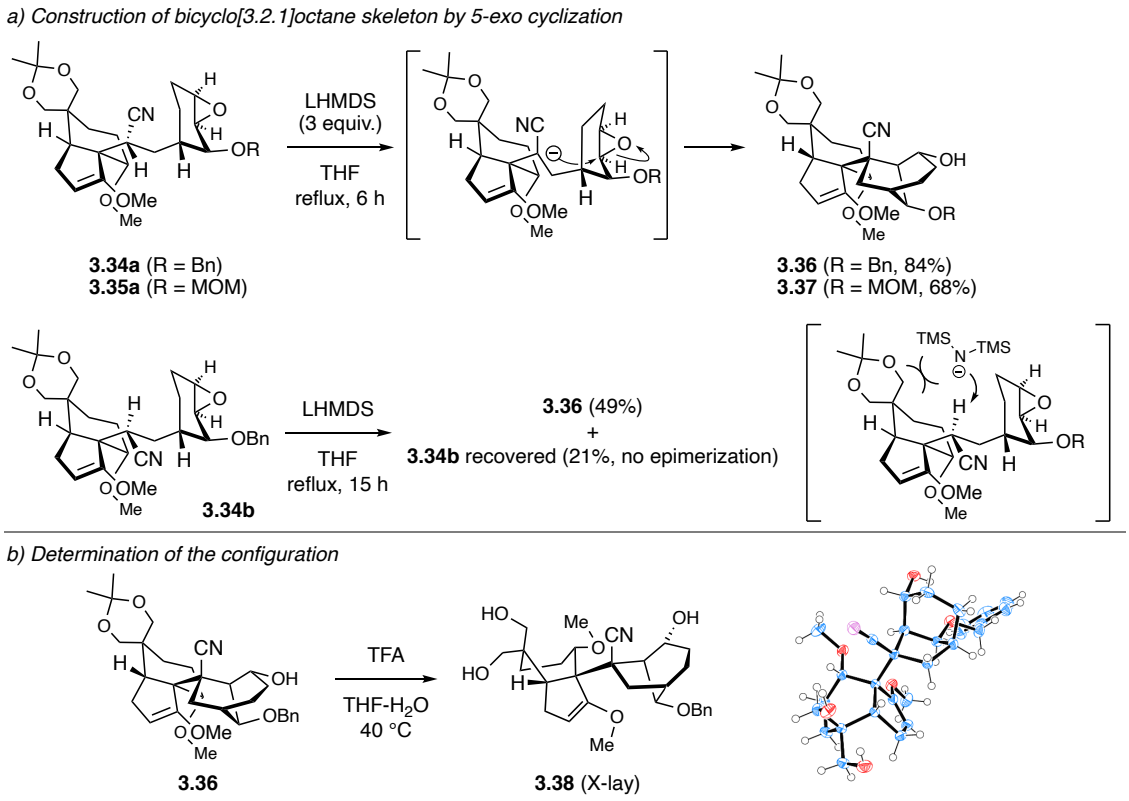
Scheme 3.10 Preparation of Optically Active Epoxyketone

Epoxyketone **3.29** was subjected to the 1,2-additon/formal rearrangement sequence with nitrile **3.25** or **3.26**, providing the corresponding keto nitriles **3.30** and **3.31** in good yields, respectively (Scheme 3.11). The hydroxy group of **3.30** was protected with a large excess amount of MeOTf and LHMDS, and the resulting mixture of mono- and bis-*O*-methylated compounds were repeatedly subjected to *O*-methylation to afford the cyclization precursors **3.34a** and **3.34b**, respectively. The stereochemical configuration of **3.34b** was determined by NOE NMR experiment. Nitrile **3.31** was also converted to the cyclization precursors **3.35a** and **3.35b**.



Scheme 3.11 Synthesis of 5-*exo* cyclization precursors

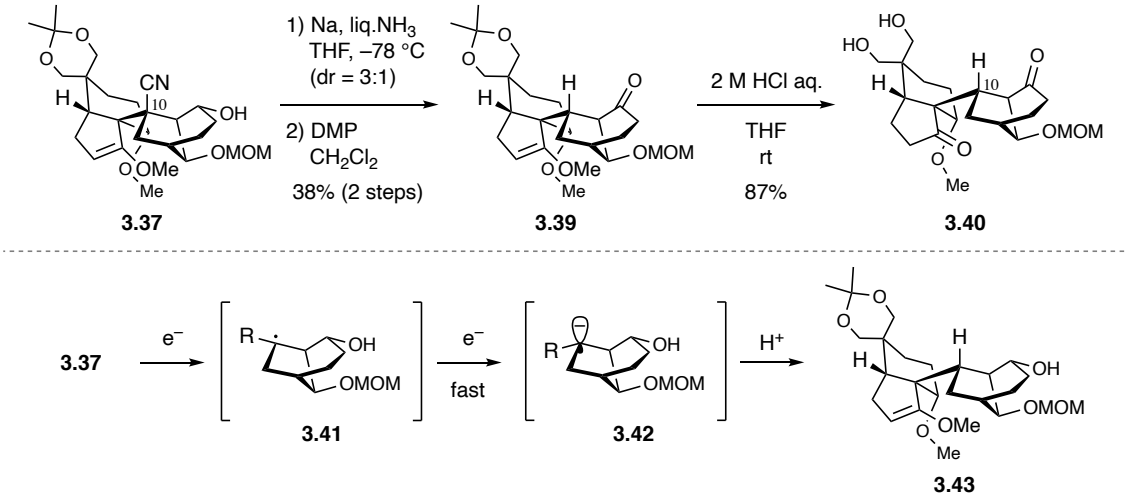
With the optically active substrates in hand, the intramolecular cyclization reactions were explored. Upon treatment with 3 equiv of LHMDS[56] under heating at 80 °C, major isomers **3.34a** or **3.35a** underwent a 5-*exo* cyclization to give tetracyclic compounds **3.36** and **3.37** in 84% and 68% yield as a single isomer, respectively (Scheme 3.12a). On the other hand, when the minor isomer **3.34b** was subjected to similar reaction conditions, the cyclization compound was produced in moderate yield along with 21% recovery of the substrate. Since the recovered **3.34b** retained the configuration at the α-position of the cyano group, the incomplete cyclization of **3.34b** would be attributable to the difficulty in deprotonation due to the steric factor. The configuration of the cyclization product **3.36** was confirmed by X-lay crystallographic analysis of diol **3.38**, which was obtained by hydrolysis under acidic conditions. It was found that the cyano group of the product was located at the concave face of the bicyclic skeleton, which was a undesired stereoisomer (Scheme 3.12b).



Scheme 3.12 5-*Exo* Cyclization and Structure Determination of the Product

The author expected that the stereochemistry at the C10 position may be inverted through reductive decyanation[57] to form a carbanion which would be protonated from the less hindered convex face of the bicyclo[3.2.1]octane skeleton (Scheme 3.13). The MOM-protected cyclization product **3.37** was subjected to a decyanation reaction under the Birch reduction conditions, yielding the decyanation product as a 3:1 mixture of diastereomers. The diastereomers were separated after

Dess-Martin oxidation of the resulting secondary alcohol, and ketone **3.39** was obtained as a major product. Upon treatment with 4 M HCl aq., the intramolecular aldol reaction did not proceed, but diketone **3.40** was obtained. X-ray crystallographic analysis of diketone **3.40** revealed that the major product of the decyanation reaction has the same stereochemical configuration as the cyclization product **3.37**. This result indicated that a protonation of the tertiary carbanion generated by reductive decyanation proceeded preferentially from the sterically hindered concave face.[58] The stereoselectivity can be interpreted as reflecting the thermodynamic stability of the carbanion intermediate. Thus, radical **3.41** generated by a single-electron reduction of nitrile **3.37** is quickly reduced by another single-electron transfer process to form carbanion intermediate **3.42**. At this time, the bulky substituent R preferentially located to the convex face of the bicyclo[3.2.1]octane skeleton, and this one is protonated to give the major product **3.43**.

