DISSERTATION

Total Synthesis of Cristaxenicin A

(クリスタキセニシン A の全合成)

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2026

Contents

Introduction

0-1.Xenicane diterpenoids

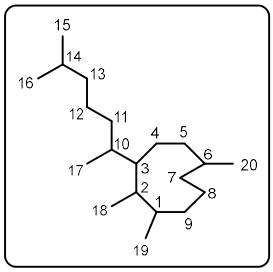


Figure 1. Xenicane scaffold

Xenicane diterpenoids are natural marine products having a highly strained nine-membered carbocycle in their core structures (Figure 1). Since the isolation of xenicin (**1**) in 1977,[1] over hundred xenicane diterpenoids with diverse oxidation patterns exhibiting a wide range of biological activities have been reported (Figure 2).[2, 3] Structurally, the xenicane family comprises two major subclasses: xenicin-type and xeniolide-type. The former features a dihydropyran moiety *trans*-fused to the nine-membered ring (e.g., xenicin (**1**));[1, 4, 5] however, the latter has a δ-lactone ring in place of the pyranoside moiety (e.g., xeniolide A (**4**)).[6-8] Additionally, there are analogues that are not included in these subclasses. Xeniaether (**7**) possesses a tetrahydrofuran ring, in which the oxygen atom cross-linked C10 and C18.[9] Furthermore, Joalin (**8**) is the only member that contains a nitrogen atom, featuring a hemiaminal structure at the C18 position.[10]

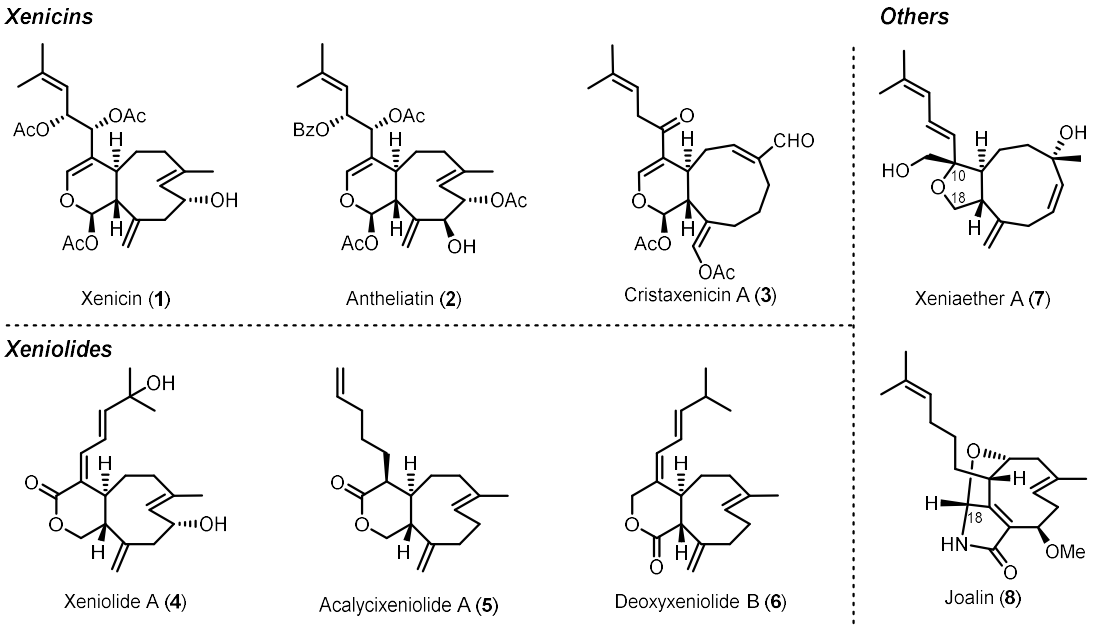


Figure 2. Xenicane diterpenoids

These diterpenoids are known to exhibit various biological activities. For example, Antheliatin (**2**) shows strong antiproliferative effects against the P-388, A-549, and MEL-28 cells, with IC50 values close to 1

μg/mL, while Xeniaether A (**7**) exhibits weak antibacterial activity against *Escherichia coli*. Furthermore, bioactivities unique to marine naturel products are also reported. For examples, Acalycixeniolide A (**5**) is known to inhibit the cell division of fertilized eggs of the starfish *Asterina pectinifera* with ED_{50} values of 20 μg/mL, and Deoxyxeniolide B (**6**) exhibits ichthyotoxicity against the mosquito fish *Orizias latipa*.

0-2. Total synthesis of xenicane diterpenoids

For its distinctive structure and promising biological activities, various total synthesis has been reported for the xenicane family.[11] The first report was the synthesis of (+)-coraxeniolide A (**13**) by Leumann and his coworkers in 2000 (Figure 3).[12] Their synthesis started from (-)-Hajos-Parrish ketone (**9**) which was transformed into a tricyclic tosylate **10** in 15 steps. Compound **10** was subjected to a Grob-fragmentation reaction by the treatment with NaH in DMSO, affording bicyclic compound **11** bearing a *trans*-cyclononenone in high yield. After conversion to lactone **12** in four steps, alkylation with allyl bromide accomplished the total synthesis of (+)-coraxeniolide A (**13**) in 7% yield. The *epi*-coraxeniolide A (**14**), obtained as the main product of the alkylation reaction, was isomerized under basic conditions to converge on the natural product.

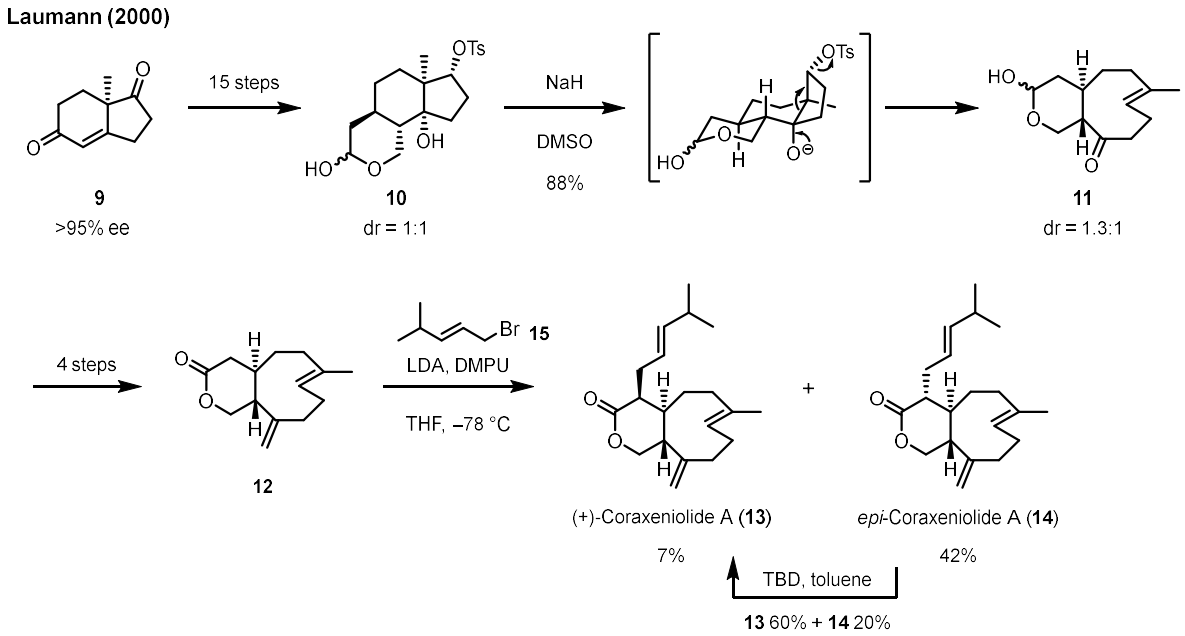


Figure 3. Leumann's total synthesis of (+)-Coraxeniolide A

Meanwhile, Corey's group also employed a similar Grob-fragmentation reaction for the synthesis of coraxeniolide A (**13**) (Figure 4).[13] An optically active diketone **16** was converted to tosylate **17** in 5 steps, which was treated with NaH in DMF, giving dienone **18** in 97% yield. In this case, the optical activity of the

starting material was transferred to the planar charity of **18**. The presence of two alkenes and the methyl group on the *E*-alkene render the compound stable enough to manage. For the total synthesis, they synthesized ***ent*-18** using the same method as **18**, and ***ent*-18** was converted to lactone **12**, the same intermediate in Leumann's synthesis, through a three-step transformation. Alkylation with allyl iodide **19** followed by isomerization with phosphazene base P_2-Et completed the total synthesis of (+)-Coraxeniolide A (**13**). This synthesis was 12 steps shorter than that of Leumann's synthesis.

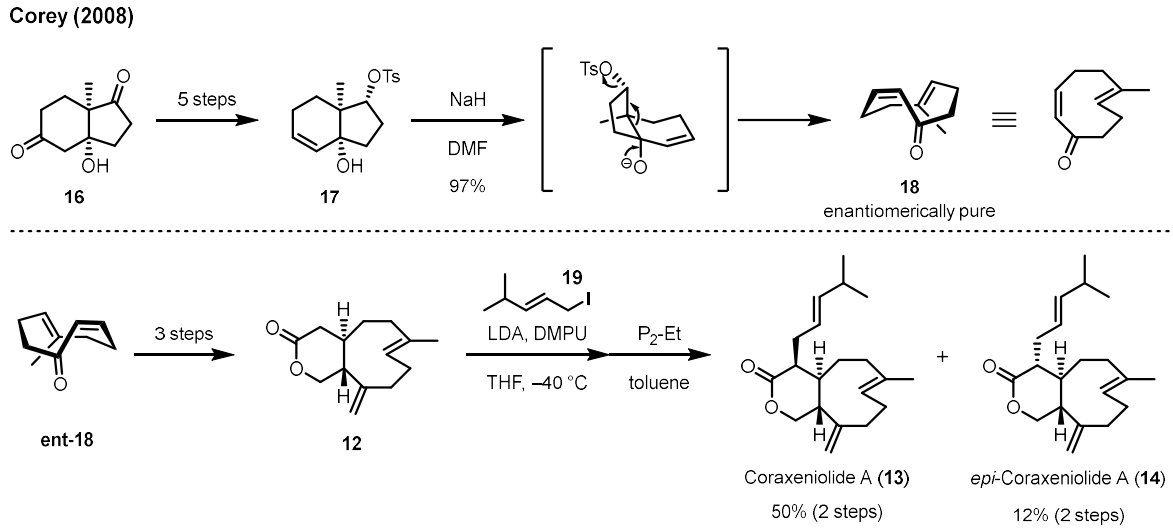


Figure 4. Corey's total synthesis of (+)-Coraxeniolide A

Altmann and his coworkers reported two total synthesis of xeniolide derivatives bearing an oxygen atom at the C8 position (Figure 5).[14, 15] In the synthesis of (+)-blumiolide C (**22**), which possesses the C6-C7 *cis*-alkene, an intramolecular alkene metathesis reaction was employed for the key nine-membered ring construction. Diene **20** was subjected to a reaction with Hoveyda–Grubbs II catalyst in the presence of benzoquinone under highly diluted condition, affording the desired cyclononene **21** as a single stereoisomer in 66% yield. Construction of the *exo*-methylene moiety and introduction of the side chain completed the total synthesis. Meanwhile, in the synthesis of (+)-isoxeniolide A (**25**), an intramolecular Nozaki-Hiyama-Kishi coupling reaction was applied for the nine-membered ring construction. Compound **23** bearing an aldehyde and a vinyl iodide side chain was treated with $CrCl_2$ and catalytic amount of $NiCl_2$ to afford *trans*-cyclononenone **24** in 71% yield. This compound was further converted to (+)-isoxeniolide A (**25**) in seven steps.

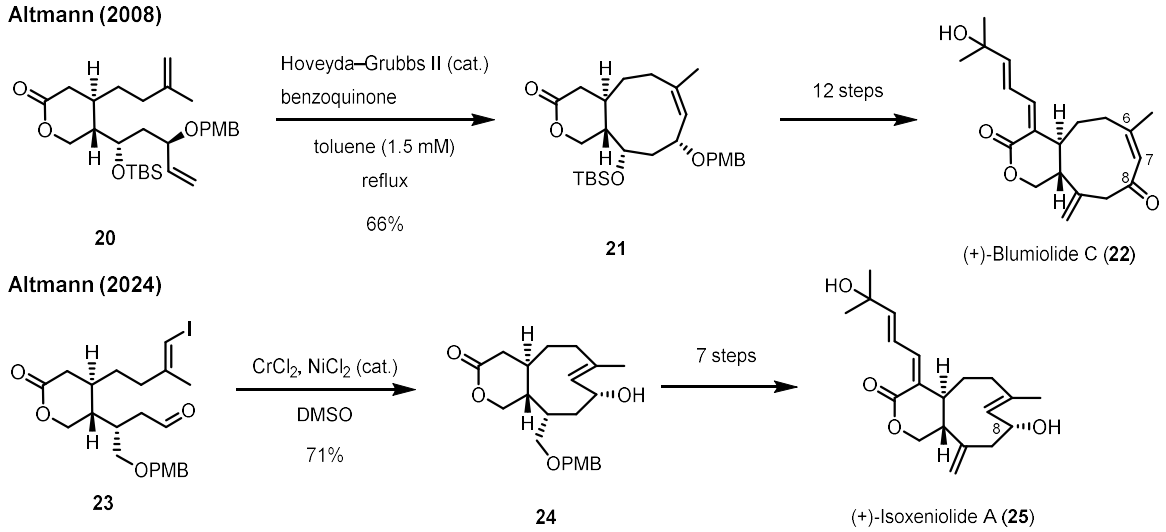


Figure 5. Altmann's synthesis of Xeniolides

In the synthesis of (-)-4-hydroxydictyolactone (**30**), which is neither a xeniolide type nor a xenicin type member of the xenicane diterpenoid, Williams and his coworkers employed an intramolecular Suzuki-Miyaura coupling reaction for the formation of the key nine-membered ring (Figure 6).[16] Chemo- and regioselective hydroboration on the terminal alkene of triene **26** afforded intermediate **27**, which was successively treated with $Pd(PPh_3)_4$ and sodium hydroxide under highly diluted condition. This gave the bicyclic compound **28**, which was further hydrolyzed with aqueous acetic acid giving hemiacetal **29** in 66% yield. The total synthesis of (-)-4-hydroxydictyolactone (**30**) was achieved after constructing the unsaturated lactone moiety and removal of the TBS group in 4 steps.

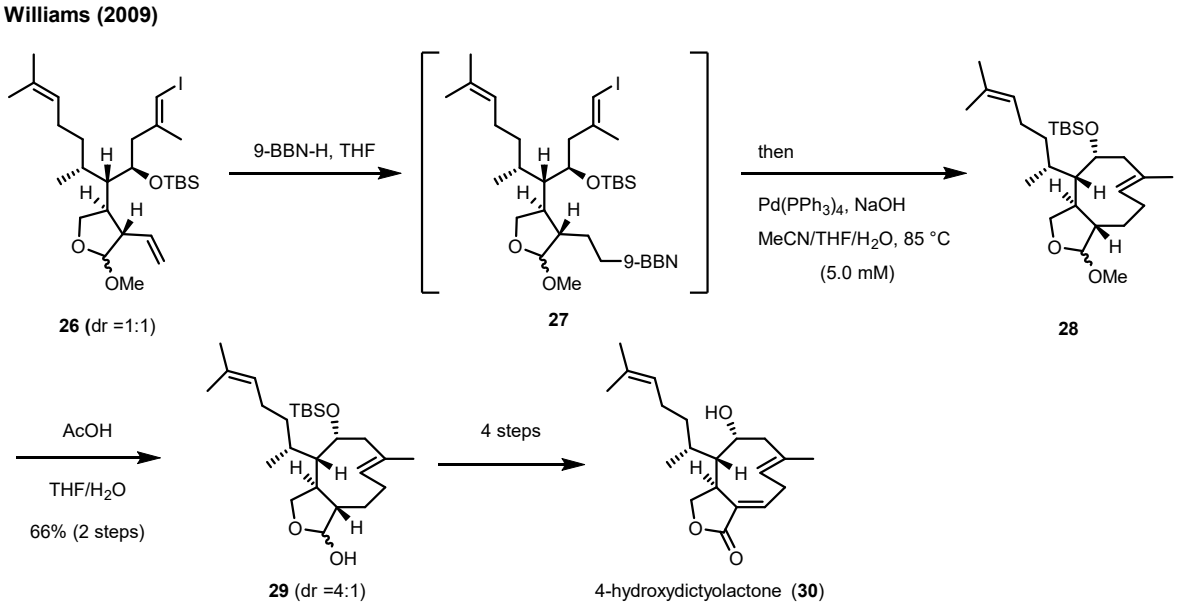


Figure 6. Williams's total synthesis of (-)-4-hydroxydictyolactone

In contrast to xeniolide type, the total synthesis of a xenicin type member has been reported only once, which was the total synthesis of (+)-waixenicin A (40), known for its specific inhibition activity against transient receptor potential melastatin 7 (TRPM7) channels, from the Magauer's group in 2023 (Figure 7).[17] In the synthesis, they efficiently constructed the characteristic dihydropyran ring of xenicin members by using a pyranone derivative as the starting material. Optically active enone **31** was converted to compound **32** via Michael addition of 1,3-dithiane followed by alkylation of the resulting enolate with allyl iodide **33**. Subsequently, treatment with KHMDS and $PhNTf_2$ afforded enol triflate **34** which possesses the dihydropyran ring. Next, β-keto ester **35** having an allyl bromide side chain was prepared from **34** in 9 steps, which was subjected to an intramolecular alkylation to form the nine-membered ring. The resulting product was subsequently treated with TASF to give compound **36** in 45% over two steps. After conversion to aldehyde **37**, acetylation of the hemiacetal moiety was achieved using AcOH, CDI, and DBU giving the desired **38** and its epimer **39** in 33% and 36% yields, respectively. The authors pointed out that the hemiacetal moiety was very reluctant for acetylation, and the condition mentioned above only worked. The undesired compound **39** was reused after conversion to **37** via solvolysis. Finally, the introduction of the side accomplished the total synthesis of (+)-Waixenicin A (**40**). Furthermore, the introduction of a prenyl side chain to aldehyde **38** enabled the total synthesis of (+)-9-Deacetoxy-14,15-deepoxyxeniculin (**41**), and treating **41** with potassium carbonate gave (−)-Xeniafaraunol A (**45**) in 88% yield. The mechanism for this transformation was proposed as follows. Solvolysis of the acetyl group followed by ring-opening would form enolate **42**, which would undergo β-elimination to give unsaturated aldehyde **43**. Deprotonation at the γ-position generates enolate **44**, which would undergo an intramolecular aldol reaction to afford (−)-Xeniafaraunol A (**45**).

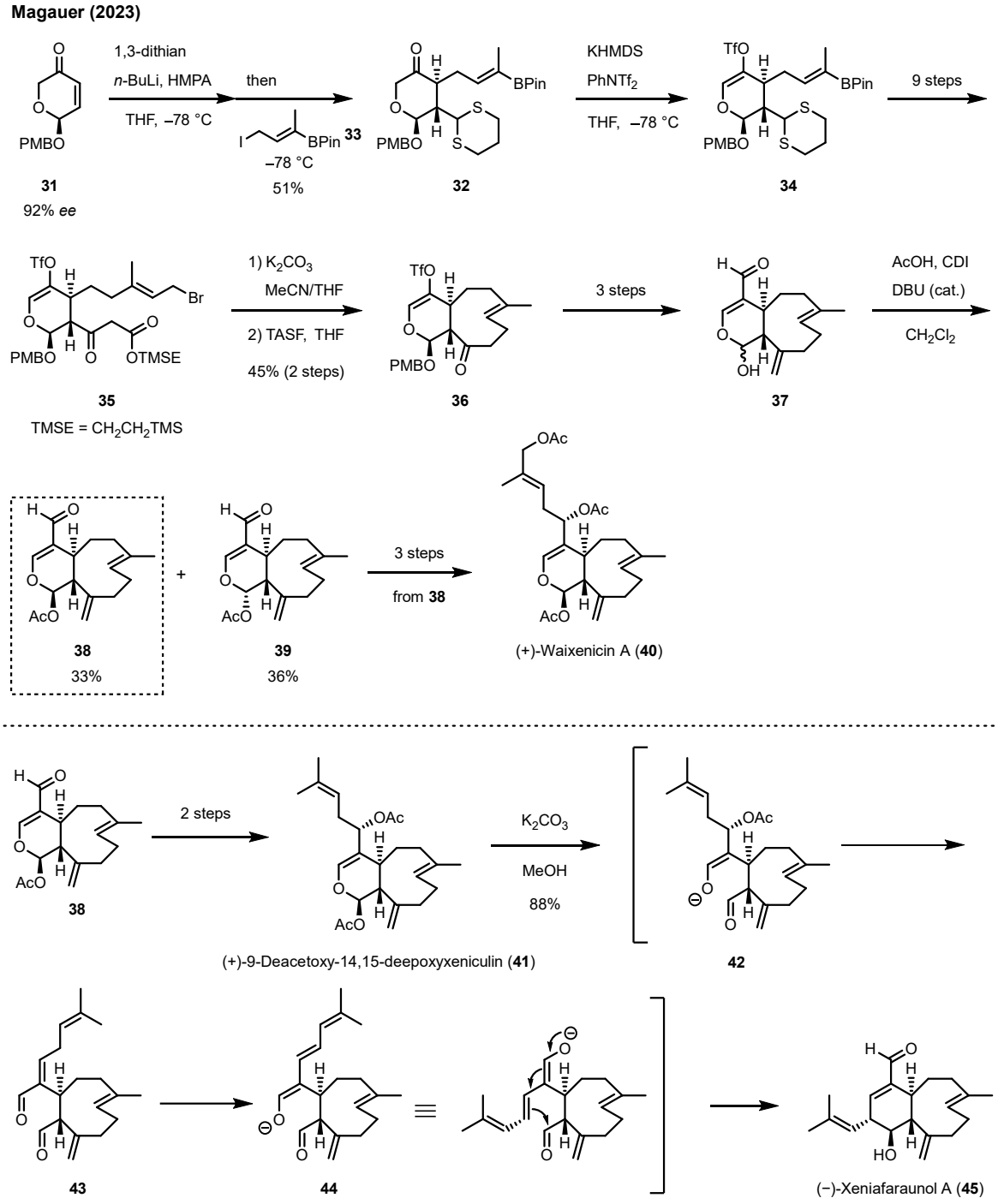


Figure 7. Magauer's total synthesis of (+)-waixenicin A and its congeners

0-3. Cristaxenicin A

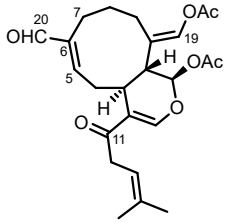


Figure 8 Cristaxenicin A (**3**)

Cristaxenicin A (**3**) is a xenicin type member of the xenicane diterpenoid which was isolated from the soft coral *Acanthoprimnoa cristata* in 2012 by Nakao and his coworkers (Figure 8).[5] Compared with other xenicin subtype family, **3** has a unique oxidizing pattern. The C11 and C20 carbons are oxidized to a ketone and an aldehyde, respectively. Representative xenicane diterpenoids have a *trans*-cyclononene skeleton with a C6-C7 double bond; however, the nine-membered ring of **3** has a *cis*-cyclononene with a C5-C6 double bond. In addition, the C1-C19 alkene moiety of **3** is functionalized as an enol acetate, which makes its synthesis difficult. This compound displayed strong antiprotozoal activity against *Leishmania amazonensis* and *Trypanosoma congolense*, which are known to cause Leishmaniasis, with IC_{50} values of 0.088 and 0.25 μM, respectively. The promising activity and unique structure of **3** have attracted considerable interest from synthetic chemists; however, only one synthetic study has been reported from Hosokawa and coworkers (Figure 9).[18]

In the study, they constructed the key dihydropyran ring via an inverse electron-demand hetero Diels–Alder reaction. Thus, the Diels–Alder reaction between unsaturated aldehyde **47** and vinyl ketone **48** was conducted at room temperature affording dihydropyran **49** in 37% yield over two steps. After converting to aldehyde **50** bearing a vinyl iodide side chain, an intramolecular Nozaki-Hiyama-Kishi coupling reaction was applied to form the nine-membered carbocycle in 87% yield. Then **51** was transformed into unsaturated aldehyde **52**, which is a cristaxenicin A (**3**) analog. They reported that the synthetic analogue exhibited antiprotozoal activity against *Leishmania donovani*, which also caused the Leishmaniasis, with IC_{50} value of 2.4 μM.

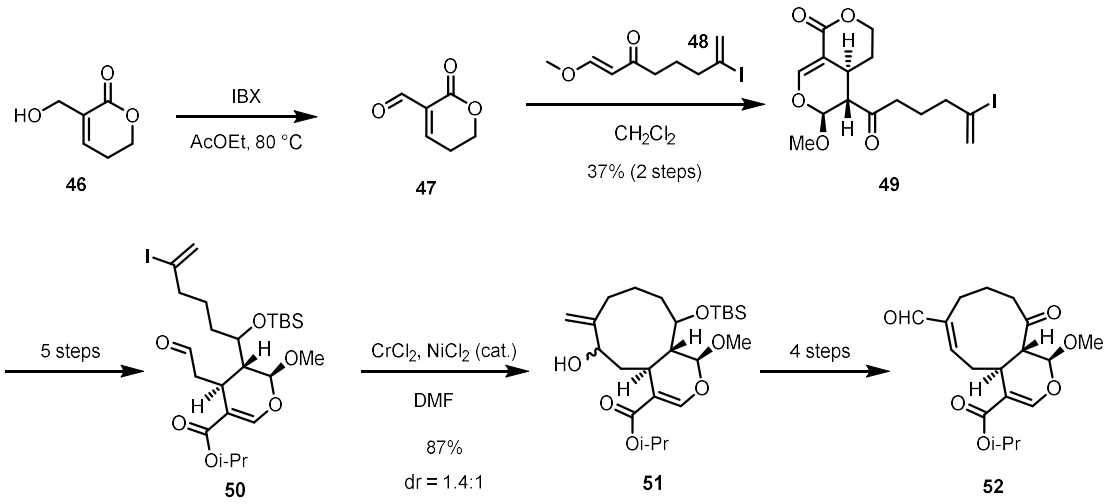


Figure 9. Hosokawa's synthetic study of cristaxenicin A

0-4. New method for the construction of a nine-membered ring developed in the author's lab

In the author's lab, Tsunoda developed a novel method for the construction of nine-membered rings (Figure 10). Allyl alcohol **55**, which was prepared from nitrile **53** and an unsaturated aldehyde, was heated with *N,N*-dimethylacetamide dimethyl acetal at 160°C in toluene, giving nine-membered compound **58**. The reaction proceeded through an Eschenmoser-Claisen reaction to form triene intermediate **56**, which underwent Cope rearrangement in one-pot. Notably, Cope rearrangements are reversible, and formation of medium-sized carbocycles, which are unstable than five- or six-membered ones, by the process is usually disfavoured. Therefore, an oxy-Cope rearrangement reaction, in which formation of an enolate anion effects stabilization of the product.[19-22] In the Tsunoda's reaction, the arising conjugated diene moiety and an α,β-unsaturated nitrile moiety would contribute stabilization of product **58**.

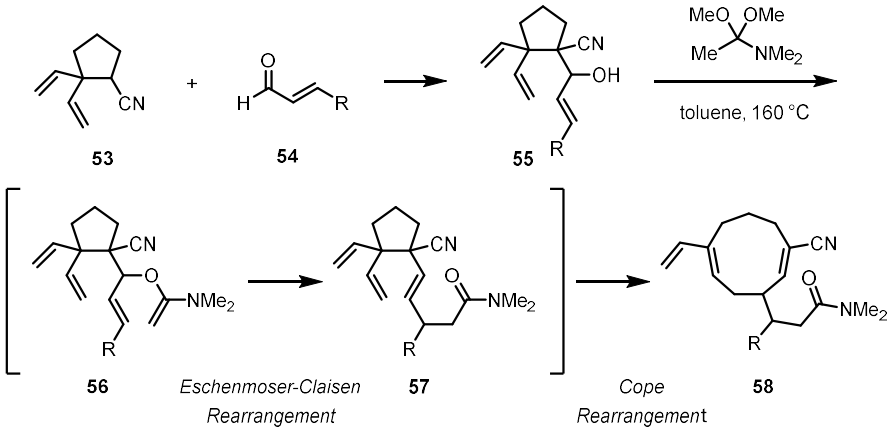


Figure 10. A new method for nine-membered ring synthesis

The synthesis of five-membered nitrile **53** is outlined in Figure 11. A commercially available silyl enol ether **59** was subjected to a Mukaiyama aldol reaction with bis(benzyloxy)methane to afford ketone **60** which was treated with an allyltitanium species generated from allyl sulfide **61**.[23,24] The resulting tertiary alcohol **62** was treated with methanesulfonic acid (MsOH) to give *gem*-divinyl compound **64** in 63% yield. The reaction proceeds through carbocation **63** which undergoes 1,2-migration of the vinyl group followed by desilylation. After removing the benzyl group with BBr_3, alcohol **65** was oxidized by Stahl's ABNO oxidation condition, and the resulting aldehyde was treated with hydroxylamine-O-sulfonic acid to afford nitrile **53**.[25, 26]

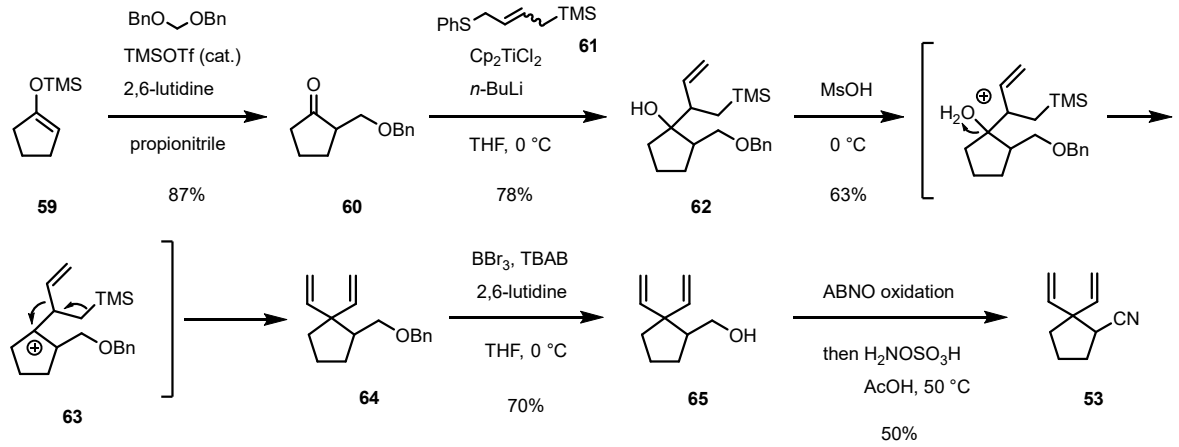


Figure 11. Synthesis of nitrile **53**

Next various unsaturated aldehydes were used in the addition reactions with nitrile **53**, and the resulting alcohols were subjected to the tandem Eschenmoser-Claisen-Cope rearrangement (Figure 12). 1,2-Addition with crotonaldehyde (**54a**) and *trans*-2-pentenal (**54b**) gave **55a** and **55b** in high yields, respectively. An aldehyde with extended conjugated system and β,β-disubstituted unsaturated aldehyde also gave the desired allyl alcohols **55c** and **55d** in high yields. Heating these alcohols with *N,N*-dimethylacetamide dimethyl acetal afforded the desired cyclononenes **58a** to **58d** in 74% to 80% yields. The reactivity of cinnamaldehyde (**54e**) and its derivative (**54f**, **54g**) were also searched and both 1,2 additions with nitril **53** and the tandem reaction also resulted high yields.

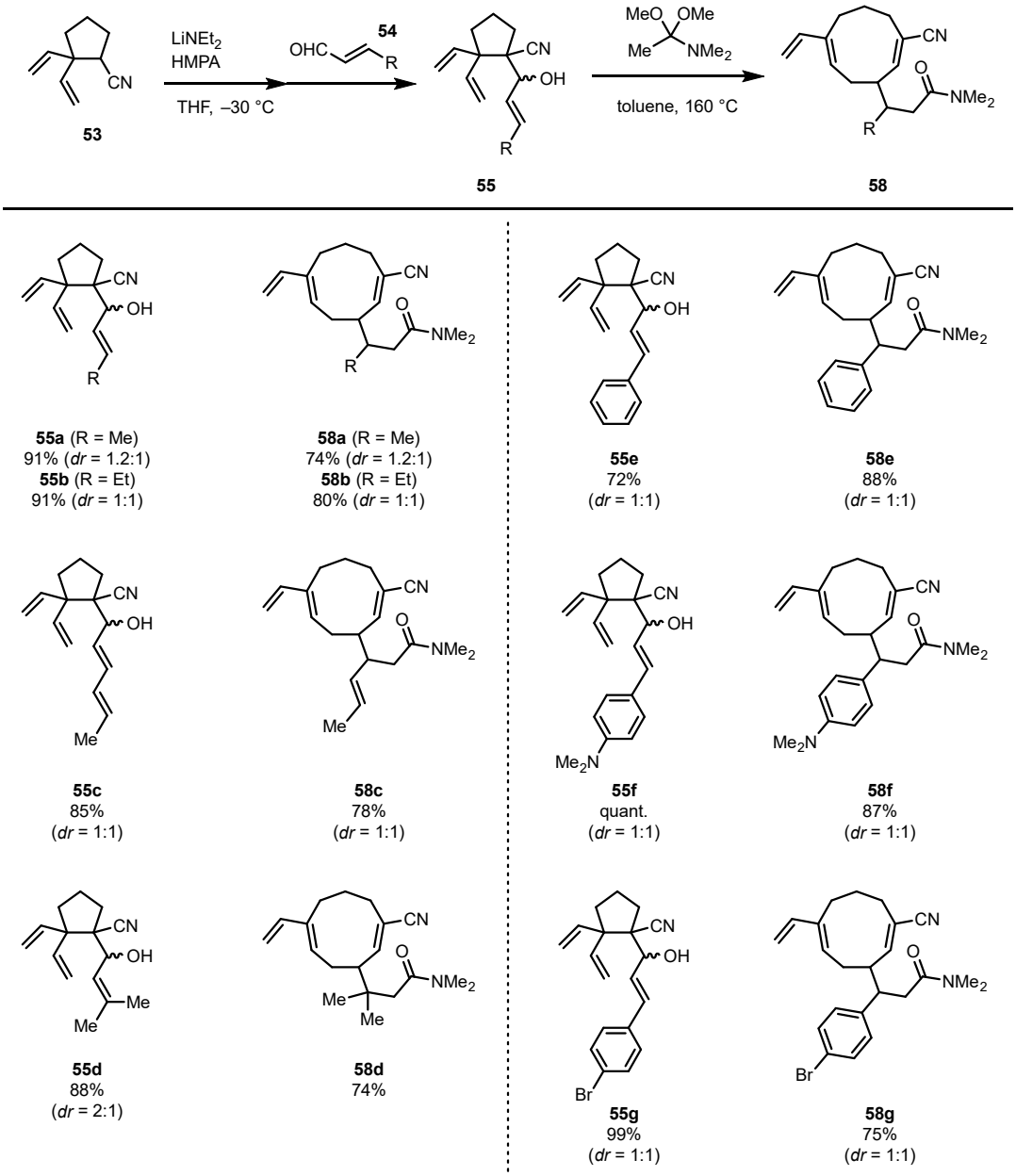


Figure 12. Scope for tandem rearrangement reaction

Tsunoda applied this tandem reaction for the synthesis of bicyclic compound **73** with a view to achieving the total synthesis of Cristaxenicin A (Figure 13). Aldol reaction of nitrile **53** with unsaturated aldehyde **66** gave two diastereomers **67** and **68** in 35% and 43% yields, respectively.[25] Diastereomer **67** was heated with dimethylacetamide dimethyl acetal at 160 °C, giving the desired nine-membered nitrile **71** as a sole product in 84% yield. A chair-like transition state of the Eschenmoser–Claisen rearrangement led to stereospecific formation of the C10 methine of intermediate **70**, as depicted, through chirality transfer. In contrast, the configuration of the C3 methine of product **71** originated from a boat-like transition state of the Cope rearrangement. Then the amide moiety of **71** was reduced with in-situ-generated Schwarz's reagent, and the

resulting aldehyde **72** was subjected to an intramolecular Stetter reaction mediated by thiazolium salt **73**.[26-28] The desired 9-5 bicyclic product **74** was obtained in as a single isomer in 69 % yield.

