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DISSERTATION

Synthetic Studies on Sanadaol based on New [5+2] Cycloaddition Reaction

（新規［5+2］型付加環化反応を基盤とするサナダオールの合成研究）

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Hokkaido University

2014

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Introduction

Cycloheptane synthesis via [5+2] cycloaddition reactions

The development of an efficient method for constructing substituted carbocycles continues to be a significant subject in modern organic synthesis. There are two types of approaches for synthesizing carbocyclic compounds, namely, an intramolecular cyclization reaction of an acyclic compound and a cycloaddition reaction of two components as depicted in Figure 1.

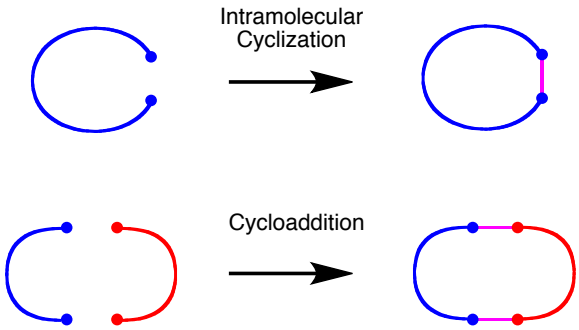
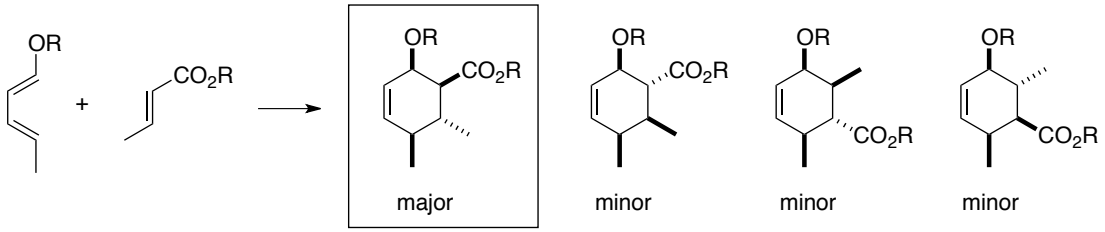


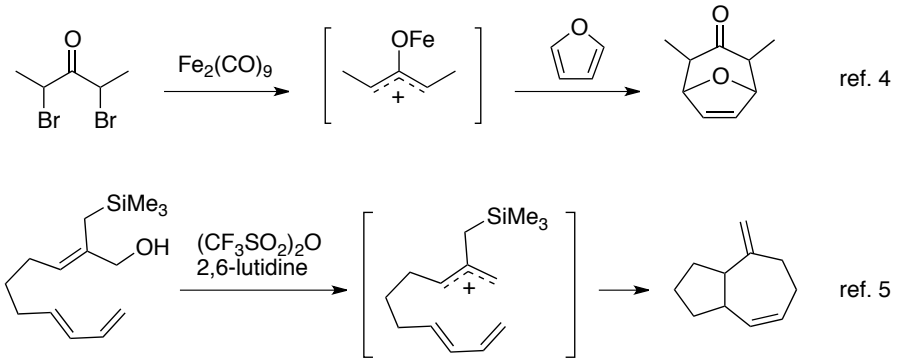
Figure 1

While a cycloaddition approach that produces two C-C bonds in one-stage is advantageous from the viewpoint of efficiency, the utility of this type of reaction is critically dependent on regio-selectivity as well as diastereoselectivity. In this regard, the Diels-Alder reaction[1] is recognized as one of the most important and powerful methods for constructing six-membered carbocycles. For example, a diene having an electron-donating group usually undergoes the Diels-Alder reaction with a dienophile possessing an electron-withdrawing group in a regio- and diastereoselective manner (Scheme 1).



Scheme 1

On the other hand, less attention has been given to the cycloaddition approach in cycloheptane synthesis.[2] It is noteworthy that the [4+3] cycloaddition reactions of a 1,3-diene and a 2-oxyallyl cation or its analogue have actually found widespread use in organic synthesis[3] (Scheme 2).

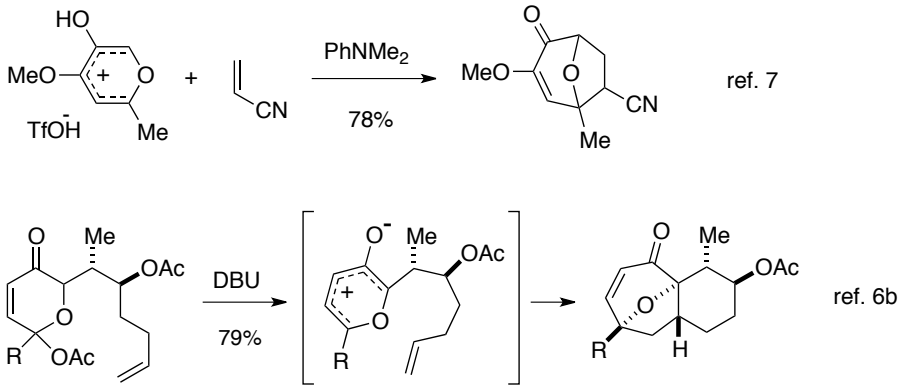


Scheme 2

In contrast, relatively small number of examples has been reported on [5+2]-type reactions,[6] because generation of a pentadienyl cation species, which readily undergoes electrocyclization, is much more difficult than allyl cations (Scheme 3).

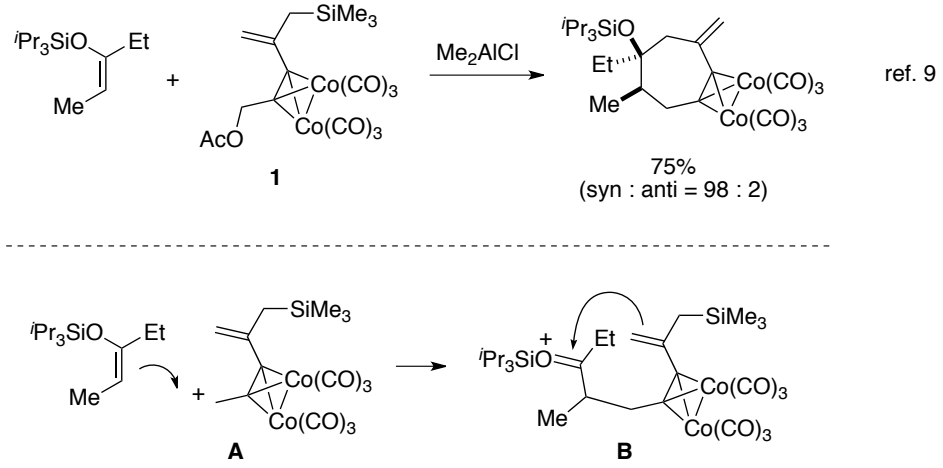
Scheme 3

One of the most ideal solutions for the problem is the use of oxidopyrylium species as a five-carbon unit, because the oxygen bridge of oxidopyrylium prohibits the electrocyclization pathway (Scheme 4).



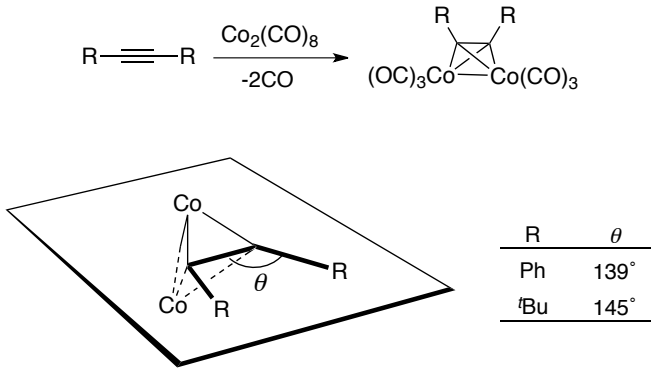
Scheme 4

In 2000, a formal [5+2] cycloaddition reaction using a dicobalt acetylene complex[8] was reported by Tanino's group (Scheme 5).[9] Thus, under the influence of a Lewis acid, cobalt complex **1** possessing a leaving group and an allylsilane moiety reacted with enol triisopropylsilyl ethers to afford cycloheptane derivatives in high regio- and stereoselectivity. The reaction proceeds through intermolecular addition of cationic species **A** with an enol silyl ether followed by the intramolecular cyclization of silyloxonium ion **B**.



Scheme 5

The successful results come from the unique property of dicobalt acetylene complexes, namely, the stabilizing effect of an α-cation[10] as well as the rigid conformation like a cis olefin (Figure 2). The large bond angles (ca. 140 °) of the cobalt complex prohibit the intramolecular cyclization of cationic species **A** in Scheme 6, leading to selective formation of a seven-membered ring[11] through the stepwise addition pathway.