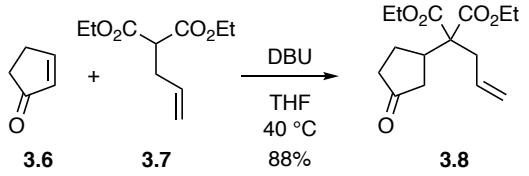


Scheme 3.13 Reductive Decyanation of Tetracyclic Compound

3-5. Conclusion

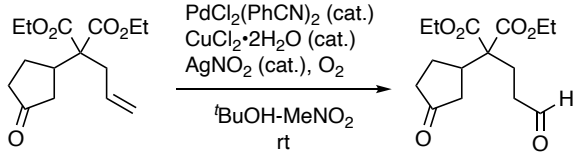
In summary, the author explored the methodology for constructing the aconitine skeleton by a convergent fragment coupling approach using nitrile derivatives. Fragment coupling was successfully performed by the 1,2-addition/formal semi-pinacol rearrangement protocol which was developed by Dr. Domon of the same laboratory. Unfortunately, the intramolecular alkylation reaction of bromonitrile described in chapter 1 could not be applied in the case of the substrate containing the bulky substituent at the α-position of cyano group. The author redesigned the cyclization precursor, and it was found that 5-*exo* cyclization of epoxynitrile was a powerful method for giving the tetracyclic compound.

3-6. Experimental section



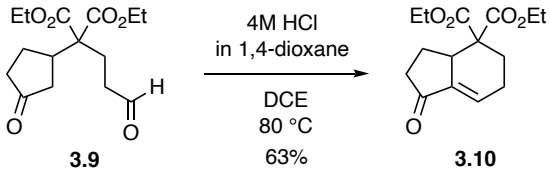
3.6 **3.7** **3.8**

1,4-adduct 3.8: To a solution of 2-cyclopenten-1-one (544 μL, 7.00 mmol) and Diethyl allylmalonate (1.41 mL, 7.00 mmol) in THF (7 mL) was added DBU (1.04 mL, 7.00 mmol). Then, the reaction mixture was warmed up to 40 °C and stirred for 13 h. After cooling to room temperature, the solvent was removed under reduced pressure. Purification by flash column chromatography (Hexane/EtOAc = 50:1 to 10:1) afforded 1,4-adduct **3.8** (1.74 g, 6.16 mmol, 88%) as pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74–5.66 (m, 1H), 5.17–5.11 (m, 2H), 4.24–4.17 (m, 4H), 2.82–2.75 (m, 1H), 2.72–2.71 (m, 2H), 2.52 (dd, 1H, *J* = 8.0, 18.4 Hz), 2.34–2.17 (m, 4H), 1.75–1.68 (m, 1H), 1.27 (t, 3H, *J* = 6.9 Hz), 1.26 (t, 3H, *J* = 6.9 Hz).



3.8 **3.9**

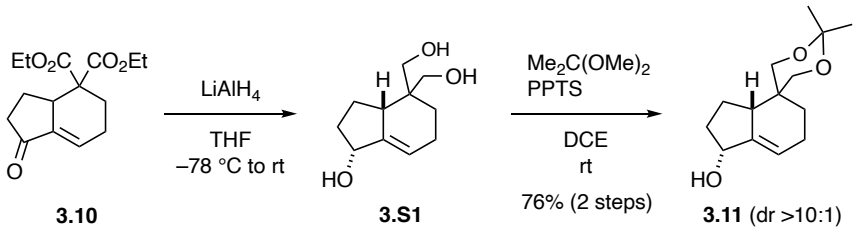
Aldehyde 3.9: To a flame-dried 500 mL 2-necked flask with a magnetic stir bar were added $PdCl_2(PhCN)_2$ (283.5 mg, 0.739 mmol), $CuCl_2$•$2H_2O$ (126.0 mg, 0.739 mmol) and $AgNO_2$ (56.9 mg, 0.370 mmol). Then, ^{t}BuOH (100 mL) and $MeNO_2$ (6.7 mL) were added to the flask, the mixture was stirred at room temperature and sparged with oxygen gas (balloon) for 10 min. Alkene **3.8** (1.74 g, 6.16 mmol) in ^{t}BuOH (15 mL) and $MeNO_2$ (1.0 mL) was added dropwise to the mixture via cannula. After stirring for 7.5 h under oxygen, the reaction mixture was diluted with H_2O (120 mL) and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash column chromatography (Hexane/EtOAc = 20:1 to 3:1) afforded aldehyde **3.9** (1.59 g, 5.33 mmol, 86%) as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.75 (s, 1H), 4.22–4.18 (m, 4H), 2.80–2.72 (m, 1H), 2.57 (td, 2 H, *J* =5.7 Hz, 9.2 Hz), 2.46 (dd, 1H, *J* = 7.4, 18.3 Hz), 2.35–2.14 (m, 6H), 1.78–1.71 (m, 1H), 1.26 (t, 6H, *J* = 6.9Hz).



3.9 **3.10**

Enone 3.10: To a solution of aldehyde **3.9** (296 mg, 0.99 mmol) in DCE (5 mL) was added 4 M HCl

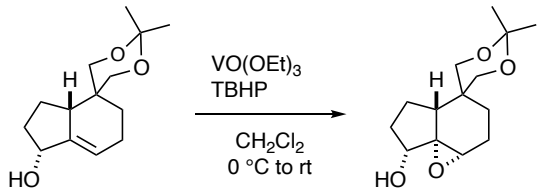
in 1,4-dioxane (24.7 µL, 98.8 µmol). Then, the reaction mixture was warmed up to 80 °C. 4 M HCl in 1,4-dioxane (50.0 µL, 0.198 mmol) was further added to the reaction mixture every 3 hours. After completion of the reaction was monitored by TLC, the reaction was quenched with saturated aqueous $NaHCO_3$ solution at room temperature. After the layers were separated, the aqueous layer was extracted with EtOAc (5 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash column chromatography (Hexane/EtOAc = 50:1 to 5:1) afforded enone **3.10** (176 mg, 0.628 mmol, 63%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.71 (d, 1H, *J* = 3.5 Hz), 4.28–4.22 (m, 2H), 4.16 (q, 2H, J = 6.9 Hz), 3.10 (br, 1H), 2.48–2.39 (m, 4H), 2.31–2.23 (m, 2H), 2.16–2.07 (m, 1H), 1.98–1.91 (m, 1H), 1.29 (t, 3H, *J* = 6.9 Hz), 1.23 (t, 3H, *J* = 6.9 Hz).



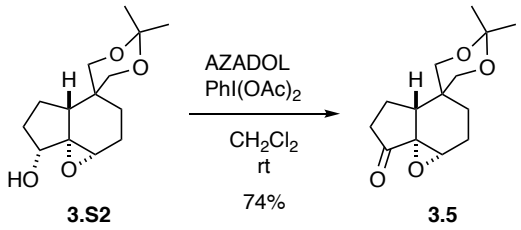
3.10 **3.S1** **3.11** (dr >10:1)

Allylic alcohol 3.11: To a suspension of LiAlH4 (576 mg, 15.2 mmol) in THF (9 mL) was added enone **3.10** (774 mg, 2.76 mmol) in THF (5 mL) via cannula at –78 °C. After stirring for 30 min, the reaction mixture was warmed up to room temperature and stirred another 1 h. To the reaction mixture was added dropwise sequentially H_2O (575 µL), 15% aqueous NaOH solution (575 µL) and H_2O (1.7 mL) at 0 °C, then diluted with Et_2O (10 mL) and stirred at room temperature for 16 h. The resulting suspension was dried over $MgSO_4$ for 1h, and filtrated through a pad of Celite. The filtrate was concentrated under reduced pressure. The obtained crude alcohol **3.S1** was used for the next step without further purification.

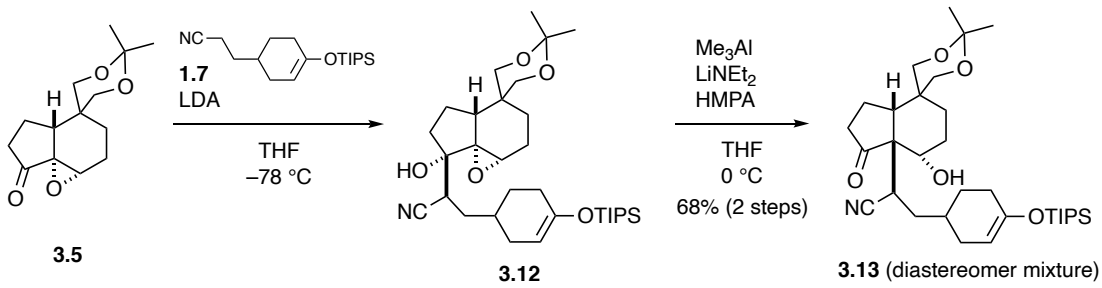
To a solution of the above crude alcohol **3.S1** and 2,2-dimethoxypropane (2.03 mL, 16.6 mmol) in CH_2Cl_2 (14 mL) was added pyridinium *p*-toluenesulfonate (PPTS) (6.9 mg, 27.6 µmol). After stirring for 6 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (15 mL). After the layers were separated, the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash column chromatography (Hexane/EtOAc = 50:1 to 1:1) afforded allylic acohol **3.11** (504 mg, 2.10 mmol, 76% for 2 steps, dr > 10:1) as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78 (s, 1H), 4.49 (s, 1H), 3.85 (d, 1H, *J* = 11.5 Hz), 3.77 (d, 1H, *J* = 12.0 Hz), 3.53 (d, 1H, *J* = 12.0 Hz), 3,47 (d, 1H, *J* = 11.5 Hz), 2.20–2.16 (m, 1H), 2.10–2.04 (m, 3H), 1.87–1.65 (m, 4H), 1.52 (s, 0.4H), 1.41 (s, 5.6H), 1.32–1.16 (m, 2H).