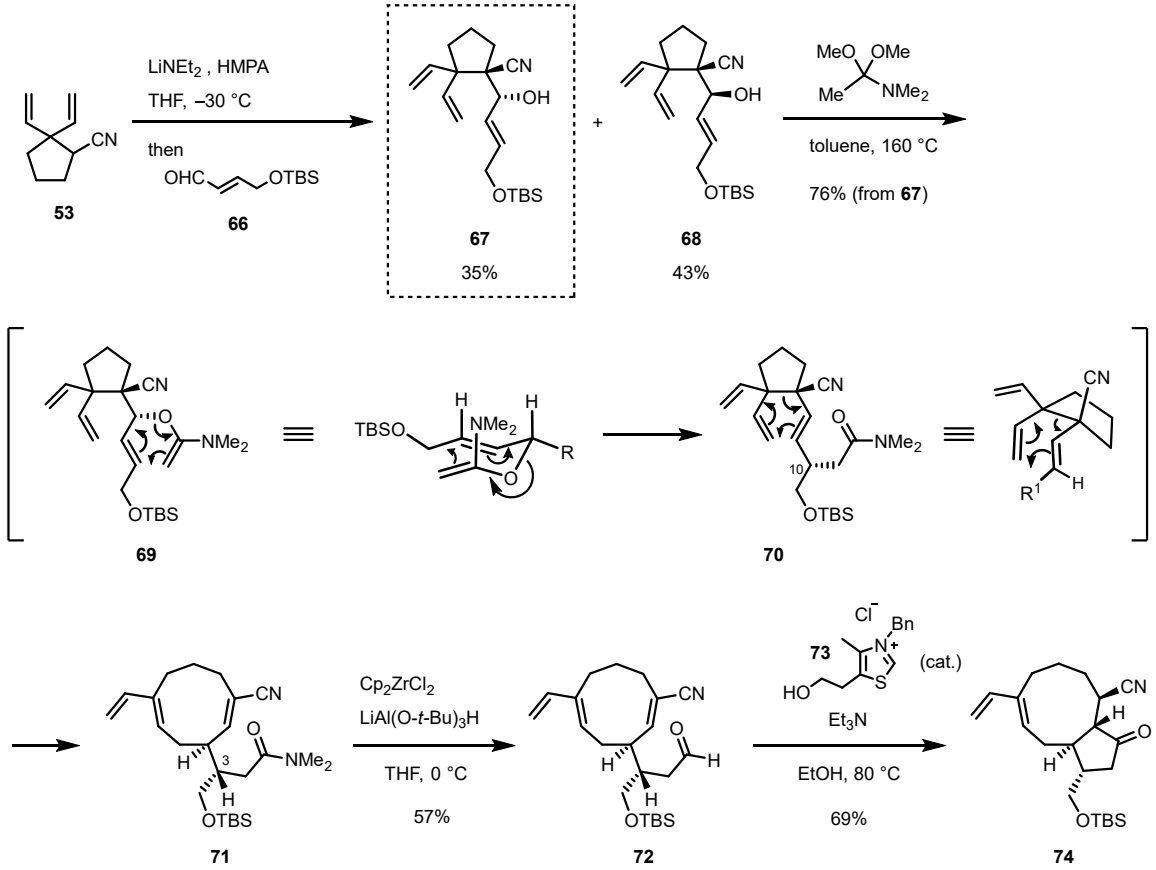


Figure 13. Synthesis of bicyclic compound **74**

In this dissertation, the author describes a preliminary examination toward the total synthesis of cristaxenicin A from 9-5 bicyclic product **74** in Chapter 1. In Chapter 2, the completion of the total synthesis of cristaxenicin A is described.

Chapter 1

Synthesis of Cristaxenicin A analog

The author's synthetic study commenced with transformation of the Tsunoda's intermediate. It was reported that the aldol reaction between nitrile **53** and unsaturated aldehyde **66** gave two diastereomers **67** and **68**, and conversion of alcohol **67** to bicyclic compound **74** was accomplished in three steps (Figure 1.1).

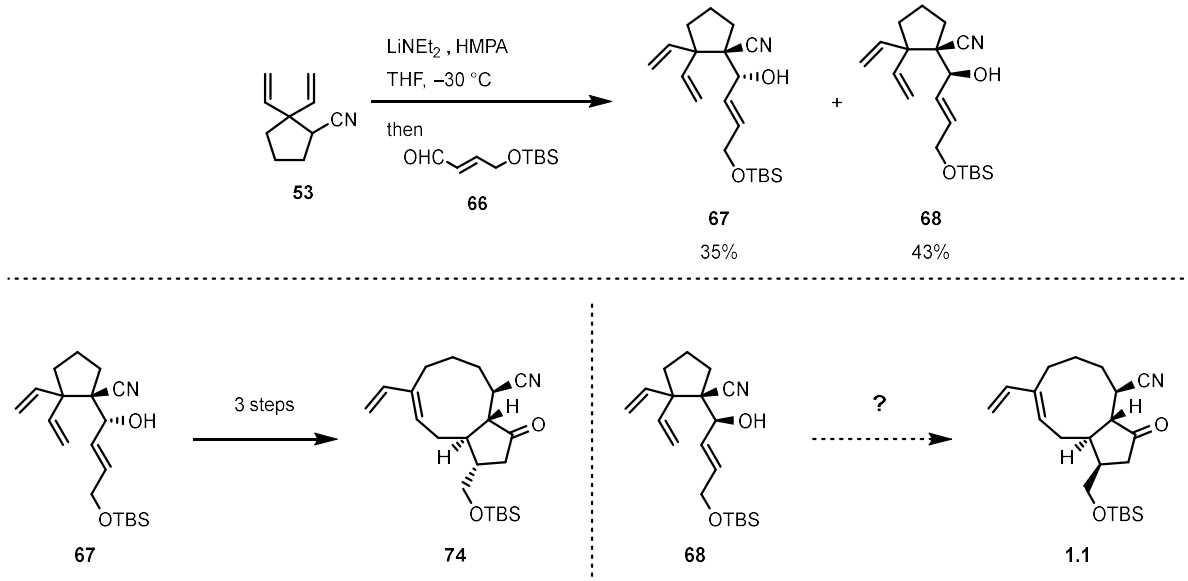


Figure 1.1. Problem in the existing route

Since similar transformation of diastereomer **68** has not yet been explored, the author first conducted the three-step construction of the bicyclic skeleton (Figure 1.2). The tandem Eschenmoser-Claisen-Cope rearrangement of alcohol **68** proceeded smoothly to afford nine-membered cyclic compound **1.2** in 76% yield. After reducing the amide group by Schwarz' reagent, the resulting aldehyde **1.3** was subjected to an intramolecular Stetter reaction using thiazolium catalyst **73**. However, it did not give the desired bicyclic compound **1.1**.

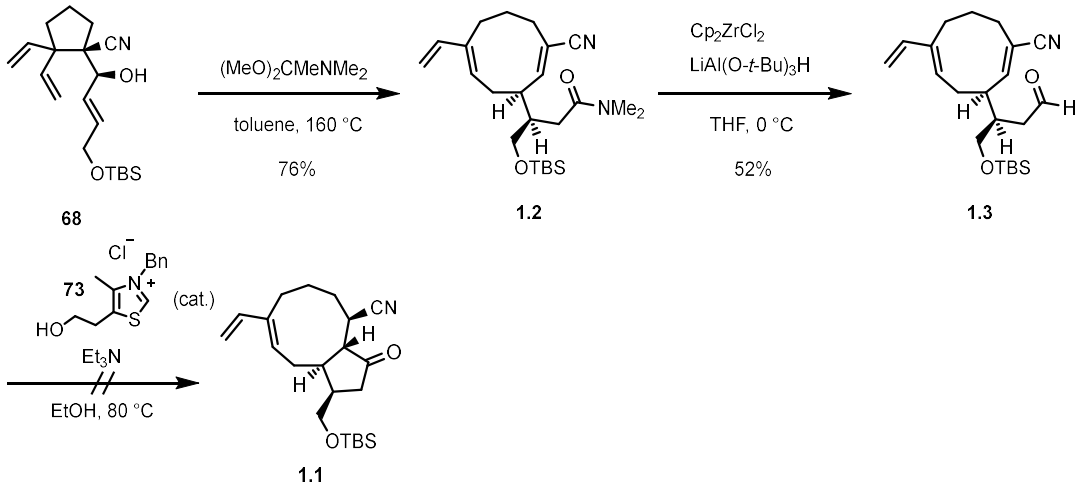


Figure 1.2. Conversion from diastereomer

The different behavior of the two isomeric aldehydes in the cyclization reaction can be explained by comparing the conformation of their transition states (Figure 1.3). As shown in the Newman projection, diastereomer **72** has its (silyloxy)methyl group oriented outward from the nine-membered ring during cyclization. On the other hand, the transition state of the cyclization of aldehyde **1.3** would suffer from steric repulsion between the (silyloxy)methyl group and nine-membered ring.

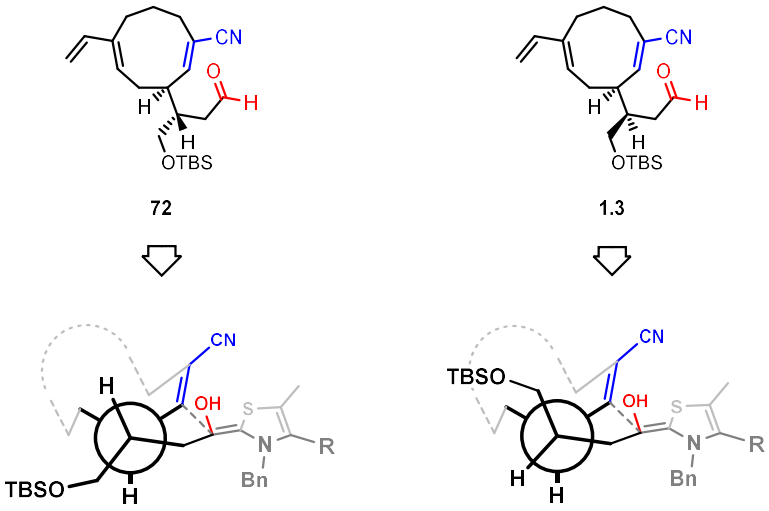


Figure 1.3. Explanation for the different behaviour between the

These results prompted the author to examine conversion of alcohol **68** to its epimer **67** (Figure 1.4). Initially, the Mitsunobu reaction was carried out to inverse the stereochemistry of the secondary alcohol moiety, but an S_N2' reaction occurred probably due to steric hindrance surrounding the hydroxyl group. On the other hand, oxidation of **68** with Dess-martin periodinane followed by Luché reduction gave **67** as an almost single isomer in 94% yield.

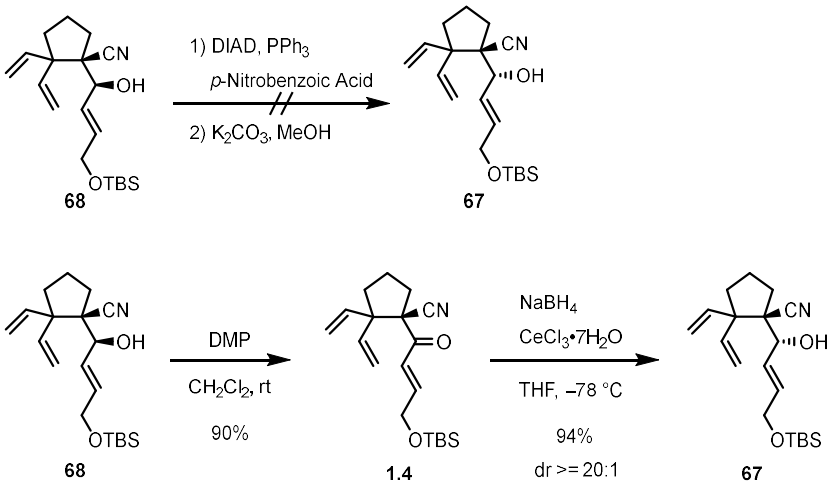


Figure 1.4. Epimerization of allyl alcohol **68**

The diastereoselectivity in the reduction step can be explained as depicted in Figure 1.5. In the Newman projection of compound **1.4** along the carbonyl carbon to the five-membered ring, the carbonyl oxygen and cyano group are oriented opposite to each other due to dipole repulsion. The attack of a reducing agent from sterically hindered left side of the ketone would be disfavored, and the desired diastereomer **67** is produced by the reaction from the right side.

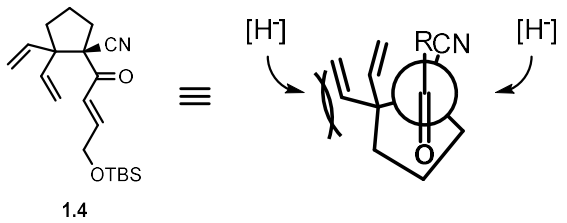


Figure 1.5. Newman projection of ketone **1.4**

Having solved the key issue by converting undesired alcohol **68** to desired isomer **67**, a sufficient amount of intermediate **74** was synthesized. Further transformations required for achieving the total synthesis are shown in Figure 1.6. It includes selective oxidation of the conjugated diene moiety giving an enal, conversion of the nitrile moiety to an enol acetate, construction of the dihydropyran ring, and installation of the side chain.

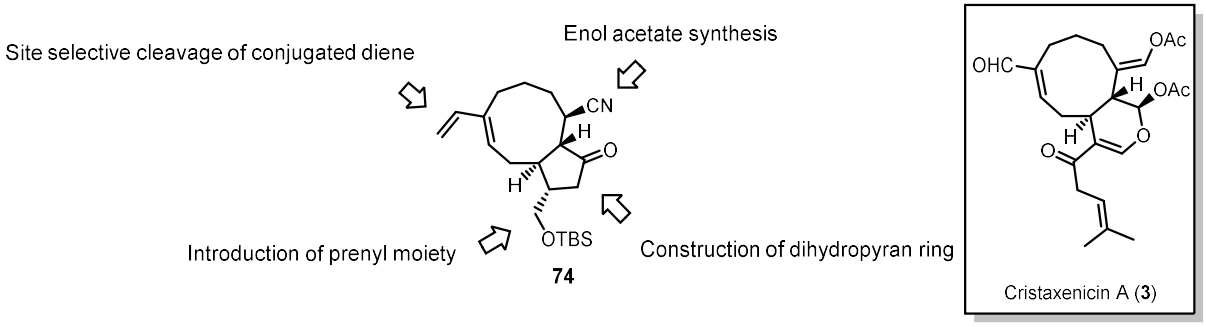


Figure 1.6. Tasks needed to be achieved

Firstly, selective oxidation of the conjugate diene moiety was examined. With a view to oxidizing the less sterically demanding vinyl group, dihydroxylation of **73** was examined (Figure 1.7). The reaction using a catalytic amount of osmium tetroxide, however, afforded a 1:1 mixture of desired compound **1.5** and its isomer **1.6** along with byproducts having the terminal vinyl group.

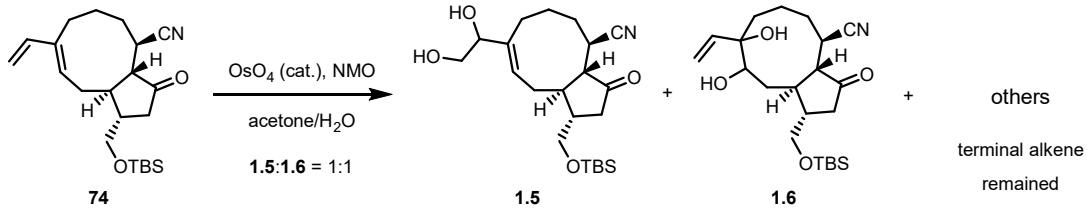


Figure 1.7. Dihydroxylation of **74**

The low selectivity of the oxidation reaction indicated the unexpectedly high reactivity of the internal alkene moiety, which led the author to protect it as an epoxide form (Figure 1.8).[29, 30] Upon treatment with methyltrioxorhenium and hydrogen peroxide in the presence of pyridine, **74** was converted to the desired epoxide **1.7**, [31] while the use of *m*-chloroperbenzoic acid was accompanied by the Baeyer–Villiger oxidation of the cyclopentanone moiety. Subsequently, ozonolysis of the remaining vinyl group afforded the corresponding aldehyde, which was subjected to the reductive cleavage of the epoxide with zinc and acetic acid, affording allyl alcohol **1.9** in 53% yield over three steps.

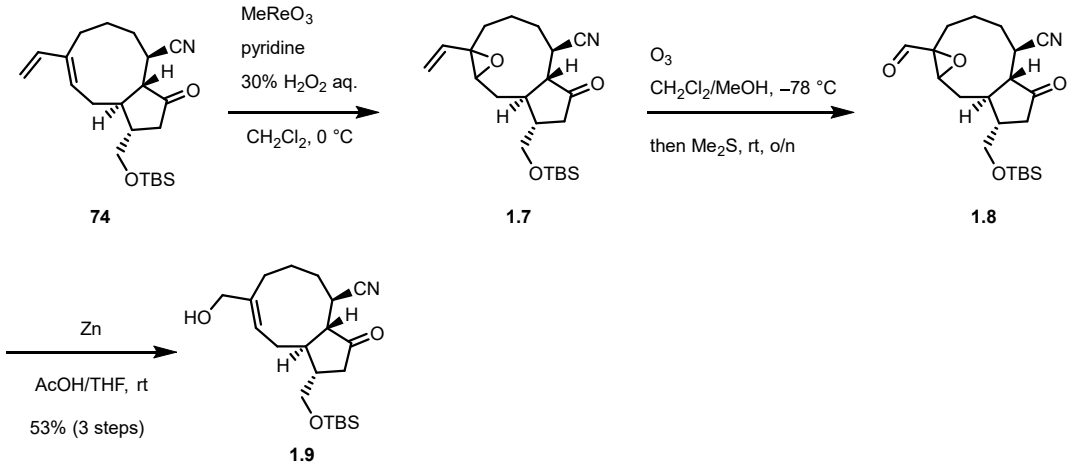


Figure 1.8. Selective cleavage of the terminal alkene

Having established a method for converting the diene moiety, the next issue was construction of the dihydropyran ring. The author designed a transformation of the cyclopentanone into a dihydropyran through oxidative cleavage of the C17-C18 (natural product numbering) bond (Figure 1.9). After introducing a methoxy group at the C17 position for enhancing the rearrangement tendency, a regioselective Baeyer-Villiger oxidation would afford lactone **1.11**. Then the lactone would be converted to aldehyde **1.12** through reductive acetylation followed by side chain manipulation, and hydrolysis of the acetate moiety would afford dihydropyran **1.15** via isomerization of tri-aldehyde intermediate **1.14**.

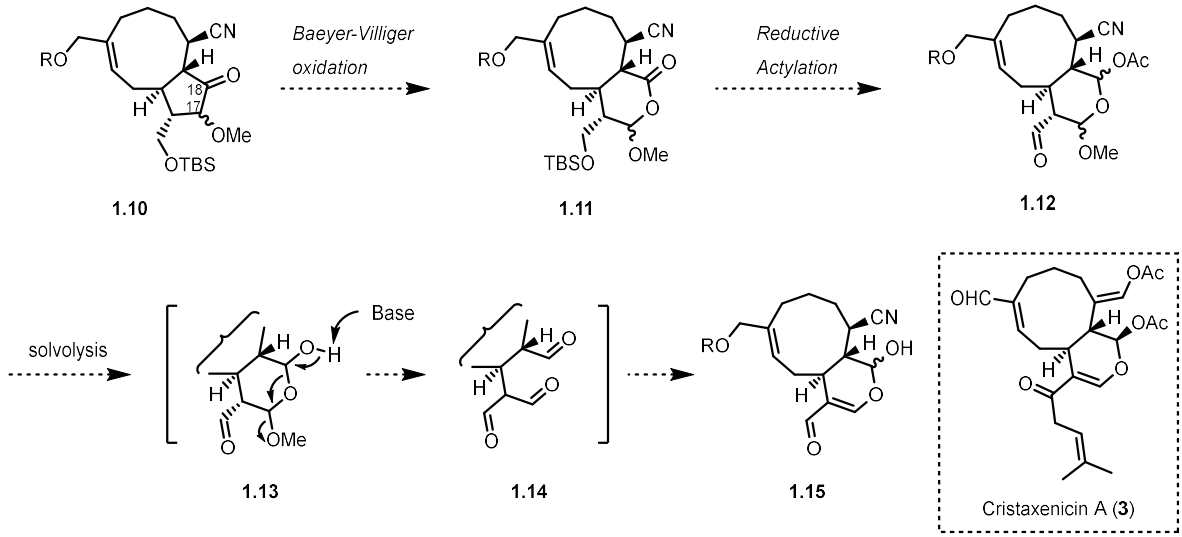


Figure 1.9. Plan for the construction of the dihydropyran ring

Based on the plan, silyl enol ether **1.20** was prepared from ketone **1.16** having a TIPS ether moiety, which is more stable to acidic conditions than TBS ether **74** (Figure 1.10). Upon treatment with iodosobenzene and BF_3•Et_2O at -30 °C,[32] **1.17** gave the desired α-methoxy ketone **1.18** as a diastereomeric mixture. After protecting the allyl alcohol moiety with a MOM group, the resulting **1.19** was treated with an equimolar amount of *m*CPBA. As was expected, the Baeyer-Villiger oxidation occurred at the C17 position, affording lactone **1.20** in 44% yield for four steps.

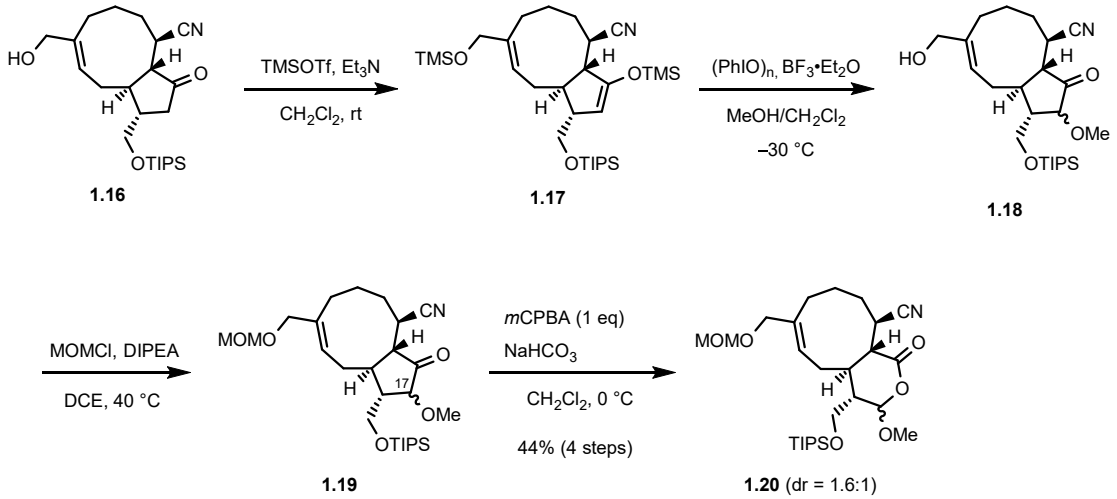


Figure 1.10. Synthesis of lactone **1.20**

Lactone **1.20** was subjected to DIBAL-H reduction followed by one-pot acetylation to give substituted tetrahydropyran **1.21**, which was treated with TAS-F giving alcohol **1.22** in 74% for two steps (Figure 1.11). Oxidation of the resulting alcohol by Dess-Martin periodinane afforded aldehyde **1.23** in 96% yield as a 2.5:1 mixture of diastereomers. The stereochemistry of the major diastereomer was established based on the NMR

coupling constants, indicating both the acetoxy and methoxy groups are directed to the α-face. The configuration of the minor isomer, which has the acetoxy and methoxy groups on the β-face, was determined similarly.

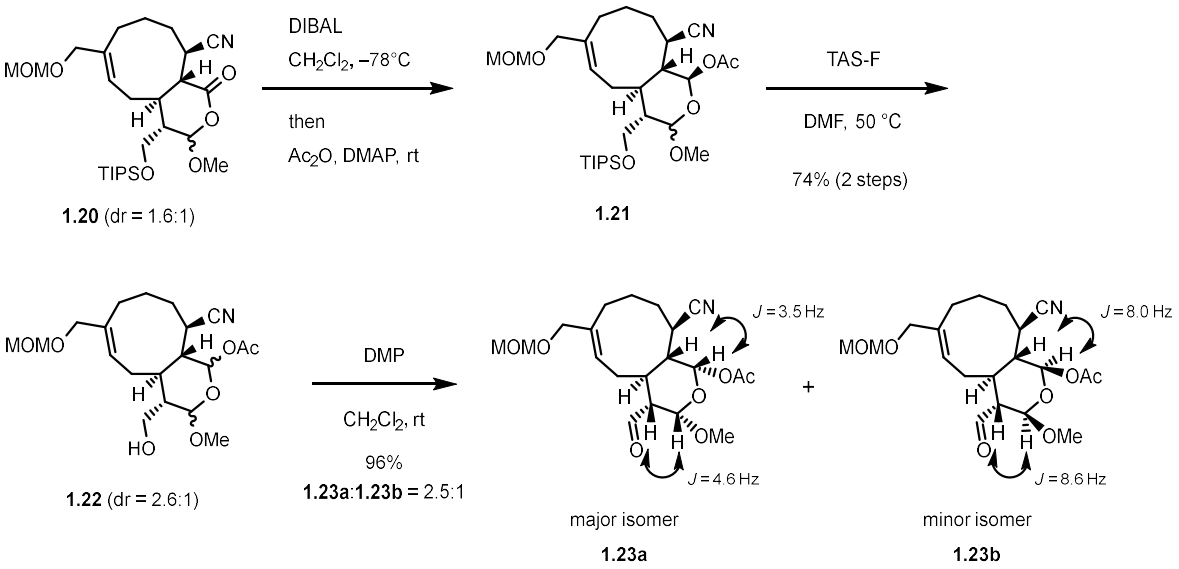
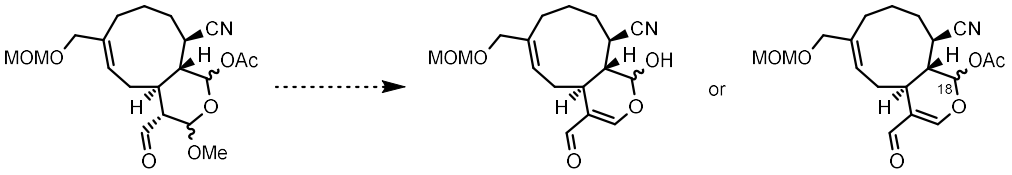


Figure 1.11. Synthesis of dihydropyran precursor **1.23**

With aldehyde **1.23** in hand, the key dihydropyran formation reaction was next examined (Figure 1.12). Treatment of **1.23** with K_2CO_3 in MeOH resulted in formation of a complex mixture, suggesting that the desired product cannot tolerate the strong basic condition. To remove the acetyl group under milder conditions, **1.23** was heated with DMAP in toluene. While most of the substrate remained unchanged, a small amount of desired compound **1.25** was found in the crude mixture. To enhance the transformation, the reaction mixture was heated with acetic acid at 120 °C, giving the desired product **1.25** in 53% yield as a 2:1 mixture of epimers. The NMR coupling constant of the C18 proton (J = 2.0 Hz) suggested that the major product was the undesired diastereomer.



Entry	conditions	results
1	K_2CO_3, MeOH	messy
2	DMAP, toluene, 120 °C	**1.25** (trace) + SM
3	DMAP, AcOH, toluene, 120 °C	**1.25** (53%, dr = 2:1) + **1.26**

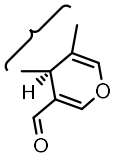


Figure 1.12. Dihydropyran ring formation

The transesterification mediated by DMAP would explain the reaction mechanism of **1.25** formation (Figure 1.13). The acetyl group of substrate **1.23** is removed by the addition reaction with DMAP, leading to ring opening and elimination of the methoxy group to afford tri-aldehyde **1.27**. The enol form of **1.27** would undergo cyclization to give hemiacetal **1.28** which is converted to **1.25** by the addition reaction with acetyl-DMAP.

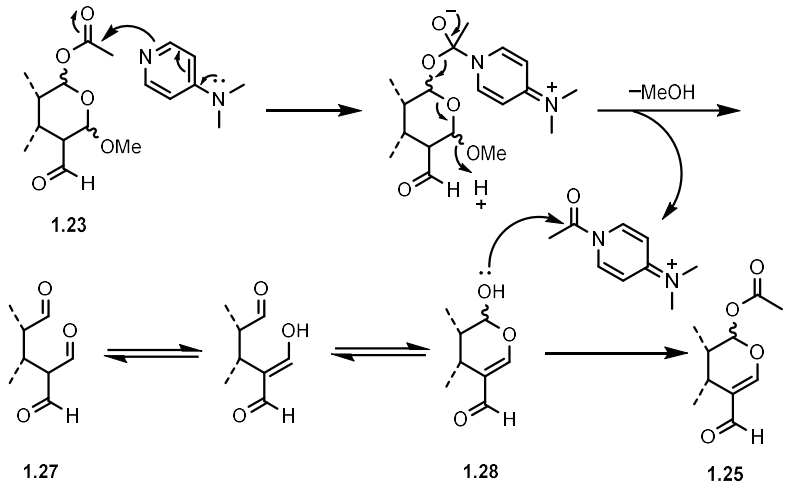


Figure 1.13. Putative mechanism for the formation of **1.25**

Elongation of the side chain was then achieved by using an allylboronate **1.30** (Figure 1.14). [33] Upon heating with **1.30** in toluene, aldehyde **1.25** was converted to alcohol **1.29** which was further oxidized with Dess-Martin periodinane to give ketone **1.30** in 44% yield for two steps.

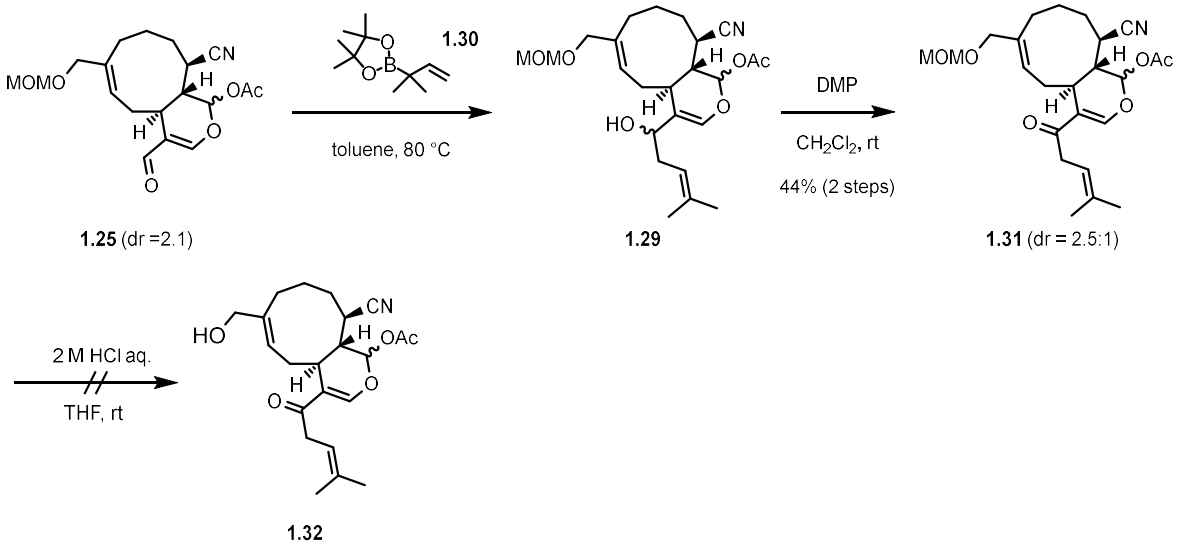


Figure 1.14. Side chain installation

Since removal of the MOM group under acidic conditions merely led to decomposition of **1.31**, PMB protected compound **1.33** was prepared through similar synthetic route (Figure 1.15). Elongation of the side chain using **1.30** followed by DMP oxidation afforded ketone **1.35**, and treatment with DDQ effected removal of the PMB group followed by oxidation of the resulting alcohol, giving Cristaxenicin A analogue **1.36**. The quantity of the product was too small for estimating the chemical yield, but its structure was confirmed by its crude NMR and mass spectrometry analysis.