R	θ
Ph	139°
tBu	145°

Figure 2

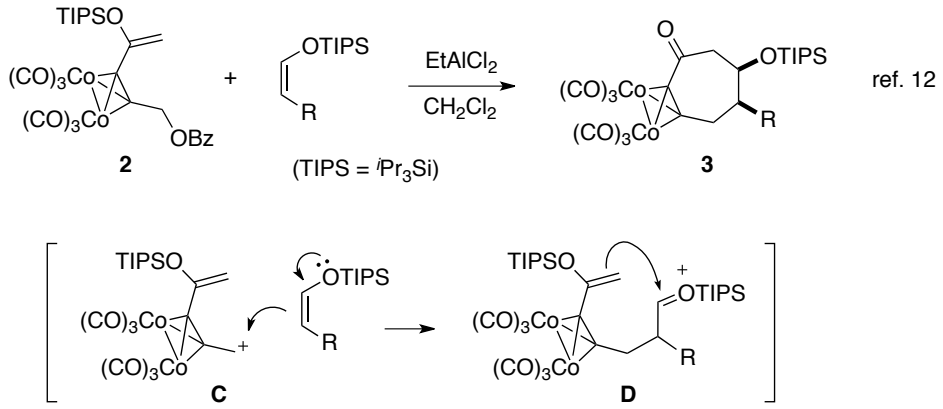
Since there are a number of natural compounds containing a cycloheptane ring with various kinds of substituents, the present [5+2] cycloaddition reaction shows promise as a key step in total synthesis of these compounds. In this thesis, the author will describe the development of a new [5+2] cycloaddition reaction based on the chemistry of acetylene dicobalt complex and the application of the reaction in studies toward the total synthesis of Sanadaol.

Chapter 1

Synthesis of 1-acetyl-2-silyoxycycloheptane derivatives via highly stereoselective formal [5+2] cycloaddition reaction

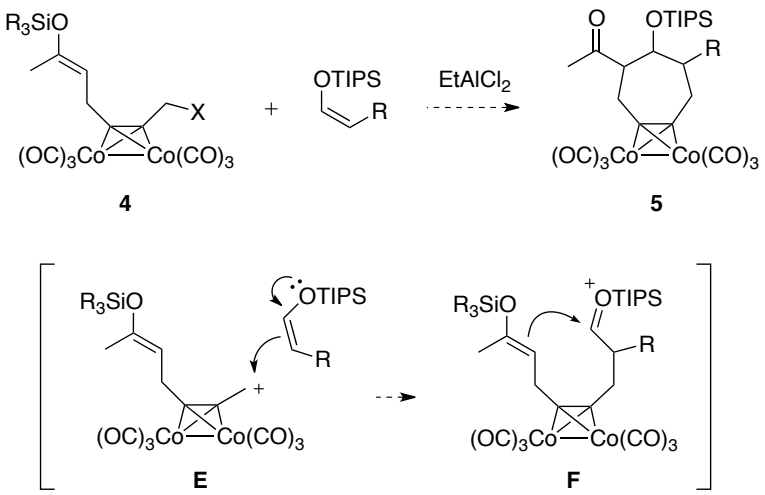
Cycloheptanone synthesis via a formal [5+2] cycloaddition reaction

As was mentioned in the introduction part, the use of acetylene dicobalt complex **1** as a five-carbon unit in the formal [5+2] cycloaddition reaction with enol silyl ethers opened the door to access cycloheptane derivatives in a straightforward manner. This idea was also applied to the synthesis of cycloheptanones by using another five-carbon unit **2** possessing an enol silyl ether moiety instead of the allylsilane moiety (Scheme 6).[12]



Scheme 6

The reaction proceeds through intermolecular addition of cationic species **C** with an enol silyl ether followed by the intramolecular cyclization of silyloxonium ion **D** to give cycloheptanone derivative **3** in a stereoselective fashion. These results led the author to develop a new synthetic method for polysubstituted cycloheptane derivatives through another type of formal [5+2] cycloaddition reaction (Scheme 7).

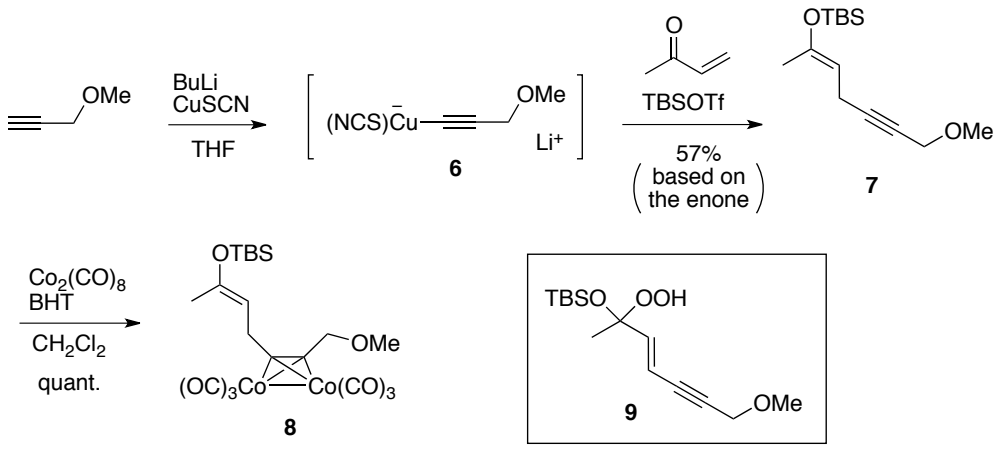


Scheme 7

Thus, the use of dicobalt acetylene complex **4** as a five-carbon unit would afford cycloheptane derivative **5** through the stepwise addition reaction involving cationic intermediates **E** and **F**. It should be noted that cycloadduct **5** possesses the ketone moiety as one of the three substituents on the seven-membered ring, while the ketone moiety of the cycloadduct **3** in Scheme 6 is incorporated in the carbocycle. Therefore, the utility of the new [5+2]-type reaction depends on the stereoselectivity at the three contiguous stereogenic centers in cycloadduct **5**. The author describe the highly stereoselective formal cycloaddition reaction of five-carbon unit **4** and its analogue with enol silyl ethers.

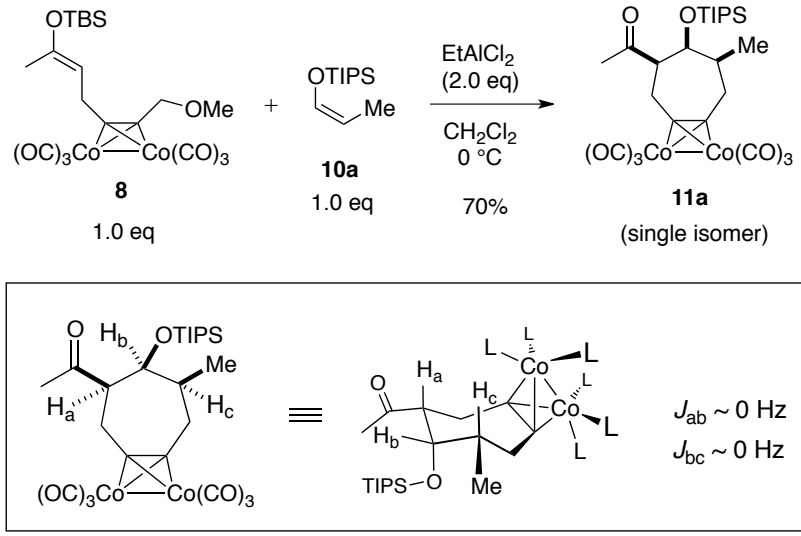
Results and Discussion

The new five-carbon unit was synthesized in only two steps as shown in Scheme 8. Methyl vinyl ketone was subjected to the conjugate addition reaction with organocopper reagent **6**,[13] which was prepared by successive treatment of methyl propargyl ether with butyllithium and copper(I) thiocyanate, in the presence of *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf). The resulting enol silyl ether **7** was then reacted with $Co_2(CO)_8$ to afford the desired dicobalt acetylene complex **8**. Although enol silyl ether **7** was found to readily undergo autooxidation of the allylic methylene group to give peroxide **9**, addition of a small amount of 2,6-di-*tert*-butyl-4-methylphenol (BHT) effectively reduced the side reaction.



Scheme 8

The reaction of dicobalt acetylene complex **8** and enol silyl ether **10a** was examined under the influence of ethylaluminum dichloride (Scheme 9). Gratifyingly, the formal [5+2] cycloaddition reaction proceeded at 0 °C in good yield, and the desired product **11a** was obtained as a single diastereomer. The stereochemistry of **11a** was determined by 1H NMR spectra. Thus, the very small vicinal coupling constants between the α-protons of the three substituents indicated that these substituents are all cis to each other.