Epoxide 3.S2: To a solution of allylic alcohol **3.11** (500 mg, 2.10 mmol, dr >10:1) and TBHP (5.5 M in nonane, 570 µL, 3.15 mmol) in CH_2Cl_2 (11 mL) was added vanadium(V) oxytriethoxide ($VO(OEt)_3$) (37.1 µL, 0.210 mmol) at 0 °C. After stirring for 1 h at the same temperature, the reaction mixture was warmed up to room temperature and stirred another 30 min. The reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ solution (10 mL) and stirred for 30 min. After the layers were separated, the aqueous layer was extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash column chromatography (Hexane/EtOAc = 20:1 to 1:1) afforded epoxide **3.S2** (438 mg, 1.72 mmol, 82%, single diastereomer) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.20 (dt, 1H, *J* = 5.2 Hz, 9.2 Hz), 4.01 (d, 1H, *J* = 12.6 Hz), 3.87 (dd, 1H, *J* = 1.8, 12.6 Hz), 3.75 (d, 1H, *J* = 11.5 Hz), 3.45 (d, 1H, *J* = 4.6 Hz), 3.25 (dd, 1H, *J* = 1.8, 11.5 Hz), 2.20–2.03 (m, 4H), 2.00–1.94 (m, 1H), 1.91–1.85 (m, 2H), 1.67–1.64 (m, 1H), 1.39 (s, 3H), 1.36 (s, 3H), 1.31–1.29 (m, 1H), 1.09–1.03 (m, 1H).

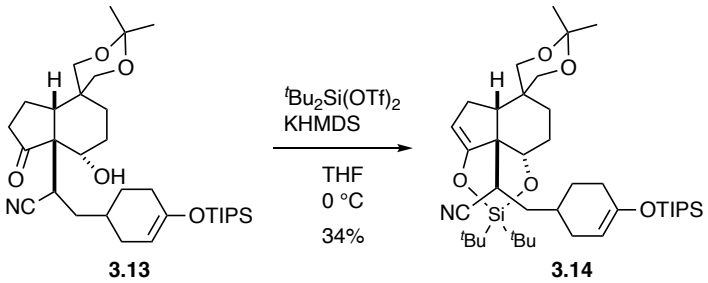


Epoxyketone 3.5: To a solution of epoxide **3.S2** (438 mg, 1.72 mmol) and iodobenzene diacetate ($PhI(OAc)_2$) (831.2 mg, 2.58 mmol) in CH_2Cl_2 (8.6 mL) was added AZADOL (13.2 mL, 86.0 µmol). After stirring for 4 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (4 mL) and saturated aqueous $Na_2S_2O_3$ solution (4 mL) and stirred for 30 min. After the layers were separated, the aqueous layer was extracted with EtOAc (8 mL × 3). The combined organic layers were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash column chromatography (Hexane/EtOAc = 20:1 to 3:1) afforded epoxide **3.5** (318 mg, 1.26 mmol, 74%) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.09. (d, 1H, *J* = 12.1 Hz), 3.793.72 (m, 3H), 3.74 (d, 1H, *J* = 11.5 Hz), 2.60–2.54 (m, 1H), 2.48–2.44 (m, 1H), 2.34–2.21 (m, 2H), 2.10–2.04 (m, 2H), 1.95–1.92 (m, 1H), 1.79 (td, 1H, *J* = 6.3, 14.3Hz), 1.41 (s, 3H), 1.40 (s, 3H), 1.24–1.17 (m, 1H).

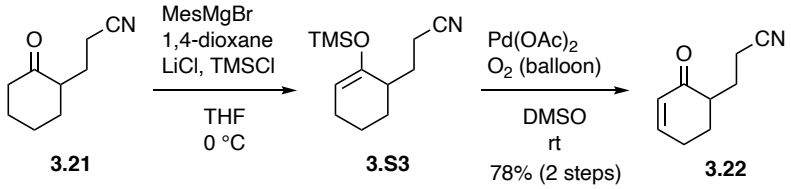


β-Hydroxyketone 3.13: To a solution of nitrile **1.7** (386 mg, 1.26 mmol) in THF (2 mL) was added LDA (1 M in THF, 1.13 mL, 1.13 mmol) at –78 °C. After stirring for 30 min at the same temperature, a solution of epoxyketone **3.5** (159 mg, 0.630 mmol) in THF (2 mL) was added to the mixture via cannula. The reaction mixture was stirred for another 30 min, the reaction was quenched with saturated aqueous $NaHCO_3$ solution (4 mL). After the layers were separated, the aqueous layer was extracted with EtOAc (4 mL × 3). The combined organic layers were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. The residue was roughly purified by column chromatography, and the obtained crude 1,2-adduct **3.12** was used for the next step without further purification.

To a solution of the above crude 1,2-adduct **3.12** (345 mg) in THF (3.1 mL) was added trimethyl aluminum (Me_3Al) (2.0 M in toluene, 462 μL, 0.924 mmol) at 0 °C and the reaction mixture was warmed up to room temperature. After stirring for 1 h, HMPA (115 μL, 0.654 mmol) was added to the reaction mixture. Then, the reaction mixture was cooled to –78 °C, $LiNEt_2$ (1.0 M in THF, 1.85 mL, 1.85 mmol) was further added and warmed up to 0 °C. After stirring for 20 min at the same temperature, the reaction was quenched by addition of AcOH (2.0 M in THF, 2.16 mL, 4.32 mmol) at –78 °C and warmed up to room temperature. Then, saturated aqueous NaCl solution was further added to the mixture. After the layers were separated, the aqueous layer was extracted with EtOAc (4 mL × 3). The combined organic layers were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by silica gel chromatography (Hexane/EtOAc = 50:1 to 2:1) afforded a β-Hydroxyketone **3.13** (239 mg, 0.420 mmol, 68% for 2 steps, 1.5:1 diastereomer mixture) as a white amorphous: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.80 (s, 0.6H), 4.56 (s, 0.4H), 4.05–4.01 (m, 1H), 3.86 (dd, 1H, J = 3.5, 12.0 Hz, 0.4 H), 3.76–3.68 (m, 1.6H), 3.64–3.51 (m, 1.6H), 3.34–3.28 (m, 0.4 H), 2.77–2.41 (m, 4H), 2.17–1.96 (m, 8H), 1.87–1.59 (m, 8H), 1.49 (s, 1.2H), 1.42 (s, 1.8H), 1.41 (s, 1.2H), 1.39 (s, 1.8H), 1.15–1.05 (m, 21H).

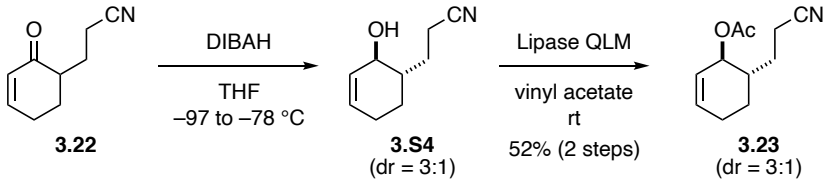


Silylene 3.14: To a solution of β-Hydroxyketone **3.13** (25.1 mg, 44.8 μmol) in THF (225 μL) was added KHMDS (1 M in THF, 98.6 μL, 98.6 μmol) at –78 °C. After stirring for 30 min at the same temperature, di-tert-butylsilyl bis(trifluoromethanesulfonate) (17.4 μL, 53.8 μmol) was added to the mixture. Then, the reaction mixture was warmed up to 0 °C and stirred for 30 min. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (0.5 mL). After the layers were separated, the aqueous layer was extracted with EtOAc (1 mL × 3). The combined organic layers were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash column chromatography (Hexane/EtOAc = 50:1 to 10:1) afforded silylene **3.14** (10.8 mg, 15.4 μmol, 34%, 1.3:1 diastereomer mixture) as a white amorphous: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.20 (s, 0.55H), 4.46–4.43 (m, 0.55H), 4.04–4.00 (m, 0.45H), 3.87 (dd, 0.55H, *J* = 5.2, 12.1 Hz), 3.78 (dd, 0.55H, *J* = 5.2, 12.0 Hz), 3.70–3.66 (m, 1H), 3.63 (d, 0.55H, *J* = 12.1 Hz), 3.55 (d, 0.45H, *J* = 12.1 Hz), 3.50–3.39 (m, 1H), 3.32–3.28 (m, 0.45H), 3.13 (dd, 0.55H, *J* = 7.5, 11.5 Hz), 2.60–2.48 (m, 1.45H), 2.39 (d, 0.55H, *J* = 16.0 Hz), 2.32–2.12 (m, 3H), 2.08–1.74 (m, 6H), 1.67–1.42 (m, 4H), 1.39–1.35 (m, 6H), 1.30–1.26 (m, 1H), 1.14–1.04 (m, 39H).