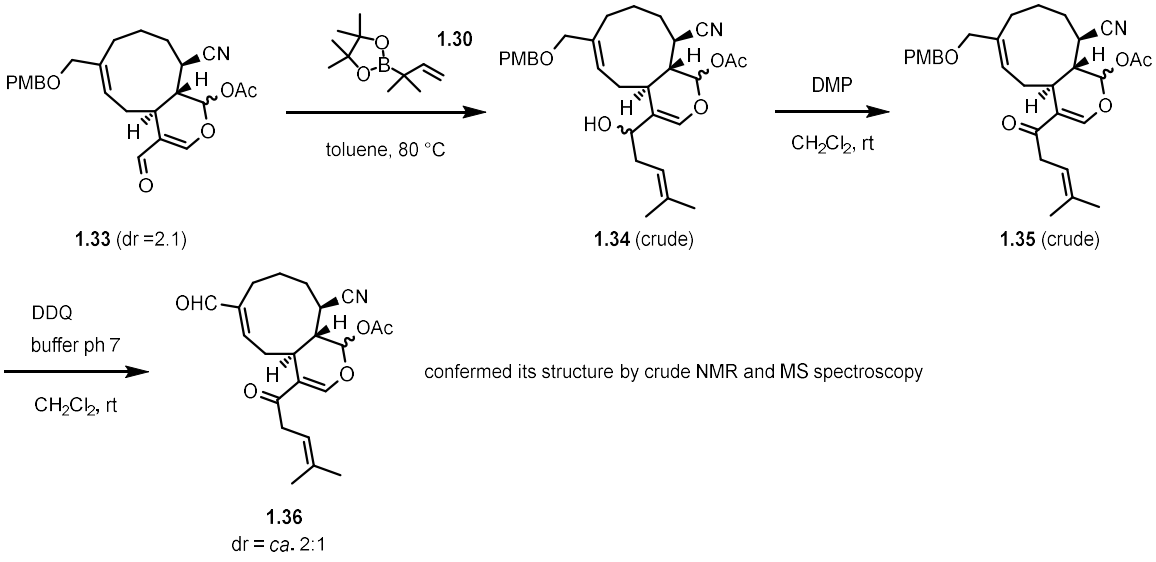


Figure 1.15. Synthesis of Cristaxenicin A analogue

Conclusion

In summary, the author accomplished the synthesis of an analogue of Cristaxenicin A. The key intermediate consisting of a 9-5 bicyclic skeleton was synthesized by an Eschenmoser-Claisen-Cope rearrangement cascade and an intramolecular Stetter reaction. The conjugated diene moiety was converted to an allyl alcohol by a unique protocol for selective cleavage of the vinyl group. A new method for constructing a dihydropyran ring from a cyclopentenone was also developed. These findings would be applied to the total synthesis of the target molecule, Cristaxenicin A.

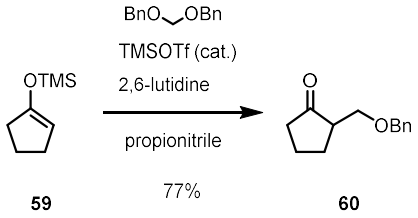
Experimental Section

All reactions were performed using flame-dried glassware under a positive pressure of argon. When necessary, the glassware was dried under reduced pressure by heating with a heat–gun. Reactions at elevated temperatures were performed under heating in an oil bath. THF and Et_2O were distilled from sodium benzophenone ketyl. Other anhydrous solvents were purchased from chemical companies. Et_2NH and Et_3N were distilled from CaH_2 under argon and stored in the presence of NaOH (pellets). Di(benzyloxy)methane,[42] Trimethyl(4-(phenylthio)but-2-en-1-yl)silane,[24] *p*-Methoxybenzyl-N-phenyl-2,2,2-trifluoroacetimidate,[34] allylboronate **1.30**,[33] neutral-silica-gel-supported $NaIO_4$,[40] and allyl carbonate **2.15**[45] were prepared according to the reported procedure. All other reagents were used as received from commercial sources without further purification.

The melting points were measured using ASONE ATM-02 apparatus and uncorrected. ^{1}H NMR spectra were measured using JEOL ECA-500 (500 MHz) in $CDCl_3$ (δ_H 7.26) or CD_3OD (δ_H 3.30). For some compounds, tetramethylsilane (δ_H 0.00) was used as an internal standard in $CDCl_3$. Chemical shifts are reported in parts per million (ppm), and signals are expressed as broad (br), singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). Coupling constants are reported in Hz. ^{13}C NMR spectra were measured using JEOL ECA-500 (126 MHz) in $CDCl_3$ (δ_C 77.0) or CD_3OD (δ_C 49.0). High-resolution mass spectra (HRMS) were recorded on JEOL JMS-T100GCV (GC-TOFMS) and Thermo Scientific Q Exactive Plus at the GC-MS & NMR Laboratory, Faculty of Agriculture, Hokkaido University, and Thermo Scientific Q Exactive Plus at the Global Research Facility Alliance Center, Hokkaido University. Fourier transform infrared (FT-IR) spectra were recorded on JASCO FT/IR-4100 spectrophotometer. Analytical thin layer chromatography (TLC) was performed using Silica Gel 60 F_{254} (E. Merck), and preparative thin layer chromatography (PTLC) was performed using PLC Silica Gel 60 F_{254} (E. Merck). Reaction components were visualized by illumination with ultraviolet light (254 nm) and by staining with 8% ethanolic phosphomolybdic acid, *p*-anisaldehyde ethanol solution, or basic potassium permanganate aqueous solution. Chromatorex PSQ 60B (Fuji Silysia Chemical Ltd.) was used for flash column chromatography. 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 column) is loaded, which is eluted completely with EtOAc. Then , the EtOAc in the silica gel column was replaced with appropriate solvent before loading the crude product.

Synthesis of 9-5 bicyclic compound 74 by the author

Synthesis of **60**

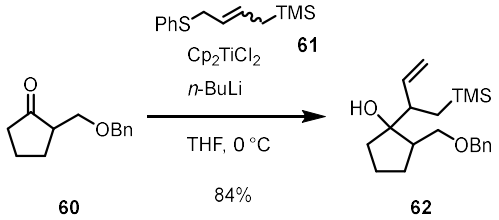


To a mixture of silyl enol ether **59** (20.0 mL, 113 mmol), di(benzyloxy)methane,[42] (27.2 g, 119 mmol) and 2,6-di-*tert*-butylpyridine (1.91 mL, 8.48 mmol) in EtCN (113 mL) was added TMSOTf (1.02 mL, 5.65 mmol) at 0 °C. After stirring at room temperature for 24 h, the reaction was quenched with saturated aqueous $NaHCO_3$ solution. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, *n*-hexane:EtOAc = 100:0 to 99:1 to 9:1 to 4:1) to afford **60** (17.7 g, 86.6 mmol, 77%) as a pale-yellow oil.

Spectral data for **60**

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.39-7.22 (m, 5H), 4.51 (d, *J* = 12.5 Hz, 1H), 4.48 (d, *J* = 12.5 Hz, 1H), 3.67 (dd, *J* = 9.0, 4.0 Hz, 1H), 3.63 (dd, *J* = 9.0, 6.0 Hz, 1H), 2.39-2.32 (m, 1H), 2.32-2.20 (m, 2H), 2.14 (dt, *J* = 14.6, 7.3 Hz, 1H), 2.08-2.00 (m, 1H), 1.92 (dtd, *J* = 12.5, 10.0, 7.0 Hz, 1H), 1.85-1.74 (m, 1H); **^{13}C{^{1}H}-NMR** (126 MHz, $CDCl_3$) δ 219.6, 138.2, 128.3 (2C), 127.6, 127.5 (2C), 73.2, 69.2, 49.4, 38.7, 27.2, 20.9; **FT-IR (ATR)**: ν_{max} 2960, 2863, 1729, 1452, 1361, 1093 cm^{-1}; **HRMS (FI)**: *m/z* Calcd for $C_{13}H_{16}O_2$ $[M]^+$: 204.1145, found: 204.1152.

Synthesis of **62**



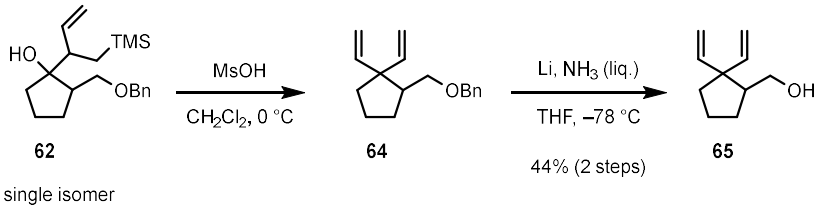
To a suspension of Cp_2TiCl_2 (27.4 g, 110 mmol) in THF (400 mL) was added *n*-BuLi (143 mL, 220 mmol, 1.54 M in hexane) dropwise over 30 min at –78 °C. After stirring at –78 °C for 30 min, allylsulfide **61**[24] (*E*/*Z* =3:1, 13.0 g, 55.0 mmol in THF 50 mL) was added dropwise over 30 min at –78 °C and warmed up to 0 °C. After stirring at 0 °C for 30 min, ketone **60** (10.2 g, 50.0 mmol) was added dropwise over 20 min at

0 °C. After the reaction mixture was stirred at 0 °C for 10 min, the reaction was quenched with 1 M aqueous NaOH solution (400 mL) and the mixture was stirred overnight. The mixture was filtered through a pad of Celite, and the Celite was rinsed with Et_2O. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to afford crude **62**. This protocol was repeated one more time (total 20.4 g (100 mmol) of ketone **60**) and the combined crude products were purified by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 100:0 to 99:1 to 19:1) to afford alcohol **62** (27.8 g, 83.6 mmol, 84% yield, single isomer, stereochemistry was not determined) as a yellow oil.

Spectral data for **62**

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.37-7.26 (m, 5H), 5.63 (dt, *J* = 16.3, 10.5 Hz, 1H), 5.07 (dd, *J* = 10.5, 2.0 Hz, 1H), 5.06 (dd, *J* = 16.3, 2.0 Hz, 1H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 3.63 (dd, *J* = 9.0, 5.5 Hz, 1H), 3.55 (dd, *J* = 9.0, 5.5 Hz, 1H), 2.64 (s, 1H), 2.31 (td, *J* = 12.1, 2.1 Hz, 1H), 2.17 (ddd, *J* = 14.0, 8.5, 5.0 Hz, 1H), 1.84-1.62 (m, 4H), 1.53-1.43 (m, 2H), 0.77 (dd, *J* = 14.5, 2.1 Hz, 1H), 0.54 (dd, *J* = 14.5, 12.3 Hz, 1H), –0.04 (s, 9H); **^{13}C{^{1}H}-NMR** (126 MHz, $CDCl_3$): δ 141.4, 138.3, 128.3 (2C), 127.5 (2C), 116.8, 84.2, 73.2, 71.0, 49.1, 44.2, 37.1, 28.8, 22.1, 16.9, –0.7 (3C) (one peak missing); **FT-IR (ATR)**: ν_{max} 3500, 2945, 2870, 1452, 1361, 1244, 1095, 858, 834 cm^{-1}; **HRMS (FI)**: *m/z* Calcd for $C_{20}H_{33}O_2Si$ $[M+H]^+$: 333.2244; found: 333.2241.

Synthesis of **65**



To a solution of alcohol **62** (17.9 g, 55.5 mmol) in CH_2Cl_2 (278 mL) was added MsOH (18.1 mL, 278 mmol) at 0 °C. After stirring at 0 °C for 10 min, 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 washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, *n*-hexane/EtOAc =100:0 to 99:1 to 97:3) to afford impure **64** as a yellow oil (8.48 g, ca. 26.3 mmol, <47%).

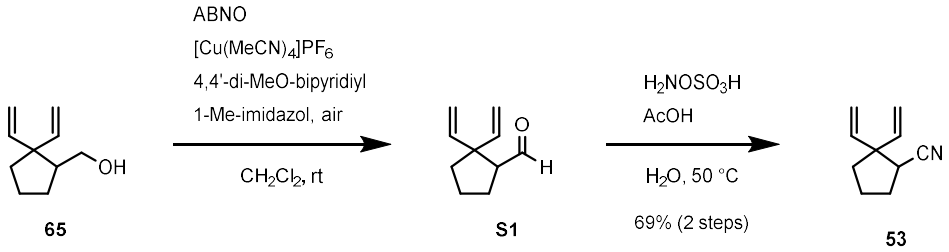
To a mixture of Li (916 mg, 132 mmol) and liquid ammonia (approx. 20 mL) was added a solution of **64** (8.48 g, ca. 26.3 mmol) in THF (52 mL) dropwise at –78 °C. After stirring at –78 °C for 30 min, the reaction

was quenched with EtOH and stirred at room temperature for 1 h. Saturated aqueous NH_4Cl solution and EtOAc was carefully added to the mixture. After the layers were separated, the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, *n*-hexane/EtOAc =97:3 to 19:1 to 9:1) to afford alcohol **65** (3.70 g, 24.3 mmol, 44% yield for two steps) as a yellow oil.

Spectral data for **65**

^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.95 (dd, *J* = 17.3, 11.0 Hz, 1H), 5.93 (dd, *J* = 17.0, 11.0 Hz, 1H), 5.16 (d, *J* = 11.0 Hz, 1H), 5.08 (d, *J* = 17.3 Hz, 1H), 5.06 (d, *J* = 11.0 Hz, 1H), 5.04 (d, *J* = 17.0 Hz, 1H), 3.70 (ddd, *J* = 10.7, 7.0, 3.8 Hz, 1H), 3.50 (dt, *J* = 10.7, 6.5 Hz, 1H), 2.09 (tt, *J* = 8.3, 7.5 Hz, 1H), 1.93-1.80 (m, 2H), 1.77-1.65 (m, 3H), 1.47-1.36 (m, 2H); **^{13}C{^{1}H}-NMR** (126 MHz, $CDCl_3$): δ 145.1, 139.9, 114.4, 112.7, 64.3, 53.3, 50.9, 36.2, 27.6, 21.7; **FT-IR (ATR)**: ν_{max} 3330, 3079, 2954, 2872, 1632, 1454, 1218, 996, 910 cm^{-1}; **HRMS (FI)**: *m/z* Calcd for $C_{10}H_{16}O$ $[M]^+$: 152.1196; found: 152.1194.

Synthesis of **53**



To a solution of alcohol **65** (3.70 g, 24.3 mmol) in CH_2Cl_2 (120 mL) were successively added $[Cu(MeCN)_4]PF_6$ (154 mg, 1.22 mmol), 4,4'-Dimethoxy-2,2'-bipyridyl (263 mg, 1.22 mmol), *N*-methylimidazole (207 µL, 2.43 mmol), and ABNO (34.0 mg, 0.243 mmol) in open air. The reaction mixture was stirred in open air at room temperature for 15 h. The mixture was directly passed through a pad of silica gel, and the gel was rinsed with Et_2O. The filtrate was carefully concentrated under reduced pressure to afford the crude aldehyde **S1** (volatile). The crude product was used for the next step without further purification.

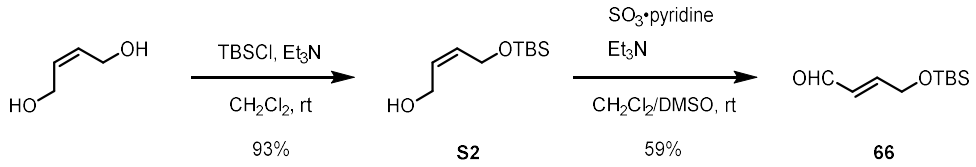
To a mixture of crude aldehyde **S1** and hydroxylamine-*O*-sulfonic acid (5.50 g, 48.6 mmol) in H_2O (120 mL) was added AcOH (2.70, 48.6 mmol). After vigorously stirring at 50 °C for 16.5 h, the reaction mixture was cooled down to room temperature, diluted with Et_2O, and quenched with saturated aqueous $NaHCO_3$ solution. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and carefully concentrated under reduced pressure.

The residue was purified by flash column chromatography (SiO_2, *n*-pentane/Et_2O = 100:0 to 99:1 to 19:1) to afford nitrile **53** (volatile, 2.47 g, 16.8 mmol, 69% yield for two steps) as a yellow oil.

Spectral data for **53**

^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.02 (dd, *J* = 18.0, 11.0 Hz, 1H), 5.84 (dd, *J* = 17.5, 10.5 Hz, 1H), 5.30 (d, *J* = 11.0 Hz, 1H), 5.20 (d, *J* = 17.5 Hz, 1H), 5.18 (d, *J* = 10.5 Hz, 1H), 5.14 (d, *J* = 18.0 Hz, 1H), 2.73 (t, *J* = 8.3 Hz, 1H), 2.19-2.10 (m, 1H), 2.03-1.93 (m, 2H), 1.92-1.82 (m, 1H), 1.82-1.68 (m, 2H); **^{13}C{^{1}H}-NMR** (126 MHz, $CDCl_3$): δ 140.8, 138.3, 120.6, 116.4, 114.8, 54.4, 39.0, 34.3, 28.6, 21.5; **FT-IR (ATR)**: ν_{max} 3086, 2959, 2880, 2237, 1636, 1456, 1415, 996, 920 cm^{-1}; **HRMS (FI)**: *m/z* Calcd for $C_{10}H_{13}N$ $[M]^+$: 147.1043; found: 147.1043.

Synthesis of **66**[25,43]

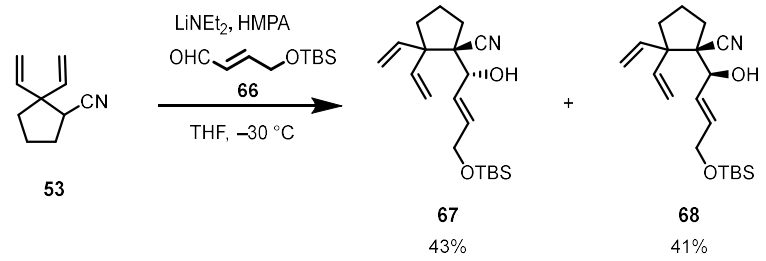


Aldehyde **66** was synthesized by a slightly modified procedure from the literature.[25]

To a mixture of *cis*-2-butene-1,4-diol (4.08 mL, 50.0 mmol) and Et_3N (10.5 mL, 75.0 mmol) in CH_2Cl_2 (200 mL) was added a solution of TBSCl (7.54 g, 50.0 mmol) in CH_2Cl_2 (50 mL) dropwise at 0 °C. After stirring at room temperature for 18 h, the reaction was quenched with saturated aqueous $NaHCO_3$ solution. After the layers were separated, the aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, *n*-pentane/Et_2O = 100:0 to 99:1 to 19:1) to afford alcohol **S2** (9.38 g, 46.4 mmol, 93%) as a colorless oil. The spectral data matched with those reported in literature.[25]

To a mixture of alcohol **S2** (9.38 g, 46.4 mmol), and Et_3N (186 mmol, 25.9 ml) in CH_2Cl_2 (186 mL) was added a solution of SO_3•pyridine (92.8 mmol, 14.8 g) in DMSO (46.4 mL) dropwise. After stirring at room temperature for 40 min, the reaction was quenched with $Na_2S_2O_3$ and water. After the layers were separated, the aqueous layer was extracted with Et_2O and the combined organic layers were washed with 1 M hydrochloric acid and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, *n*-pentane/Et_2O = 100:0 to 99:1 to 19:1) to afford alcohol **66** (5.47 g, 27.6 mmol, 59%) as a yellow oil. The spectral data matched with those reported in literature.[25]

Synthesis of **67** and **68**



A $LiNEt_2$ solution (1.0 M THF/*n*–hexane) was prepared as following. To a solution of Et_2NH (2.10 mL, 20.3 mmol) in THF (5.1 mL) was added *n*-BuLi (13.1 mL, 20.3 mmol, 1.55 M in *n*–hexane) dropwise at 0 °C and stirred at the same temperature for 10 min.

A mixture of nitrile **53** (2.30 g, 15.6 mmol) and HMPA (3.64 mL, 20.3 mmol) in THF (76 mL) was cooled to –30 °C and the above $LiNEt_2$ solution was added dropwise. After stirring at the same temperature for 2 h, a solution of aldehyde **66** (4.02g, 20.3 mmol) in THF (20 mL) was added dropwise at –30 °C and stirred at the same temperature for 10 min. The reaction was quenched with saturated aqueous NH_4Cl solution and the mixture was diluted with EtOAc. After the layers were separated, the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 24:1 to 23:2 to 9:1 to 4:1) to afford allyl alcohol **67** (2.31 g, 6.65 mmol, 43% yield) as a pale-yellow solid and **68** (2.24 g 6.44 mmol, 41% yield).

Spectral data for **67**

^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.50 (dd, *J* = 17.3, 11.0 Hz, 1H), 6.02 (dd, *J* = 17.9, 10.7 Hz, 1H), 5.89-5.86 (m, 2H), 5.35 (dd, *J* = 10.7, 1.5 Hz, 1H), 5.27 (dd, *J* = 17.9, 1.5 Hz, 1H), 5.22 (dd, *J* = 11.0, 1.5 Hz, 1H), 5.13 (dd, *J* = 17.3, 1.5 Hz, 1H), 4.21 (d, *J* = 3.0 Hz, 2H), 4.19 (t, *J* = 5.0 Hz, 1H), 2.20 (dt, *J* = 14.0, 9.5 Hz, 1H), 1.96 (dd, *J* = 8.8, 2.8 Hz, 1H), 1.96-1.92 (m, 2H), 1.90 (d, *J* = 5.0 Hz, 1H), 1.85-1.77 (m, 1H), 1.77-1.69 (m, 1H), 0.91 (s, 9H), 0.078 (s, 3H), 0.076 (s, 3H); **^{13}C{^{1}H}-NMR** (126 MHz, $CDCl_3$): δ 141.5, 136.9, 134.0, 127.8, 121.2, 117.0, 115.3, 74.2, 62.7, 57.6, 56.9, 33.7, 33.5, 25.9 (3C), 20.1, 18.3, –5.27, –5.29; **FT-IR (ATR)**: ν_{max} 3471, 2951, 2926, 2856, 2237, 1729, 1252, 833, 777 cm^{-1}; **HRMS (FI)**: *m/z* Calcd for $C_{20}H_{33}NO_2Si$ $[M]^+$: 347.2275; found: 347.2276. **Melting point**: 61 to 64 °C ($CHCl_3$).

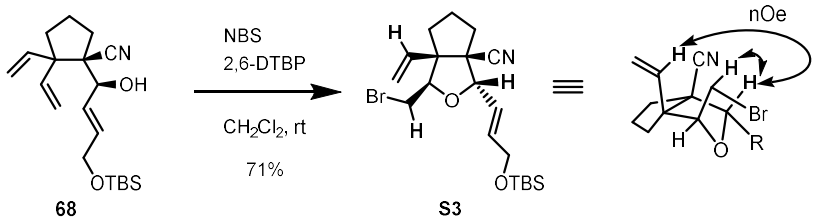
Spectral data for **68**

^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.16 (dd, *J* = 17.3, 11.0 Hz, 1H), 5.96-5.84 (m, 3H), 5.29 (dd, *J* = 11.0, 1.0 Hz, 1H), 5.20 (dd, *J* = 17.3, 1.0 Hz, 1H), 5.17 (dd, *J* = 10.0, 1.0 Hz, 1H), 5.06 (d, *J* = 16.5 Hz, 1H), 4.20 (d, *J* = 3.0 Hz, 2H), 4.16 (d, *J* = 6.5 Hz, 1H), 2.41 (ddd, *J* = 15.5, 6.5, 3.5 Hz, 1H), 2.19-2.07 (m, 2H), 2.01-1.90

(m, 3H), 1.89-1.78 (m, 1H), 0.92 (s, 9H), 0.08 (s, 6H); **^{13}C{^{1}H}-NMR** (126 MHz, $CDCl_3$): δ 140.2, 137.0, 133.9, 127.5, 121.3, 116.8, 115.9, 74.0, 62.6, 57.8, 56.0, 34.7, 34.3, 25.8 (3C), 19.9, 18.3, –5.36 (2C); **FT-IR (ATR)**: ν_{max} 3455, 2954, 2932, 2856, 2237, 1731, 1254, 1108, 833 cm^{-1}; **HRMS (FI)**: *m/z* Calcd for $C_{20}H_{33}NO_2Si$ $[M]^+$: 347.2275; found: 347.2276.

Synthesis of **S3**

The relative stereochemistry of **68** was determined from its derivative **S3** by measuring its nOe correlation.

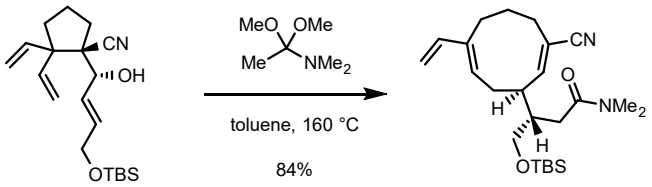


To a mixture of allyl alcohol **68** (11.0 mg, 0.0316 mmol) and 2,6-di-*tert*-butylpyridine (13.9 μL, 0.0632 mmol) in CH_2Cl_2 (300 μL) was added NBS (8.8 mg, 0.049 mmol). After stirring at room temperature for 2.5 h, another portion of NBS (9.2 mg, 0.052 mmol) and di-*tert*-butylpyridine (14.0 μL, 0.0637 mmol) were added and stirred for 2 h at room temperature. Then another portion of NBS (4.2 mg, 0.024 mmol) was added and stirred for further 30 min. The reaction was quenched with $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ solution. The mixture was diluted with Et_2O and the layers were separated. The aqueous layer was extracted with Et_2O, and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 99:1 to 19:1) to afford bromoether **S3** (9.3 mg, 0.023 mmol, 71% yield) as a white solid.

Spectral data for **S3**

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.06 (dt, *J* = 15.0, 2.5 Hz, 1H), 6.92 (dt, *J* = 15.0, 2.5 Hz, 1H), 6.28 (dd, *J* = 17.0, 11.0 Hz, 1H), 5.65 (dd, *J* = 17.3, 11.0 Hz, 1H), 5.32 (d, *J* = 11.0 Hz, 1H), 5.23 (d, *J* = 11.0 Hz, 1H), 5.20 (d, *J* = 17.3 Hz, 1H), 5.15 (d, *J* = 17.0 Hz, 1H), 4.39 (t, *J* = 2.5 Hz, 2H), 2.58 (ddd, *J* = 13.8, 9.3, 7.5 Hz, 1H), 2.14-2.08 (m, 2H), 2.06-2.00 (m, 1H), 1.98-1.91 (m, 2H), 0.95 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); **^{13}C{^{1}H}-NMR** (126 MHz, $CDCl_3$): δ 190.6, 149.1, 139.0, 136.2, 123.9, 120.2, 117.2, 117.0, 62.3, 61.7, 58.9, 33.2, 32.3, 25.8 (3C), 20.4, 18.2, –5.4, –5.5; **FT-IR (ATR)**: ν_{max} 2956, 2928, 2857, 2361, 1698, 1629, 1132, 832, 771 cm^{-1}; **HRMS (FI)**: *m/z* Calcd for $C_{20}H_{31}NO_2Si$ $[M]^+$: 345.2119; found: 345.2125. **Melting point**: 35 to 37 °C ($CHCl_3$).

Synthesis of **71**



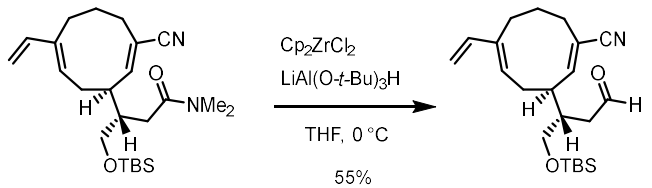
67 **71**

In a sealed tube, allyl alcohol **67** (4.21 g, 12.1 mmol) and *N*,*N*-Dimethylacetamide Dimethyl Acetal (8.85 mL, ca. 60.5 mmol, contains 5-10% Methanol) were dissolved in toluene (40 mL) and heated to 160 °C. After stirring for 3 h, the mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 4:1 to 3:2) to afford **71** (4.26 g, 10.2 mmol, 84% yield) as a yellow oil.

Spectral data for **71**

^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.56 (d, *J* = 9.0 Hz, 1H), 6.22 (dd, *J* = 17.5, 11.0 Hz, 1H), 5.83 (t, *J* = 8.5 Hz, 1H), 5.16 (d, *J* = 17.5 Hz, 1H), 5.01 (d, *J* = 11.0 Hz, 1H), 3.70 (dd, *J* = 10.5, 4.0 Hz, 1H), 3.55 (dd, *J* = 10.5, 4.5 Hz, 1H), 3.02 (s, 3H), 2.96 (s, 3H), 2.63-2.55 (m, 1H), 2.49 (dd, *J* = 10.5, 9.0 Hz, 1H), 2.40-2.31 (m, 2H), 2.23-2.04 (m, 5H), 2.00 (dt, *J* = 13.5, 8.3 Hz, 1H), 1.93-1.81 (m, 2H), 0.87 (s, 9H), 0.04 (s, 3H), 0.00 (s, 3H); **^{13}C{^{1}H}-NMR** (126 MHz, $CDCl_3$): δ 171.4, 151.2, 138.9, 138.1, 132.1, 120.0, 114.6, 112.2, 63.0, 41.7, 40.4, 37.2, 35.5, 31.3, 31.1, 26.9, 26.8, 25.7 (3C), 22.5, 18.1, –5.6, –5.8; **FT-IR (ATR)**: ν_{max} 2954, 2927, 2857, 2213, 1644, 1103, 834, 773 cm^{-1}; **HRMS (FI)**: *m/z* Calcd for $C_{24}H_{40}N_2O_2Si$ $[M]^+$: 416.2854; found:416.2848.

Synthesis of **72**



71 **72**

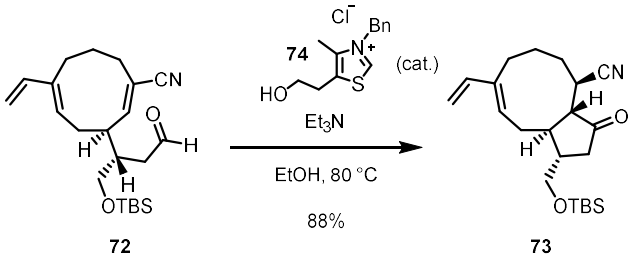
To a solution of amide **71** (4.26 g, 10.2 mmol) and Cp_2ZrCl_2 (8.94 g, 30.6 mmol) in THF (100 mL) was added $LiAlH(O\text{-}t\text{-}Bu)_3$ (15.3 mL, 15.3 mmol, 1.0 M THF solution) dropwise for 1 h at 0 °C. After stirring at the same temperature for 1 h, another portion of $LiAlH(O\text{-}t\text{-}Bu)_3$ (5.10 mL, 5.10 mmol, 1.0 M THF solution) was added dropwise for 30 min. After stirring at the same temperature for 10 min, another portion of

$LiAlH(O\text{-}t\text{-}Bu)_3$ (1.53 mL, 1.53 mmol, 1.0 M THF solution) was added dropwise for 10 min. After stirring at the same temperature for 5 min, the reaction was quenched with saturated aqueous NH_4Cl solution and the mixture was diluted with Et_2O and water. The mixture was vigorously stirred at room temperature until both phases became clear. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 97:3 to 19:1 to 9:1) to afford aldehyde **72** (2.10 g, 5.62 mmol, 55% yield) as a yellow oil.

Spectral data for **72**

^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.78 (s, 1H), 6.47 (d, *J* = 9.3 Hz, 1H), 6.22 (dd, *J* = 17.3, 11.0 Hz, 1H), 5.82 (t, *J* = 8.5 Hz, 1H), 5.18 (d, *J* = 17.3 Hz, 1H), 5.03 (d, *J* = 9.3 Hz, 1H), 3.57 (d, *J* = 5.5 Hz, 2H), 2.59-2.50 (m, 2H), 2.42-2.32 (m, 3H), 2.20-1.99 (m, 5H), 1.95-1.82 (m, 2H), 0.87 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); **^{13}C{^{1}H}-NMR** (126 MHz, $CDCl_3$): δ 200.8, 149.7, 138.8, 138.6, 131.4, 119.7, 115.6, 112.6, 63.6, 42.9, 40.4, 40.3, 31.6, 27.1, 26.9, 25.8 (3C), 22.6, 18.1, –5.6, –5.7; **FT-IR (ATR)**: ν_{max} 2952, 2929, 2857, 2216, 1725, 1461, 1252, 1093, 835 cm^{-1}; **HRMS (FD)**: Calcd for $C_{22}H_{35}NO_2Si$ $[M]^+$: 373.2432; found: 373.2432.

Synthesis of **73**



In a sealed tube, aldehyde **72** (2.10 g, 5.62 mmol), Et_3N (783 µL, 5.62 mmol) and thiazolium catalyst **74** (758 mg, 2.81 mmol) were dissolved in EtOH (28.1 mL) and heated to 80 °C. After stirring for 36 h, the reaction was cooled down to room temperature, quenched with water and the mixture was diluted with Et_2O. The mixture was directly passed through a pad of silica gel, and the gel was rinsed with Et_2O. The filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 19:1 to 9:1) to afford ketone **73** (1.85 g, 4.95 mmol, 88% yield) as a pale-yellow solid.

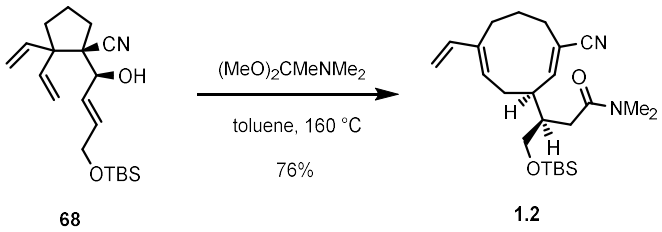
Spectral data for **73**

^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.26 (d, *J* = 17.5, 11.0 Hz, 1H), 5.73 (dd, *J* = 9.3, 7.8 Hz, 1H), 5.15 (d, *J* = 17.5 Hz, 1H), 5.02 (d, *J* = 11.0 Hz, 1H), 3.74 (dd, *J* = 10.5, 3.8 Hz, 1H), 3.70 (dd, *J* = 10.5, 3.8 Hz, 1H), 2.66-

2.60 (m, 1H), 2.48 (ddd, *J* = 14.5, 10.5, 3.5 Hz, 1H), 2.45-2.27 (m, 5H), 2.24 (dd, *J* = 18.5, 10.5 Hz, 1H), 2.05-1.85 (m, 4H), 1.80-1.67 (m, 2H), 0.87 (s, 9H), 0.051 (s, 3H), 0.048 (s, 3H); **^{13}C{^{1}H}-NMR** (126 MHz, $CDCl_3$): δ 214.7, 141.6, 138.7, 128.7, 120.7, 112.6, 62.5, 54.0, 42.2, 41.6, 39.9, 31.9, 31.7, 27.0, 25.8 (3C), 24.9, 22.5, 18.2, –5.5, –5.6; **FT-IR (ATR)**: ν_{max} 2951, 2927, 2857, 2237, 1745, 1469, 1100, 833, 774 cm^{-1}; **HRMS (FI)**: *m/z* Calcd for $C_{22}H_{35}NO_2Si$ $[M]^+$: 373.2432; found: 373.2440. **Melting point**: 106 to 108 °C ($CHCl_3$).