Scheme 9

Next, enol silyl ether **10c** possessing a terminal chloro group was examined, but the adduct **11c** was obtained in only 35% yield (Figure 3). After several trials, an alternative procedure was established for obtaining the desired product in high yield. In the advanced procedure, the mixture of enol silyl ether **10c** and cobalt complex **8** in dichloromethane was added to a cooled solution of $EtAlCl_2$, giving rise to adduct **11c** in 70% yield.

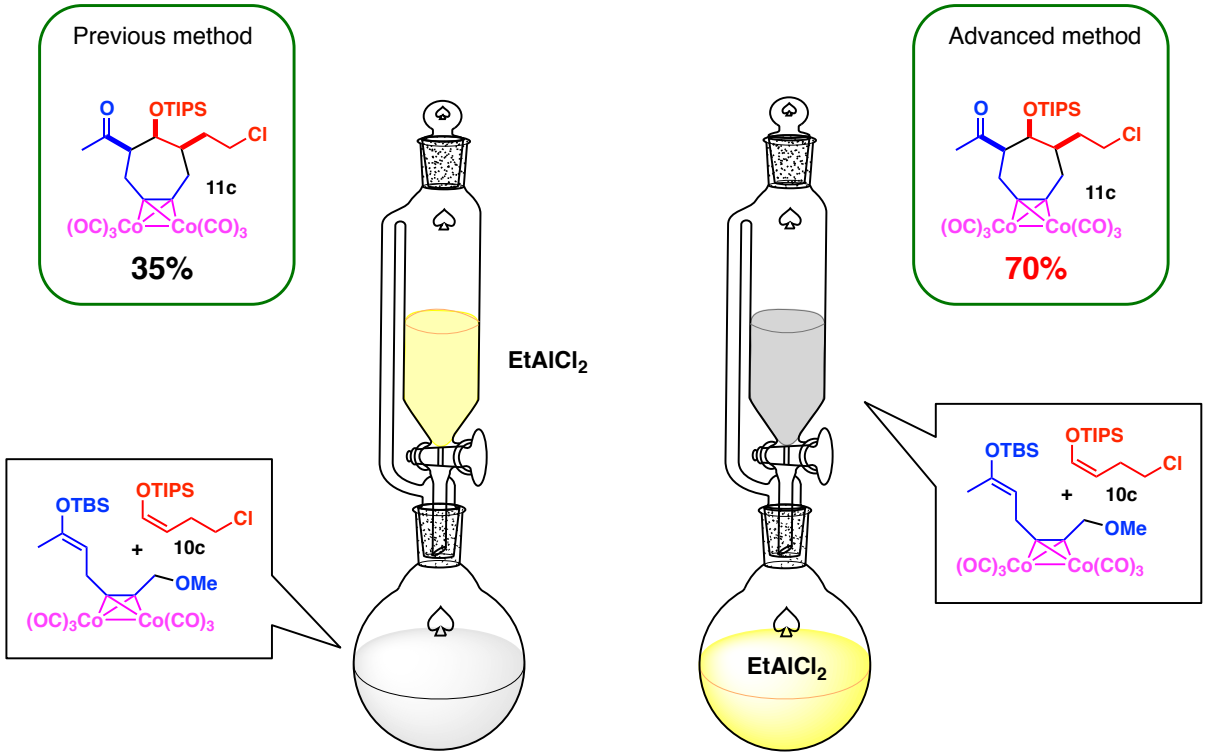
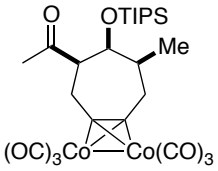
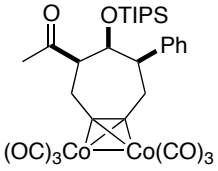
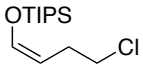
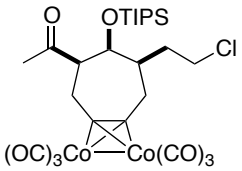
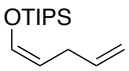
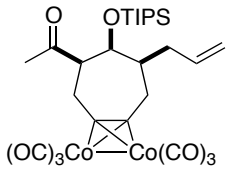
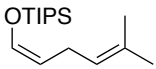
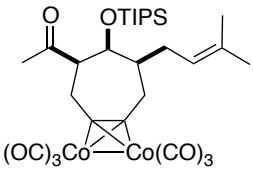
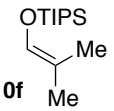
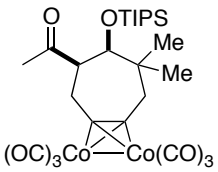


Figure 3

While the origin of the increased yield is not clear, the advanced method was applied to the [5+2] cycloaddition reactions of various enol silyl ethers (Table 1). The reaction of **8** with enol silyl ether **10f** derived from isobutyraldehyde also occurred smoothly to afford a cycloheptane derivative **11f** having a quaternary carbon atom as a single diastereomer (entry 6).

Table 1

Stereoselective synthesis of cycloheptane derivatives by formal [5+2] cycloaddition reactions.[a,b]

Entry	Enol silyl ether	Product	yield (%)
1	**10a**		**11a** 69
2	**10b**		**11b** 77
3	 **10c**		**11c** 70
4	 **10d**		**11d** 76
5	 **10e**		**11e** 86
6	 **10f**		**11f** 78

[a] The general procedure is described in ref. 9. [b] Minor diastereomers were not detected by proton NMR spectra.

The stereochemical outcome of the cycloaddition reaction can be rationalized by the transition state models which correspond to the intramolecular cyclization step of the silyloxonium ion intermediate **F** in Scheme 7. Taking into account the rigidity as well as the bulkiness of the cobalt complex moiety,[14] transition state models in which the R group occupies an equatorial position can be depicted (Figure 4). In these models, **F-2** would suffer from the serious steric repulsion between the two bulky silyl groups, while **F-3** having the enol silyl ether at the pseudo axial position would also be disfavored. Therefore, the diastereomer with all-cis substituents is formed through transition state **F-1**.

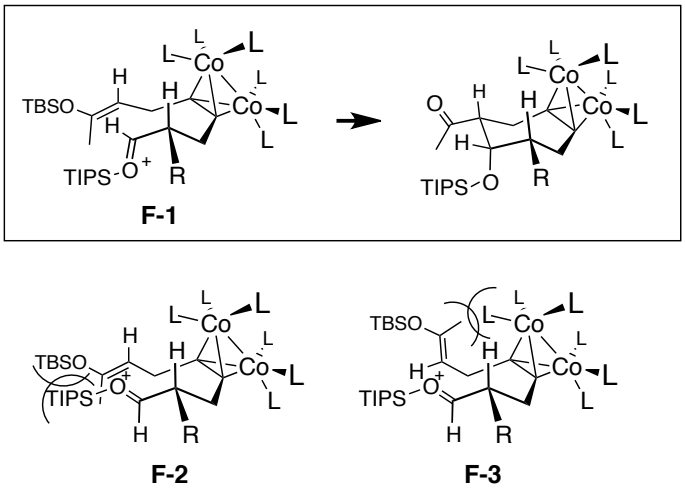
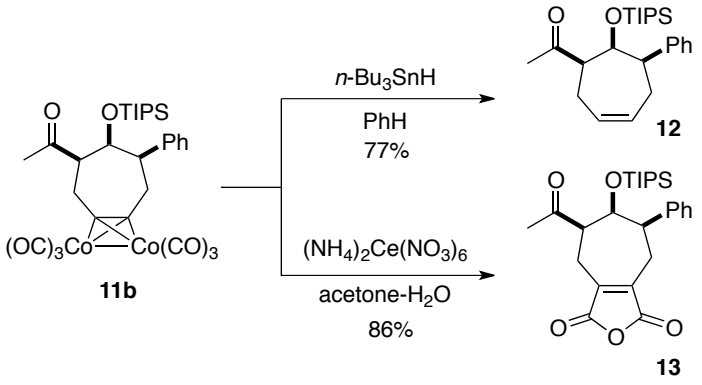