Enone 3.22: Ketone **3.21** was prepared by the known procedure.[53] A 500 mL 2-necked flask was charged with LiCl (4.07 g, 96.0 mmol) and flame-dried under vacuum. The flask was purged three times with Argon and charging with MesMgBr (1 M solution in Et_2O, 48.0 mL, 48.0 mmol), 1,4-dioxane (4.31 mL, 50.4 mmol) and THF (112 mL). The mixture was stirred for 15 min at room temperature before cooling to 0 ◦C. TMSCl (6.06 mL, 48 mmol) was added and the mixture was stirred for 5 min before addition of a solution of the ketone **3.21** (0.5 M in THF, 48.0 mL, 24.0 mmol) over 1 h via syringe pump. After stirring at the same temperature for 30 min, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (150 mL). After the layers were separated, the aqueous layer was extracted with Et_2O (100 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. The obtained crude silyl enol ether **3.S3** was used for the next step without further purification.

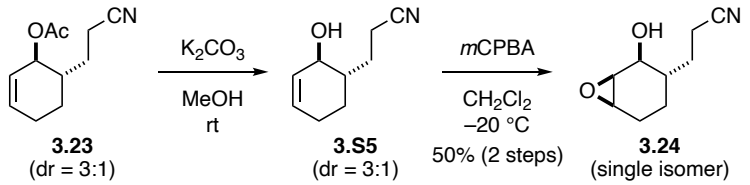
To a solution of the above crude silyl enol ether **3.S3** (13.93 g) in DMSO (120 mL) was added palladium diacetate ($Pd(OAc)_2$) (538 mg, 2.40 mmol). The reaction mixture was stirred under O_2 atmosphere (balloon) for 18 h. Then, $Pd(OAc)_2$ (538 mg, 2.40 mmol) was further added to the reaction mixture and the reaction mixture was stirred for another 10 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (150 mL). After the layers were separated, the aqueous layer was extracted with EtOAc (100 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash column chromatography (Hexane/EtOAc = 10:1 to 5:4) afforded enone **3.22** (2.79 g, 18.7 mmol, 78% for 2 steps) as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 (td, 1H, *J* = 5.2, 10.3 Hz), 6.02 (d, 1H, *J* = 10.3 Hz), 2.64–2.45 (m, 5H), 2.20–2.10 (m, 2H), 1.84–1.76 (m, 1H), 1.72–1.65 (m, 1H).



3.22 **3.S4** (dr = 3:1) **3.23** (dr = 3:1)

Allylic acetate 3.23: To a solution of enone **3.22** (2.74 g, 18.4 mmol) in THF (91 mL) was added DIBAH (1.03 M in Hexane, 26.8 mL, 27.6 mmol) at –97 °C. Then, the reaction mixture was gradually warmed up to –78 °C over 1 h, and quenched with saturated aqueous Rochelle salt solution (100 mL). The mixture was stirred at room temperature for 1 h. After the layers were separated, the aqueous layer was extracted with EtOAc (100 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. The obtained crude allylic alcohol **3.S4** was used for the next step without further purification.

To a solution of the above allylic alcohol **3.S4** (2.88 g) in vinyl acetate (37 mL) was added Lipase QLM (1.44 g). After stirring for 18 h, the suspension was filtrated through a pad of Celite, and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (Hexane/EtOAc = 20:1 to 10:1) afforded optically active allylic acetate **3.23** (1.86 g, 9.62 mmol, 52% for 2 steps, 3:1 diastereomer mixture) as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.01–5.98 (m, 0.25H), 5.91–5.89 (m, 0.75H), 5.83–5.80 (m, 0.25H), 5.60 (dd, 0.75H, *J* = 2.3, 10.3 Hz), 5.22 (t, 0.25H, *J* = 4.0 Hz), 5.07 (dd, 0.75H, *J* = 2.3, 4.6 Hz), 2.49–2.31 (m, 3H), 2.16–2.06 (m, 5H), 1.89–1.80 (m, 2H), 1.66–1.41 (m, 2H).

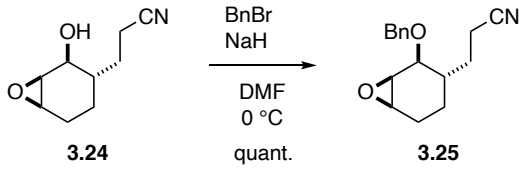


3.23 (dr = 3:1) **3.S5** (dr = 3:1) **3.24** (single isomer)

Epoxy alcohol 3.24: To a solution of allyl acetate (1.74 g, 9.00 mmol) in MeOH (30 mL) was added

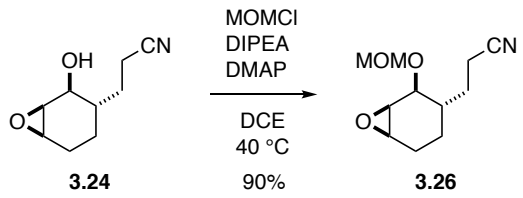
potassium carbonate (2.49 g, 18.0 mmol) at 0 °C. Then, the reaction mixture was warmed up to room temperature and stirred for 1 h. Then, the reaction mixture was diluted with H_2O (30 mL) and MeOH was removed under reduced pressure. The residue was extracted with EtOAc (30 mL × 3) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. The obtained crude allyl alcohol **3.S5** was used for the next step without further purification.

To a solution of the above crude allyl alcohol **3.S5** (1.45 g) in CH_2Cl_2 (60 mL) was added mCPBA (3.58 g, 13.5 mmol) in four portions at –20 °C. After stirring for 6 h, the reaction was quenched with 2-methyl-2-butene (6 mL) at the same temperature. Then, the mixture was stirred at room temperature for 30 min and saturated aqueous $NaHCO_3$ solution (50 mL) was added. After the layers were separated, the aqueous layer was extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash column chromatography (Hexane/EtOAc = 4:1 to 2:3) afforded epoxy alcohol **3.24** (748 mg, 4.5 mmol, 50% for 2 steps) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.61 (t, 1H, *J* = 8.6 Hz), 3.38 (t, 1H, *J* = 4.0 Hz), 3.30–3.29 (m, 1H), 2.52–2.38 (m, 2H), 2.08–2.01 (m, 1H), 1.97–1.90 (m, 1H), 1.88–1.78 (m, 2H), 1.56–1.48 (m, 2H), 1.11–1.02 (m, 1H).

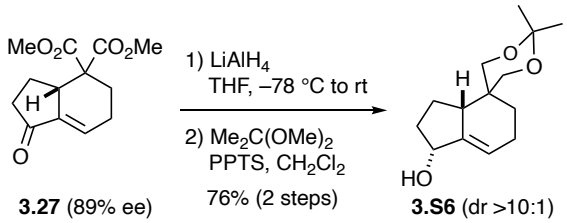


3.24 quant. **3.25**

Benzyl ether 3.25: To a solution of alcohol **3.24** (50.4 mg, 0.301 mmol) and benzyl bromide (53.6 μL, 0.542 mmol) in DMF (1.5 mL) was added NaH (55% dispersion, 39.4 mg, 0.903 mmol) at 0 °C. After stirring for 1 h at the same temperature, MeOH (60 μL) was added to the reaction mixture and the reaction mixture was stirred another 30 min. The reaction was quenched with saturated aqueous NH_4Cl solution (2 mL) and extracted with EtOAc (1 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash column chromatography (Hexane/EtOAc = 20:1 to 3:1) afforded benzyl ether **3.25** (78.2 mg, 0.301 mmol, quant., 87% ee) as a pale yellow oil. The enantiomeric excess (ee) was determined by HPLC analysis (CIRALCEL AS-H column, 5.0 μm, 250×4.6 mm, Hexane/^{i}PrOH (85:15 as an eluent), flow rate = 1.0 mL/min, λ = 220 nm, major enantiomer t_R = 20.1 min, minor enantiomer t_R = 17.8 min: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.30 (m, 5H), 4.81 (d, 1H, *J* = 11.5 Hz), 4.4.64 (d, 1H, *J* = 11.5 Hz), 3.49 (dd, 1H, *J* = 1.8, 9.7 Hz), 3.38 (dd, 1H, *J* = 1.8, 4.0 Hz), 3.31 (t, 1H, *J* = 4.0 Hz), 2.36–2.24 (m, 2H), 2.05–1.98 (m, 1H), 1.96–1.74 (m, 3H), 1.59–1.57 (m, 1H), 1.47–1.40 (m, 1H), 1.10–1.02 (m, 1H).