Experimental date for Chapter 1

Synthesis of **1.2**



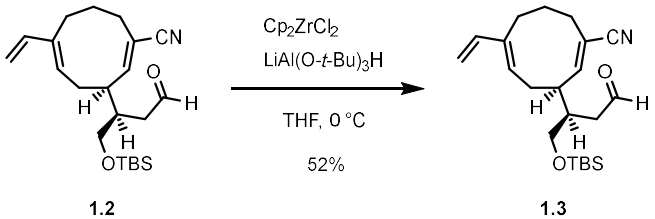
68 **1.2**

In a sealed tube, allyl alcohol **68** (1.16 g, 3.34 mmol) and *N*,*N*-Dimethylacetamide Dimethyl Acetal (2.44 mL, ca. 16.7 mmol, contains 5-10% Methanol) were dissolved in toluene (40 mL) and heated to 160 °C. After stirring for 3 h, the mixture was cooled down to room temperature and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 6:1 to 3:1) to afford **1.2** (1.06 g, 2.54 mmol, 76% yield) as a yellow oil.

Spectral data for **1.2**

^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.74 (d, *J* = 8.2 Hz, 1H), 6.23 (dd, *J* = 17.5, 11.0 Hz, 1H), 5.84 (t, *J* = 8.5 Hz, 1H), 5.17 (d, *J* = 17.5 Hz, 1H), 5.02 (d, *J* = 11.0 Hz, 1H), 3.68 (dd, *J* = 10.0, 4.0 Hz, 1H), 3.64 (dd, *J* = 10.0, 3.8 Hz, 1H), 3.03 (s, 3H), 2.96 (s, 3H), 2.60 (dd, *J* = 15.3, 8.2 Hz, 1H), 2.55-2.47 (m, 1H), 2.37 (dt, *J* = 13.5, 3.0 Hz, 1H), 2.32-2.25 (m, 1H), 2.20-2.11 (m, 4H), 2.11-2.02 (m, 2H), 1.93-1.83 (m, 2H), 0.88 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); **^{13}C{^{1}H}-NMR** (126 MHz, $CDCl_3$): δ 171.5, 151.2, 139.0, 138.3, 132.3, 120.0, 114.8, 112.3, 62.5, 41.6, 41.3, 37.3, 35.5, 32.1, 31.7, 26.9, 26.8, 25.8 (3C), 22.5, 18.1, –5.5, –5.7; **FT-IR (ATR)**: ν 2952, 2927, 2857, 2213, 1644, 1252, 1100, 835, 775 cm^{-1}; **HRMS (FD)**: *m/z* Calcd for $C_{24}H_{40}N_2O_2Si$ $[M]^+$: 416.2854; found: 416.2856.

Synthesis of **1.3**



1.2 **1.3**

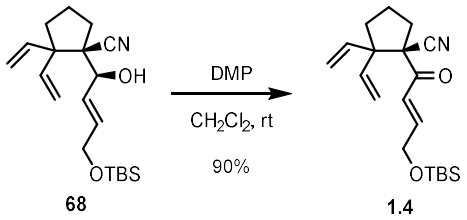
To a solution of amide **1.2** (283 mg, 0.679 mmol) and Cp_2ZrCl_2 (596 mg, 2.04 mmol) in THF (6.8 mL) was added $LiAlH(O\text{-}t\text{-}Bu)_3$ (1.02 mL, 1.02 mmol, 1.0 M THF solution) dropwise at 0 °C. After stirring at the same temperature for 5 min, the reaction was quenched with water, and the mixture was diluted with Et_2O.

After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 97:3) to afford aldehyde **1.3** (132 mg, 0.353 mmol, 52% yield) as a pale-yellow oil.

Spectral data for **1.3**

^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.79 (s, 1H), 6.58 (d, *J* = 8.5 Hz, 1H), 6.22 (dd, *J* = 18.0, 10.5 Hz, 1H), 5.80 (t, *J* = 8.8 Hz, 1H), 5.17 (d, *J* = 18.0 Hz, 1H), 5.03 (d, *J* = 10.5 Hz, 1H), 3.64 (dd, *J* = 10.5, 4.0 Hz, 1H), 3.57 (dd, *J* = 10.5, 5.3 Hz, 1H), 2.64 (ddd, *J* = 17.0, 8.5, 1.5 Hz, 1H), 2.44 (dd, *J* = 17.5, 4.5 Hz, 1H), 2.41-2.34 (m, 2H), 2.31-2.23 (m, 1H), 2.18-2.00 (m, 5H), 1.94-1.82 (m, 2H), 0.87 (s, 9H), 0.024 (s, 3H), 0.019 (s, 3H); **^{13}C{^{1}H}-NMR** (126 MHz, $CDCl_3$): δ 201.0, 150.1, 138.8, 138.6, 131.5, 119.7, 115.3, 112.6, 63.1, 43.9, 41.0, 40.0, 31.3, 27.0, 26.9, 25.8 (3C), 22.6, 18.1, –5.7 (2C); **FT-IR (ATR)**: ν_{max} 2953, 2927, 2857, 2214, 1722, 1462, 1252, 1105, 836, 755 cm^{-1}; **HRMS (FD)**: *m/z* Calcd for $C_{22}H_{35}NO_2Si$ $[M]^+$: 373.2432; found: 373.2427.

Synthesis of **1.4**



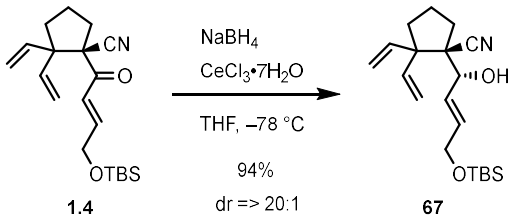
To a solution of allyl alcohol **67** (2.24 g, 6.44 mmol) in CH_2Cl_2 (32.2 mL) was added Dess-Martin Periodinane (3.55 g, 8.37 mmol). After stirrin9g for 1 h at room temperature, the reaction was quenched with $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ solution and the mixture was diluted with Et_2O. After the layers were separated, the aqueous layer was extracted with Et_2O and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 19:1) to afford ketone **1.4** (2.00 g, 5.79 mmol, 90% yield) as a white solid.

Spectral data for **1.4**

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.06 (dt, *J* = 15.0, 2.5 Hz, 1H), 6.92 (dt, *J* = 15.0, 2.5 Hz, 1H), 6.28 (dd, *J* = 17.0, 11.0 Hz, 1H), 5.65 (dd, *J* = 17.3, 11.0 Hz, 1H), 5.32 (d, *J* = 11.0 Hz, 1H), 5.23 (d, *J* = 11.0 Hz, 1H), 5.20 (d, *J* = 17.3 Hz, 1H), 5.15 (d, *J* = 17.0 Hz, 1H), 4.39 (t, *J* = 2.5 Hz, 2H), 2.58 (ddd, *J* = 13.8, 9.3, 7.5 Hz, 1H), 2.14-2.08 (m, 2H), 2.06-2.00 (m, 1H), 1.98-1.91 (m, 2H), 0.95 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H);

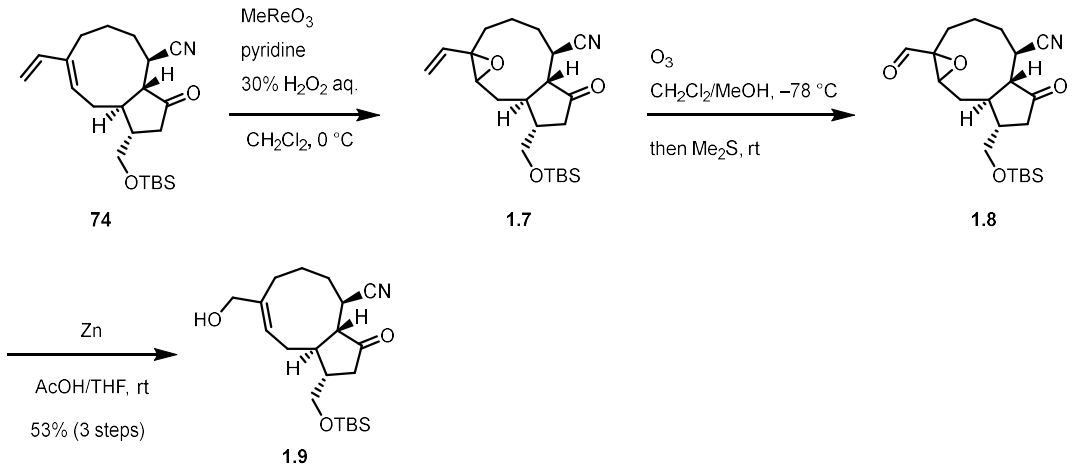
$^{13}C\{^1H\}$-NMR (126 MHz, $CDCl_3$): δ 190.6, 149.1, 139.0, 136.2, 123.9, 120.2, 117.2, 117.0, 62.3, 61.7, 58.9, 33.2, 32.3, 25.8 (3C), 20.4, 18.2, –5.4, –5.5; **FT-IR (ATR)**: ν_{max} 2956, 2928, 2857, 2361, 1698, 1629, 1132, 832, 771 cm^{-1}; **HRMS (FI)**: *m/z* Calcd for $C_{20}H_{31}NO_2Si$ $[M]^+$: 345.2119; found: 345.2125. **Melting point**: 35 to 37 °C ($CHCl_3$).

Synthesis of **67**



To a solution of ketone **1.4** (2.00 g, 5.79 mmol) and $CeCl_3 \cdot 7H_2O$ (3.45 g, 9.26 mmol) in MeOH (29 mL) was added $NaBH_4$ (329 mg, 8.69 mmol) at –78 °C. After stirring at –78 °C for 1 h, the reaction was quenched with saturated aqueous NH_4Cl solution, and the mixture was diluted with Et_2O and H_2O. After the layers were separated, the aqueous layer was extracted with Et_2O and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 47:3 to 23:2 to 7:3) to afford **67** (1.90 g, 5.47 mmol, 94% yield) and **68** (61.7 mg, 0.178 mmol, 3% yield).

Synthesis of **1.9**



To a mixture of ketone **74** (1.33 g, 3.56 mmol), methyltrioxorhenium (88.7 mg, 0.356 mmol) and pyridine (64.3 μL, 0.854 mmol) in CH_2Cl_2 (17.8 mL) was added H_2O_2 (727 μL, 7.12 mmol, 30% aqueous solution)

at 0 °C. After stirring at 0 °C for 1.5 h, another portion of methyltrioxorhenium (88.7 mg, 0.356 mmol) and pyridine (64.3 μL, 0.854 mmol) were added and stirred for 1 h at the same temperature. The reaction was quenched with 10% aqueous Na_2EDTA solution and $Na_2S_2O_3$. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were washed with aqueous 1 M HCl solution and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford crude allyl epoxide **1.7**. The crude product was used for the next step without further purification.

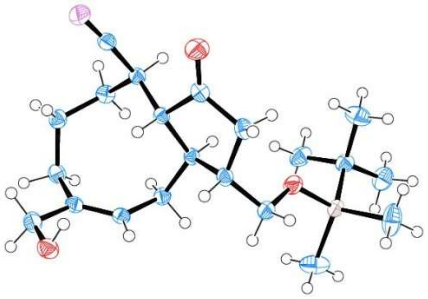
A solution of crude allyl epoxide **1.7** in CH_2Cl_2-MeOH (1:1, 25 mL) was cooled at –78 °C, and O_3 was passed through until the solution changed from a colorless solution to a very slight, pale blue color. Then O_2 was sparged through the solution to purge out excess O_3, and Me_2S (316 μL, 4.27 mmol) was added at –78 °C. The mixture was allowed to warm up to room temperature and stirred overnight under argon gas. The mixture was concentrated under reduced pressure to afford crude aldehyde **1.8**. The crude product was used for the next step without further purification.

To a mixture of crude **1.8** in AcOH-THF(1:1, 20 mL) was added zinc powder (2.33 g, 35.6 mmol) and stirred for 4 h at room temperature. The reaction mixture was diluted with Et_2O and filtered. The filtrate was washed with water, saturated aqueous $NaHCO_3$ solution, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 3:1 to 7:3) to afford allyl alcohol **1.9** (708 mg, 1.88 mmol, 53% yield for three steps) as a colorless oil. For X-ray analysis, it was partially recrystallized from *n*-hexane/EtOAc.

Spectral data for **1.9**

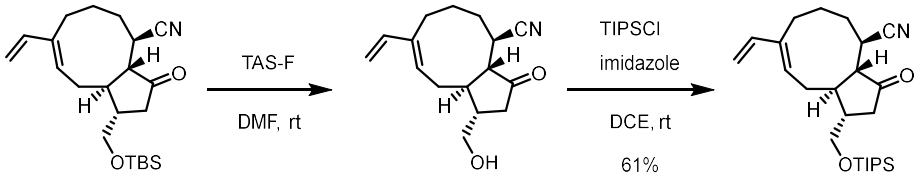
^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.70 (t, *J* = 8.3 Hz, 1H), 4.10 (d, *J* = 13.5 Hz, 1H), 4.06 (d, *J* = 13.5 Hz, 1H), 3.74 (ddd, *J* = 10.3, 3.5, 1.8 Hz, 1H), 3.70 (dt, *J* = 10.3, 3.0, 2.5 Hz, 1H), 2.68-2.62 (m, 1H), 2.49–2.35 (m, 3H), 2.32 (dt, *J* = 8.5, 5.5 Hz, 1H), 2.22 (td, *J* = 5.5, 3.5 Hz, 1H), 2.19-2.13 (m, 2H), 2.11-2.02 (m, 2H), 1.99-1.89 (m, 2H), 1.76 (t, *J* = 12.3 Hz, 1H), 1.70-1.59 (m ,1H), 0.87 (s, 4.5H), 0.86 (s, 4.5H), 0.04 (s, 6H); **^{13}C{^{1}H}-NMR** (126 MHz, $CDCl_3$): δ 215.6, 143.7, 121.1, 120.8, 66.5, 62.2, 52.9, 42.0, 40.7, 39.8, 31.9, 29.7, 28.0, 27.8, 25.8 (3C), 23.0, 18.2, –5.48, –5.54; **FT-IR (ATR)**: ν_{max} 3474, 2950, 2928, 2857, 2235, 1735, 1101, 835, 776, 753 cm^{-1}; **HRMS (ESI)**: *m/z* Calcd for $C_{21}H_{35}NO_3NaSi$ $[M + Na]^+$: 400.2278; found: 400.2272. **Melting point**: 101 to 103 °C (*n*-hexane/EtOAc).

Crystallographic Information of 1.9



CCDC.No	2492823	
Empirical formula	$C_{21}H_{35}NO_3Si$	
Formula weight	377.59	
Temperature	150 K	
Crystal system	monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 12.9377(4) Å	α = 90°
	b = 14.5274(5) Å	β = 98.458(3)°
	c = 11.8214(4) Å	γ = 90°
Volume	2197.68(13) $Å^3$	
Z	4	
ρ_{calc}g	1.141 cm^3	
Absorption coefficient	1.086 mm^{-1}	
F(000)	824.0	
Crystal size	0.439 × 0.25 × 0.138 mm^3	
Radiation	Cu Kα (λ = 1.54184)	
2Θ range for data collection	6.908 to 136.424°	
Index ranges	$-15 \le h \le 15, -17 \le k \le 17, -13 \le l \le 14$	
Reflections collected	13619	
Independent reflections	4036 [R_{int} = 0.0337, R_{sigma} = 0.0312]	
Data/restraints/parameters	4036/0/375	
Goodness-of-fit on F^2	1.042	
Final R indexes [I>=2 σ (I)]	R_1 = 0.0358, wR_2 = 0.0960	
Final R indexes [all data]	R_1 = 0.0384, wR_2 = 0.0984	
Largest diff. peak/hole	0.27/-0.26 e $Å^{-3}$	

Synthesis of **S1.2**



73 **S1.1** **S1.2**

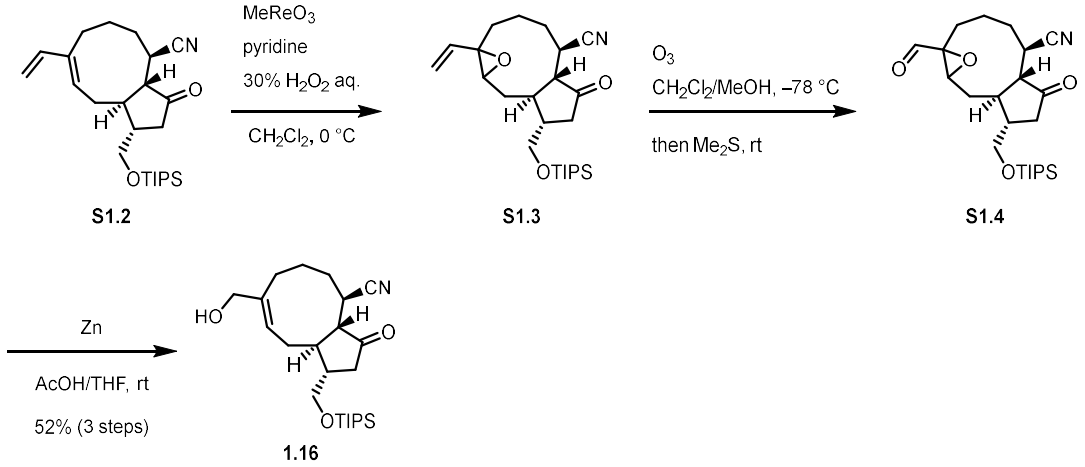
A mixture of ketone **73** (214 mg, 0.573 mmol) and TAS-F (317 mg, 1.15 mmol) in DMF (3.0 mL) was stirred at room temperature for 15 h. The reaction was quenched with water, and the reaction mixture was extracted with Et_2O. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford crude **S1.1**. The crude product was used for the next step without further purification.

To a solution of crude **S1.1** and imidazole (156 mg, 2.29 mmol) in DCE (5.7 mL) was added TIPSCl (244 μL, 1.15 mmol). After stirring at room temperature for 18 h, the reaction was quenched with saturated aqueous $NaHCO_3$ solution. After the layers were separated, the aqueous layer was extracted with Et_2O and the combined organic layers were washed with 1 M hydrochloric acid and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 19:1 to 4:1) to afford **S1.2** with a mixture of silanols. It was further recrystallized from *n*-hexane/EtOAc to afford **S1.2** (146 mg, 0.352 mmol, 61% for 2 steps) as a white crystal.

Spectral data for **S1.2**

^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.27 (dd, *J* = 17.8, 10.5 Hz, 1H), 5.70 (dd, *J* = 10.0, 7.5 Hz, 1H), 5.16 (d, *J* = 17.8 Hz, 1H), 5.04 (d, *J* = 10.5 Hz, 1H), 3.88 (dd, *J* = 10.0, 3.0 Hz, 1H), 3.81 (dd, *J* = 10.0, 3.0 Hz, 1H), 2.66-2.61 (m, 1H), 2.50 (ddd, *J* = 14.5, 10.5, 3.0 Hz, 1H), 2.46-2.29 (m, 6H), 2.07-1.91 (m, 4H), 1.81-1.71 (m, 2H), 1.11 (sept, *J* = 5.5 Hz, 3H), 1.06 (s, 18H).

Synthesis of **1.16**



To a mixture of ketone **S1.2** (135 g, 0.325 mmol), methyltrioxorhenium (8.1 mg, 0.033 mmol) and pyridine (6.3 μL, 0.078 mmol) in CH_2Cl_2 (3.3mL) was added H_2O_2 (99.2 μL, 0.972 mmol, 30% aqueous solution) at 0 °C. After stirring at the same temperature for 4 h, the reaction was quenched with 10% aqueous Na_2EDTA solution and $Na_2S_2O_3$. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were washed with aqueous 1 M HCl solution and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 9:1 to 17:3) to afford impure allyl epoxide **S1.3**.

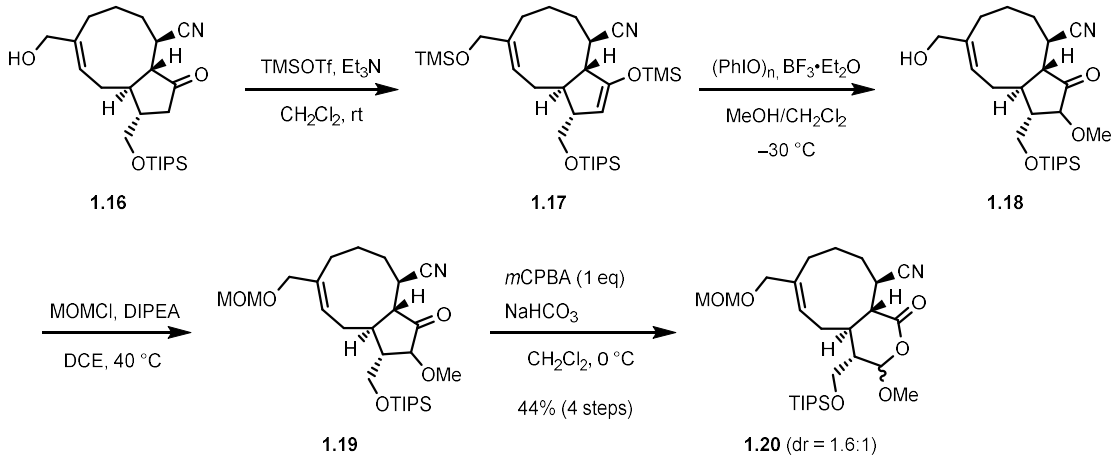
A solution of crude allyl epoxide **S1.3** in CH_2Cl_2-MeOH (1:1, 3.3 mL) was cooled at –78 °C, and O_3 was passed through until the solution changed from a colorless solution to a very slight, pale blue color. Then O_2 was sparged through the solution to purge out excess O_3, and Me_2S (24.0 μL, 0.650 mmol) was added at –78 °C. The mixture was allowed to warm up to room temperature and stirred overnight under argon gas. The mixture was concentrated under reduced pressure to afford crude aldehyde **S1.4**. The crude product was used for the next step without further purification.

To a mixture of crude **S1.4** in AcOH-THF(1:1, 3.3 mL) was added zinc powder (212 mg, 3.25 mmol) and stirred for 4 h at room temperature. The reaction mixture was diluted with Et_2O and filtered. The filtrate was washed with water, saturated aqueous $NaHCO_3$ solution, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 4:1 to 3:1 to 7:3) to afford allyl alcohol **1.16** (70.0 mg, 0.168 mmol, 52% yield for three steps) as a white solid.

Spectral data for **1.16**

^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.72 (dd, *J* = 9.8, 6.8 Hz, 1H), 4.11 (d, *J* = 13.5 Hz, 1H), 4.07 (d, *J* = 13.5 Hz, 1H), 3.88 (dd, *J* = 10.0, 3.0 Hz, 1H), 3.81 (dd, *J* = 10.0, 3.0 Hz, 1H), 2.69 (ddd, *J* = 10.8, 5.3, 3.0 Hz, 1H), 2.48 (ddd, *J* = 17.5, 10.5, 3.5 Hz, 1H), 2.43 (d, *J* = 7.5 Hz, 1H), 2.40-2.29 (m, 3H), 2.19 (t, *J* = 6.0 Hz, 2H), 2.10-2.02 (m, 3H), 1.98-1.89 (m, 1H), 1.86-1.67 (m, 2H), 1.10 (sept, *J* = 6.7 Hz, 3H), 1.06 (s, 18H).

Synthesis of **1.20**



To a solution of alcohol **1.16** (22.7 mg, 0.0543 mmol) and Et_3N (45.4 μL, 0.326 mmol) in CH_2Cl_2 (540 μL) was added TMSOTf (31.8 μL, 0.163 mmol) at 0 °C. After stirring at room temperature 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, and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the crude enol silyl ether **1.17**. The crude product was used for the next step without farther purification.

A suspension of iodosobenzene (14.3 mg, 0.652 mmol) in MeOH (540 μL) was cooled to –78 °C, and BF_3•Et_2O (17.1 μL, 0.0652 mmol, distilled before use) was added. To this mixture was added silyl enol ether **1.17** in CH_2Cl_2 (540 μL) and slowly warm up to –30 °C over 30 min. After stirring at the same temperature for 1 h, the reaction was quenched with saturated aqueous $NaHCO_3$ solution. After the layers were separated, the aqueous layer was extracted with Et_2O and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 4:1 to 3:1 to 7:3) to afford impure α-methoxyketone **1.18** (19.5 mg, ca. 0.0434 mmol, ca. 80% for two steps).

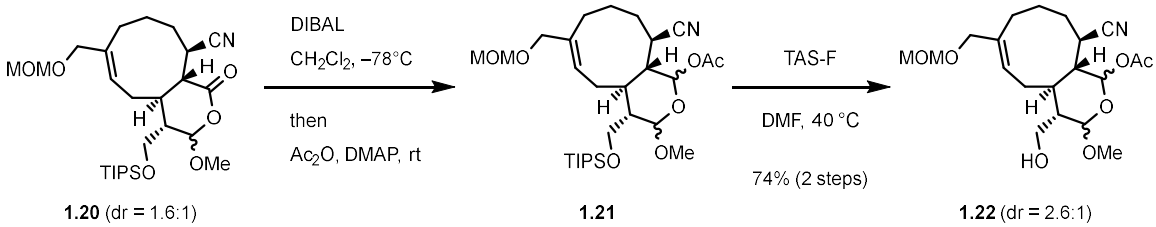
To a solution of **1.18** (19.5 mg, ca. 0.0434 mmol) and DIPEA (44.2 μL, 0.260 mmol) in DCE (440 μL) was added MOMCl (9.8 μL, 0.130 mmol). After stirring at 40 °C for 12 h, The reaction was quenched with saturated aqueous $NaHCO_3$ solution. After the layers were separated, the aqueous layer was extracted with Et_2O and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 4:1 to 3:1 to 7:3) to afford impure α-methoxyketone **1.19** (17.7 mg, ca. 0.0434 mmol, ca. 66% for three steps).

To a solution of impure α-methoxyketone **1.19** (17.7 mg, 0.0358 mmol) and $NaHCO_3$ (30.1 mg, 0.358 mmol) in CH_2Cl_2 (360 μL) was added dry *m*CPBA (6.8 mg, 0.0394 mmol). After stirring for 20 min at 0 °C, the reaction was quenched with 2-methyl-2-butene, saturated aqueous $NaHCO_3$ solution and $NaHCO_3$, and the slurry was vigorously stirred for 1 h at room temperature. After the layers were separated, the aqueous layer was extracted with Et_2O, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC to afford lactone **1.20** (12.3 mg, 0.0241 mmol, 44%, dr = 1.6:1) as a colorless oil.

Spectral data for **1.20**

^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.56 (dd, *J* = 9.5, 7.5 Hz, 0.62 × 1H), 5.47 (dd, *J* = 10.3, 7.8 Hz, 0.38 × 1H), 5.30 (d, *J* = 2.5 Hz, 0.62 × 1H), 5.22 (d, *J* = 5.5 Hz, 0.38 × 1H), 4.46 (m, 2H), 4.02-3.88 (m, 3H), 3.83 (dd, *J* = 10.5, 5.5 Hz, 0.38 × 1H), 3.71 (t, *J* = 9.5 Hz, 0.62 × 1H), 3.54 (s, 3H), 3.38 (s, 3H), 3.38-3.33 (m, 0.38 × 1H), 3.26 (dt, *J* = 10.0, 4.3 Hz, 0.62 × 1H), 2.90-2.85 (m, 1H), 2.53 (ddd, *J* = 14.5, 5.5, 4.0 Hz, 0.38 × 1H), 2.44-2.24 (m, 2H), 2.24-2.16 (m, 1H + 0.62 × 1H), 2.14-1.91 (m, 5H), 1.73-1.66 (m, 1H), 1.17-1.07 (m, 3H), 1.08 (s, 0.62 × 18H), 1.07 (s, 0.38 × 18H).

Synthesis of **1.22**



1.20 (dr = 1.6:1) **1.21** **1.22** (dr = 2.6:1)

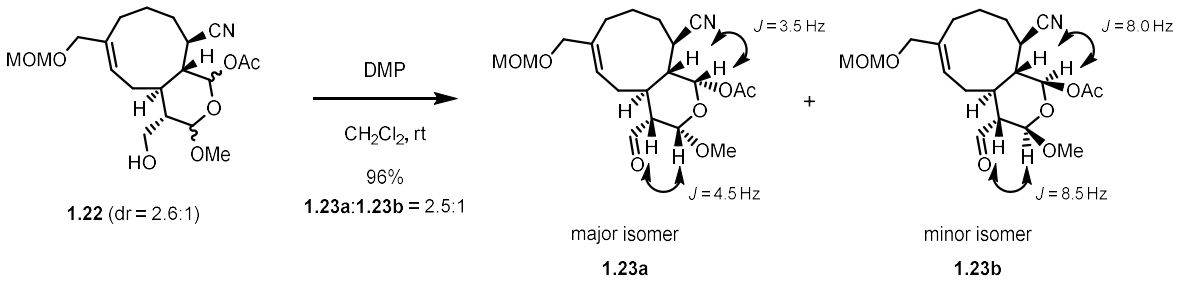
To a solution of lactone **1.20** (9.0 mg, 0.18 mmol) in CH_2Cl_2 (200 μL) was added DIBAL (35.4 μL, 0.0354 mmol, 1.0 M in *n*-hexane) at –78 °C. After stirring at –78 °C for 30 min, DMAP (8.6 mg, 0.071 mmol) and acetic anhydride (6.7 μL, 0.071 mmol) was added to the reaction mixture at –78 °C, and the mixture was allowed to warm up to room temperature. After stirring at room temperature for 10 min, the reaction was quenched with saturated aqueous $NaHCO_3$ solution and saturated aqueous sodium potassium tartrate solution. The mixture was vigorously stirred at room temperature for 1 h. After the pH was adjusted to 4-5, the layers were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford crude acetal **1.21**. The crude product was used for the next step without farther purification.

A mixture of crude acetal **1.21** and TAS-F (13.8 mg, 0.0500 mmol) in DMF (200 μL) was stirred at for 25 min. The reaction was quenched with water, and the reaction mixture was extracted with Et_2O. The combined organic layers were washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 7.3 to 3:2 to 1:1 to 2:3) to afford alcohol **1.22** (5.2 mg, 0.013 mmol, 74% yield for two steps, dr = 2.5:1).

Spectral data for **1.22**

^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.15 (d, *J* = 3.5 Hz, 0.72 × 1H), 5.85 (d, *J* = 9.0 Hz, 0.28 × 1H), 5.64 (t, *J* = 8.3 Hz, 0.72 × 1H), 5.50 (dd, *J* = 10.8, 7.3 Hz, 0.28 × 1H), 4.77 (d, *J* = 4.0 Hz, 0.72 × 1H), 4.631 (s, 2H), 4.626 (d, *J* = 4.0 Hz, 0.72 × 1H), 4.61-4.57 (m, 0.28 × 2H), 3.96 (s, 2H), 3.93-3.84 (m, 1H), 3.72 (d, *J* = 13.0 Hz, 0.72 × 1H), 3.72-3.68 (m, 0.28 × 1H), 3.52 (s, 0.28 × 3H), 3.39 (s, 0.72 × 3H), 3.382 (s, 0.72 × 3H), 3.375 (s, 0.28 × 3H), 3.29-3.20 (m, 1H), 2.96 (s, 0.28 × 1H), 2.89 (s, 0.28 × 1H), 2.71 (d, *J* = 11.0 Hz , 0.72 × 1H), 2.60 (tdd, *J* = 11.5, 6.2, 5.3 Hz , 0.72 × 1H), 2.55-2.47 (m, 1H), 2.44-2.38 (m, 1H), 2.37-2.23 (m, 2H). 2.14 (s, 3H), 2.11-2.05 (m, 1H + 0.28 × 1H), 2.03-1.95 (m, 1H), 1.95-1.87 (m, 0.72 × 1H), 1.77-1.69 (m, 1H).

Synthesis of **1.23**

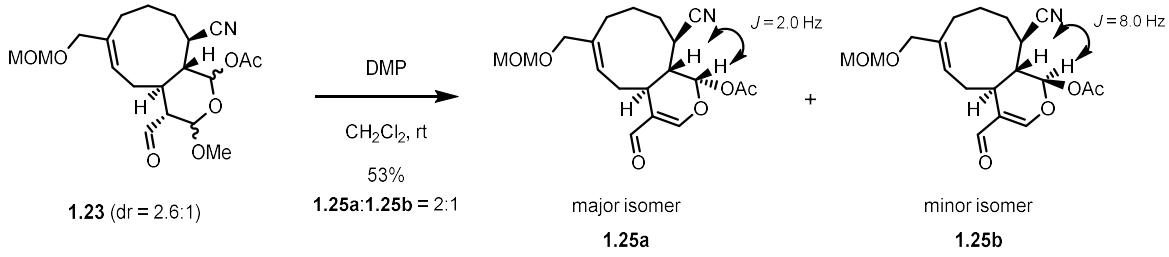


To a solution of allyl alcohol **1.22** (5.2 mg, 0.013 mmol) in CH_2Cl_2 (200 mL) was added Dess-Martin Periodinane (11.1 mg, 0.0262 mmol). After stirring at room temperature for 40 min, the reaction was quenched with saturated aqueous $Na_2S_2O_3$ solution and $NaHCO_3$ and the mixture was diluted with Et_2O. After the layers were separated, the aqueous layer was extracted with Et_2O and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford aldehyde **1.23** (5.0 mg, 0.013 mmol, 96% yield, dr = 2.5.1) as a white solid.