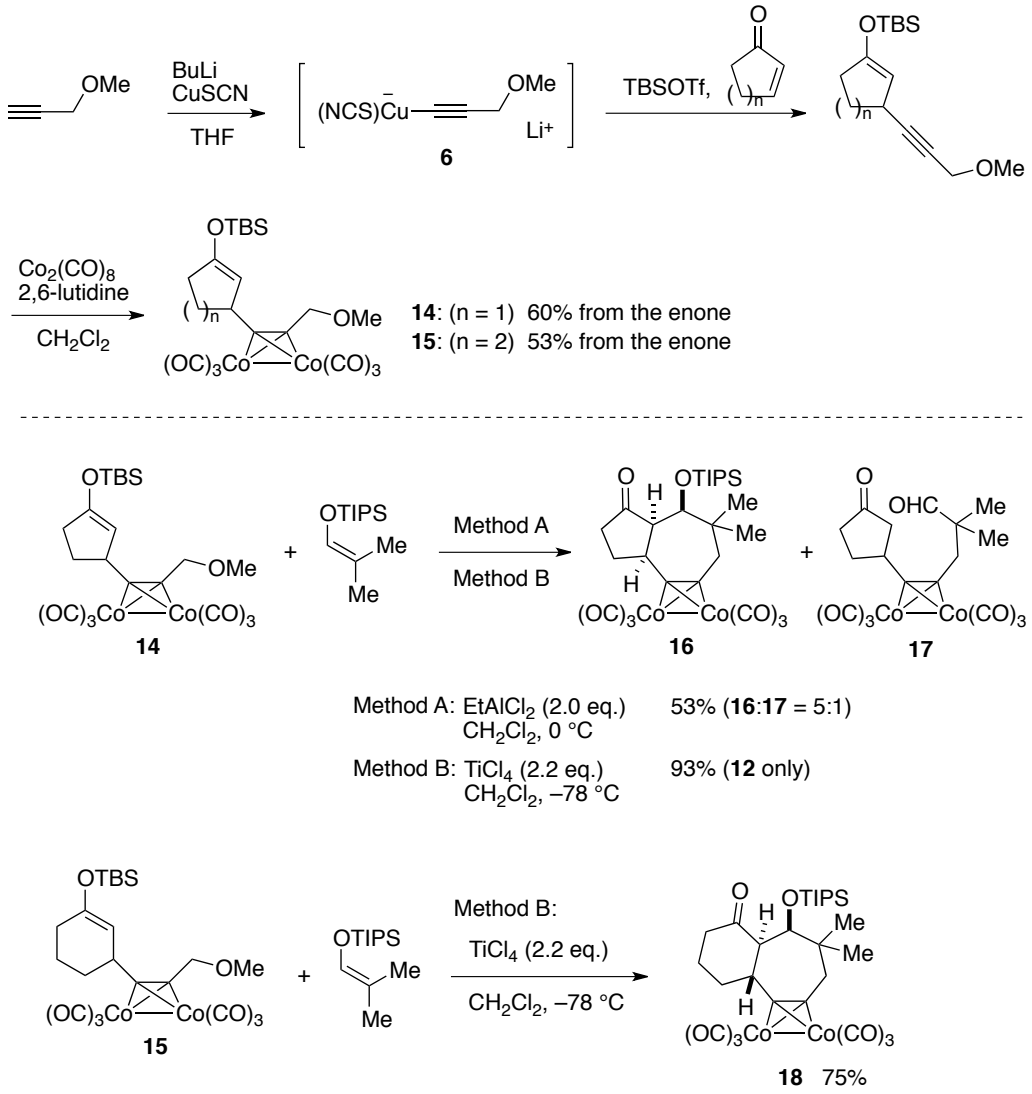
Figure 4

As was reported previously, the cyclic dicobalt acetylene complexes can be transformed into useful compounds in one step (Scheme 10). For example, cycloaddition product **11b** underwent reductive decomplexation[15] by refluxing with tributyltin hydride in benzene to afford the corresponding cycloheptene **12**. On the other hand, oxidation of **11b** with cerium(IV) ammonium nitrate resulted in formation of maleic anhydride **13** in high yield.[9,12,16]



Scheme 10

Next, the formal [5+2] cycloaddition reaction was applied to the synthesis of bicyclic compounds. New five-carbon units **14** and **15** having a cyclic enol silyl ether moiety were prepared from the corresponding 2-cycloalken-1-ones through a similar method for the synthesis of **8** (Scheme 11).[13] In these cases, the use of 2,6-lutidine instead of BHT was found to give the better results, because the enol silyl ethers tend to undergo hydrolysis rather than autooxidation.



Scheme 11

The enol silyl ether derived from isobutyraldehyde was chosen as the coupling partner with cobalt complex **14**, so as to avoid the formation of the product as a mixture of four diastereomers. The reaction under the previous conditions using ethylaluminum dichloride at 0 °C (Method A) gave the desired bicyclic ketone **16** in moderate yield along with by-product **17** which arose from desilylation of the silyloxonium ion intermediate.

It was found, however, that the reaction under the influence of titanium(IV) chloride proceeds even at –78 °C (Method B), giving rise to the desired product **16** in 93% yield as a single diastereomer. The reaction of six-membered substrate **15** by adopting Method B resulted in formation of bicyclic ketone **18** in good yield. Judging from the coupling constants in the 1H NMR spectra, compound **16** possessed a cis-fused 5-7 skeleton, and the configuration of the 6-7 bicyclic system of **18** was suggested to be trans. Although the origin of the different stereochemical outcome depending on the ring size of the substrates is not clear, the present cycloaddition reaction shows promise for constructing highly substituted bicyclic systems in short steps.

Conclusion

In conclusion, the author has developed an efficient method for the synthesis of substituted cycloheptane derivatives on the basis of a formal [5+2] cycloaddition reaction. The five-carbon unit **8**, a dicobalt acetylene complex possessing a leaving group and an enol silyl ether moiety, was prepared from commercially available compounds in only two steps. Under the influence of a Lewis acid, the cobalt complex reacted with enol triisopropylsilyl ethers to afford cycloheptane derivatives having three substituents as a single diastereomer. The formal [5+2] cycloaddition reaction was applied to constructing bicyclic skeleton, and applications in total synthesis of polycyclic natural compounds are under investigation.

Experimental Section

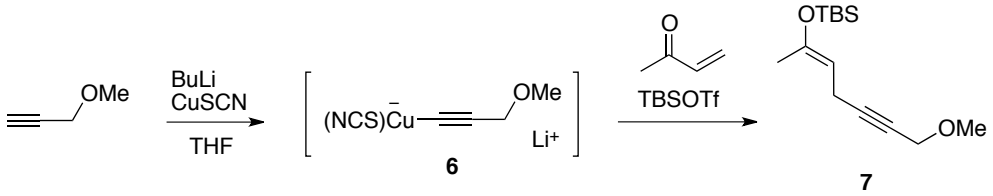
General Methods

Air– and moisture-sensitive compounds were performed using flame-dried glassware under a positive pressure of argon and introduced via syringe or Teflon cannula through a rubber septum. THF and diethylether was distilled from sodium benzophenone ketyl. Anhydrous CH_2Cl_2 was purchased from Kanto Chemical Co. Inc. Triethylamine and diisopropylamine were distilled from CaH_2 under argon and stirred in the presence of NaOH.

All reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25-nm Merck Kieselgel 60 F_{254} plates. Components were visualized by illumination with ultraviolet light (254 nm) and by staining with one of the following reagents: 6% ethanolic *p*-anisaldehyde (with 6% conc. sulfuric acid and 1% acetic acid), 8% ethanolic phosphomolybdoic acid, or ceric ammonium molybdate in 10% sulfuric acid. E. Merck silica gel (60 particle size 0.040-0.063 mm) was used for flush column chromatography.

^{1}H-NMR spectra were measured at 500MHz using a JEOL ECA-500 instrument. Chemical shifts are reported in parts per million (ppm) from internal tetramethylsilane, and signal are expressed as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m). Coupling constants are reported in Hz.

1-Methoxy-6-(*tert*-butyldimethylsilyloxy)-hept-5-en-2-yne 7



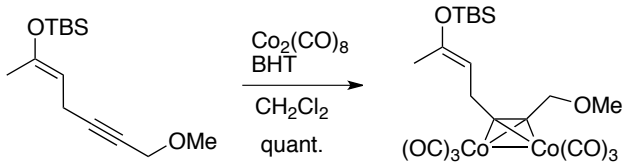
To a solution of methyl propargyl ether (2.55 mL, 30.0 mmol) in THF (80.0 mL) was added ^{n}BuLi (11.0 mL, 30 mmol, 2.77 M solution in hexane) at –78 °C. After stirring for 10 min at room temperature, the solution of lithium acetylide was added *via* cannula to a suspension of CuSCN (3.65 g, 30.0 mmol) at –78 °C in ether (80.0 mL). After stirring for 2 h, the resulting heterogeneous mixture was added *via* cannula to *tert*-butyldimethylsilyl triflate (5.00 mL, 22.0 mmol) and methyl vinyl ketone (1.63 mL, 20.0 mmol) in ether (80.0 mL). The reaction mixture was stirred at –78 °C for 2 h, quenched with 28% aqueous NH_3 and extracted three times with ether, washed with brine and dried over $MgSO_4$. The combined organic layers were concentrated *in vacuo*. The crude product was purified by silica gel column chromatography to give enol silyl ether **7** (2.92 g, 11.5 mmol, 57%) as a pale yellow oil.

^{1}H NMR (500MHz, $CDCl_3$) *E* isomer: δ 4.38 (t, *J* = 6.9 Hz, 1H), 3.98 (s, 2H), 3.26 (s, 3H), 2.86 (dd, *J*

= 6.9, 1.1 Hz, 2H), 1.68 (d, *J* = 1.1 Hz, 3H), 0.95 (s, 9H), 0.15 (s, 6H)

Z isomer: δ 4.58 (t, *J* = 7.5 Hz, 1H), 4.07 (s, 2H), 3.30 (s, 3H), 2.77 (d, *J* = 7.5 Hz, 2H), 1.62 (s, 3H), 0.92 (s, 9H), 0.13 (s, 6H).