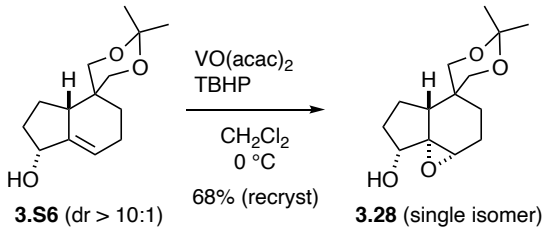
MOM ether 3.26: To a solution of alcohol **3.24** (35.4 mg, 0.212 mmol) and *N,N*-diisopropylethylamine (DIPEA) (148 μL, 0.848 mmol) in DCE (1 mL) was sequentially added chloromethyl methyl ether (MOMCl) (33.5 μL, 0.424 mmol) and *N,N*-dimethylaminopyridine (DMAP) (1 tip). Then, the reaction mixture was warmed up to 40 °C and stirred for 14 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (1 mL). After the layers were separated, the aqueous layer was extracted with EtOAc (1 mL × 3). The combined organic layers were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash column chromatography (Hexane/EtOAc = 20:1 to 5:4) afforded MOM ether **3.26** (40.1 mg, 0.190 mmol, 90%) as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.89 (d, 1H, *J* = 6.9 Hz), 4.75 (d, 1H, *J* = 6.9 Hz), 3.58 (dd, 1H, *J* = 1.7, 9.9 Hz), 3.45 (s, 3H), 3.38 (dd, 1H, *J* = 1.7, 4.0 Hz), 3.30 (t, 1H, *J* = 4.0 Hz), 2.38 (d, 1H, *J* = 11.5 Hz), 2.42–2.31 (m, 2H), 2.10–2.03 (m, 1H), 1.97–1.91 (m, 1H), 1.88–1.81 (m, 1H), 1.73–1.66 (m, 1H), 1.50–1.43 (m, 1H), 1.11–1.02 (m, 1H).



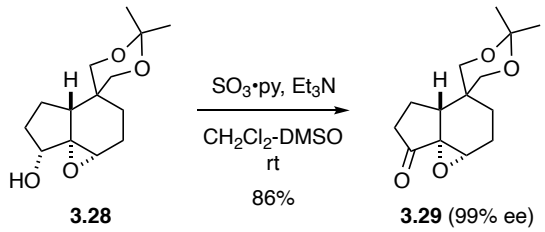
Allylic alcohol 3.S6: Enone **3.27** was synthesized by the known procedure. To a suspension of $LiAlH_4$ (4.29 mg, 124 mmol) in THF (90 mL) was added enone **3.27** (5.71 g, 22.6 mmol) in THF (25 mL) via cannula at –78 °C. After stirring for 30 min, the reaction mixture was warmed up to room temperature and stirred another 1 h. To the reaction mixture was added dropwise sequentially H_2O (4.3 mL), 15% aqueous NaOH solution (4.3 mL) and H_2O (13 mL) at 0 °C, then diluted with Et_2O (200 mL) and stirred at room temperature for 16 h. The resulting suspension was dried over $MgSO_4$ for 1h, and filtrated through a pad of Celite. The filtrate was concentrated under reduced pressure. The obtained crude alcohol was used for the next step without further purification.

To a solution of the above crude alcohol and 2,2-dimethoxypropane (16.6 mL, 136 mmol) in CH_2Cl_2 (113 mL) was added pyridinium *p*-toluenesulfonate (PPTS) (56.8 mg, 0.226 μmol). After stirring for 3 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (100 mL). After the layers were separated, the aqueous layer was extracted with EtOAc (100 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated, and concentrated under reduced

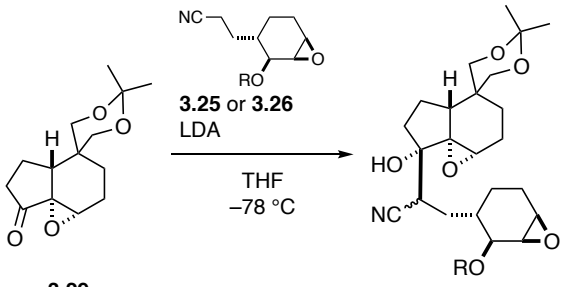
pressure. Purification by flash column chromatography (Hexane/EtOAc = 50:1 to 1:1) afforded allylic acohol **3.S6** (4.09 g, 17.2 mmol, 76% for 2 steps, dr > 10:1) as a pale yellow oil. The ^{1}H NMR spectra were identical to those of racemic compound **3.11**.



Epoxide 3.28: To a solution of allylic alcohol **3.S6** (4.14 g, 17.4 mmol, dr > 10:1) and TBHP (5.5 M in decane, 3.8 mL, 20.9 mmol) in CH_2Cl_2 (87 mL) was added vanadium(V)-oxy acetyacetonate ($VO(acac)_2$) (231 mg, 0.870 mmol) at 0 °C. After stirring for 1.5 h at the same temperature, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ solution (45 mL) and saturated aqueous $NaHCO_3$ solution (45 mL), and stirred for 30 min. After the layers were separated, the aqueous layer was extracted with EtOAc (100 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash column chromatography (Hexane/EtOAc = 10:1 to 4:5) and recrystallization from Hexane-Et_2O afforded epoxide **3.28** (2.99 g, 11.8 mmol, 68%, single diastereomer) as a colorless oil. ^{1}H NMR spectra were identical to those of racemic compound **3.S2**.



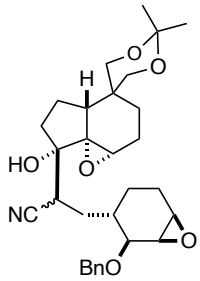
Epoxyketone 3.29: To a solution of alcohol **3.28** (1.26 g, 4.94 mmol) and Et3N (2.07 mL, 14.8 mmol) in CH_2Cl_2 (20 mL) was added a solution of SO_3•py (1.24 g, 7.41 g) in DMSO (4 mL) at 0 °C. Then, the reaction mixture was warmed up to room temperature and stirred for 5 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (100 mL). After the layers were separated, the aqueous layer was extracted with EtOAc (30 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash column chromatography (Hexane/EtOAc = 50:1 to 1:1) afforded epoxyketone **3.29** (1.07 g, 4.25 mmol, 86%, 98% ee) as a white solid. The enantiomeric excess (ee) was determined by HPLC analysis (CIRALCEL OD-H column, 5.0 μm, 250×4.6 mm, Hexane/^{i}PrOH (60:40 as an eluent), flow rate = 1.0 mL/min, λ = 220 nm, major enantiomer t_R = 7.3 min, minor enantiomer t_R = 6.4 min. ^{1}H NMR spectra were identical to those of racemic compound **3.5**.



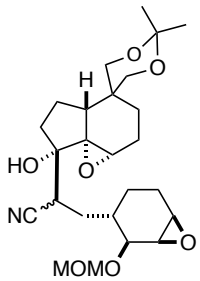
3.29

3.30 (R = Bn, 87%, dr = 1.2:1)
3.31 (R = MOM, 93%, dr = 1:1)

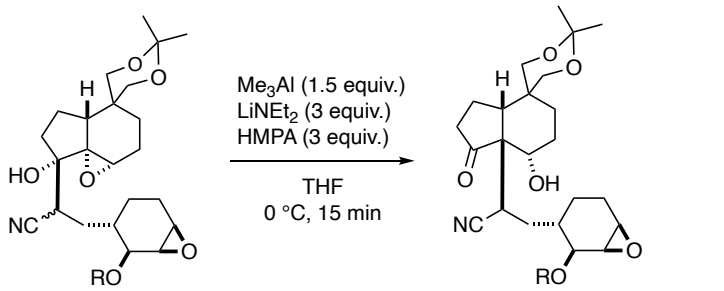
1,2-adducts 3.30 and **3.31**: To a solution of nitrile **3.25** or **3.26** (1.1 equiv.) in THF (0.4 M) was added LDA (1.0 M in THF, 1.2 equiv.) at –78 °C. After stirring for 30 min at the same temperature, a solution of epoxyketone **3.29** (1.0 equiv.) in THF (0.4 M) was added to the mixture via cannula and stirred for 40 min. The reaction mixture was quenched with brine. After the layers were separated, the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by flash column chromatography afforded 1,2-adducts **3.30** and **3.31**.