Spectral data for **1.23**

^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.78 (d, *J* = 2.5 Hz, 0.29 × 1H), 9.59 (d, *J* = 3.0 Hz, 0.71 × 1H), 6.18 (d, *J* = 3.5 Hz, 0.71 × 1H), 5.88 (d, *J* = 8.0 Hz, 0.29 × 1H), 5.69 (t, *J* = 8.8 Hz, 0.71 × 1H), 5.52 (dd, *J* = 8.8, 6.8 Hz, 0.29 × 1H), 4.96 (d, *J* = 4.5 Hz, 0.71 × 1H), 4.68 (d, *J* = 8.5 Hz, 0.29 × 1H), 4.64 (s, 0.71 × 2H), 4.63-4.59 (m, 0.29 × 2H), 3.99-3.91 (m, 1H), 3.98 (s, 2H), 3.48 (s, 0.29 × 3H), 3.39 (s, 0.71 × 3H), 3.38 (s, 0.29 × 3H), 3.34 (s, 0.71 × 3H), 3.28-3.23 (m, 0.71 × 1H), 3.23-3.18 (m, 0.29 × 1H), 2.82 (ddd, *J* = 11.0, 7.0, 2.0 Hz, 0.71 × 1H), 2.66 (ddd, *J* = 11.0, 8.5, 2.5 Hz, 0.29 × 1H), 2.61 (ddd, *J* = 11.5, 4.5, 2.5 Hz, 0.71 × 1H), 2.52-2.44 (m, 0.29 × 1H), 2.4-2.29 (m, 3H), 2.29-2.19 (m, 2H), 2.15 (s, 3H), 2.12-2.04 (m, 2H), 2.03-1.89 (m, 2H), 1.78-1.70 (m, 1H).

Synthesis of **1.25**

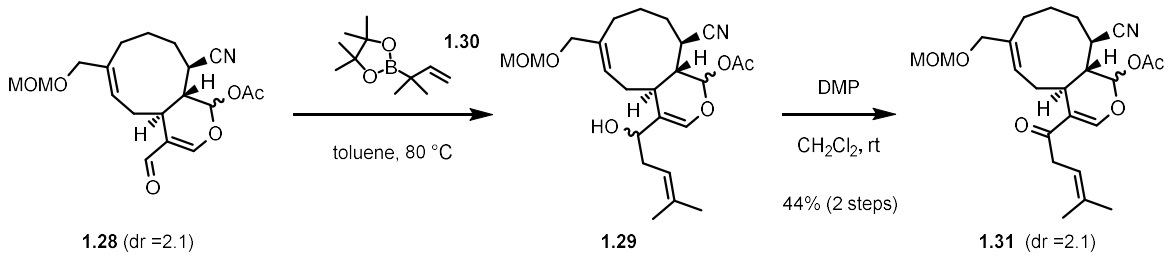


A mixture of aldehyde **1.22** (3.9 mg, 0.0099 mmol), DMAP (10.1 mg, 0.0827 mmol) and AcOH (3.2 µL, 0.055 mmol) in toluene (200 µL) was heated to 120 °C and stirred for 1 h. The reaction mixture was cooled down to room temperature and quenched with saturated aqueous NH_4Cl solution. After the layers were separated, the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC to afford lactone **1.25** (1.9 mg, 0.0052 mmol, 53%, dr = 2:1) as a colorless oil.

Spectral data for **1.25**

^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.30 (s, 0.33 × 1H), 9.29 (s, 0.67 × 1H), 7.18 (d, *J* = 2.0 Hz, 0.33 × 1H), 7.15 (*J* = 2.0 Hz, 0.67 × 1H), 6.55 (*J* = 2.0 Hz, 0.67 × 1H), 6.25 (d, *J* = 8.0 Hz, 0.33 × 1H), 5.37-5.29 (m, 1H), 4.64-4.57 (m, 2H), 4.00-3.90 (m, 2H), 3.363 (s, 0.33 × 3H), 3.360 (s, 0.67 × 2H), 3.15-3.05 (m, 1H), 3.03 (td, *J* = 7.0 4.5 Hz, 0.67 × 1H), 2.29-2.94 (m, 0.33 × 1H), 2.82-2.74 (m, 1H), 2.63 (ddd, *J* = 14.5, 9.5, 4.0 Hz, 0.33 × 1H), 2.54 (ddd, *J* = 14.5, 11.0, 2.5 Hz, 0.67 × 1H), 2.41 (td, *J* = 8.0, 3.5 Hz, 0.33 × 1H), 2.23-2.04 (m, 6H + 0.67 × 1H), 2.19 (s, 0.33 × 3H), 2.17 (s, 0.67 × 3H).

Synthesis of **1.31**



1.28 (dr =2.1) **1.29** **1.31** (dr =2.1)

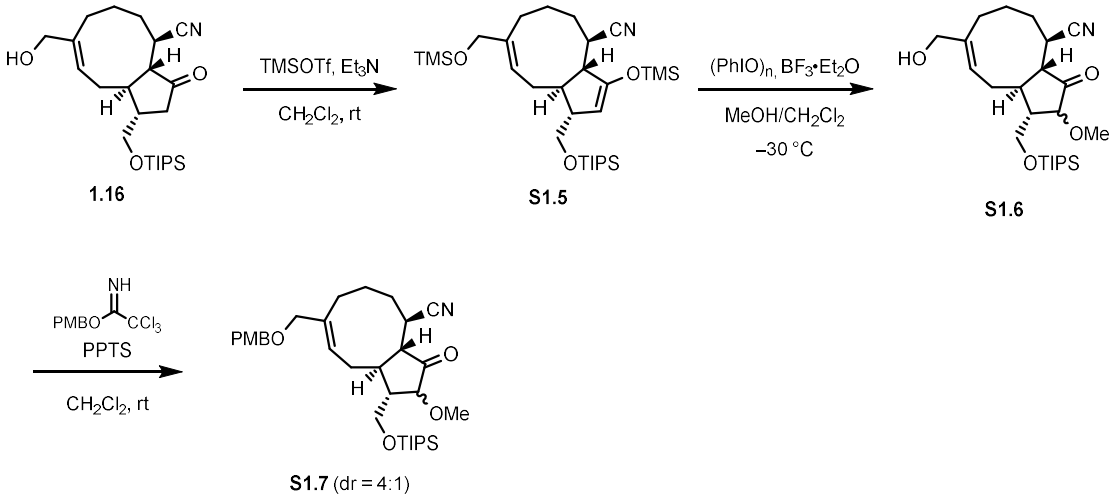
A mixture of crude ketone **1.28** (1.9 mg, 0.0052 mmol) and allylboronate **1.30**[33] (10.8 mg, 0.0551 mmol) in toluene (200 μL) was heated to 80 °C and stirring for 16.5 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 4:1 to 3:1 to 7:3 to 1:1) to afford impure alcohol **1.29**.

To a solution of alcohol **1.29** in CH_2Cl_2 (200 μL) was added Dess-Martin Periodinane (8.2 mg, 0.0193 mmol). After stirring at room temperature for 10 min, the reaction mixture was diluted with Et_2O and quenched with 10% aqueous $Na_2S_2O_3$ solution and $NaHCO_3$. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC to afford lactone **1.31** (1.0 mg, 0.023 mmol, 44%, dr = 2:1) as a colorless oil.

Spectral data for **1.31**

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.41 (s, 0.33 × 1H), 7.35 (s, 0.67 × 1H), 6.45 (d, *J* = 2.5 Hz, 0.67 × 1H), 6.22 (d, *J* = 5.5 Hz, 0.33 × 1H), 5.43 (t, *J* = 8.0 Hz, 0.33 × 1H), 5.5.34 (dd, *J* = 9.5, 6.5 Hz, 0.67 × 1H), 5.29-5.24 (m, 1H), 4.64-4.58 (m, 2H), 4.00-3.91 (m, 2H), 3.40-3.34 (m, 1H), 3.369 (s, 0.33 × 3H), 3.365 (s, 0.33 × 3H), 3.30-3.24 (m, 1H), 2.97-2.88 (m, 2H), 2.82-2.77 (m, 1H), 2.62-2.56 (m, 1H), 2.49-2.41 (m, 1H), 2.36-2.28 (m, 2H), 2.21-2.13 (m, 2H), 2.17 (s, 3H), 2.11-1.99 (m, 3H), 1.76 (s, 3H), 1.66 (s, 3H).

Synthesis of **S1.7**



To a solution of alcohol **1.16** (81.2 mg, 0.194 mmol) and Et_3N (161 µL, 1.16 mmol) in CH_2Cl_2 (2.0 µL) was added TMSOTf (113 µL, 0.582 mmol) at 0 °C. After stirring at room temperature for 10 min, the reaction was quenched with saturated aqueous $NaHCO_3$ solution. After the layers were separated, the aqueous layer was extracted with Et_2O, and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the crude enol silyl ether **S1.5**. The crude product was used for the next step without farther purification.

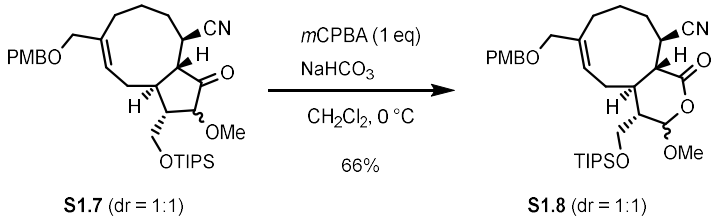
A suspension of iodosobenzene (46.9 mg, 0.213 mmol) in MeOH (2.0 mL) was cooled to –78 °C, and $BF_3 \cdot Et_2O$ (48.7 µL, 0.388 mmol, distilled before use) was added. To this mixture was added silyl enol ether **S1.5** in CH_2Cl_2 (2.0 mL) and slowly warm up to –30 °C over 30 min. After stirring at the same temperature for 20, the reaction was quenched with saturated aqueous $NaHCO_3$ solution. After the layers were separated, the aqueous layer was extracted with Et_2O and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 17.3 to 4:1 to 1:1) to afford impure α-methoxyketone **S1.6**.

To a solution of α-methoxyketone **S1.6** and PPTS (97.5 mg, 0.388 mmol) in CH_2Cl_2 (2.0 mL) was added imidate (60.5 µL, 0.291 mmol). After stirring at room temperature for 3 h, The reaction was quenched with saturated aqueous $NaHCO_3$ solution. After the layers were separated, the aqueous layer was extracted with Et_2O and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC to afford α-methoxyketone **S1.7** (35.0 mg, 0.0614 mmol, 32% for 3 steps, dr = 4:1) as a colorless oil.

Spectral data for **S1.7**

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.24 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.86 (t, *J* = 8.0 Hz, 0.8 × 1H), 5.73 (t, *J* = 8.3 Hz, 0.20 × 1H), 4.44 (d, *J* = 11.3 Hz, 0.80 × 1H), 4.43 (d, *J* = 12.0 Hz, 0.20 × 1H), 4.38 (d, *J* = 11.3 Hz, 0.80 × 1H), 4.35 (d, *J* = 12.0 Hz, 0.20 × 1H), 3.95-3.85 (m, 2H + 0.20 × 1H), 3.85-3.79 (m, 1H), 3.81 (s, 3H), 3.79-3.74 (m, 1H), 3.70 (d, *J* = 5.5 Hz, 0.80 × 1H), 3.60 (s, 0.20 × 3H), 3.41 (s, 0.80 × 3H), 2.78-2.72 (m, 0.80 × 1H), 2.62-2.57 (m, 0.20 × 3H), 2.45-2.32 (m, 2H), 2.30-2.17 (m, 3H), 2.14-2.08 (m, 0.20 × 3H), 2.03-1.87 (m, 1H + 0.80 × 1H), 1.84-1.66 (m, 4H), 1.17-1.04 (m, 3H), 1.08 (s, 0.20 × 18H), 1.06 (s, 0.80 × 18H).

Synthesis of **S1.8**



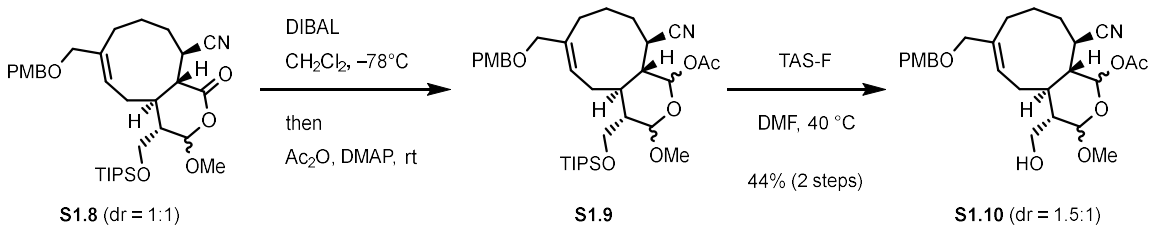
S1.7 (dr = 1:1) **S1.8** (dr = 1:1)

To a solution of α-methoxyketone **S1.7** (17.0 mg, 0.0298 mmol) and $NaHCO_3$ (26.5 mg, 0.298 mmol) in CH_2Cl_2 (300 µL) was added dry *m*CPBA (5.7 mg, 0.0318 mmol). After stirring for 50 min at –20 °C, another portion of dry *m*CPBA (3.2 mg, 0.0185 mmol) was added and stirred for additional 15 min. The reaction was quenched with 2-methyl-2-butene, saturated aqueous $NaHCO_3$ solution and $NaHCO_3$, and the slurry was vigorously stirred for 1 h at room temperature. After the layers were separated, the aqueous layer was extracted with Et_2O, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC to afford lactone **S1.8** (11.6 mg, 0.0198 mmol, 66%, dr = 1:1) as a colorless oil.

Spectral data for **S1.8**

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.234 (d, *J* = 8.8 Hz, 0.50 × 1H), 7.295 (d, *J* = 8.5 Hz, 0.50 × 1H), 6.872 (d, *J* = 8.8 Hz, 0.50 × 1H), 6.870 (d, *J* = 8.5 Hz, 0.50 × 1H), 5.53 (t, *J* = 8.3 Hz, 0.50 × 1H), 5.44 (dd, *J* = 9.8, 7.3 Hz, 0.50 × 1H), 5.28 (d, *J* = 2.0 Hz, 0.50 × 1H), 5.20 (d, *J* = 5.5 Hz, 0.50 × 1H), 4.43 (d, *J* = 11.5 Hz, 0.50 × 1H), 4.42 (d, *J* = 11.5 Hz, 0.50 × 1H), 4.39 (d, *J* = 11.5 Hz, 0.50 × 1H), 4.37 (d, *J* = 8.8 Hz, 0.50 × 1H), 3.98 (m, 2H), 3.87-3.81 (m, 1H + 0.50 × 1H), 3.81 (s, 3H), 3.70 (t, *J* = 9.5 Hz, 0.50 × 1H), 3.53 (s, 0.50 × 3H), 3.52 (s, 0.50 × 3H), 3.39-3.33 (s, 0.50 × 1H), 3.24 (dt, *J* = 10.0, 4.8 Hz, 0.50 × 1H), 2.88-2.83 (m,1H), 2.52 (ddd, *J* = 14.5, 10.5 4.0 Hz, 0.50 × 1H), 2.43-2.23 (m, 2H), 2.23 (m, 1H + 0.50 × 1H), 2.13- 1.89 (m, 5H), 1.71-1.59 (m, 1H), 1.59-1.46 (m, 1H), 1.16-1.06 (m, 3H), 1.074 (s, 0.50 × 18H), 1.070 (s, 0.50 × 18H).

Synthesis of **S1.10**



S1.8 (dr = 1:1) **S1.9** **S1.10** (dr = 1.5:1)

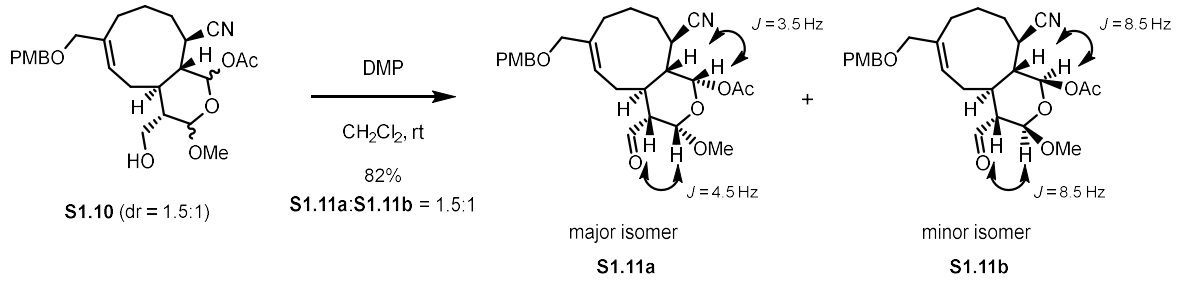
To a solution of lactone **S1.8** (12.2 mg, 0.0208 mmol) in CH_2Cl_2 (400 µL) was added DIBAL (41.6 µL, 0.0416 mmol, 1.0 M in *n*-hexane) at –78 °C. After stirring at –78 °C for 15 min, DMAP (10.2 mg, 0.0832 mmol) and acetic anhydride (7.9 µL, 0.0832 mmol) was added to the reaction mixture at –78 °C, and the mixture was allowed to warm up to room temperature. After stirring at room temperature for 5 min, the reaction was quenched with saturated aqueous $NaHCO_3$ solution and saturated aqueous sodium potassium tartrate solution. The mixture was vigorously stirred at room temperature for 1 h. After the pH was adjusted 4-5, the layers were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford crude acetal **S1.9**. The crude product was used for the next step without farther purification.

A mixture of crude acetal **S1.9** and TAS-F (26.8 mg, 0.0973 mmol) in DMF (200 µL) was stirred at for 22.5 h. The reaction was quenched with water, and the reaction mixture was extracted with Et_2O. The combined organic layers were washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 3:2 to 1:1 to 2:3) to afford alcohol **S1.10** (4.3 mg, 0.0091 mmol, 44% for two steps, dr = 1.5:1).

Spectral data for **S1.10**

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 6.15 (d, *J* = 3.0 Hz, 0.60 × 1H), 5.84 (d, *J* = 8.5 Hz, 0.40 × 1H), 5.62 (t, *J* = 8.0 Hz, 0.60 × 1H), 5.48 (t, *J* = 8.0 Hz, 0.40 × 1H), 4.77 (d, *J* = 3.5 Hz, 0.40 × 1H), 4.58 (d, *J* = 8.0 Hz, 0.40 × 1H), 4.42 (s, 0.60 × 2H), 4.41 (s, *J* = 11.5 Hz, 0.40 × 1H), 4.36 (d, *J* = 8.0 Hz, 0.40 × 1H), 3.97-3.84 (m, 3H), 3.84-3.78 (m, 1H), 3.81 (s, 3H), 3.74-3.66 (m, 1H), 3.52 (s, 0.40 × 3H), 3.39 (s, 0.60 × 3H), 3.30-3.20 (m, 1H), 2.76-2.69 (m, 0.40 × 1H), 2.64-2.55 (m, 0.60 × 1H), 2.55-2.47 (m, 1H), 2.46-2.36 (m, 1H), 2.36-2.26 (m, 2H), 2.26-1.85 (m, 5H), 2.14 (s, 3H), 1.83-1.77 (m, 1H), 1.74-1.63 (m, 1H).

Synthesis of **S1.11**

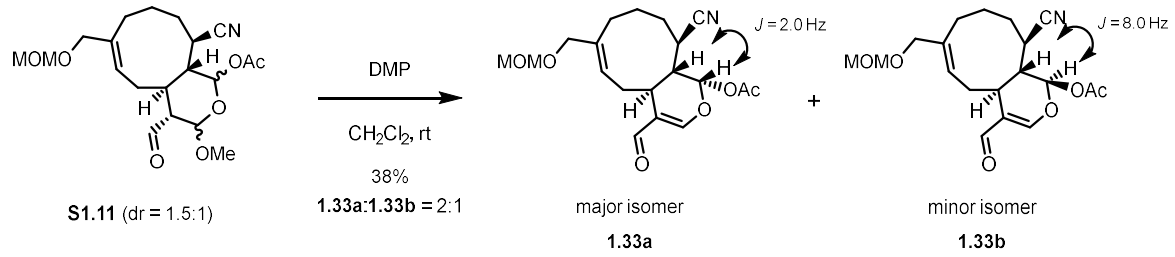


To a solution of allyl alcohol **S1.10** (4.4 mg, 0.0091 mmol) in CH_2Cl_2 (200 mL) was added Dess-Martin Periodinane (7.7 mg, 0.018 mmol). After stirring at room temperature for 75 min, the reaction was quenched with saturated aqueous $Na_2S_2O_3$ solution and $NaHCO_3$ and the mixture was diluted with Et_2O. After the layers were separated, the aqueous layer was extracted with Et_2O and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford aldehyde **S1.11** (3.5 mg, 0.0074 mmol, 82% yield, dr = 1.5:1) as a colorless oil.

Spectral data for **S1.11**

^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.78 (d, *J* = 2.0 Hz, 0.40 × 1H), 9.58 (d, *J* = 2.5 Hz, 0.60 × 1H), 7.25 (d, *J* = 8.5 Hz, 0.60 × 1H), 7.24 (d, *J* = 9.0 Hz, 0.40 × 1H), 6.90 (d, *J* = 8.5 Hz, 0.60 × 1H), 6.89 (d, *J* = 9.0 Hz, 0.40 × 1H), 6.17 (d, *J* = 3.5 Hz, 0.60 × 1H), 5.87 (d, *J* = 8.5 Hz, 0.40 × 1H), 5.67 (d, *J* = 8.5 Hz, 0.60 × 1H), 5.67 (d, *J* = 7.5 Hz, 0.40 × 1H), 4.95 (d, *J* = 4.5 Hz, 0.60 × 1H), 4.68 (d, *J* = 8.5 Hz, 0.40 × 1H), 4.27 (s, 2H), 3.96-3.89 (m, 1H), 3.86-3.79 (m, 1H), 3.82 (s, 1H), 3.48 (s, 0.40 × 3H), 3.48 (s, 0.40 × 3H), 3.30 (s. 0.60 × 3H), 3.29-3.24 (m, 0.60 × 1H), 3.23-3.17 (m, 0.40 × 1H), 2.85-2.77 (m, 0.60 × 1H), 2.69-2.58 (m, 1H + 0.40 × 1H), 2.54-2.44 (m, 0.40 × 1H), 2.42-2.29 (m, 1H + 0.60 × 1H), 2.29-2.20 (m, 1H), 2.20-1.88 (m, 5H), 2.15 (s, 3H), 1.74-1.66 (m, 1H).

Synthesis of **1.33**



A mixture of aldehyde **S1.11** (3.1 mg, 0.0066 mmol), DMAP (12.1 mg, 0.0099 mmol) and AcOH (3.8 μL, 0.0066 mmol) in toluene (200 μL). After stirring at 80 °C for 1 h, the reaction mixture was stirred at 100 °C for additional 30 min. The reaction mixture was cooled down to room temperature and quenched with saturated aqueous NH_4Cl solution. After the layers were separated, the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC to afford lactone **1.33** (1.1 mg, 0.0025 mmol, 38%, dr = 1.5:1) as a colorless oil.

Spectral data for **1.33**

^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.29 (s, 0.40 × 1H), 9.28 (s, 0.60 × 1H), 7.24 (d, *J* = 8.5 Hz, 0.40 × 1H), 7.23 (d, *J* = 8.5 Hz, 0.60 × 1H), 7.18 (s, 0.40 × 1H), 7.14 (s, 0.60 × 1H), 6.88 (d, *J* = 8.5 Hz, 1H), 6.54 (d, *J* = 2.0 Hz, 0.60 × 1H), 6.24 (d, *J* = 8.0 Hz, 0.40 × 1H), 5.36-5.26 (m, 1H), 4.42-4.32 (m, 2H), 3.97 (d, 12.5 Hz, 1H), 3.93 (d, 1H), 3.86-3.78 (m, 2H), 3.81 (s, 3H), 3.16-3.07 (m, 1H), 3.07-2.98 (m, 1H), 2.82 (m, 1H), 2.63 (ddd, *J* = 14.5, 9.0, 5.3 Hz, 0.40 × 1H), 2.54 (ddd, *J* = 14.0, 11.3, 5.0 Hz, 0.60 × 1H), 2.44-2.34 (m, 1H), 2.31-2.25 (m, 1H), 2.25-1.91 (m, 5H), 2.19 (s, 0.40 × 3H), 2.13 (s, 0.60 × 3H).

Chapter 2

Total Synthesis of Cristaxenicin A

In Chapter 1, the synthesis of an analogue of Cristaxenicin A was described. To achieve the total synthesis, the nitrile moiety should be converted to the enol acetate of Cristaxenicin A. Keeping the cyano group transformation in mind, a new synthetic route was designed (Figure 2.1). Starting from PMB protected bicyclic compound **2.1**, the cyclopentanone would be transformed into a cyclopentene which could serve as a precursor of dialdehyde. This transformation of the ketone moiety enables conversion of the nitrile moiety to an enol acetate through reduction to an aldehyde. Dihydroxylation of cyclopentene **2.3** would give triol **2.4**, and oxidation of the primary alcohol followed by elongation of the side chain would afford diol **2.5**. Oxidative cleavage of the 1,2-diol would afford dihydropyran **2.7** via isomerization of di-aldehyde **2.6**. Finaly, acetylation of the lactol, and DDQ oxidation will give the natural product, cristaxenicin A (**3**).

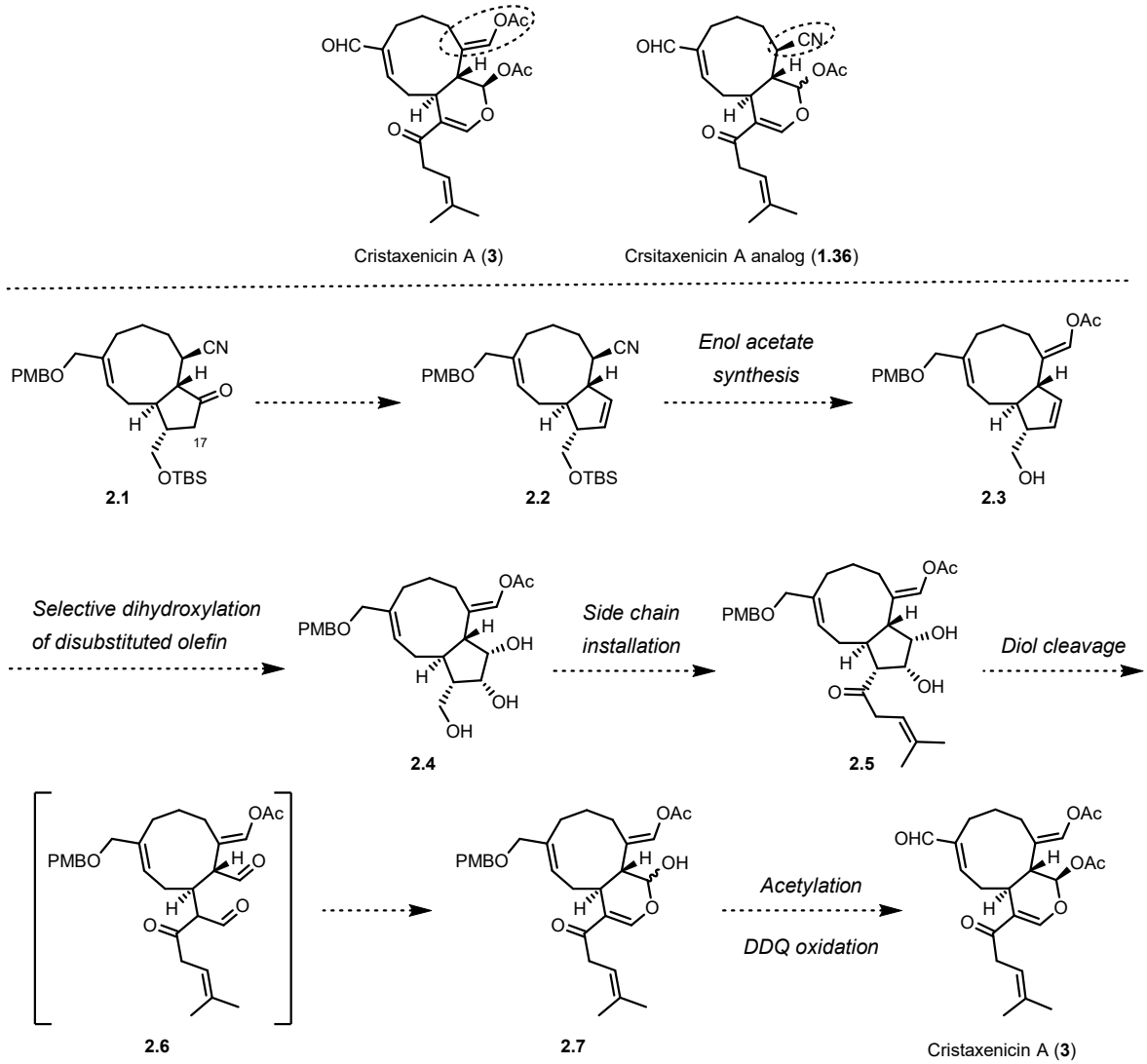


Figure 2.1. New synthetic plan

Firstly, cyclopentene **2.2** was synthesized from allyl alcohol **1.9** which was obtained in Chapter 1 (Figure 1.8). Protection of alcohol **1.9** as a PMB ether was achieved by using the corresponding trifluoroacetimidate.[34] Regioselective enolate formation with LHMDS followed by treatment with Tf_2O afforded enol triflate **2.8** which was reduced by $Pd(PPh_3)_4$ and ammonium formate, giving cyclopentene **2.2**. At this stage, construction of the enol acetate moiety was accomplished in two steps. The reduction of nitrile **2.2** with DIBAL-H in toluene at 0 °C afforded aldehyde **2.9** in 91% yield as a 19:1 diastereomeric mixture. Upon successive treatment with *t*-BuOK and acetic anhydride at -78 °C, aldehyde **2.9** was converted to enol acetate **2.10**. Removal of the TBS group gave alcohol **2.3** as a 10:1 mixture of *E*- and *Z*-isomers in 69% yield for two steps. The stereochemistry of the major isomer was confirmed by nOe experiments.

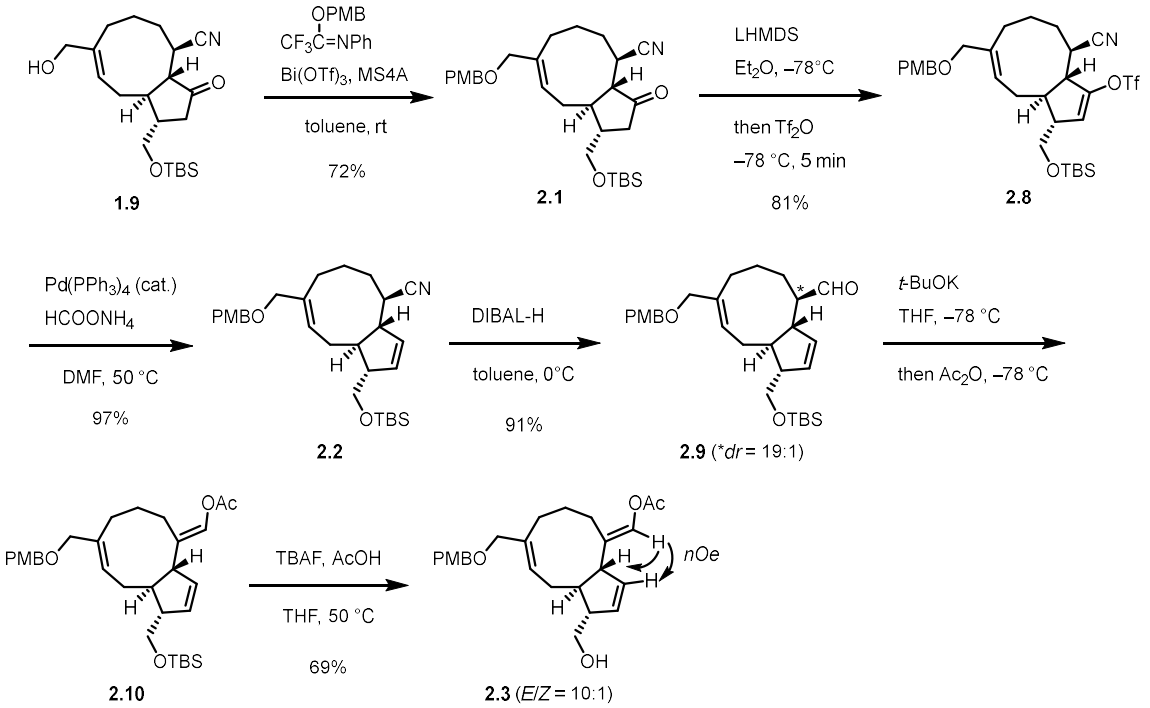


Figure 2.2 Synthesis of cyclopentene **2.3**

With the key intermediate in hand, selective oxidation of the cyclopentene moiety was examined (Figure 2.3). Judging from the experiments described in Chapter 1 (Figure 1.7), the trisubstituted alkene on the nine-membered ring was expected to exhibit high reactivity toward dihydroxylation. The author planned to use the primary alcohol moiety of **2.3** as an anchor of hydrogen-bond-induced dihydroxylation reported by Donohoe. [35,36] Upon treatment with an equimolar amount of OsO_4 and an excess amount of TMEDA ligand, **2.3** underwent smooth oxidation to afford the desire triol **2.4** as a single isomer in 71% yield.

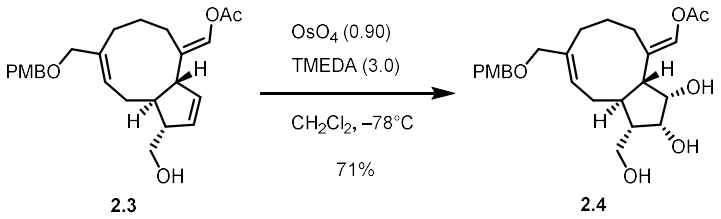


Figure 2.3. Chemoselective dihydroxylation

The 1,2-diol moiety of triol **2.4** was selectively protected with phenylboronic acid under low-temperature, and the remaining primary alcohol was oxidized to an aldehyde (Figure 2.4). Allylboronate **1.30** was used for installation of a prenyl side chain to aldehyde **2.12**, giving alcohol **2.13** in 68% overall yield from triol **2.4**.[33] The resulting alcohol was oxidized to ketone, and the boronate group was removed using a large excess amount of pinacol under weakly acidic conditions, giving diol **2.5** in 57% yield for two steps.