[1-Methoxy-6-(*tert*-butyldimethylsiloxy)-hept-5-en-2-yne] dicobalthexacarbonyl 8



7 **8**

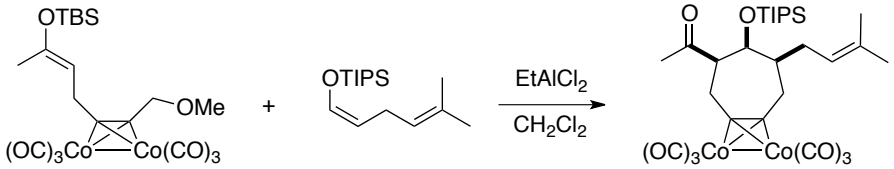
To a solution of $Co_2(CO)_8$ (4.12 g, 12.1 mmol) and 2,6-*di*-*t*-butyl-*p*-cresol (0.130 g, 0.574 mmol) in CH_2Cl_2 (36.5 mL) was added a solution of **7** (2.92 g, 11.5 mmol) in CH_2Cl_2 (35.0 mL) at room temperature. After being stirred for 1 h, the mixture was filtered through a pad of celite. Concentration under reduced pressure followed by purification by column chromatography afforded cobalt complex **8** (6.20 g, 11.5 mmol, 100%) as a dark brown oil.

^{1}H NMR (500MHz, $CDCl_3$) *E* isomer: δ 4.59 (s, 2H), 4.55 (t, *J* = 6.9 Hz, 1H), 3.56 (d, *J* = 6.9 Hz, 2H), 3.50 (s, 3H), 1.80 (s, 3H), 0.91 (s, 9H), 0.16 (s, 6H).

Z isomer: δ 4.65 (s, 2H), 4.80 (t, *J* = 6.3 Hz, 1H), 4.59 (s, 2H), 3.50 (s, 3H), 3.49 (d, *J* = 6.3 Hz, 2H), 1.80 (s, 3H), 0.91 (s, 9H), 0.16 (s, 6H).

Typical Procedure for [5+2] cycloaddition reactions.

[(1R*, 2S*, 3S*)-1-Acetyl-3-(3-methyl-2-butenyl)-2-triisopropyolsilyloxycyclohept-5-yne] dicobalthexacarbonyl



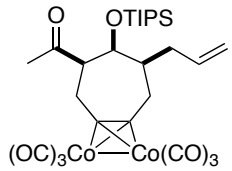
8 **10e** **11e**

To a solution of $EtAlCl_2$ (1.04 M solution of hexane,0.960 mL, 1.0 mmol) in CH_2Cl_2 (3.00 mL) was added a solution of enol silyl ether **10e** (184 mg, 0.500 mmol) and dicobalt complex **8** (270 mg, 0.500 mmol) in CH_2Cl_2 (2.00 mL) *via* cannula at 0 °C. After stirring at 0 °C for 9 minutes, the reaction mixture was quenched with a saturated aqueous NaK tartrate (aqueous Roschell's salt) and stirred at room temperature vigorously for 1 h under argon atmosphere. Then the aqueous layer was extracted three times with ether and the organic layer was washed with brine and dried over $MgSO_4$. The combined organic layers were concentrated *in vacuo*. The crude product was purified by silica gel

column chromatography to give [5+2] cycloaddition product **11e** (292 mg, 0.428 mmol, 85.7%) as a dark brown oil.

^{1}H NMR (500MHz, $CDCl_3$) δ 5.10 (t, *J* = 7.1 Hz, 1H), 3.72 (s, 1H), 3.41 (dd, *J* = 16.1 Hz, 13.2 Hz, 1H), 3.15 (d, *J* = 16.1 Hz, 1H), 2.94 (dd, *J* = 15.5 Hz, 12.1 Hz, 1H), 2.90 (dd, *J* = 15.5 Hz, 13.2 Hz, 1H), 2.47 (d, *J* = 12.1 Hz, 1H), 2.28 (m, 2H), 2.25 (s, 3H), 2.19 (m, 1H), 1.73 (s, 3H), 1.61 (s, 3H), 1.05 (m, 21 H)

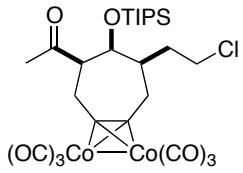
[(1R*, 2S*, 3S*)-1-Acetyl-3-(2-propenyl)-2-triisopropyolsilyloxycyclohept-5-yne] dicobalt-hexacarbonyl



11d

^{1}H NMR (500MHz, $CDCl_3$) δ 5.82 (dddd, *J* = 17.8, 12.1, 6.8, 4.6 Hz, 1H), 5.13 (d, *J* = 12.1 Hz, 1H), 5.10 (d, *J* = 17.8 Hz, 1H), 4.75 (s, 1H), 3.43 (dd, *J* = 16.1, 12.6 Hz, 1H), 3.18 (dd, *J* = 16.1, 2.3 Hz, 1H), 3.01 (dd, *J* = 16.1, 12.0 Hz, 1H), 2.94 (dd, *J* = 16.1, 3.5 Hz, 1H), 2.50 (dd, *J* = 12.6, 2.9 Hz, 1H), 2.38 (dd, *J* = 12.6, 4.6 Hz, 1H), 2.29 (dd, *J* = 7.5, 6.9 Hz, 1H), 2.25 (s, 3H), 1.74 (ddd, *J* = 6.3, 3.5, 2.9 Hz, 1H), 1.09 (m, 21H).

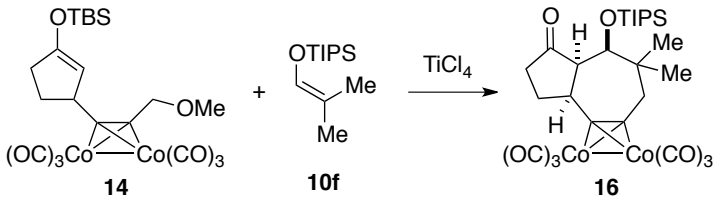
[(1R*, 2S*, 3S*)-1-Acetyl-3-(2-chloroethyl)-2-triisopropyolsilyloxycyclohept-5-yne] dicobalt-hexacarbonyl



11c

^{1}H NMR (500MHz, $CDCl_3$) δ 4.72 (s, 1H), 3.67 (ddd, *J* = 10.9, 6.3, 5.8 Hz, 1H), 3.61 (ddd, *J* = 12.1, 9.8, 2.9 Hz, 1H), 3.38 (dd, *J* = 16.0, 12.6 Hz, 1H), 3.19 (dd, *J* = 15.5, 2.3 Hz, 1H), 3.02 (dd, *J* = 15.5, 11.5 Hz, 1H), 2.90 (dd, *J* = 18.4, 2.9 Hz, 1H), 2.48 (dd, *J* = 12.1, 2.9 Hz, 1H), 2.23 (s, 3H), 2.04 – 1.94 (m, 3H), 1.05 (m, 21H).

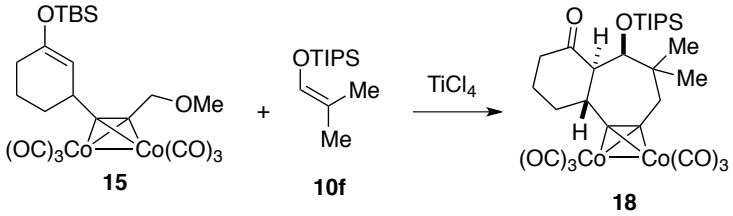
[(3S*, 7R*)-1,1-dimethyl-4-oxo-2-triisopropyolsilylbicyclo[5.3.0]dec-8-yne]-dicobalthexacarbonyl



To a solution of $TiCl_4$ (41.7 μL, 0.220 mmol) in CH_2Cl_2 (0.300 mL) was added a solution of enol silyl ether **10f** (22.8 mg, 0.100 mmol) and cobalt complex **14** (60.8 mg, 0.110 mmol) in CH_2Cl_2 (0.200 mL) *via* cannula at –78 °C. After stirring at –78 °C for 30 minutes, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ and separated. Then the aqueous layer was extracted three times with ether and the organic layer was washed with brine and dried over $MgSO_4$. The combined organic layers were concentrated *in vacuo*. The crude product was purified by silica gel column chromatography to give [5+2] cycloaddition product **16** (59.7 mg, 0.0934 mmol, 93.4%).