Benzyl ether 3.30: Purification by flash column chromatography (Hexane/EtOAc = 4:1 to 3:2) afforded benzyl ether **3.30** (121.3 mg, 0.238 mmol, 87%, 1.2:1 diastereomer mixture) from epoxyketone **3.29** (69.2 mg, 0.274 mmol) as a white amorphous: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.30 (m, 5H), 4.89 (d, 0.45H, *J* = 11.5 Hz), 4.80 (d, 0.55H, *J* = 11.5 Hz), 4.66 (d, 1H, *J* = 11.5 Hz), 4.56 (d, 1H, *J* = 11.5 Hz), 3.96–3.90 (m, 1H), 3.79–3.68 (m, 2H), 3.61 (dd, 0.55H, *J* = 1.7, 9.2 Hz), 3.54–.3.46 (m, 1.55H), 3.42–3.37 (m, 1H), 3.33–3.30 (m, 1.45H), 3.11 (d, 1H, *J* = 11.5 Hz), 2.93 (s, 0.55H), 2.87–2.84 (m, 0.9H), 2.54 (dd, 1H, *J* = 4.0, 11.5 Hz), 2.10–1.48 (m, 7H), 1.38 (s, 1.35H), 1.38–1.35 (m, 6H), 1.32–1.15 (m, 3H), 1.06–0.90 (m, 1H)

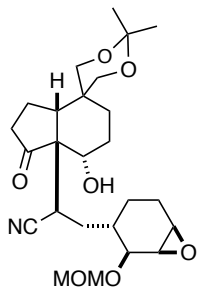


MOM ether 3.31: Purification by flash column chromatography (Hexane/EtOAc = 1:1 to 2:3) afforded benzyl ether **3.31** (73.7 mg, 0.160 mmol, 93%, 1:1 diastereomer mixture) from epoxyketone **3.29** (43.5 mg, 0.172 mmol) as a white amorphous: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.89 (d, 0.5H, *J* = 7.5 Hz), 4.86 (d, 0.5H, *J* = 6.3 Hz), 4.79 (d, 0.5H, *J* = 6.3 Hz), 4.77 (d, 0.5H, *J* = 7.5 Hz), 4.01 (d, 0.5H, *J* = 12.6 Hz), 3.97 (d, 0.5H, *J* = 12.1 Hz), 3.83–3.67 (m, 2.5H), 3.61–3.54 (m, 1.5H), 3.46 (s, 1.5H), 3.45 (s, 1.5H), 3.38 (br s, 1H), 3.31–3.29 (m, 2H), 2.97 (s, 0.5H), 2.89 (s, 0.5H), 2.77 (dd, 0.5H, *J* = 3.5, 10.9 Hz), 2.49 (dd, 0.5H, *J* = 4.0, 12.0 Hz), 2.14–1.73 (m, 14H), 1.38 (s, 1.5H), 1.37 (s, 1.5H), 1.36 (s, 3H), 1.31–0.97 (m, 2H).

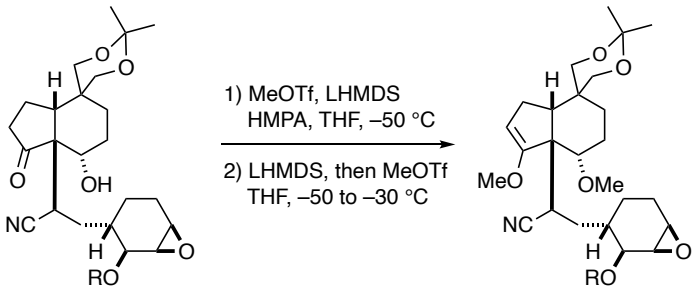


β-Hydroxy ketone 3.32 and **3.33**: To a solution of 1,2-adduct **3.30** or **3.31** (1.0 equiv.) in THF (0.1 M) was added trimethyl aluminum (Me_3Al) (2.0 M in toluene, 1.5 equiv.) at 0 °C and the reaction mixture was warmed up to room temperature. After stirring for 1 h, HMPA (3.0 equiv.) was added to the reaction mixture. Then, the reaction mixture was cooled to –78 °C, $LiNEt_2$ (1.0 M in THF, 3.0 equiv.) was further added and warmed up to –40 °C. After stirring for 30 min at the same temperature, the reaction was quenched by addition of AcOH (2.0 M in THF, 7.0 equiv.) at –78 °C and warmed up to room temperature. Then, saturated aqueous NaCl solution was further added to the mixture. After the layers were separated, the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by column chromatography afforded β-Hydroxy ketone **3.32** and **3.33**.

The obtained crude of Benzyl ether **3.32** (1.3:1 diastereomer mixture) was roughly purified by column chromatography and used for the next step without further purification.



MOM ether 3.33: Purification by flash column chromatography (Hexane/EtOAc = 1:1 to 2:3) afforded benzyl ether **3.33** (32.6 mg, 70.2 μmol, 88%, 2.7:1 diastereomer mixture) from 1,2-adduct **3.31** (37.0 mg, 79.8 μmol) as a white amorphous: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.89 (d, 0.7H, J = 6.9 Hz), 4.81–4.78 (m, 0.6H), 4.75 (d, 0.7H, J = 6.9 Hz), 4.52 (br s, 0.3H), 4.05 (d, 0.7H, J = 12.1 Hz), 3.97 (br s, 0.7H), 3.83 (d, 0.7H, J = 12.1 Hz), 3.74–3.51 (m, 3.6H), 3.46 (s, 2.1H), 3.44 (s, 0.9H), 3.39–3.35 (m, 1H), 3.30–3.27 (m, 1.7H), 2.92 (dd, 0.3H, J = 3.5, 12.1 Hz), 2.75–2.65 (m, 1H), 2.52–2.40 (m, 1H), 2.32–2.16 (m, 1H), 2.13–1.60 (m, 12H), 1.45–1.29 (m, 7H), 0.94–0.87 (m, 0.3H), 0.73–0.67 (m, 0.7H).



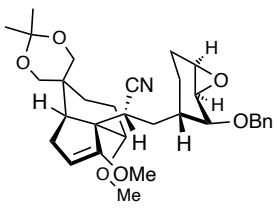
3.32 (R = Bn)
3.33 (R = MOM)

3.34a,b (R = Bn)
3.35a,b (R = MOM)

Bis-methyl ether 3.34a,b and **3.35a,b**: To a solution of β-Hydroxyketone **3.32** or **3.33** (1.0 equiv.) and HMPA (3.0 equiv.) in THF (0.1 M) was sequentially added methyl trifluoromethanesulfonate (MeOTf) (5.0 equiv.) and LHMDS (1 M in THF, 5.0 equiv.) at –50 °C. After stirring for 1 h at the same temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution. After the layers were separated, the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. The residue was filtered through a short pad of silica gel to remove HMPA. The obtained crude mixture of mono- and bis methyl ether were used for next step without further purification.

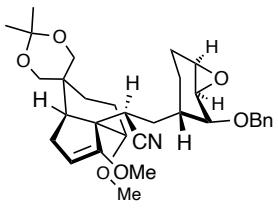
To a solution of the above crude (1.0 equiv.) in THF (0.1 M) was added LHMDS (1 M in THF, 2.0 equiv.) at –40 °C. After stirring for 30 min at the same temperature, MeOTf (2.0 equiv.) was added to the mixture. Then, the reaction mixture was stirred for 30 min at a temperature below –30 °C and quenched with saturated aqueous $NaHCO_3$ solution. After the layers were separated, the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by column chromatography afforded bis-methyl ether **3.34a,b** and **3.35a,b**.

Benzyl ether 3.34a,b: Purification by column chromatography (Hexane/EtOAc = 20:1 to 7:3) and Preparative TLC (Hexane/EtOAc = 7:3) afforded benzyl ether **3.34a** (38.5 mg, 71.6 μmol, 61% for 3 steps, single isomer) and **3.34b** (13.8 mg, 25.7 μmol, 22% for 3 steps, single isomer) from 1,2-adduct **3.32** (60.0 mg, 0.115 mmol) as a white amorphous.