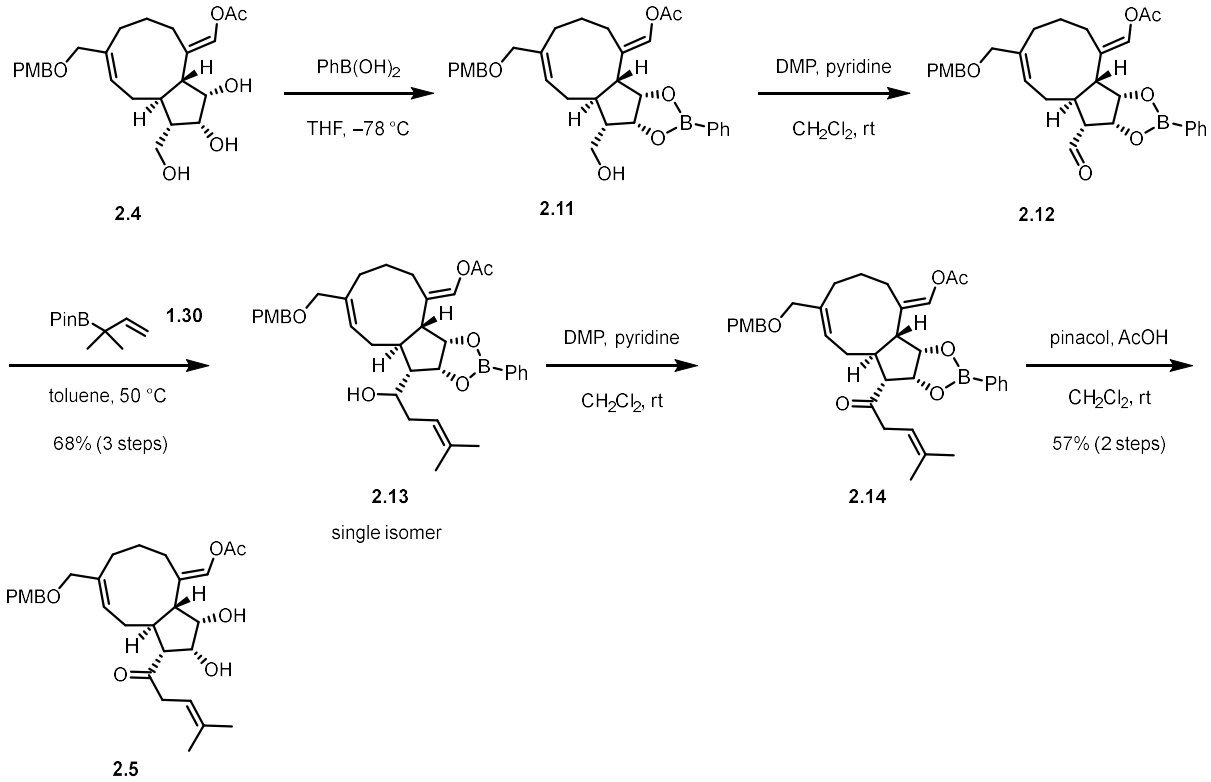


Figure 2.4. Synthesis of dihydropyran precursor **2.5**

Having established the synthetic route to diol **2.5**, the key dihydropyran construction step was examined using lead tetraacetate or sodium periodate (Figure 2.5). These conventional methods for oxidative cleavage

of a 1,2-diol, however, gave complex mixtures. The results led the author to explore other reaction conditions by using a model substrate having a substructure of diol **2.5**.

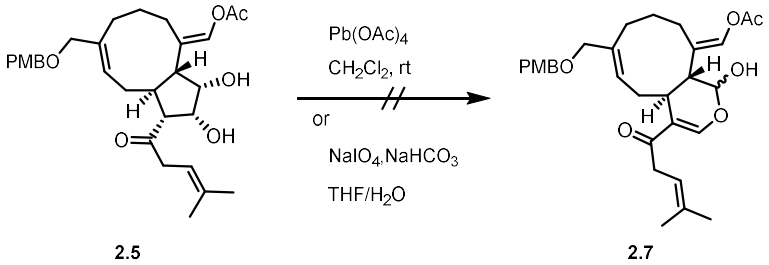


Figure 2.5. Initial attempts for dihydropyran ring construction

The synthesis of model substrate **2.21** is shown in Figure 2.6. Nitrile **2.16**, which was prepared from allyl carbonate **2.15** by using a palladium catalyst and TMSCN, was subjected to a dihydroxylation reaction to afford diol **2.17** as a diastereomeric mixture.[37,38] Protection of the diol with TBS groups enabled separation of the diastereomers, and the desired *syn*-nitrile **2.18** and *anti*-nitrile **2.19** were obtained in 31% and 23% yields for three steps, respectively. The *syn*-nitrile **2.18** was reduced with DIBAL-H to give aldehyde **2.20** in high yield. After three-step transformation, including introduction of the prenyl side chain, oxidation of the resulting alcohol, and removal of the TBS group, model substrate **2.21** was obtained in 38% yield from **2.20**.[38] The ketone-epimer of the model substrate was also synthesized in a similar way.

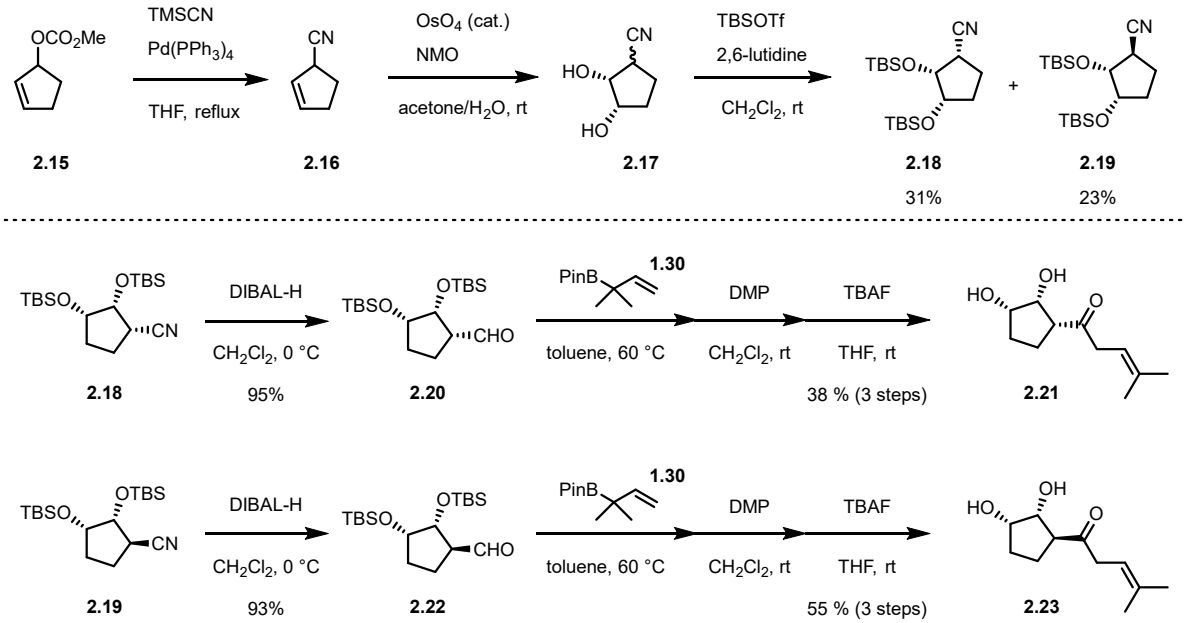


Figure 2.6. Synthesis of model compounds

The two diols **2.21** and **2.23** were subjected to a conventional oxidation reaction using sodium periodate and a buffer solution (Figure 2.7). Model compound **2.21**, having the same stereochemistry as that of **2.5**, resulted in formation of a complex mixture. In contrast, the ketone-epimer **2.23** gave the desired dihydropyran **2.24** in 64% NMR yield along with its isomer **2.25** in 4% NMR yield. The origin of the different behavior between the two epimers is not clear, but the intramolecular hydrogen bonding in **2.21**, which was observed in a proton NMR chart, might affect the unsuccessful transformation.

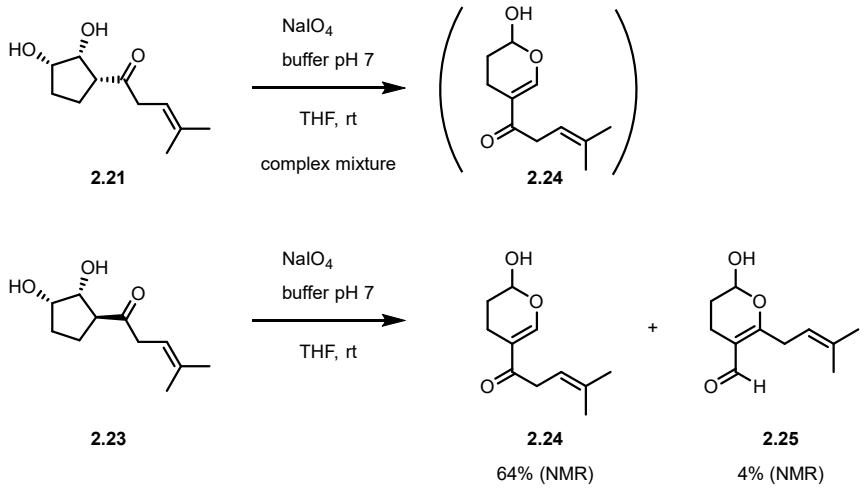


Figure 2.7. Dihydropyran synthesis with model compounds

The contrasting result observed for ketone-epimer **2.23** led the author to examine isomerization of diol substrate **2.5** to the corresponding ketone-epimer (Figure 2.8). Since a strong base was expected to induce β-elimination of the hydroxy group or a retro-aldol reaction, proline or a combined use of pyrrolidine and acetic acid were examined. These mild conditions were expected to produce an enamine intermediate for the epimerization of the ketone side chain, but the desired product was not obtained.

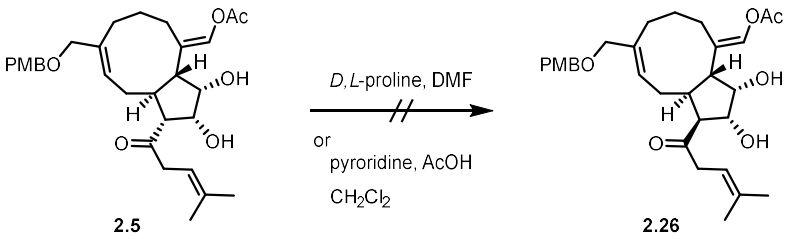
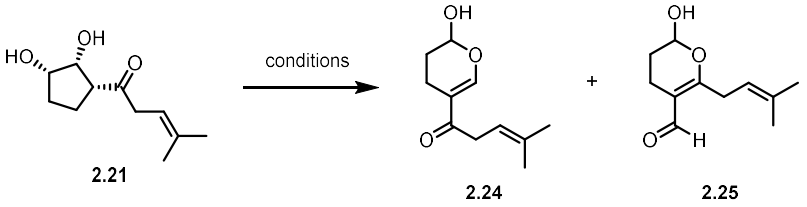


Figure 2.8. Sidechain isomerization with diol **2.5**

Since the alternative route involving isomerization of **2.5** to the ketone-epimer was fruitless, further investigation was continued by using only *syn*-**2.21** as a model substrate (Figure 2.9). As was shown in Figure 2.9, the use of sodium periodate gave a complex mixture (entry 1). The reaction with lead tetraacetate or

iodobenzenediacetate (PIDA) in CH_2Cl_2 resulted in substrate decomposition (entries 2 and 3). On the other hand, unexpected information was obtained by the use of tetrabutylammonium periodate (entry 4). [39] The TLC monitoring during the reaction indicated partial conversion of *syn*-**2.21** to a new product, but the starting material was recovered unchanged after usual workup. The result suggested that silica gel on the TLC plate might facilitate the oxidation reaction. Indeed, treatment of *syn*-**2.21** with tetrabutylammonium periodate in the presence of silica gel powder produced a small amount of the desired product **2.24** (entry 5). Further examinations were conducted by using silica-gel-supported $NaIO_4$,[40] and dihydropyran **2.24** was obtained in 70% NMR yield along with 8% of its isomer **2.25** (entry 6). The silica-gel-supported $NaIO_4$ prepared from neutral-type silica gel gave better result than that prepared from acidic-type one (entry 7). The use of other solvents led to decreased yield of desired product **2.24** (entries 8-10).



2.21 **2.24** **2.25**

Entry[a]	Reagents	Solvents	Yield[b] **2.24**	**2.25**
1	$NaIO_4$	THF/H_2O[c]	decomp.	
2	$Pb(OAc)_4$	CH_2Cl_2	decomp.	
3	PIDA	CH_2Cl_2	decomp.	
4[d]	*n*-Bu_4NIO_4	CH_2Cl_2	**2.21** 91%	
5	*n*-Bu_4NIO_4, SiO_2	CH_2Cl_2	6%	N.D.
6	$NaIO_4/SiO_2$ (N)	CH_2Cl_2	70%	8%
7	$NaIO_4/SiO_2$ (A)	CH_2Cl_2	53%	5%
8	$NaIO_4/SiO_2$ (N)	THF	<12%	trace
9	$NaIO_4/SiO_2$ (N)	MeCN	18%	trace
10	$NaIO_4/SiO_2$ (N)	toluene	<6%	trace

[a]15 mg scale. [b]NMR yield. [c]Phosphate buffer ph 7. [d]Partial conversion by TLC monitoring
N = neutral silica gel. A = acidic silicagel

Figure 2.9. Examination of oxidative cleavage condition

These results led the author to apply the best condition (entry 6 in Figure 2.9) to the oxidation of substrate **2.5**. The TLC monitoring during the reaction showed a clean formation of a new spot, the strong UV absorption of which suggested presence of a dihydropyran structure (Figure 2.10). However, the proton NMR

chart of the crude mixture indicated that the primary product was dialdehyde **2.6**. Fortunately, **2.6** was found to undergo a cyclization reaction during the silica gel column chromatography, affording dihydropyran **2.7** as an equilibrium mixture with its isomer **2.27** in 55% yield.

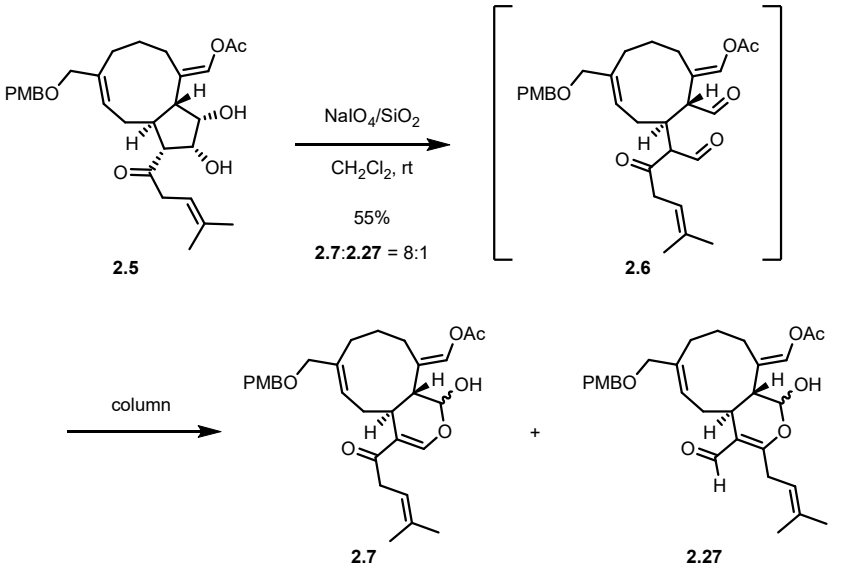


Figure 2.10. Dihydropyran ring synthesis

The next task was acetylation of the hemiacetal moiety. Conventional methods by using acetic anhydride and amines were applied to dihydropyran **2.7**, but desired acetate **2.28** was not obtained (Figure 2.11). It was reported that the combined use of acetic acid, carbonyldiimidazole (CDI), and DBU gave a successful result in the total synthesis of waixenicin A,[17] but the conditions were not effective for the acetylation of **2.7**.

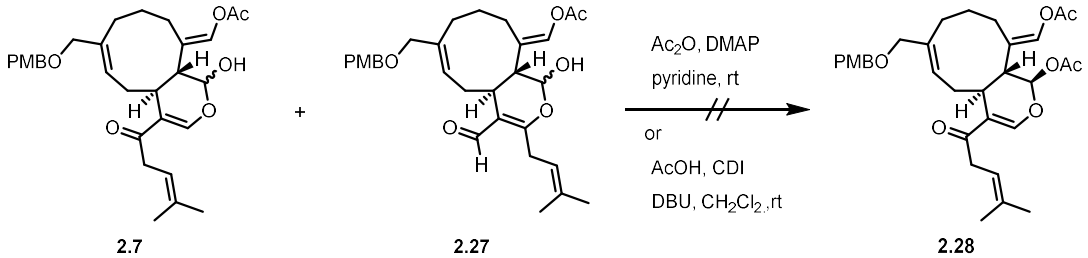
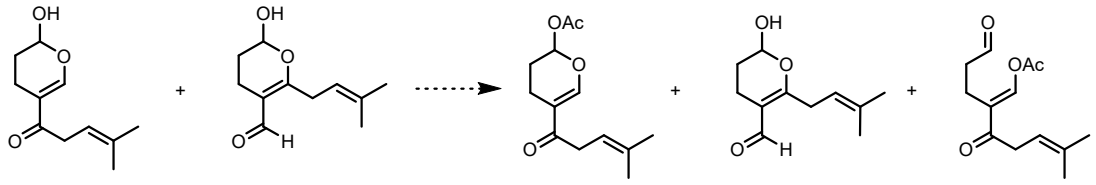


Figure 2.11 Unsuccessful results for acetylation

The author decided to explore the acetylation reactions using a model substrate which was prepared by the oxidation reaction of model 1,2-diol **2.21** or **2.23** (Figure 2.12). Firstly, the mixture of hemiacetals **2.24** and **2.25** was treated with acetic anhydride and amines. Use of a catalytic amount of DMAP and pyridine afforded a complex mixture containing the desired product **2.29** (9% NMR yield) and enol acetate **2.31** (2% NMR yield). Interestingly, the reaction with a catalytic amount of DMAP only gave the desired product **2.29** in 24% NMR yield (entry 2). The use of pyridine only also afforded **2.29** in 21% NMR yield (entry 3), but

the yield of enol acetate **2.31** was increased to 58% NMR yield. Predominant formation (92% NMR yield) of enol acetate **2.31** was observed by using triethylamine, a stronger base than pyridine (entry 4).



2.24 8.8:1 **2.25** **2.29** **2.30** **2.31**

Entry	Conditions	Results[a]		
		2.29	**2.30**	**2.31**
1	Ac_2O, DMAP (cat.), rt, pyridine	9%	2%	2%
2	Ac_2O, DMAP (cat.), rt, CH_2Cl_2	24%	trace	trace
3	Ac_2O, pyridine, rt, CH_2Cl_2	21%	3%	58%
4	Ac_2O, Et_3N, rt, CH_2Cl_2	-	-	92%
5	AcOH, CDI, DBU (cat.), rt, CH_2Cl_2	42%	5%	-
6	AcOH (1.5), EDCI•HCl (1.5), DMAP (0.2), rt, CH_2Cl_2	44%	4%	27%
7	AcOH (3.0), EDCI•HCl (3.0), DMAP (1.0), rt, CH_2Cl_2	56%	7%	-
8	AcOH, EDCI•HCl, CH_2Cl_2	-	-	91%

[a]NMR yield.

Figure 2.12. Examination of acetylation condition

Next, the condensation reactions with acetic acid were examined. In contrast to the reaction of **2.7** (Figure 2.11), the reaction conditions reported in the total synthesis of waixenicin A afforded the desired acetate **2.29** in 42% NMR yield (entry 5). Similarly, the reaction mediated with EDCI•HCl and DMAP, which was reported in Hosokawa's total synthesis of Alycyonolide, also gave **2.29** in 44% NMR yield (entry 6).[41] Upon trucking these reactions with TLC, formation of enol acetate **2.31** was observed at an early period. Then the initial product **2.31** decreased gradually, during which the desired acetate **2.29** increased. Since **2.29** has a vinylogous anhydride structure, it may work as an acetylating agent in the presence of DMAP as a catalyst for transesterification. Indeed, the reaction without DMAP afforded only enol acetate **2.31** in 91% NMR yield (entry 8). Although the reaction under the conditions in entry 6 showed poor reproducibility, which was also mentioned by Hosokawa *et al.*, increasing the quantities of the reagents improved the results. The desired product **2.29** was obtained in 56% NMR yield along with its isomer **2.30** in 7% NMR yield (entry 7).

The optimal reaction conditions were applied to acetylation of dihydropyran **2.7** (Figure 2.13). Although enol acetate **2.32** was formed as a major product along with a small amount of the desired product **2.28**, the reaction at higher temperature in 1,2-dichloroethane afforded **2.28** in 46% isolated yield as a 10:1 mixture with its regio isomer **2.33**. Epimers of both products were also obtained as a 5.9:1 mixture in 16% yield.

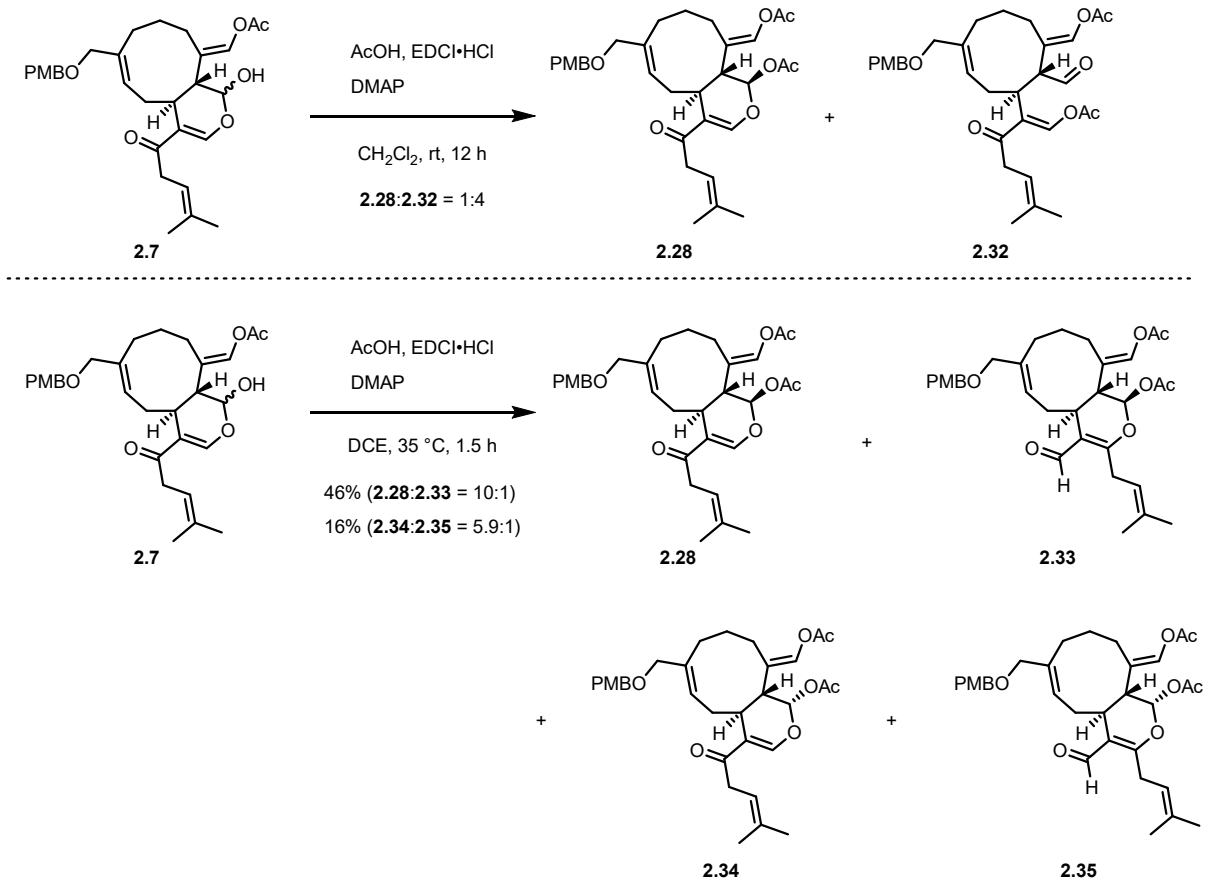


Figure 2.13. Acetylation of hemiacetal **2.7**

Finally, the 10:1 mixture of **2.28** and **2.33** was subjected to DDQ oxidation, affording Cristaxenicin A (**5**) in 57% isolated yield (Figure 2.14). The reaction proceeded through removal of the PMB group to give alcohol **2.36**, which was also isolated in 25% yield. The spectral data of the synthetic compound were identical to those of the natural product (Figure 2.16, see page 60).[5]

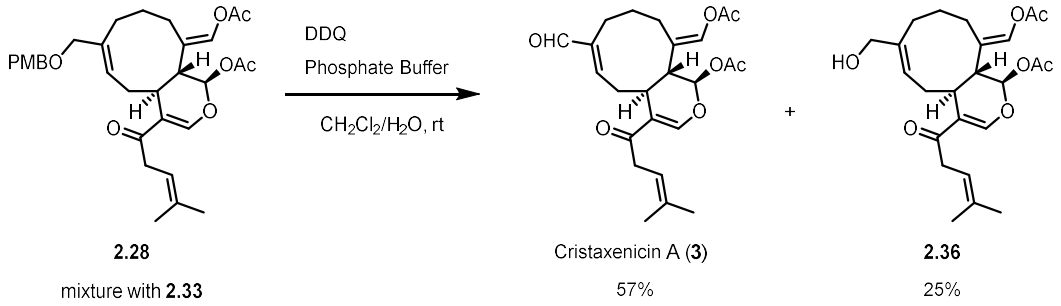


Figure 2.14. Completion of the total synthesis

Conclusion

In summary, the author achieved the first total synthesis of Cristaxenicin A (Figure 2.15). The key intermediate ketone **2.1** was converted to cyclopentene intermediate **2.2**, which enabled the transformation of the cyano group into the enol acetate moiety. After regioselective dihydroxylation directed by the primary alcohol moiety, the side chain was introduced by using an allylboronate reagent. Then construction of the dihydropyran ring was achieved through oxidative cleavage of the 1,2-diol **2.5** giving a dialdehyde followed by silica gel-mediated cyclization. Finally, the synthesis of Cristaxenicin A was accomplished through acetylation under finely tuned conditions followed by oxidative removal of the PMB group.

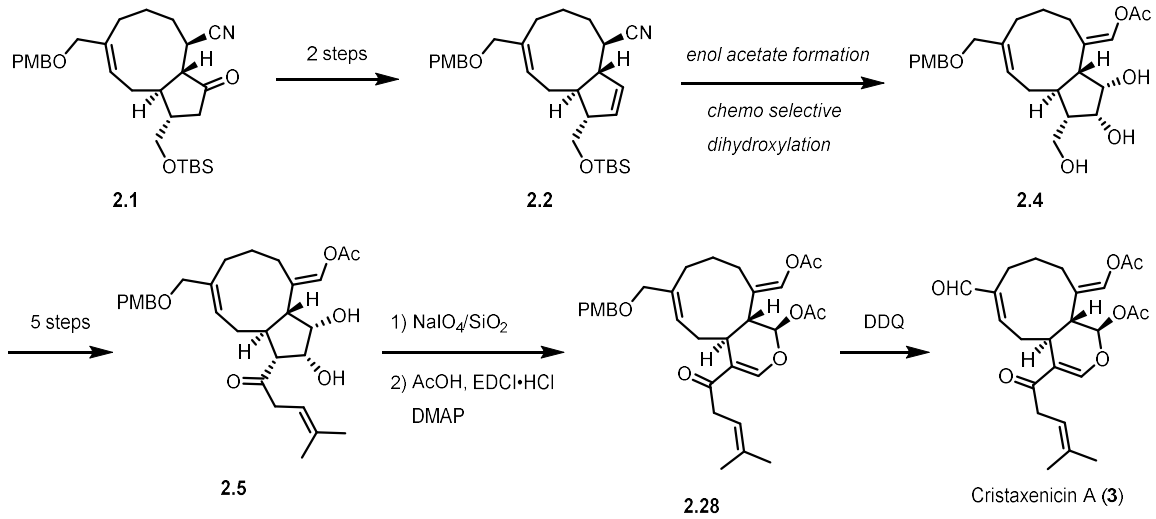
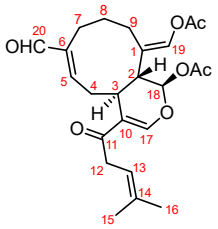


Figure 2.15. Summary of the total synthesis

Figure 2.16. Comparision of NMR spectra between natural and synthetic Cristaxenicin A (**3**)

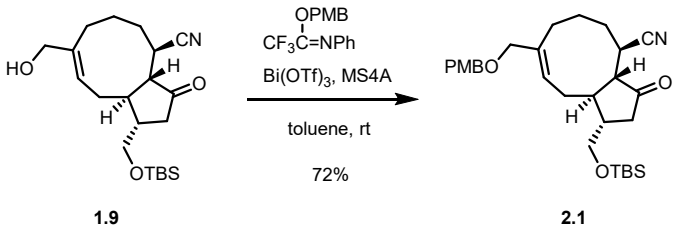


[a]Overlap with the solvent peak.

	natural **3** (400/not described. MHz, CD_3OD)		synthetic **3** (500/126 MHz, CD_3OD)		^{13}C difference
No.	^{1}H (δ, multi)	$^{13}C\{^{1}H\}$ (δ)	^{1}H (δ, multi)	$^{13}C\{^{1}H\}$ (δ)	Δδ ppm
1		120.6		122.0	1.4
2	2.48 (dd)	49[a]	2.48 (dd)	50[a]	-
3	3.04 (m)	35.9	3.07-3.01 (m)	37.3	1.4
4	2.86 (ddd)	30.0	2.86 (ddd)	31.4	1.4
4’	2.65 (ddd)		2.65 (ddd)		-
5	6.65 (t)	153.4	6.65 (t)	154.8	1.4
6		144.9		146.3	1.4
7	2.39 (dd)	21.2	2.41-2.30 (m, 2H)	22.6	1.4
7’	2.32 (dd)				-
8	1.83 (m)	22.5	1.87-1.79 (m)	24.2	1.7
9	2.54 (dd)	28.8	2.54 (dd)	30.1	1.3
9’	2.00 (dd)		2.00 (dd)		-
10		120.2		121.6	1.4
11		198.2		199.6	1.4
12	3.40 (dd)	37.6	3.40 (dd)	39.0	1.4
12’	3.33 (dd)		3.33 (dd)		-
13	5.30 (t)	116.9	5.30 (t)	118.3	1.4
14		134.9		136.3	1.4
15	1.68 (s)	16.7	1.68 (s)	18.1	1.4
16	1.75 (s)	24.5	1.75 (s)	25.9	1.4
17	7.68 (s)	154.6	7.68 (s)	156.0	1.4
18	5.86 (d)	94.5	5.86 (d)	95.9	1.4
19	6.98 (s)	136.0	6.98 (s)	137.4	1.4
20	9.27 (s)	195.8	9.27 (s)	197.2	1.4
OAc-18	2.05 (s)	19.1	2.05 (s)	20.5	1.4
		168.9		170.3	1.4
OAc-19	2.10 (s)	19.0	2.10 (s)	20.4	1.4
		167.8		169.2	1.4

Experimental Section

Synthesis of **2.1**

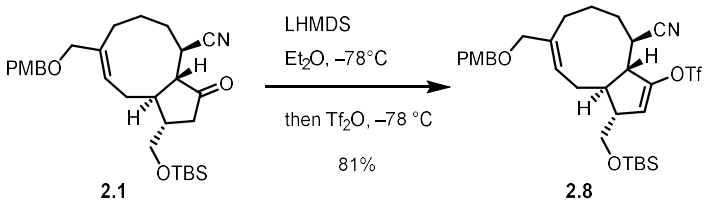


To a mixture of allyl alcohol **1.9** (356 mg, 0.943 mmol), PMB-imidate[34] (349 mg, 1.13 mmol) and MS 4 Å (214 mg) in toluene (4.7 mL) was added $Bi(OTf)_3$ (18.6 mg, 0.0283 mmol). After stirring at room temperature for 20 min, the reaction was quenched with Et_3N (131 µL, 0.943 mmol) and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 9:1 to 17:3 to 4:1) to afford ketone **2.1** (340 mg, 0.527 mmol, 72% yield) as a colorless oil.

Spectral data for **2.1**

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.26 (d, *J* = 9.0 Hz, 2H), 6.88 (d, *J* = 9.0 Hz, 2H), 5.72 (dd, *J* = 10.0, 7.0 Hz, 1H), 4.44 (d, *J* = 12.3 Hz, 1H), 4.41 (d, *J* = 12.3 Hz, 1H), 3.91 (s, 2H), 3.81 (s, 3H), 3.73 (dd, *J* = 10.5, 4.0 Hz, 1H), 3.70 (dd, *J* = 10.5, 3.5 Hz, 1H), 2.65 (ddd, *J* = 11.0, 4.5, 3.5 Hz, 1H), 2.48-2.39 (m, 2H), 2.35 (t, *J* = 10.8 Hz, 1H), 2.36-2.29 (m, 1H), 2.26-2.18 (m, 1H), 2.22 (dd, *J* = 18.8, 10.5 Hz, 1H), 2.18-2.12 (m, 1H), 2.08-1.98 (m, 2H), 1.95-1.85 (m, 2H), 1.81-1.74 (m, 1H), 1.74-1.65 (m, 1H), 0.88 (s, 9H), 0.06 (s, 6H); **^{13}C{^{1}H}-NMR** (126 MHz, $CDCl_3$): δ 214.9, 159.2, 141.0, 130.2 , 129.3 (2C), 123.4, 120.9, 113.8 (2C), 73.3, 72.0, 62.4, 55.3, 53.4, 42.0, 41.0, 39.8, 31.9, 30.3, 27.7, 27.5, 25.8 (3C), 22.6, 18.3, –5.4, –5.5; **FT-IR (ATR)**: ν_{max} 2950, 2927, 2857, 2236, 1740, 1511, 1246, 1094, 834, 776 cm^{-1}; **HRMS (FD)**: *m/z* Calcd for $C_{29}H_{43}NO_4Si$ $[M]^+$: 497.2956; found: 497.2960.