^{1}H NMR (500MHz, $CDCl_3$) δ 4.51 (d, *J* = 4.0 Hz, 1H), 4.19 (dd, *J* = 8.6, 6.9 Hz, 1H), 3.38 (d, *J* = 17.2 Hz, 1H), 2.86 (dd, *J* = 8.6, 4.0 Hz, 1H), 2.71 (d, *J* = 17.2 Hz, 1H), 2,47 (ddd, *J* = 16.6, 9.8 Hz, 1H), 2.35 (ddd, *J* = 16.6, 10.3 Hz, 2H), 2.28 (dd, *J* = 10.3, 9.8 Hz, 1H), 1.11 (m, 21H), 0.87 (s, 3H), 0.85 (s, 3H).

[(3S*, 8S*)-1,1-dimethyl-4-oxo-2-triisopropyolsilylbicyclo[5.5.0]undec-9-yne]dicobalt-hexacarbonyl



To a solution of $TiCl_4$ (41.7 μl, 0.220 mmol) in CH_2Cl_2 (0.300 mL) was added a solution of enol silyl ether **10f** (22.8 mg, 0.100 mmol) and dicobalt complex **15** (62.3 mg, 0.110 mmol) in CH_2Cl_2 (0.200 mL) *via* cannula at –78 °C. After stirring at –78 °C for 30 minutes, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ and separated. Then the aqueous layer was extracted three times with ether and the organic layer was washed with brine and dried over $MgSO_4$. The combined organic layers were concentrated *in vacuo*. The crude product was purified by silica gel column chromatography to give [5+2] cycloaddition product **18** (45.6mg, 0.0752 mmol, 75.2%).

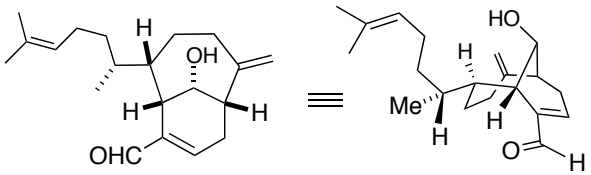
^{1}H NMR (500MHz, $CDCl_3$) δ 4.82 (s, 1H), 3.54 (dt, *J* = 12.0, 4.1 Hz, 1H), 3.25 (d, *J* = 16.6 Hz, 1H), 2.71 (d, *J* = 16.6 Hz, 1H), 2.56 (d, *J* = 15.5 Hz, 1H), 2.48 (d, *J* = 12.0 Hz, 1H), 2.29 (d, *J* = 11,5 Hz, 1H), 2.24 (dd, *J* = 15.5, 6.3 Hz, 1H), 2.09 (ddd, *J* = 11.5 , 6.3, 2.9 Hz, 1H), 1.86 (ddt, *J* = 25.8, 13.8, 2.9 Hz, 1H), 1.72 (ddd, *J* = 25.8, 13.8, 4.1 Hz, 1H), 1.08 (m, 21H), 0.91 (s, 3H), 0.88 (s, 3H).

Chapter 2

Synthetic Studies on Sanadaol Based on Stereoselective Formal [5+2] Cycloaddition Reaction

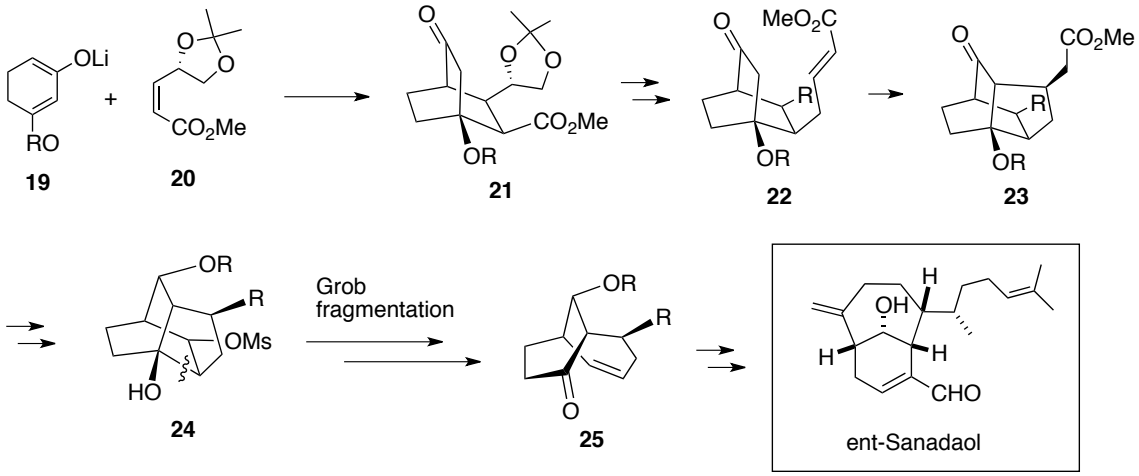
About Sanadaol

Sanadaol is a diterpene isolated from *Pachydicton coriaceum* (sanadagusa, in Japanese), the algae from Izu-Shimoda beach in 1982 by Kakisawa and co-workers.[17] Moore also isolated Sanadaol in 1983 from *Dictyota crenulata*, the algae populations in Hawaii.[18] The unique cage structure of Sanadaol contains the bicyclo[4.3.1]decane skeleton and the five contiguous asymmetric centers.



Sanadaol

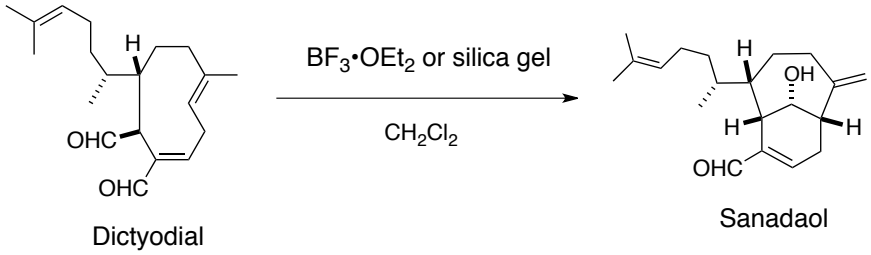
In 1988, Yamada and co-workers have accomplished the total synthesis of racemic Sanadaol, (+)-Sanadaol, and (-)-Sanadaol to confirm its absolute configuration by using their own method to construct the bicyclo[4.3.1]skeleton.[19] The report is the only one example describing the total synthesis until now (Scheme 12).



Scheme 12

They used a formal cycloaddition reaction via sequential Michael reactions to construct the bicyclo[2.2.2]octane skeleton starting from cyclohexenone derivative **19** and unsaturated ester **20**. After synthesis of tricyclic keto ester **23** by intramolecular Michael addition of **22**, they conducted the Grob fragmentation reaction of mesylate **24** to construct the basic skeleton of Sanadaol. The total synthesis was accomplished through introduction of the side chain.

By reason of its peculiar structure, Sanadaol has attracted attention for its physiological activities, but biological activity has never been reported to date. In the meanwhile, Dictyodial, a main component of *Dictyota crenulata* that can be converted into Sanadaol in acidic condition (Scheme 13), has antibacterial activity against *Straphylococcus acureu* and *Bacillis subilis*, and also has antifungal activity against *Candida albican*[20, 21].