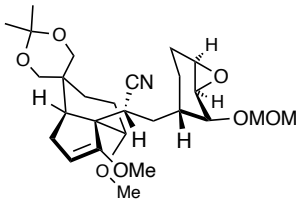
3.34a

Major isomer 3.34a: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, 2H, J = 7.5 Hz), 7.34 (t, 2H, J = 7.5 Hz), 7.27 (t, 1H, J = 7.5 Hz), 4.76 (d, 1H, J = 11.5 Hz), 4.70 (s, 1H), 4.68 (d, 1H, J = 11.5 Hz), 3.86 (s, 2H), 3.67 (d, 1H, J = 11.5 Hz), 3.54–3.53 (m, 4H), 3.44 (d, 1H, J = 11.5 Hz), 3.36–3.32 (m, 2H), 3.27 (br s, 1H), 3.23 (s, 3H), 3.07 (dd, 1H, J = 3.4, 12.6 Hz), 2.41–2.33 (m, 2H), 2.14–2.05 (m, 3H), 1.90–1.87 (m, 1H), 1.77–1.74 (m, 2H), 1.67–1.49 (m, 3H), 1.39 (s, 3H), 1.34 (s, 3H), 1.04 (ddd, 1H, J = 3.5, 10.9, 13.8Hz), 0.94–0.90 (m, 1H)



3.34b

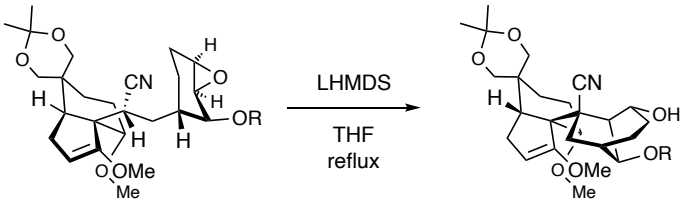
Minor isomer 3.34b: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, 2H, *J* = 7.5 Hz), 7.35 (t, 2H, *J* = 7.5 Hz), 7.28 (t, 1H, *J* = 7.5 Hz), 4.86 (d, 1H, *J* = 11.5 Hz), 4.68 (s, 1H), 4.65 (d, 1H, *J* = 11.5 Hz), 3.71 (br s, 1H), 3.60–3.58 (m, 4H), 3.51 (d, 1H, *J* = 11.4 Hz), 3.37–3.27 (m, 5H), 3.23 (s, 3H), 2.75 (dd, 1H, *J* = 2.9, 11.5 Hz), 2.38 (t, 1H, *J* = 9.2 Hz), 2.07–1.88 (m, 6H), 1.76–1.72 (m, 1H), 1.67 (dd, 1H, *J* = 4.0, 14.9 Hz), 1.42–1.33 (m, 5H), 1.28 (s, 3H), 1.22–1.14 (m, 1H), 1.11 (d, 1H, *J* = 13.8 Hz), 1.02–0.96 (m, 1H)



3.35a

MOM ether 3.35a: Purification by column chromatography (Hexane/EtOAc = 4:1 to 2:3) afforded MOM ether **3.35a** (17.0 mg, 34.6 μmol, 49% for 2 steps, single isomer) and mixture of **3.35a** and **3.35b** (11.9 mg, 24.2 μmol, 35% for 2 steps, **3.35a**:**3.35b** = 1:2) from β-hydroxyketone **3.33** (32.5 mg, 70.1 μmol) as a white amorphous.

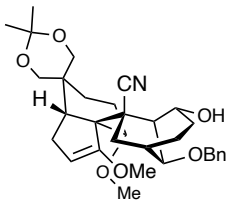
Major isomer **3.35a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.88 (d, 1H, *J* = 6.9 Hz), 4.76 (d, 1H, *J* = 6.9 Hz), 4.72 (s, 1H), 3.96 (d, 1H, *J* = 12.1 Hz), 3.81 (d, 1H, *J* = 12.1 Hz), 3.65 (dd, 1H, *J* = 1.2, 11.5 Hz), 3.57 (s, 3H), 3.52 (dd, 1H, *J* = 1.7, 9.2 Hz), 3.47 (s, 3H), 3.46–3.43 (m, 1H), 3.36–3.33 (m, 2H), 3.30–3.28 (m, 1H), 3.24 (m, 3H), 3.09 (dd, 1H, *J* = 2.9, 13.8 Hz), 2.51b(t, 1H, *J* = 9.2 Hz), 2.26 (dt, 1H, *J* = 2.3, 13.2 Hz), 2.19–2.07 (m, 2H), 1.92–1.74 (m, 5H), 1.66–1.61 (m, 1H), 1.50–1.47 (m, 2H), 1.40–1.36 (m, 7H), 1.06 (ddd, 1H, *J* = 3.4, 10.9, 13.8 Hz).



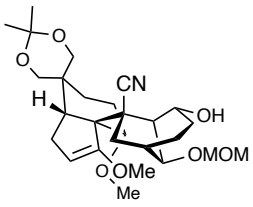
3.34a (R = Bn)
3.35a (R = MOM)

3.36 (R = Bn)
3.37 (R = MOM)

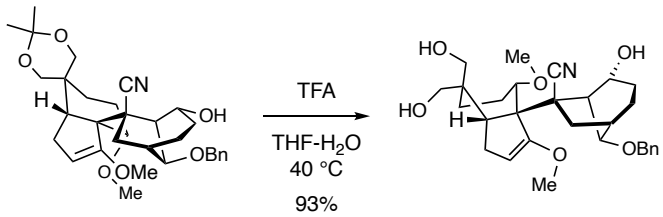
Tetracyclic compound 3.36 and **3.37**: The reaction were performed in a sealed tube. To a solution of bis-methyl ether **3.34a** or **3.35a** (1.0 equiv.) in THF (0.04 M) was added LHMDS (1.0 M in THF, 3.0 equiv.). The reaction mixture was stirred for 2 h at 60 °C, and then warmed up to 80 °C. The reaction was monitored by TLC, and the reaction mixture was quenched with brine at room temperature. After the layers were separated, the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by column chromatography afforded tetracyclic compound **3.36** and **3.37**.



Benzyl ether 3.36: Purification by flash column chromatography (Hexane/EtOAc = 10:1 to 1:1) afforded benzyl ether **3.36** (7.0 mg, 13 μmol, 84%, single isomer) from bis-methyl ether **3.34a** (8.3 mg, 15 μmol) as a white amorphos: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.30 (m, 5H), 4.70 (s, 1H), 4.61 (s, 1H), 4.61 (d, 1H, *J* = 10.9 Hz), 4.48 (d, 1H, *J* = 10.9 Hz), 4.14–4.08 (m, 1H), 4.02 (d, 1H, *J* = 11.5 Hz), 3.91 (dd, 1H, *J* = 5.8, 9.8 Hz), 3.68–3.63 (m, 1H), 3.50 (br s, 1H), 3.45 (d, 1H, *J* = 11.5 Hz), 3.36 (s, 3H), 3.35 (s, 3H), 2.44–2.20 (m, 6H), 2.14–2.08 (m, 4H), 1.86 (dt, 1H, *J* = 5.2, 14.9 Hz), 1.80 (dd, 1H, *J* = 6.3, 15.5 Hz), 1.63–1.44 (m, 3H), 1.40–1.36 (m, 7H).

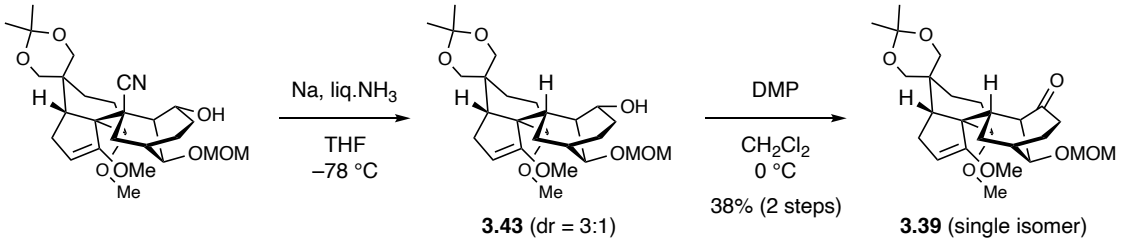


MOM ether 3.37: Purification by column chromatography (Hexane/EtOAc = 1:1 to 1:4) afforded MOM ether **3.37** (7.3 mg, 14.8 μmol, 68%, single isomer) from bis-methyl ether **3.35a** (10.7 mg, 21.8 μmol) as a white amorphous: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.79 (s, 1H), 4.67 (d, 1H, *J* = 6.9 Hz), 4.62 (d, 1H, *J* = 6.9 Hz), 4.46 (d, 1H, *J* = 10.9 Hz), 4.10–4.08 (m, 1H), 4.03 (d, 1H, *J* = 11.5 Hz), 3.94 (dd, 1H, *J* = 5.8, 9.8 Hz), 3.83 (br s, 1H), 3.70 (d, 1H, *J* = 12.1 Hz), 3.59 (s, 3H), 3.44–3.42 (m, 2H), 3.39 (s, 3H), 3.38 (s, 3H), 2.44–2..06 (m, 9H), 1.88 (dt, 1H, *J* = 4.6, 10.9 Hz), 1.79 (dd, 1H, *J* = 6.3, 15.5 Hz), 1.63–1.45 (m, 3H), 1.39–1.36 (m, 7H).