Synthesis of **2.8**



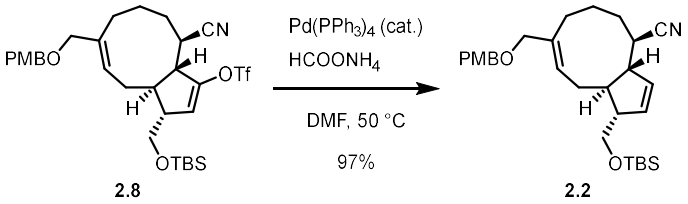
To a solution of ketone **2.1** (324 mg, 0.651 mmol) in Et_2O was added LHMDS (1.20 mL, 1.20 mmol, 1 M THF solution) dropwise at –78 °C. After stirring at the same temperature for 30 min, Tf_2O (197 µL, 1.20

mmol) was added dropwise and the mixture was stirred at the same temperature for 10 min. The reaction was quenched with Et_3N (106 μL, 1.80 mmol) and saturated aqueous $NaHCO_3$ solution. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 19:1 to 9:1 to 4:1) to afford vinyl triflate **2.8** (332 mg, 0.683 mmol, 81% yield) as a colorless oil.

Spectral data for **2.8**

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 5.90 (t, *J* = 8.3 Hz, 1H), 5.66 (s, 1H), 4.44 (d, *J* = 11.3 Hz, 1H), 4.37 (d, *J* = 11.3 Hz, 1H), 3.93 (d, *J* = 11.8 Hz, 1H), 3.811 (d, *J* = 11.8 Hz, 1H), 3.807 (s, 3H), 3.58 (dd, *J* = 10.3, 4.8 Hz, 1H), 3.53 (dd, *J* = 10.3, 5.3 Hz, 1H), 3.13 (dd, *J* = 6.8, 5.3 Hz, 1H), 2.60-2.55 (m, 1H), 2.55-2.49 (m, 1H), 2.39-2.31 (m, 1H), 2.29-2.19 (m, 3H), 2.03-1.91 (m, 1H), 1.84-1.65 (m, 4H), 0.88 (s, 9H), 0.04 (s, 6H); **^{13}C{^{1}H}-NMR** (125 MHz, $CDCl_3$): δ 159.2, 147.3, 138.1, 130.2, 129.2 (2C), 126.9, 120.3, 118.8, 118.5 (q, *J* = 319.5 Hz), 113.8 (2C), 72.5, 71.9, 64.7, 55.3, 52.4, 51.7, 43.0, 35.1, 34.9, 27.8, 25.8 (3C), 24.5, 21.4, 18.2, –5.4, –5.5; **FT-IR (ATR)**: ν_{max} 2954, 2936, 2925, 2857, 2237, 1424, 1209, 1139, 837 cm^{-1}; **HRMS (FD)**: *m/z* Calcd for $C_{30}H_{42}F_3NO_6SSi$ $[M]^+$: 629.2449; found: 629.2466.

Synthesis of **2.2**

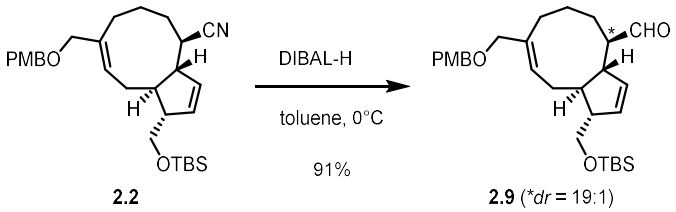


A mixture of vinyl triflate **2.8** (308 mg, 0.489 mmol), $Pd(PPh_3)_4$ (113 mg, 0.0978 mmol) and ammonium formate (92.7 mg, 1.47 mmol) in DMF (4.9 mL) was heated to 50 °C. After stirring for 1.5 h, the reaction mixture was cooled down to room temperature, diluted with Et_2O, and quenched with water. After the layers were separated, the organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 19:1 to 9:1) to afford cyclopentene **2.2** as a yellow oil (229 mg, 0.476 mmol, 97% yield).

Spectral data for **2.2**

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 5.91 (t, *J* = 8.3 Hz, 1H), 5.81 (dt, *J* = 5.5, 2.0 Hz, 1H), 5.65 (dt, *J* = 5.5, 2.0 Hz, 1H), 4.44 (d, *J* = 11.5 Hz, 1H), 4.37 (d, *J* = 11.5 Hz, 1H), 3.93 (d, *J* = 12.0 Hz, 1H), 3.81 (s, 3H), 3.79 (d, *J* = 12.0 Hz, 1H), 3.56 (dd, *J* = 10.0, 6.0 Hz, 1H), 3.52 (dd, *J* = 10.0, 6.0 Hz, 1H), 3.00-2.92 (m, 1H), 2.62-2.55 (m, 1H), 2.41 (td, *J* = 13.3, 5.0 Hz, 1H), 2.34 (dt, *J* = 12.0, 3.5 Hz, 1H), 2.27 (dd, *J* = 8.3, 5.8 Hz, 1H), 2.27-2.19 (m, 2H), 1.93-1.83 (m, 1H), 1.77-1.67 (m, 3H), 1.47 (quin, *J* = 6.0 Hz, 1H), 0.87 (s, 9H), 0.040 (s, 3H), 0.037 (s, 3H); **^{13}C{^{1}H}-NMR** (126 MHz, $CDCl_3$): δ 159.1, 137.2, 132.8, 132.4, 130.4, 129.2 (2C), 128.4, 122.3, 113.8 (2C), 72.7, 71.7, 66.1, 58.6, 55.3, 54.7, 45.4, 38.3, 34.6, 27.6, 25.9 (3C), 24.0, 21.3, 18.3, –5.3, –5.4; **FT-IR (ATR)**: ν_{max} 2952, 2927, 2855, 2234, 1512, 1246, 1093, 1068, 831 cm^{-1}; **HRMS (FD)**: *m/z* Calcd for $C_{29}H_{43}NO_3Si$ $[M]^+$: 481.3007; found: 481.3010.

Synthesis of **2.9**



2.2 **2.9** (**dr* = 19:1)

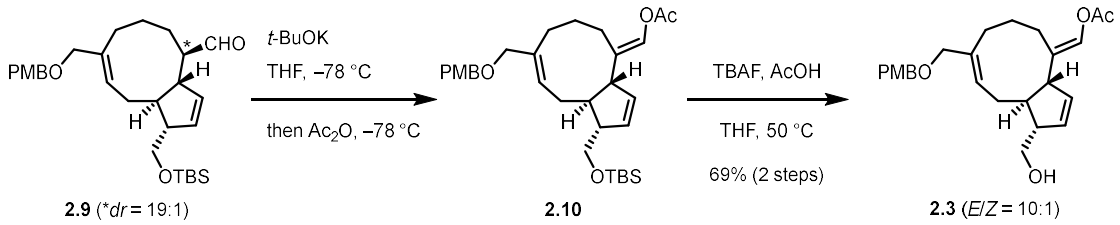
To a solution of cyclopentene **2.2** (213 mg, 0.442 mmol) in toluene (4.4 mL) was added DIBAL-H (875 µL, 0.884 mmol, 1.01 M *n*-hexane solution) at 0 °C. After stirring at the same temperature for 10 min, the reaction was quenched with 10% aqueous *L*-Tartaric Acid solution. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 19:1 to 9:1) to afford aldehyde **2.9** (195 mg, 0.402 mmol, 91% yield, dr = 19:1) as a colorless oil.

Spectral data for **2.9** (major isomer only)

^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.75 (s, 1H), 7.25 (d, *J* = 9.0 Hz, 2H), 6.84 (d, *J* = 9.0 Hz, 2H), 5.92 (t, *J* = 8.3 Hz, 1H), 5.61 (d, *J* = 5.5 Hz, 1H), 5.56 (d, *J* = 5.5 Hz, 1H), 4.43 (d, *J* = 11.5 Hz, 1H), 4.36 (d, *J* = 11.5 Hz, 1H), 3.94 (d, *J* = 12.0 Hz, 1H), 3.81 (s, 3H), 3.79 (d, *J* = 12.0 Hz, 1H), 3.54 (d, *J* = 6.5 Hz, 2H), 3.05 (dd, *J* = 9.5, 6.5 Hz, 1H), 2.58-2.51 (m, 1H), 2.37 (td, *J* = 13.5, 5.0 Hz, 1H), 2.31 (dd, *J* = 7.5, 5.0 Hz, 2H), 2.25 (dt, *J* = 12.0, 3.8 Hz, 1H), 2.14 (dt, *J* = 12.5, 4.0 Hz, 1H), 1.91-1.83 (m, 1H), 1.75 (td, *J* = 13.5, 4.0 Hz, 1H), 1.58-1.50 (m, 2H), 1.42-1.32 (m, 1H), 0.90 (s, 9H), 0.049 (s, 3H), 0.046 (s, 3H); **^{13}C{^{1}H}-NMR** (126 MHz,

$CDCl_3$): δ 205.0, 159.1, 136.8, 134.0, 130.9, 130.5, 129.2 (2C), 128.9, 113.7 (2C), 72.8, 71.5, 66.8, 58.4, 57.7, 55.3, 51.4, 45.2, 34.8, 27.5, 25.9 (3C), 21.5, 21.2, 18.3, –5.3, –5.4 ; **FT-IR (ATR)**: ν_{max} 2928, 2855, 1720, 1513, 1246, 1074, 835, 774 cm^{-1}; **HRMS (FD)**: *m/z* Calcd for $C_{29}H_{44}O_4Si$ $[M]^+$: 484.3003; found: 484.3011.

Synthesis of **2.3**



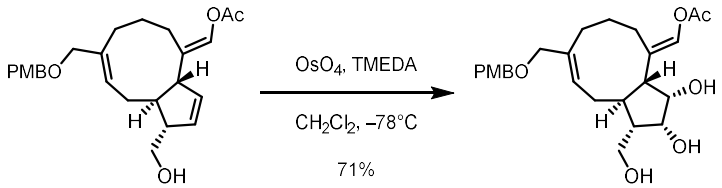
To a solution of aldehyde **2.9** (179 mg, 0.369 mmol) in THF (3.7 mL) was added *t*-BuOK (554 µL, 0.554 mmol, 1 M THF solution) dropwise at –78 °C. After stirring at the same temperature for 30 min, Ac_2O (69.8 µL, 0.738 mmol) was added dropwise and the mixture was stirred at the same temperature for 10 min. The reaction was quenched with saturated aqueous $NaHCO_3$ solution and, the mixture was diluted with Et_2O. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the crude enol acetate **2.10**.

To a solution of crude enol acetate **2.10** and AcOH (84.6 µL, 1.48 mmol) in THF was added TBAF (738 µL, 0.738 mmol, 1.0 M THF solution). After stirring at 40 °C for 30 h, the reaction was quenched with saturated aqueous $NaHCO_3$ solution, and the mixture was diluted with Et_2O. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (*n*-hexane/EtOAc = 7:3) to afford alcohol **2.3** (105 mg, 0.255 mmol, 69% yield, E/Z =10:1) as a colorless oil.

Spectral data for **2.3** (major isomer only)

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 6.83 (s, 1H), 5.71-5.66 (m, 2H), 5.56 (d, *J* = 6.0 Hz, 1H), 4.40 (d, *J* =11.5 Hz, 1H), 4.34 (d, *J* = 11.5 Hz, 1H), 3.93 (d, *J* = 11.5 Hz, 1H), 3.805 (d, *J* = 11.5 Hz, 1H), 3.800 (s, 3H), 3.69 (dd, *J* = 11.0, 5.0 Hz, 1H), 3.58 (dd, *J* = 11.0, 5.5 Hz, 1H), 3.08 (d, *J* = 4.5 Hz, 1H), 2.57-2.45 (m, 2H), 2.41 (ddd, *J* = 13.3, 9.3, 4.5 Hz, 1H), 2.34-2.15 (m, 5H), 2.09 (s, 3H), 1.85-1.65 (m, 2H), 1.62 (br, 1H); **^{13}C{^{1}H}-NMR** (126 MHz, $CDCl_3$): δ 168.0, 159.0, 137.4, 135.3, 131.7, 131.1, 130.5, 129.7, 129.2 (2C), 127.1, 113.7 (2C), 73.3, 71.2, 65.4, 56.7, 55.20, 55.18, 47.8, 33.4, 26.9, 26.4, 23.8, 20.7; **FT-IR (ATR)**: ν_{max} 3449, 2919, 2856, 1748, 1512, 1220, 1095, 1033, 819 cm^{-1}; **HRMS (FD)**: *m/z* Calcd for $C_{25}H_{32}O_5$ $[M]^+$: 412.2244; found: 412.2257.

Synthesis of **2.4**



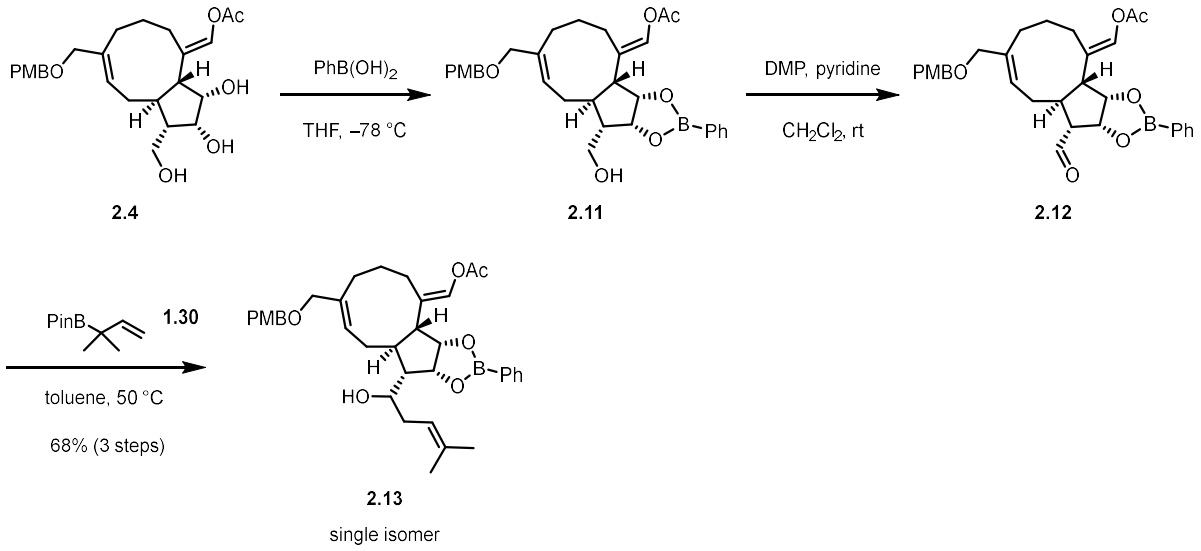
2.3 **2.4**

To a solution of alcohol **2.3** (90.0 mg, 0.218 mmol) and TMEDA (76.0 μL, 0.654 mmol) in CH_2Cl_2 (4.4 mL) was added OsO_4 (1.00 mL, 0.197 mmol, 0.197 M CH_2Cl_2 solution) dropwise at –78 °C. After stirring at the same temperature for 30 min, the mixture was concentrated under reduced pressure. The residue was dissolved in THF/H_2O (1:1, 20 mL) and quenched with $Na_2S_2O_3$ (1.2 g) and 1 M hydrochloric acid (5 mL). The mixture was stirred overnight and diluted with EtOAc. The two layers were separated, and the aqueous layer was extracted with EtOAc until the absence of the target product was confirmed on TLC. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified with flash column chromatography (SiO_2, *n*-hexane/EtOAc = 7:3 to 1:1 to 1:3) to afford triol **2.4** as a colorless oil (69.5 mg, 0.156 mmol, 71% yield), along with impure alcohol **2.3** (25.0 mg). The mixture containing **2.3** was further purified by preparative TLC to recover **2.3** (10.1 mg, 0.0245 mmol, 11% yield) as a colorless oil.

Spectral data for **2.4**

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.24 (d, *J* = 8.5 Hz, 2H), 7.01 (s, 1H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.53 (t, *J* = 8.5 Hz, 1H), 4.37 (d, *J* = 12.0 Hz, 1H), 4.34 (d, *J* = 12.0 Hz, 1H), 4.31 (dd, *J* = 8.3, 4.8 Hz, 1H), 3.93-3.87 (m, 3H), 3.84 (dd, *J* = 11.5, 3.0 Hz, 1H), 3.80 (s, 3H), 3.77 (dd, *J* = 11.5, 6.5 Hz, 1H), 3.31 (br, 1H), 2.78 (br, 2H), 2.61-2.52 (m, 1H), 2.43 (ddd, *J* = 13.8, 8.3, 4.0 Hz, 1H), 2.30-2.23 (m 1H), 2.22-2.10 (m, 4H), 2.12 (s, 3H), 2.05 (ddd, *J* = 13.5, 7.5, 6.0 Hz , 1H), 1.94-1.82 (m, 3H), 1.81-1.71 (m, 1H); **^{13}C{^{1}H}-NMR** (126 MHz, $CDCl_3$): δ 168.1, 159.1, 139.6, 134.7, 130.5, 129.3 (2C), 125.0, 121.9, 113.7 (2C), 74.1, 73.7, 73.3, 71.3, 61.5, 55.2, 51.7, 47.6, 41.8, 29.5, 28.4, 24.5, 23.3, 20.7 ; **FT-IR (ATR)**: ν_{max} 3392, 2917, 2856, 1745, 1511, 1219, 1087, 1033, 752 cm^{-1}; **HRMS (FD)**: *m/z* Calcd for $C_{25}H_{35}O_7$ $[M+H]^+$: 447.2377; found: 447.2374.

Synthesis of **2.13**



To a solution of triol **2.4** (65.1 mg, 0.146 mmol) in THF (1.5 mL) was added phenylboronic acid (18.8 mg, 0.184 mmol) at –78 °C. After stirring at –78 °C for 1 h, the reaction mixture was warm up to room temperature and concentrated under reduced pressure to afford crude boronate **2.11** (about 10:1 ratio of 1,2- and 1,3-protected compounds).

To a solution of the crude alcohol **2.11** and pyridine (28.6 µL, 0.355 mmol) in CH_2Cl_2 (1.5 mL) was added Dess-Martin Periodinane (124 mg, 0.292 mmol). After stirring at room temperature for 1.5 h, the reaction mixture was diluted with Et_2O and quenched with $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ solution. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford crude ketone **2.12** (mixture with pyridine).

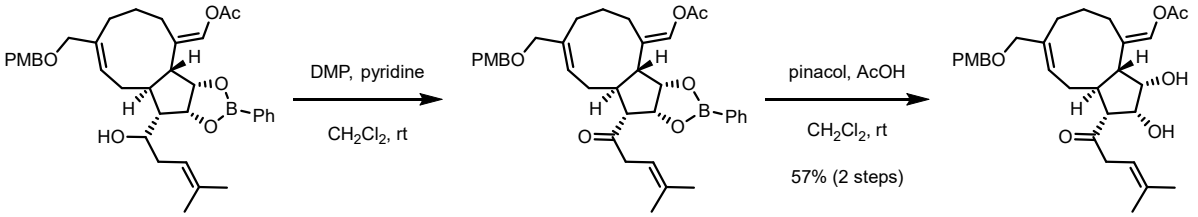
A mixture of **2.12** and allylboronate **1.30**[33] (57.3 mg, 0.292 mmol) in toluene was heated to 50 °C and stirring for 2.5 h. The reaction mixture was concentrated under reduced pressure, and the crude product was purified by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 9:1 to 4:1) to afford alcohol **2.13** (single isomer, 59.2 mg, 0.0986 mmol, 68% yield for three steps) as a colorless oil.

Spectral data for **2.13**

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.97 (d, *J* = 7.5 Hz, 2H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.17 (s, 1H), 6.85 (d, *J* = 8.0 Hz, 2H), 5.65 (t, *J* = 8.8 Hz, 1H), 5.28 (t, *J* = 7.3 Hz, 1H), 4.92 (t, *J* = 6.0 Hz, 1H), 4.71 (t, *J* = 6.0 Hz, 1H), 4.34 (s, 2H), 4.00 (ddd, *J* = 8.8, 7.0, 3.8 Hz, 1H), 3.87 (s, 2H), 3.80 (s, 3H), 2.61 (ddd, *J* = 14.0, 9.5, 4.0 Hz, 1H), 2.59-2.53 (m, 1H), 2.41 (dt, *J* = 14.5, 8.5 Hz, 1H),

2.38-2.28 (m, 1H), 2.27 (ddd, *J* = 14.0, 8.3, 3.8 Hz, 1H), 2.22-2.14 (m, 4H), 2.18 (s, 3H), 2.13-2.06 (m, 1H), 2.00-1.92 (m, 1H), 1.92-1.82 (m, 1H), 1.78 (s, 3H), 1.78-1.65 (m, 2H), 1.73 (s, 3H); **^{13}C{^{1}H}-NMR** (126 MHz, $CDCl_3$): δ 167.7, 159.1, 138.1, 135.8, 135.3, 135.0 (2C), 131.6, 130.6, 129.3 (2C), 127.9 (2C), 126.8, 120.2, 119.9, 113.7 (2C), 83.1, 83.0, 73.7, 72.3, 71.2, 55.3, 53.8, 52.1, 41.8, 34.9, 27.8, 26.2, 26.0, 24.0, 23.3, 20.9, 18.1 (one peak missing); **FT-IR (ATR)**: ν_{max} 3502, 2921, 2857, 1750, 1367, 1213, 1098 cm^{-1}; **HRMS (FD)**: *m/z* Calcd for $C_{36}H_{45}BO_7$ $[M]^+$: 599.3289; found: 599.3288.

Synthesis of **2.5**



2.13 single isomer **2.14** **2.5**

To a solution of alcohol **2.13** (37.1 mg, 0.0618 mmol) and pyridine (19.9 μL, 0.247 mmol) in CH_2Cl_2 (1.2 mL) was added Dess-Martin Periodinane (53.8 mg, 0.127 mmol). After stirring for 3.5 h at room temperature, the reaction was quenched with $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ solution and the mixture was diluted with Et_2O. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford crude ketone **2.14**.

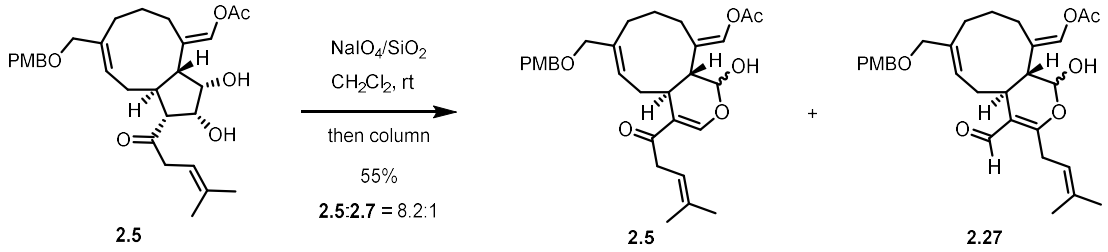
To a solution of the crude ketone **2.14** in CH_2Cl_2 (1.2 mL) were added pinacol (146 mg, 1.24 mmol) and AcOH (60 μL). After stirring at room temperature for 13 h, another portion of pinacol (292 mg, 2.48 mmol) was added and stirred for additional 6 h. Then another portion of pinacol (146 mg, 1.24 mmol) was added and stirred for further 6 h. The reaction mixture was concentrated under reduced pressure, and the crude product was purified by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 4:1 to 3:2) to afford diol **2.5** as a colorless oil (18.1 mg, 0.0353 mmol, 57% yield for two steps).

Spectral data for **2.5**

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.24 (d, *J* = 9.0 Hz, 2H), 7.03 (s, 1H), 6.87 (d, *J* = 9.0 Hz, 2H), 5.50 (t, *J* = 7.7 Hz, 1H), 5.33 (tt, *J* = 6.8, 1.5 Hz, 1H), 4.42 (td, *J* = 8.0, 5.0 Hz, 1H), 4.37 (d, *J* = 11.5 Hz, 1H), 4.34 (d, *J* = 11.5 Hz, 1H), 3.95-3.90 (m, 1H), 3.90 (d, *J* = 12.5 Hz, 1H), 3.85 (d, *J* = 12.5 Hz, 1H), 3.81 (s, 3H), 3.28 (dd, *J* = 17.5, 7.7 Hz, 1H), 3.23 (dd, *J* = 17.5, 7.7 Hz, 1H), 3.07 (d, *J* = 8.0 Hz, 1H), 2.89 (dd, *J* = 10.3, 8.3

Hz, 1H), 2.80-2.70 (m, 1H), 2.57 (d, *J* = 5.5 Hz, 1H), 2.52 (ddd, *J* = 14.0, 8.0, 6.0 Hz, 1H), 2.42 (ddd, *J* = 18.5, 8.0, 4.5 Hz, 1H), 2.25 (ddd, *J* = 13.5, 10.0, 3.0 Hz, 1H), 2.19-2.09 (m, 2H), 2.13 (s, 3H), 2.01-1.92 (m, 2H), 1.90-1.80 (m, 1H), 1.80-1.70 (m, 1H), 1.78 (s, 3H), 1.66 (s, 3H); **^{13}C{^{1}H}-NMR** (126 MHz, $CDCl_3$): δ 209.9, 167.9, 159.1, 139.9, 136.5, 135.0, 130.5, 129.3 (2C), 124.3, 121.5, 115.3, 113.7 (2C), 73.9, 73.2, 72.8, 71.4, 58.7, 55.3, 51.5, 44.2, 42.6, 28.9, 28.5, 25.7, 24.7, 23.3, 20.7, 18.2; **FT-IR (ATR)**: ν_{max} 3425, 2934, 1748, 1712, 1512, 1246, 1098 cm^{-1}; **HRMS (FD)**: *m/z* Calcd for $C_{30}H_{41}O_7$ $[M+H]^+$: 513.2847; found: 513.2847.

Synthesis of **2.7**



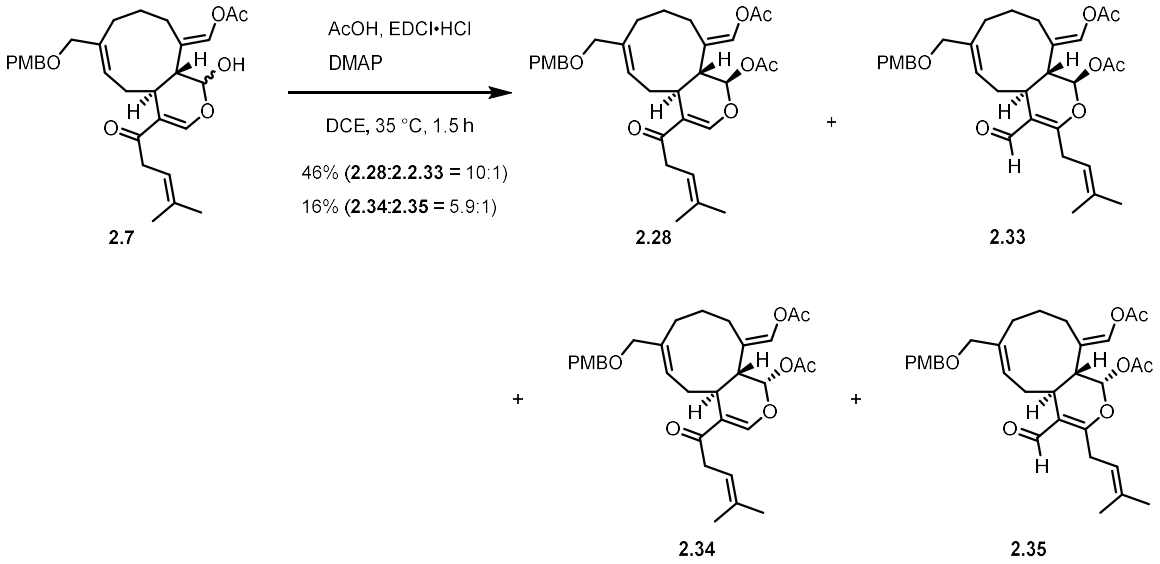
To a solution of diol **2.5** (18.1 mg, 0.0787 mmol) in CH_2Cl_2 (800 μL) was added neutral-silica-gel-supported $NaIO_4$ (77.6 mg, 0.117 mmol, 0.146 g per 1 g of silica gel).[40] After stirring at room temperature for 15 min, the mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, *n*-hexane:EtOAc = 7:3) to afford an equilibrium mixture of dihydropyran **2.5** and **2.27** (10.0 mg, 0.0530 mmol, 55%, ratio = 12.0:8.0:1.5:1 (not assigned)) as a colorless oil.

Spectral data for **2.5** and **2.27** mixture

^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.87 (s, 0.07 × 1H), 9.84 (s, 0.04 × 1H), 7.37 (s, 0.36 × 1H), 7.31 (d, *J* = 1.5 Hz, 0.53 × 1H), 7.25-7.19 (m, 2H + 0.53 × 1H + 0.04 × 1H), 7.04 (s, 0.36 × 1H), 7.02 (s, 0.07 × 1H), 6.86 (d, *J* = 9.0 Hz, 2H), 5.70-5.65 (m, 0.07 × 1H), 5.68-5.58 (m, 0.53 × 1H), 5.47-5.41 (m, 0.04 × 1H), 5.39-5.33 (m, 0.36 × 1H), 5.33-5.23 (m, 0.53 × 2H + 0.36 × 1H + 0.04 × 1H), 5.17-5.10 (m, 0.07 × 1H + 0.04 × 1H), 4.93 (dd, *J* = 8.8, 6.3 Hz, 0.31 × 1H), 4.90 (dd, *J* = 7.5, 6.5 Hz, 0.07 × 1H), 4.38-4.29 (m, 2H), 3.97-3.82 (m, 2H), 3.80 (s, 3H), 3.42-3.32 (m, 0.07 × 1H + 0.06 × 1H), 3.32-3.23 (m, 0.53 × 2H + 0.36 × 2H), 3.19-3.11 (m, 0.07 × 1H + 0.04 × 1H), 3.11-3.04 (m, 0.53 × 1H + 0.7 × 1H), 2.91-2.80 (m, 1H), 2.73-2.63 (m, 0.36 × 1H + 0.4 × 1H), 2.58-2.38 (m, 2H), 2.37-2.28 (m, 1H), 2.23-2.08 (m, 5H), 2.03-1.89 (m, 2H), 1.88-1.77 (m, 1H), 1.74 (m, 0.53 × 3H + 0.36 × 3H), 1.71 (m, 0.07 × 3H + 0.04 × 3H), 1.67 (m, 0.07 × 3H + 0.04 × 3H), 1.65 (m, 0.53 × 3H + 0.36 × 3H); **^{13}C{^{1}H}-NMR** (126 MHz, $CDCl_3$): δ 197.6, 197.4, 167.72, 167.65, 159.0, 153.5, 151.9, 137.8, 136.2, 136.1, 135.1, 134.9, 134.5, 130.6, 130.5, 129.3, 122.5, 121.7, 121.0, 120.8, 117.19,

117.6, 113.7, 99.2, 94.5, 74.0, 73.8, 71.2, 71.1, 55.3, 46.3, 38.5, 38.2, 37.8, 36.9, 30.7, 30.3, 29.9, 29.7, 27.3, 27.0, 25.8, 25.7, 24.1, 23.8, 23.4, 23.3, 20.8, 20.7, 18.1 (Only the visible peaks are described); **FT-IR (ATR)**: ν_{max} 3390, 2923, 2927, 1751, 1611, 1512, 1245, 1225 cm^{-1}; **HRMS (FD)**: *m/z* Calcd for $C_{30}H_{38}O_7$ $[M]^+$: 510.2612; found: 510.2627.

Synthesis of **2.28**



To a solution of dihydropyran **2.5** and **2.27** (9.3 mg, 0.018 mmol), EDCI•HCl (10.6 mg, 0.055 mmol) and DMAP (2.2 mg, 0.018 mmol) in dichloroethane (400 μL) was added AcOH (3.2 μL, 0.055 mmol) at room temperature. After stirring at 35 °C for 1.5 h, the reaction was quenched with saturated aqueous $NaHCO_3$ solution and the mixture was diluted with Et_2O. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were washed with 1 M hydrochloric acid dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (*n*-hexane/EtOAc = 4:1) to afford a mixture of **2.28** and **2.33** (4.7 mg, 0.0085 mmol, 46% yield, **2.28**:**2.33**=10:1) as a colorless oil and a mixture of **2.34** and **2.35** (1.6 mg, 0.0029 mmol, 16% yield, **2.34**:**2.35** = 5.9:1) as a colorless oil.

Only the spectral date of major isomers is described below.

Spectral data for **2.28**

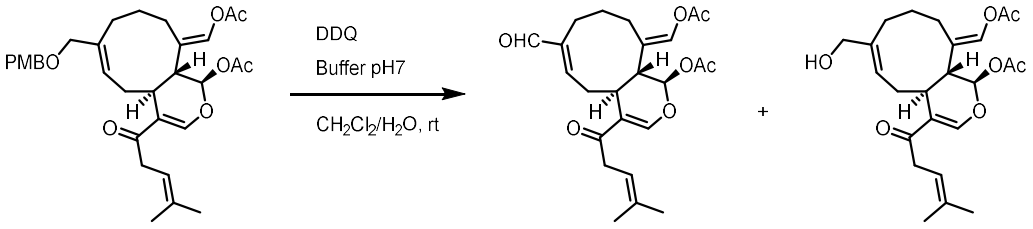
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.34 (s, 1H), 7.24 (d, *J* = 8.5 Hz, 2H), 7.04 (s, 1H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.78 (d, *J* = 10.0 Hz, 1H), 5.41-5.33 (m, 1H), 5.27 (t, *J* = 6.8 Hz, 1H), 4.36 (d, *J* = 11.5 Hz, 1H), 4.32 (d, *J* = 11.5 Hz, 1H), 3.95 (d, *J* = 12.0 Hz, 1H), 3.84 (d, *J* = 12.0 Hz, 1H), 3.80 (s, 3H), 3.25 (d, *J* = 6.5 Hz, 2H), 2.93-2.86 (m, 1H), 2.70-2.53 (m, 3H), 2.49 (dd, *J* = 11.5, 10.0 Hz, 1H), 2.25-2.16 (m, 1H), 2.16-2.06 (m,

1H), 2.15 (s, 3H), 2.09 (s, 3H), 1.98-1.87 (m, 2H), 1.83-1.73 (m, 1H), 1.73 (s, 3H), 1.65 (s, 3H); **^{13}C{^{1}H}-NMR** (126 MHz, $CDCl_3$): δ 197.1, 169.0, 167.4, 159.1, 152.9, 139.8, 135.31, 135.25, 130.5, 129.3 (2C), 125.0, 120.85, 120.76, 117.0, 113.7 (2C), 95.3, 73.7, 71.2, 55.3, 38.6, 36.4, 29.7, 29.5, 25.7, 25.6, 24.1, 23.3, 20.8, 20.7, 18.1; **FT-IR (ATR)**: ν_{max} 2949, 2937, 2920, 1757, 1656, 1615, 1512, 1216, 1178 cm^{-1}; **HRMS (ESI)**: *m/z* Calcd for $C_{32}H_{40}O_8Na$ $[M+Na]^+$: 575.2615; found: 575.2620.