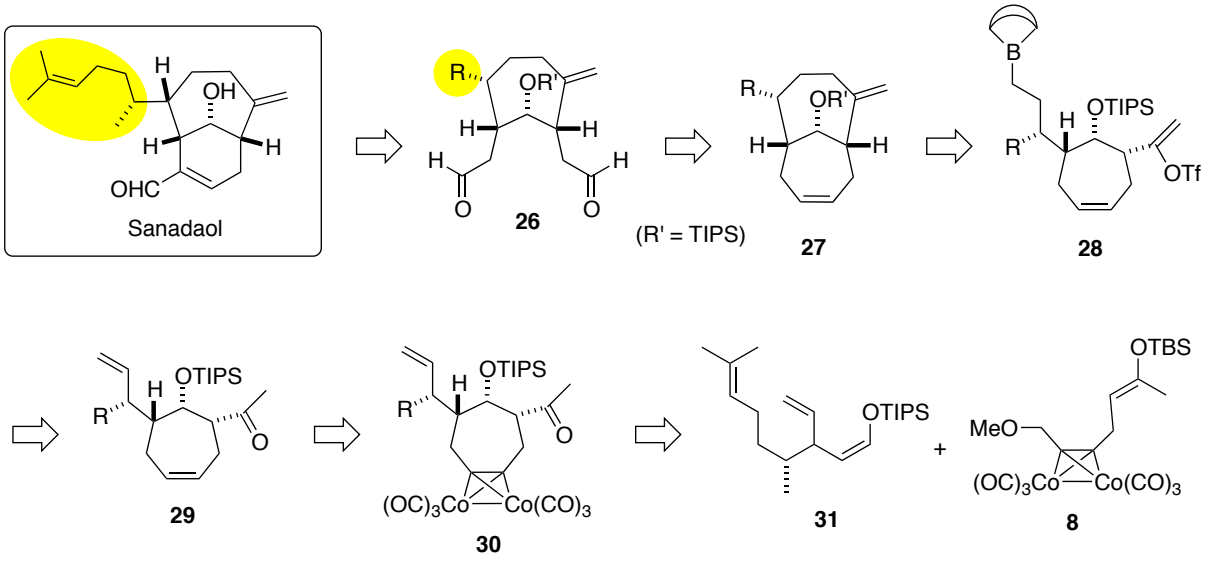


Scheme 13

The Synthetic Strategy

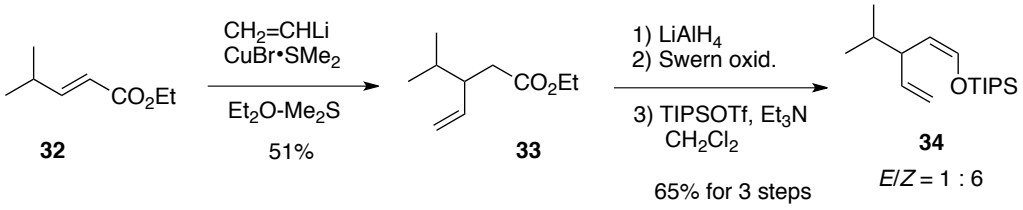
As described in Chapter 1, the [5+2] cycloaddition reaction is useful to construct cycloheptane derivatives having three contiguous stereogenic centers, the relative configuration of the substituents are controlled as *syn–syn*. At the sight of the structure of Sanadaol, there can be found three contiguous stereogenic centers in a similar *syn–syn* configuration. Thus, the author planed to construct the bicyclic system of the natural product through the [5+2] cycloaddition reaction as a key step.

The first synthetic strategy for Sanadaol is based on the intramolecular Suzuki–Miyaura coupling reaction (Scheme 14). Thus, the cyclohexene ring involving the unsaturated aldehyde moiety is to be constructed by intramolecular aldol condensation of dialdehyde **28**.[22] Dialdehyde **28** is supposed to be obtained from bicyclic alkene **27** by oxidative cleavage such as the osmium-catalyzed reaction with $NaIO_4$. With a view to obtaining bicyclo[4.4.1]undecane derivative **27**, the author planed to employ the intramolecular Suzuki–Miyaura coupling reaction of organoboron compound **28** which would come from ketone **29** having a side chain with a vinyl group. The cycloheptene ring of **29** is to be constructed through the [5+2] cycloaddition reaction of enol silyl ether **31** with five-carbon unit **8** followed by reductive decomplexation reaction of cycloadduct **30**.



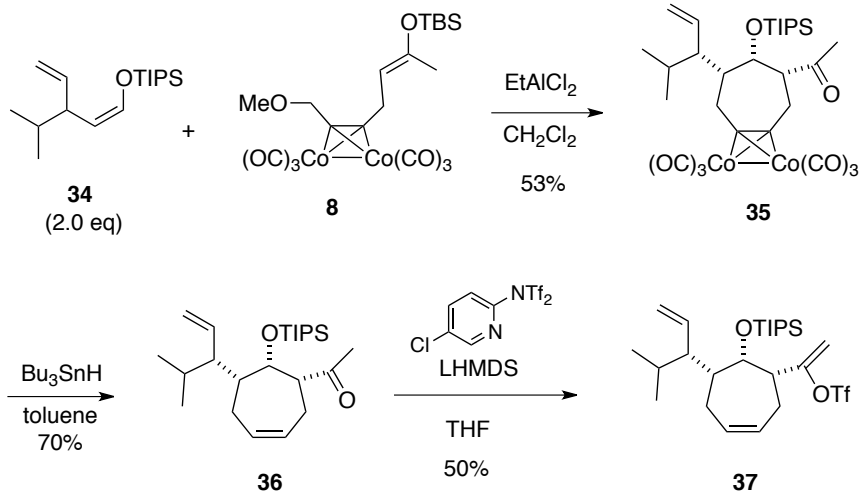
Scheme 14

At first, a model compound having an isopropyl group instead of the side chain of Sanadaol was prepared (Scheme 15). In the presence of a copper salt, commercially available ester **32** underwent conjugate addition with vinyllithium to afford ester **33**. Reduction of **33** gave the corresponding alcohol which was subjected to Swern oxidation to give an aldehyde that in turn was treated with TIPSOTf and triethylamine to afford **34** in moderate yield.



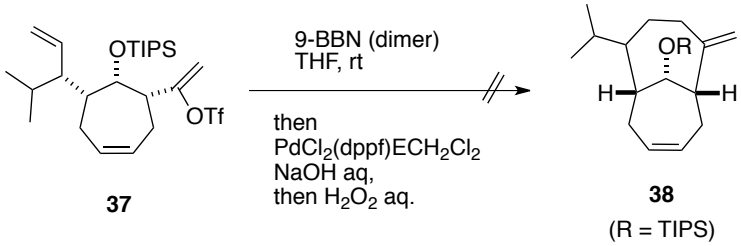
Scheme 15

The formal [5+2] cycloaddition reaction of **34** with **8** mediated by $EtAlCl_2$ gave cycloheptane derivative **35** in 53% yield. The product was subjected to decomplexation by heating with tributyltin hydride[15] to afford ketone **36**. Enol triflate **37** was then obtained from **36** in moderate yield by the reaction with Commins' reagent and LHMDS (Scheme 16).



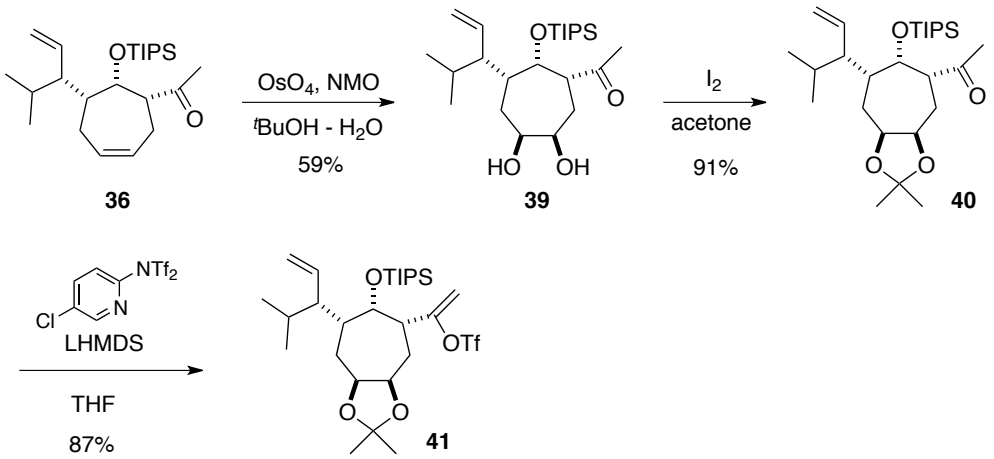
Scheme 16

With the coupling precursor **37** in hand, the stage was set for the intramolecular coupling reaction. However, the reaction of **37** with 9-BBN led to formation of a complex mixture after applying the Suzuki–Miyaura coupling conditions (Scheme 17).



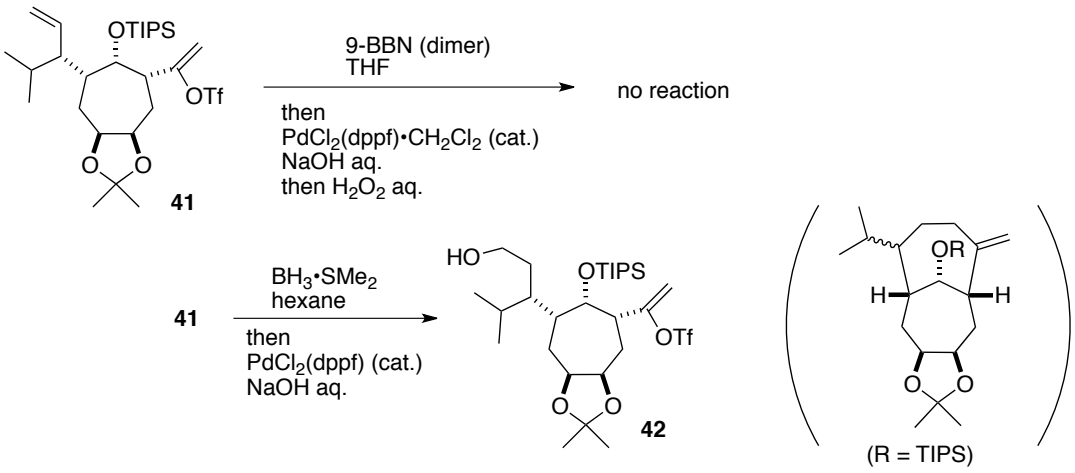
Scheme 17

Analysis of the products suggested that the endo-cyclic alkene moiety of **37** might undergo hydroboration faster rather than the vinyl group. Indeed, the reaction of diene **36** with osmium(VIII) oxide and N-methylmorpholine oxide (NMO) afforded diol **39** as the main product, indicating that the sterically hindered vinyl group exhibits low reactivity. After protection of the 1,2-diol by an acetonide group, the resulting ketone **40** was converted to enol triflate **41** (Scheme 18).