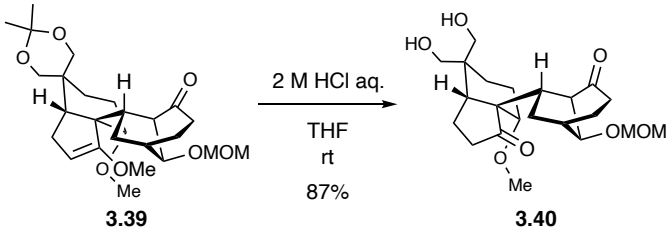
3.36 **3.38**

Triol 3.38: To a solution of tetracyclic compound **3.36** (3.7 mg, 6.9 μmol) in CH_2Cl_2 (200 μL) and H_2O (40 μL) was added trifluoroacetic acid (TFA) (2.7 μL, 35 μmol). Then, the reaction mixture was warmed up to 40 °C and stirred for 8 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (0.5 mL). After the layers were separated, the aqueous layer was extracted with EtOAc (0.5 mL × 5). The combined organic layers were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by column chromatography (Hexane/EtOAc = 1:4 to 0:1) afforded triol **3.38** (3.2 mg, 6.4 μmol, 93%) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.30 (m, 5H), 4.80 (s, 1H), 4.65–4.59 (m, 2H), 4.49 (d, 1H, *J* = 11.5 Hz), 4.30–4.24 (m, 2H), 4.12–4.07 (m, 1H), 3.70 (br s, 1H), 3.65–3.60 (m, 3H), 3.54 (t, 1H, *J* = 10.3 Hz), 3.41 (s, 3H), 3.35 (s, 3H), 3.23–3.21 (m, 1H), 2.71–2.69 (m, 2H), 2.50 (dd, 1H, *J* = 9.2, 16.0 Hz), 2.43–2.36 (m, 3H), 2.29 (dd, 1H, *J* = 6.3, 13.8 Hz), 2.17–2.10 (m, 2H), 2.05–1.98 (m, 1H), 1.82 (dd, 1H, *J* = 6.9, 16.1 Hz), 1.48–1.37 (m, 3H), 1.30–1.19 (m, 1H).



Ketone 3.39: To a solution of tetracyclic compound (8.6 mg, 17.5μmol) in THF (500 μL) was added sodium (1 tips, 7.7 mg, excess) at –78 °C. Then, liq. NH_3 was added until the mixture turned dark blue, and the reaction mixture was stirring for another 30 min at the same temperature. The reaction mixture was quenched with MeOH (100 μL) and the remaining NH_3 was volatilized at the room temperature. Then, saturated aqueous NH_4Cl (1 mL) solution was added to the mixture and extracted with EtOAc (1 mL × 3). The combined organic layers were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. The obtained crude reduced product **3.43** was used for the next step without further purification.

To a solution of the above crude alcohol **3.43** (6.1mg, dr = 3:1) in CH_2Cl_2 (200 μL) was added Dess-Martin periodinane (14.8 mg, 35.0 μmol) at 0 °C. After stirring for 40 min at the same temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (300 μL) and saturated aqueous $Na_2S_2O_3$ solution (300 μL). After the mixture was stirred for 30 min at room temperature, extracted with EtOAc (0.5 mL × 3). The combined organic layers were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by column chromatography (Hexane/EtOAc = 4:1 to 2:1) afforded ketone **3.39** (3.1 mg, 6.7 μmol, 38% for 2 steps) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.70 (s, 1H), 4.64 (d, 1H, *J* = 6.3 Hz), 4.61 (d, 1H, *J* = 6.3 Hz), 4.48 (t, 1H, *J* = 5.4 Hz), 3.75 (d, 1H, *J* = 11.5 Hz), 3.69 (d, 1H, *J* = 11.5 Hz), 3.65 (d, 1H, *J* = 11.5 Hz), 3.54 (s, 3H), 3.42 (br s, 1H), 3.40 (d, 1H, *J* = 11.5 Hz), 3.35 (s, 3H), 3.23 (s, 3H), 3.18 (d, 1H, *J* = 5.8 Hz), 2.46–2.37 (m, 2H), 2.27–2.22 (m, 2H), 2.18–2.11 (m, 1H), 2.09–1.99 (m, 3H), 1.90–1.80 (m, 2H), 1.75–1.70 (m, 2H), 1.48–1.34 (m, 9H).



Diol 3.40: To a solution of ketone **3.40** (3.1 mg, 6.7 μmol) in THF (200 μL) was added aqueous 2 M HCl solution (100 μL) at 0 °C. Then, the reaction mixture was warmed up to room temperature and stirred for 1 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution and extracted with EtOAc (0.5 mL × 5). The combined organic layers were dried over $MgSO_4$, filtrated,

and concentrated under reduced pressure. Purification by column chromatography (EtOAc/MeOH = 1:0 to 10:1) afforded diol **3.40** (2.4 mg, 5.8 μmol, 87%) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.71 (d, 1H, *J* = 6.3 Hz), 4.66 (d, 1H, *J* = 6.3 Hz), 4.41 (t, 1H, *J* = 5.2 Hz), 3.77–3.71 (m, 3H), 3.66 (br s, 1H), 3.59 (d, 1H, *J* = 9.8 Hz), 3.50 (d, 1H, *J* = 5.8 Hz), 3.38 (s, 3H), 3.14 (s, 3H), 2.83 (br s, 1H), 2.67–2.63 (m, 1H), 2.42 (td, 1H, *J* = 9.2, 17.8 Hz), 2.35–2.24 (m, 3H), 2.21–1.93 (m, 7H), 1.77–1.67 (m, 2H), 1.52–1.46 (m, 2H), 1.29 (t, 1H, *J* = 13.8 Hz), 1.00 (t, 1H, *J* = 13.8 Hz).

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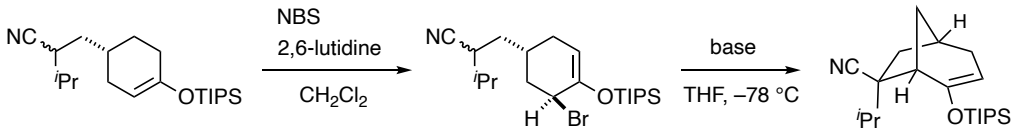
25. $LiNEt_2$ was superior to LDA especially in the reactions of hindered α-substituted nitriles such as **1.9d**.



1.7d **1.8d** **1.9d**

LDA : 30% (2 steps)
$LiNEt_2$: 71% (2 steps)

26. For selected examples of the syntheses of caged skeletons via intramolecular Mukaiyama aldol reaction, see: (a) Kuo, D.; Money, T. *Can. J. Chem.* **1988**, *66*, 1794. (b) Mehta, G.; Murty, A. N. *J. Org. Chem.* **1990**, *55*, 3568. (c) Hagiwara, K.; Tabuchi, T.; Urabe, D.; Inoue, M. *Chem. Sci.* **2016**, *7*, 4372.
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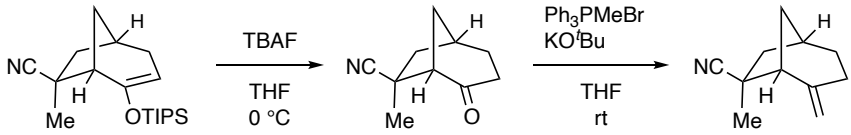
29. The stereochemistry of the cyclization products **1.22** and **1.26** was determined by the following method. The transformation of TIPS enol ether **1.9a** into alkene **1.22** via deprotection, followed by Wittig reaction. The ^{1}H NMR spectra of which were identical to those of the major isomer obtained in Scheme 1.8. On the other hand, the ^{1}H NMR spectra of the major isomer of **1.26** did not match with **1.10a** obtained in the scheme below.



1.9a **1.10a** **1.22**

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