Spectral data for **2.34**

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.28 (d, *J* = 2.0 Hz, 1H), 7.23 (d, *J* = 8.8 Hz, 2H), 7.15 (s, 1H), 6.87 (d, *J* = 8.8, 2H), 6.12 (d, *J* = 1.5 Hz, 1H), 5.50-5.40 (m, 1H), 5.29 (t, *J* = 7.5 Hz, 1H), 4.37 (d, *J* = 12.0 Hz, 1H), 4.33 (d, *J* = 12.0 Hz, 1H), 3.93 (d, *J* = 12.0 Hz, 1H), 3.84 (d, *J* = 12.0 Hz, 1H), 3.80 (s, 3H), 3.27 (d, *J* = 7.5 Hz, 2H), 2.90 (d, *J* = 12.0 Hz, 1H), 2.63-2.50 (m, 3H), 2.46 (dd, *J* = 13.3, 1.8 Hz, 1H), 2.26-2.18 (m, 1H), 2.15 (s, 3H), 2.15-2.08 (m, 1H), 2.08 (s, 3H), 1.93-1.74 (m, 3H), 1.74 (s, 3H), 1.65 (s, 3H); **^{13}C{^{1}H}-NMR** (126 MHz, $CDCl_3$): δ 197.7, 169.8, 167.5, 159.1, 151.6, 136.4, 135.3, 130.5, 129.3 (2C), 121.8, 119.5, 116.8, 113.8 (2C), 90.5, 73.8, 71.3, 55.3, 38.4, 31.3, 25.8, 23.7, 23.5, 20.8, 20.7, 18.1 (Only the visible peaks are described); **FT-IR (ATR)**: ν_{max} 2938, 2923, 1755, 1743, 1656, 1613, 1509,1220, 1116 cm^{-1}; **HRMS (ESI)**: *m/z* Calcd for $C_{32}H_{40}O_8Na$ $[M+Na]^+$: 575.2615; found: 575.2627.

Synthesis of Cristaxenicin A (**3**)



2.28 Cristaxenicin A (**3**) 57% **2.36** 25%

A mixture of **2.28** and **2.33** (4.7 mg, 0.0085 mmol, **2.28**:**2.33** =10:1) was dissolved in CH_2Cl_2 (400 µL) and phosphate buffer (pH 7, 400 µL). To the mixture was added DDQ (2.9 mg, 0.013 mmol) and stirred at room temperature for 1 h. Another portion of DDQ (5.8 mg, 0.026 mmol) was added and stirred for additional 30 min. Another portion of DDQ (5.8 mg, 0.026 mmol) was added and stirred for additional 30 min. The reaction mixture was diluted with Et_2O and quenched with saturated aqueous $NaHCO_3$ solution and *L*-ascorbic acid. After the layers were separated, the aqueous layer was extracted with Et_2O and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, *n*-hexane:EtOAc = 4:1 to 1:1) to afford Cristaxenicin A (**3**) (2.1 mg, 0.0049 mmol, 57%) and alcohol **2.36** (1.0 mg, 0.0023 mmol, 27%).

Spectral data for Cristaxenicin A (**3**)

^{1}H-NMR (500 MHz, CD_3OD): δ 9.27 (s, 1H), 7.68 (s, 1H), 6.97 (s, 1H), 6.65 (t, *J* = 8.5 Hz, 1H), 5.86 (d, *J* = 10.0 Hz, 1H) 5.30 (t, *J* = 7.1 Hz, 1H), 3.40 (dd, *J* = 16.5, 7.1 Hz, 1H), 3.33 (dd, *J* = 16.5, 7.1 Hz, 1H), 3.07-3.01 (m, 1H), 2.86 (ddd, *J* = 13.0, 8.5, 3.5 Hz, 1H), 2.65 (ddd, *J* = 13.0, 8.5, 3.5 Hz, 1H), 2.54 (dd, *J* = 14.3, 7.3 Hz, 1H), 2.48 (dd, *J* = 11.3, 9.8 Hz, 1H), 2.41-2.30 (m, 2H), 2.10 (s, 3H), 2.05 (s, 3H), 2.01 (dd, *J* = 14.3, 6.8 Hz, 1H), 1.87-1.79 (m, 2H), 1.75 (s, 3H), 1.68 (s, 3H); **^{13}C{^{1}H}-NMR** (126 MHz, CD_3OD): δ 199.6, 197.2, 170.3, 169.2, 156.0, 154.8, 146.3, 137.4, 136.3, 122.0, 121.6, 118.3, 95.9, 39.0, 37.3, 31.4, 30.1, 25.9, 24.2, 22.6, 20.5, 20.4, 18.1 (one peak overlapped with the solvent); **FT-IR (ATR)**: ν_{max} 2936, 1759, 1683, 1619, 1373, 1217, 1179, 1115, 1084 cm^{-1} ; **HRMS (FD)**: *m/z* Calcd for $C_{24}H_{30}O_8$ $[M]^+$: 430.1986; found: 430.1992.

Spectral data for **2.36**

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.35 (s, 1H), 7.02 (s, 1H), 5.78 (d, *J* = 9.5 Hz, 1H), 5.38 (t, *J* = 8.3 Hz, 1H), 5.28 (t, *J* = 7.0 Hz, 1H), 4.03 (d, *J* = 5.5 Hz, 1H), 3.53 (br, 1H), 3.26 (d, *J* = 7.0 Hz, 1H), 2.95-2.87 (m, 1H), 2.69-2.60 (m, 1H), 2.60-2.52 (m, 2H), 2.49 (dd, *J* = 12.0, 9.5 Hz, 1H), 2.26-2.18 (m, 1H), 2.17 (s, 3H), 2.15-2.11 (m, 1H), 2.10 (s, 3H), 2.00-1.91 (s, 2H), 1.85-1.75 (s, 1H), 1.75 (s, 3H), 1.66 (s, 3H); **^{13}C{^{1}H}-NMR** (126 MHz, $CDCl_3$): δ 197.1, 169.0, 167.5, 153.0, 135.4, 120.9, 117.0, 95.3, 67.0, 38.6, 36.4, 29.7, 29.5, 25.8, 24.3, 23.6, 20.8, 20.7, 18.1 (Only the visible peaks are described); **FT-IR (ATR)**: ν_{max} 3649, 2928, 1757, 1653, 1617, 1372, 1212, 1181, 1181, 1107 cm^{-1} ; **HRMS (FD)**: *m/z* Calcd for $C_{24}H_{30}O_7$ $[M]^+$: 432.2143; found: 432.2155.

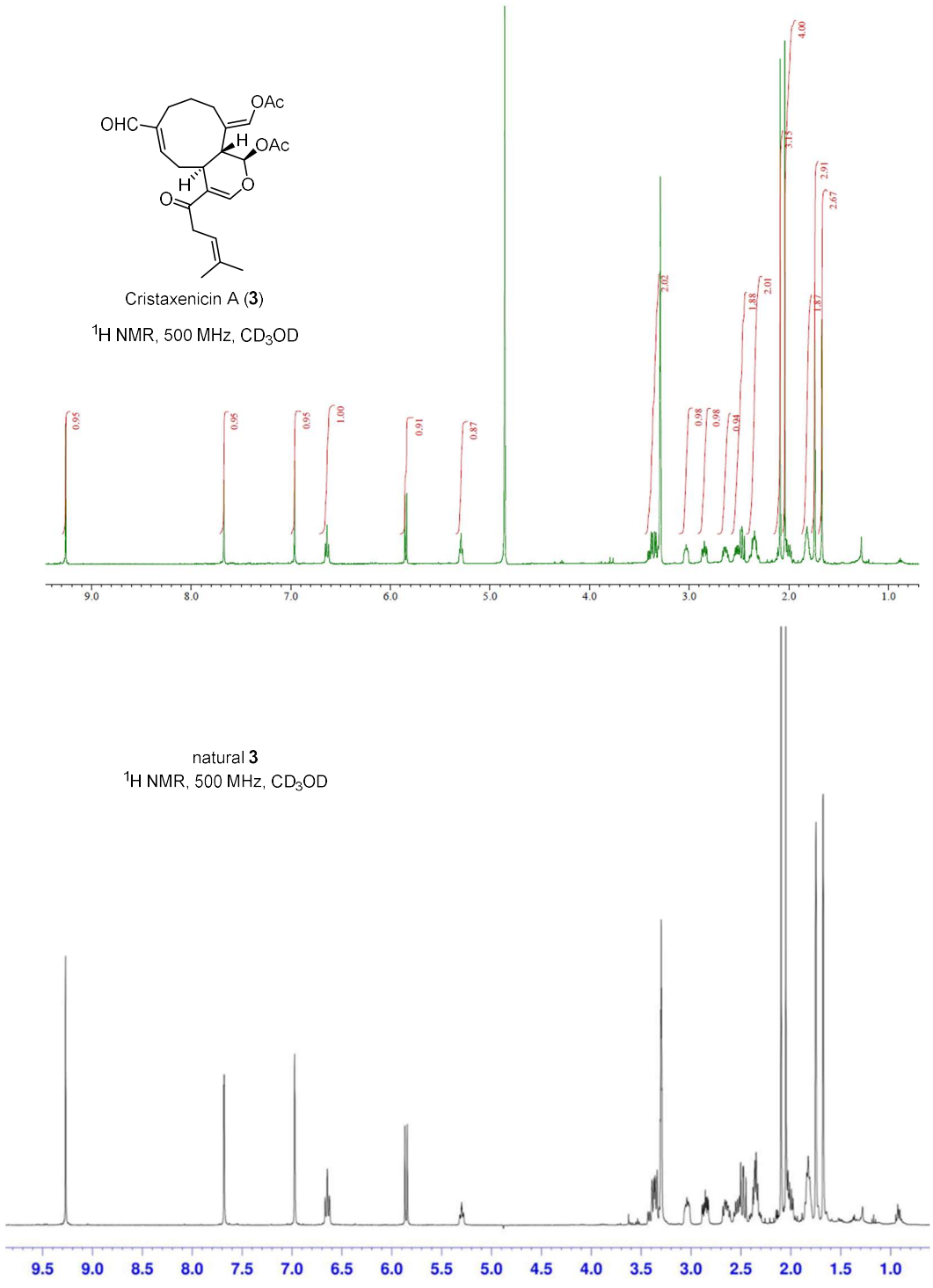
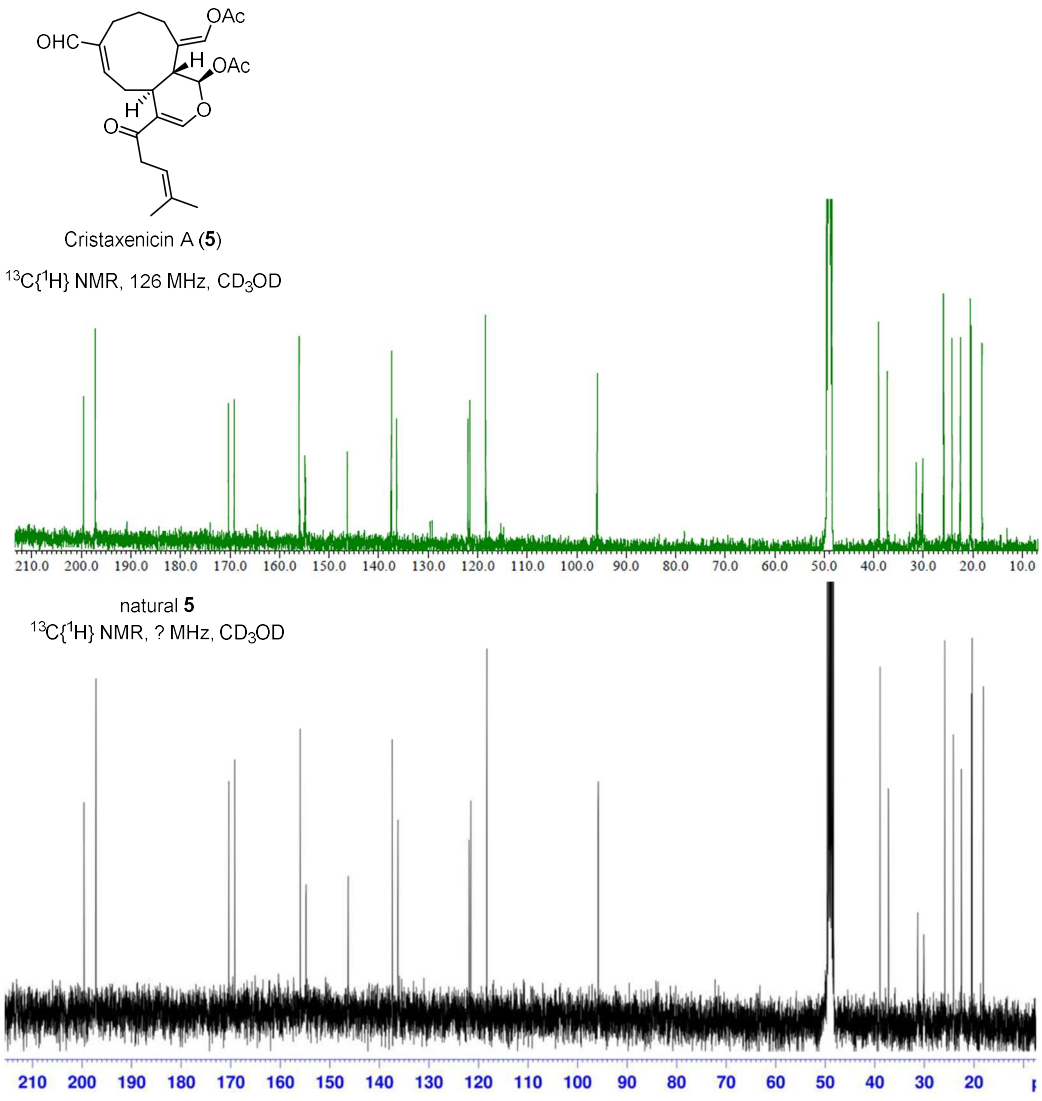


Figure S1. ^{1}H NMR spectra of synthetic and natural **3**[5]

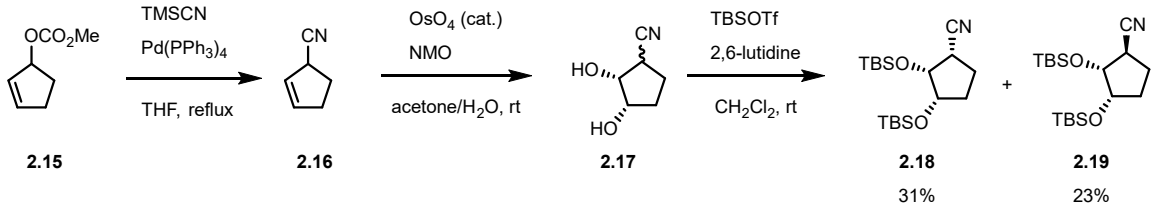


The ^{13}C NMR chart of synthetic **5** was identical to that of natural **5**.

Figure S2. ^{13}C NMR spectra of synthetic natural **3**[5]

Model compound synthesis

Synthesis of **2.18** and **2.19**



2.15 **2.16** **2.17** **2.18** 31% **2.19** 23%

A mixture of allyl carbonate **2.15**[37] (4.07 g, 28.6 mmol), TMSCN (3.94 mL, 31.5mmol), and $Pd(PPh_3)_4$ (661 mg, 0.572 mmol) in THF (114 mL) was refluxed for 11 h. After cooling down to room temperature, the mixture was passed through a pad of silica gel, and the silica gel was washed with Et_2O. The filtrate was carefully concentrated under reduced pressure to afford the crude allyl nitrile **2.16** (containing triphenylphosphine).

To a solution of the crude allyl nitrile **2.16** and NMO (6.70 g, 57.2 mol) in acetone (114 mL) and H_2O (28.6 mL) was added OsO_4 (3.64 mL, 0.572 mmol, 0.157 M *t*-BuOH solution). After stirring for 19 h at room temperature, the reaction was quenched with $Na_2S_2O_3$. The mixture was diluted with EtOAc and the layers were separated. The aqueous layer was extracted with EtOAc until the absence of the target product was confirmed on TLC. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, *n*-hexane:EtOAc = 7:3 to 3:7) to afford diol **2.17** (3.10 g, 17.8 mmol, 73% purity, containing triphenylphosphine oxide).

To a solution of the diol **2.17** in CH_2Cl_2 (89 mL) were added 2,6-lutidine (8.25 mL, 71.2 mmol) and TMSOTf (9.65 mL, 53.4 mmol). After stirring at room temperature for 30 min, the reaction was quenched with aqueous saturated $NaHCO_3$ solution. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, *n*-hexane:EtOAc = 10:1 to 3:1) to afford **2.18** (3.12 g, 8.77 mmol, 31 % yield for three steps) as a white solid, along with **2.19** (2.38 g, 6.69 mmol, 23% yield for three steps) as a white solid.

Spectral data for **2.18**

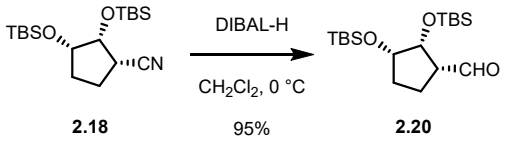
^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.03 (dd, *J* = 11.5, 3.0 Hz, 1H), 3.95 (td, *J* = 5.7, 3.0 Hz, 1H), 2.81 (ddd, *J* = 9.6, 7.4, 5.7 Hz, 1H), 2.27-2.16 (m, 1H), 2.04 (dtd, *J* = 13.5, 8.9, 4.5 Hz, 1H), 1.83-1.74 (m, 1H), 1.73-1.65

(m, 1H), 0.95 (s, 9H), 0.91(s, 9H), 0.15 (s, 3H), 0.12 (s, 3H), 0.09 (s, 3 H), 0.06 (s, 3H); **$^{13}C\{^{1}H\}$-NMR** (126 MHz, $CDCl_3$): δ 120.8, 75.4, 75.1, 32.0, 29.4, 25.9 (3C), 25.8 (3C), 25.5, 18.2 (2C), –4.4, –4.6, –4.76, –4.82; **FT-IR (ATR)**: ν_{max} 2942, 2929, 2855, 2242, 1148, 835, 771 cm^{-1}; **HRMS (FD)**: *m/z* Calcd for $C_{18}H_{37}NO_2Si_2$ $[M]^+$: 355.2357; found 355.2362. Melting point: 65 to 69 °C (*n*-hexane).

Spectral data for **2.19**

^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.07 (dd, *J* = 8.3, 3.2 Hz, 1H), 4.00 (dd = 9.8, 3.2 Hz, 1H), 2.90 (dt, *J* = 9.8, 7.5 Hz, 1H), 2.30-2.20 (m, 1H), 1.90-1.75 (m, 2H), 1.65 (dd, *J* = 13.0, 10.5 Hz, 1H), 0.92 (s, 9H), 0.88 (s, 9H), 0.17 (s, 3H). 0.10 (s, 3H), 0.06 (s, 3H), 0.05, (s, 3H); **$^{13}C\{^{1}H\}$-NMR** (126 MHz, $CDCl_3$): δ 122.8, 78.9, 74.1, 32.4, 30.0, 25.8 (3C), 25.7 (3C), 24.7, 18.03, 18.02, –4.4, –4.66, –4.69, –4.9; **FT-IR (ATR)**: ν_{max} 2954, 2928, 2857, 2240, 1150, 835, 771 cm^{-1}; **HRMS (FD)**: *m/z* Calcd for $C_{18}H_{38}NO_2Si_2$ $[M+H]^+$: 356.2436; found: 356.2442. Melting point: 54 to 57 °C (*n*-hexane).

Synthesis of **2.20**



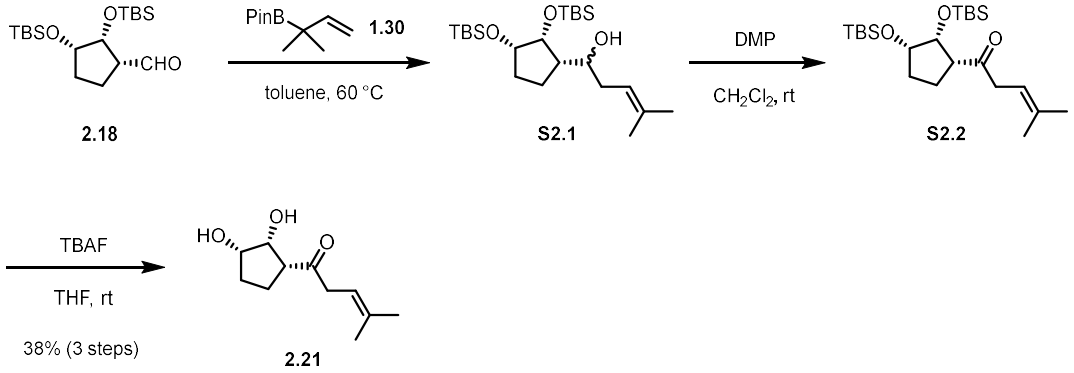
2.18 95% **2.20**

A solution of **2.18** (2.99 g, 8.41 mmol) in CH_2Cl_2 (33.6 mL) was cooled to 0 °C, and DIBAL-H (12.5 mL, 12.6 mmol, 1.01 M hexane solution) was added to the solution dropwise. After stirring at the same temperature for 5 min, the reaction was quenched with aqueous 10% aqueous *L*-Tartaric Acid solution. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, *n*-hexane:EtOAc = 19:1) to afford **2.20** (2.88 g, 8.03 mmol, 95% yield) as a colorless oil.

Spectral data for **2.20**

^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.82 (d, *J* = 2.5 Hz, 1H), 4.22 (dd, *J* = 7.2, 3.5 Hz, 1H), 3.99 (dt, *J* = 3.5, 2.5, 1H), 2.60-2.53 (m, 1H), 2.28-2.18 (m, 1H), 1.77-1.63 (m, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.093 (s, 3H), 0.085 (s, 3H), 0.06 (s, 6H); **$^{13}C\{^{1}H\}$-NMR** (126 MHz, $CDCl_3$): δ 203.6, 76.2, 75.2, 56.1, 30.2, 25.9 (6C), 20.0, 18.12, 18.09, –4.2, –4.5, –4.6, –4.9; **FT-IR (ATR)**: ν_{max} 2952, 2928, 2857, 1721, 1251, 1123, 833, 773 cm^{-1}; **HRMS (FD)**: *m/z* Calcd for $C_{18}H_{39}O_3Si_2$ $[M+H]^+$: 359.2432, found: 359.2441.

Synthesis of **2.21**



A solution of **2.18** (2.74 g, 7.91 mmol) and allylboronate **1.30**[33] (1.80 g, 9.17 mmol) in toluene (31 mL) was warmed up to 60 °C and stirred for 14 h. Another portion of allylbronate **1.30** (449 mg, 2.75 mmol) was added and the mixture was stirred for additional 12 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography (SiO_2, *n*-hexane:Et_2O = 99:1 to 90:10) to afford crude alcohol **S2.1**.

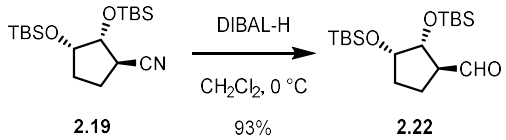
To a solution of the crude alcohol **S2.1** in CH_2Cl_2 (31 mL) was added Dess-Martin Periodinane (6.49 g, 15.3 mmol). After stirring for 30 min at room temperature, the reaction was quenched with $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ solution and the mixture was diluted with Et_2O. After the layers were separated, the aqueous layer was extracted with Et_2O, and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford crude ketone **S2.2**.

To a solution of the crude ketone **S2.2** in THF (31 mL) was added TBAF (22.9 mL, 16.3 mmol, 1.0 M THF solution). After stirring for 1 h at room temperature, the reaction was quenched with saturated aqueous NH_4Cl solution. The mixture was diluted with EtOAc and the layers were separated. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, *n*-hexane:EtOAc = 4:1 to 3:1 to 7:3 to 3:2) to afford diol **2.21** (567 mg, 2.98 mmol, 38% yield for three steps) as a yellow oil.

Spectral data for **2.21**

^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.26 (t, *J* = 6.8 Hz, 1H), 4.03 (t, *J* = 7.0 Hz, 1H), 3.95 (dt, *J* = 7.8, 7.0 Hz, 1H), 3.94 (br, 2H), 3.19 (d, *J* = 6.8 Hz, 2H), 2.87 (dt, *J* = 9.0, 7.8 Hz, 1H), 2.02-1.93 (m, 1H), 1.93-1.85 (m, 1H), 1.84-1.75 (m, 1H), 1.72 (s, 3H), 1.62-1.53 (m, 1H), 1.59 (s, 3H); **^{13}C{^{1}H}-NMR** (126 MHz, $CDCl_3$): 211.4, 135.9, 115.4, 79.8, 78.1, 54.7, 42.1, 29.6, 25.6, 22.7, 18.0; **FT-IR (ATR)**: ν_{max} 3384, 2965, 2919, 2877, 1701, 1098, 771, 730; **HRMS (FD)**: *m/z* Calcd for $C_{11}H_{18}O_3$ $[M]^+$: 198.1251, found: 198.1257.

Synthesis of **2.23**

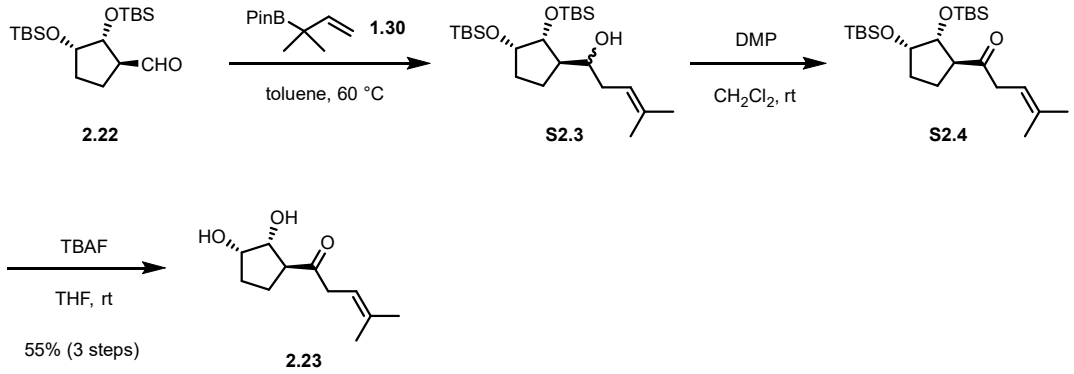


To a solution of **2.19** (2.20 g, 6.19 mmol) in CH_2Cl_2 (31 mL) was cooled to 0 °C, and was added DIBAL-H (9.20 mL, 9.29 mmol, 1.01 M hexane solution) dropwise. After stirring at the same temperature for 25 min, the reaction was quenched with aqueous 10% tartaric acid solution. After the layers were separated, the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over MgSO4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, hexane:EtOAc = 19:1) to afford **2.22** (2.07 g, 5.77 mmol, 93% yield) as a colorless oil.

Spectral data for **2.22**

^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.75 (d, *J* = 3.0 Hz, 1H), 4.10 (dd, *J* = 7.0, 3.5 Hz, 1H), 3.93 (dt, *J* = 4.0, 3.8 Hz, 1H), 2.98 (dtd, *J* = 10.8, 6.8, 3.0 Hz, 1H), 2.03-1.93 (m, 1H), 1.84-1.75 (m, 1H), 1.69 (dd, *J* = 8.0, 4.0 Hz, 1H), 1.7-1.66 (m, 1H), 0.894 (s, 9H), 0.890 (s, 9H), 0.064 (s, 6H), 0.055 (s, 3H), 0.05 (s, 3H); **^{13}C{^{1}H}-NMR** (126 MHz, $CDCl_3$): 203.4, 76.1, 75.2, 56.1, 30.2, 25.9 (3C), 25.8 (3C), 19.9, 18.10, 18.06, –4.3, –4.5, –4.6, –4.9; **FT-IR (ATR)**: ν_{max} 2953, 2929, 2857, 1725, 1143, 833, 772; **HRMS (FI)**: *m/z* Calcd for $C_{18}H_{39}O_3Si_2$ $[M+H]^+$: 359.2432, found: 359.2429.

Synthesis of **2.23**



A solution of **2.22** (1.95 g, 5.44 mmol) and allyl borane **1.30**[33] (1.60 g, 8.16 mmol) in toluene (27.2 mL) was warmed up to 60 °C and stirred for 12 h. The reaction mixture was concentrated under reduced pressure

and the residue was purified by flash column chromatography (SiO_2, hexane:Et_2O = 99:1 to 19:1 to 90:10) to afford crude alcohol **S2.3**.

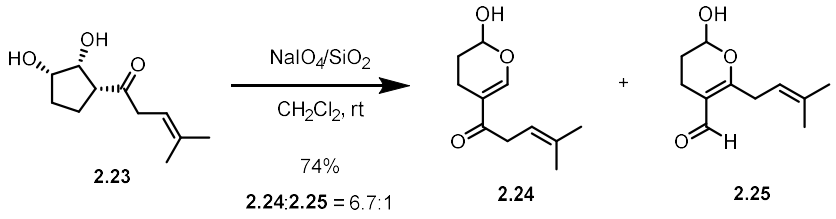
To a solution of the crude alcohol **S3** in CH_2Cl_2 (27.2 mL) was added Dess-Martin Periodinane (4.62 g, 10.9 mmol). After stirring 1 h at room temperature, the reaction was quenched with $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ solution. Et_2O was added and the layers were separated. The aqueous layer was extracted with Et_2O, and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford crude ketone **S2.4**.

To a solution of the crude ketone **S4** in THF (21.8 mL) was added TBAF (16.3 mL, 16. 3 mmol, 1.0 M THF solution).After stirring 1h at room temperature, the reaction was quenched with saturated aqueous NH_4Cl solution. EtOAc was added and the layers were separated. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, hexane:EtOAc = 4:1 to 3:1 to 7:3 to 3:2) to afford diol **2.23** (590 mg, 2.98 mmol, 55% yield for three steps) as a yellow oil.

Spectral data for **2.23**

^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.30 (t, *J* = 7.5, 1H), 4.15 (dd, *J* = 8.0, 4.5, 1H), 4.12-4.08 (m, 1H), 3.22 (d, *J* = 7.5, 2H), 3.06 (q, *J* = 8.5, 1H), 2.82 (br, 2H), 2.15-2.05 (m, 1H), 1.95-1.86 (m, 1H), 1.80-1.72 (m, 1H), 1.75 (s, 3H), 1.72-1.62 (m, 1H), 1.63 (s, 3H).; **^{13}C{^{1}H}-NMR** (126 MHz, $CDCl_3$): 211.4, 135.9, 115.4, 75.9, 73.2, 54.7, 42.5, 30.0, 25.7, 23.7, 18.0; **FT-IR** (ATR): ν_{max} 3376, 2932, 2914, 1702, 1088, 771; **HRMS (FI)**: *m/z* Calcd for $C_{11}H_{18}O_3$ $[M]^+$: 198.1251, found: 198.1258.

Synthesis of **2.24** and **2.25**



To a solution of diol **2.23** (15.6 mg, 0.0787 mmol) in CH_2Cl_2 (800 µL) was added neutral-silica-gel-supported $NaIO_4$ (173 mg, 0.117 mmol, 0.146 g per 1 g of silica gel).[42] After stirring at room temperature for 10 min, the mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, *n*-hexane:EtOAc = 9:1 to 17:3 to 7:3) to afford an equilibrium mixture of dihydropyran **2.24** and **2.25** (11.4 mg, 0.0581 mmol, 74%, **2.24**:**2.25** = 6.7:1) as a pale-yellow oil.

Spectral data for **2.24** and **2.25** mixture

^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.85 (s, 0.13 × 1H), 7.50 (s, 0.87 × 1H), 5.50-5.46 (m, 0.13 × 1H), 5.47 (dd, *J* = 4.5, 2.0 Hz, 0.87 × 1H), 5.29 (t, *J* = 7.0 Hz, 0.87 × 1H), 5.17 (t, *J* = 7.0 Hz, 0.13 × 1H), 3.60 (br, 1H), 3.27 (d, *J* = 6.0 Hz, 0.13 × 1H), 3.26 (d, *J* = 7.0 Hz, 0.87 × 2H), 3.15 (d, *J* = 6.0 Hz, 0.13 × 1H), 2.64 (t, *J* = 7.0 Hz, 0.13 × 1H), 2.52 (t, *J* = 7.0 Hz, 0.13 × 1H), 2.38-2.29 (m, 0.87 × 2H), 1.95-1.81 (m, 2H), 1.73 (s, 0.87 × 3H), 1.72 (s, 0.13 × 3H), 1.68 (s, 0.13 × 3H), 1.64 (s, 0.87 × 3H); **^{13}C{^{1}H}-NMR** (126 MHz, $CDCl_3$): δ 197.9, 189.4, 154.4, 134.7, 118.7, 117.2, 116.3, 113.2, 93.8, 93.2, 37.0, 29.7, 26.4, 26.3, 25.7, 25.6, 19.5, 18.0, 17.9, 14.9, 14.2 (one peak missing); **FT-IR (ATR)**: ν_{max} 3376, 2932, 2914, 1702, 1088, 771; **HRMS (FD)**: m/z Calcd for $C_{11}H_{16}O_3$ $[M]^+$: 196.1094, found: 196.1096.

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Acknowledgement

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

The author would also like to express the major gratitude to Associate Professor Dr. Takahiro Suzuki, Department of Chemistry, Faculty of Science, Hokkaido University and assistant professor Dr. Junya Takino, Department of Chemistry, Faculty of Science, Hokkaido University.

The author would sincerely appreciate Professor Dr. Masaya Sawamura, Department of Chemistry, Faculty of Science, Hokkaido University, Professor Dr. Takanori Suzuki, Department of Chemistry, Faculty of Science, Hokkaido University and Professor Dr. Yasuhide Inokuma, Department of Chemistry, Faculty of Science, Hokkaido University.

This research was economically supported by Hokkaido University Ambitious Doctoral Fellowship and Hokkaido University EXEX Doctoral Fellowship. The author would also like to express great thanks to them.

Furthermore, the author would like to express special thanks to Dr. Kosuke Kato for thoughtful guidance and continuous support.

The author is grateful to the laboratory members for the daily discussion and support in the research life.

Finally, the author would sincerely like to thank his family, Masatoshi, Lien. Pin and Haruka for their understanding and support.