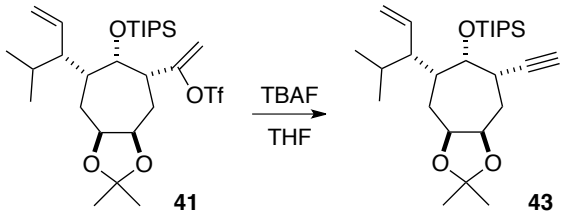
Scheme 18

Treatment of **41** with 9-BBN merely resulted in recovery of the starting material, which is consistent with the low reactivity of the vinyl group surrounded by the seven-membered ring and the isopropyl group (Scheme 19). The result led the author to use the sterically less demanding borane reagent, namely, borane-dimethyl sulfide complex. The reaction with **41**, however, led to formation of alcohol **42** after work-up, which suggests that the steric hindrance around the enol triflate moiety also prevented the desired coupling reaction.



Scheme 19

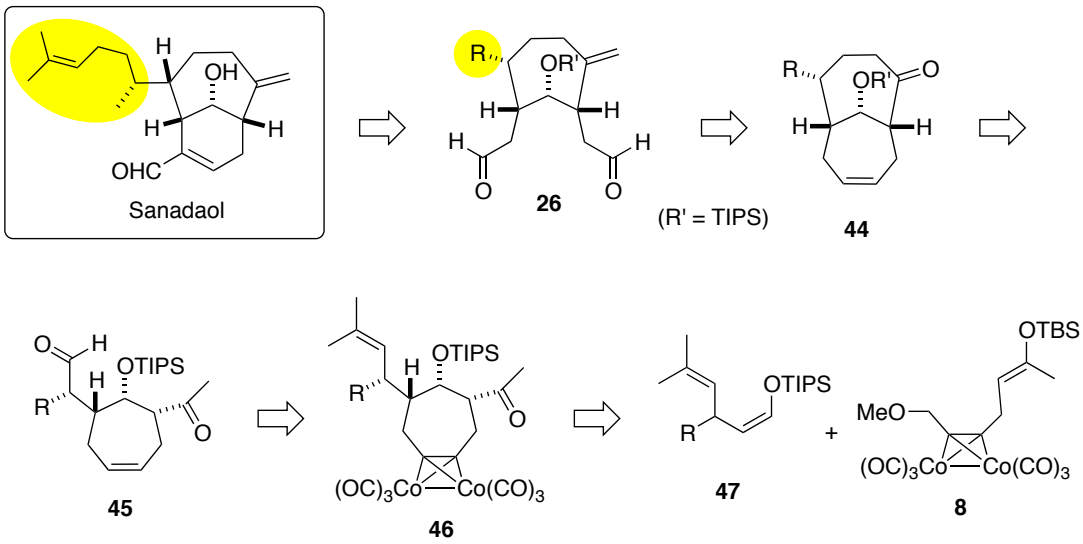
Removal of the bulky TIPS group was expected to reduce steric hindrance around the enol triflate moiety. However, the reaction of enol triflate **41** with TBAF caused β-elimination to afford acetylene **43** without cleaving the Si-O bond (Scheme 20). These results led the author to change the strategy for constructing the bicyclo[4.4.1]undecane skeleton.



Scheme 20

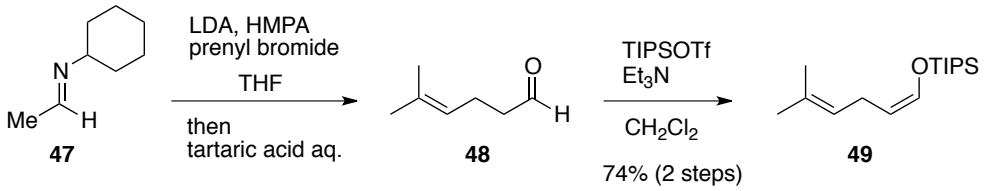
The Second Synthetic Strategy

The alternative synthetic strategy for Sanadaol is shown in Scheme 21. With a view to obtaining bicyclic compound **44**, the author planed to employ an intramolecular aldol reaction of ketoaldehyde **45**, which would be synthesized from cycloheptane derivative **46** having hexacarbonyl dicobalt acetylene complex moiety. The cycloheptane derivative **46** was to be obtained by the [5+2] cycloaddition reaction between enol silyl ether **47** and the five-carbon unit **8**.



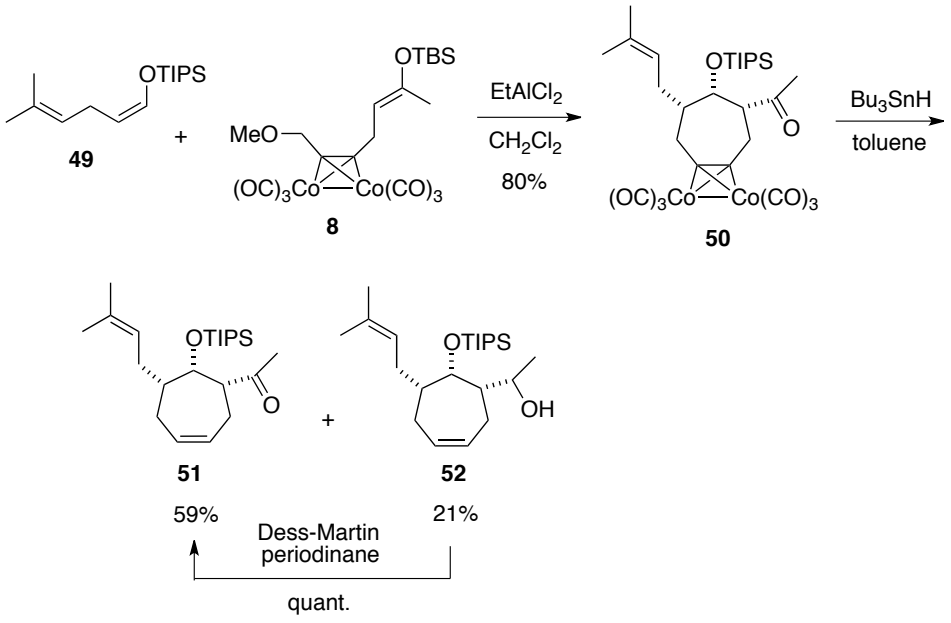
Scheme 21

At first, the author explored a model study by omitting the side chain R' in Scheme 2.10, and enol silyl ether **49** was prepared as shown in Scheme 22. Successive treatment of imine **47** with LDA, prenyl bromide, and an aqueous solution of tartaric acid afforded aldehyde **48** that was converted to enol silyl ether **49** in 74% yield for two steps.



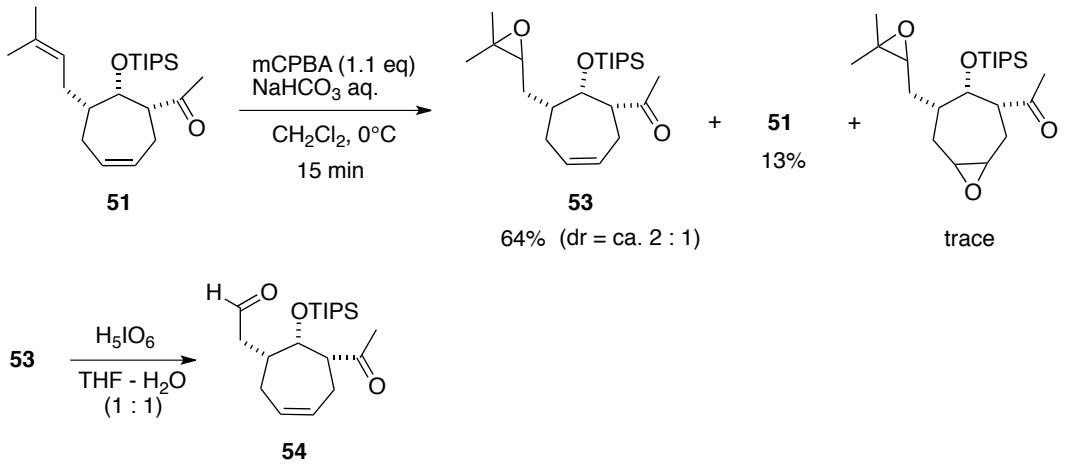
Scheme 22

The formal [5+2] cycloaddition reaction of **49** gave cycloheptane derivative **50** in 80% yield. The product was then heated with tributyltin hydride to afford the desired ketone **51** along with secondary alcohol **52** arising from over reduction of the carbonyl group of **51**. Oxidation of secondary alcohol **52** with Dess–Martin periodinane resulted in quantitative formation of ketone **51** (Scheme 23).



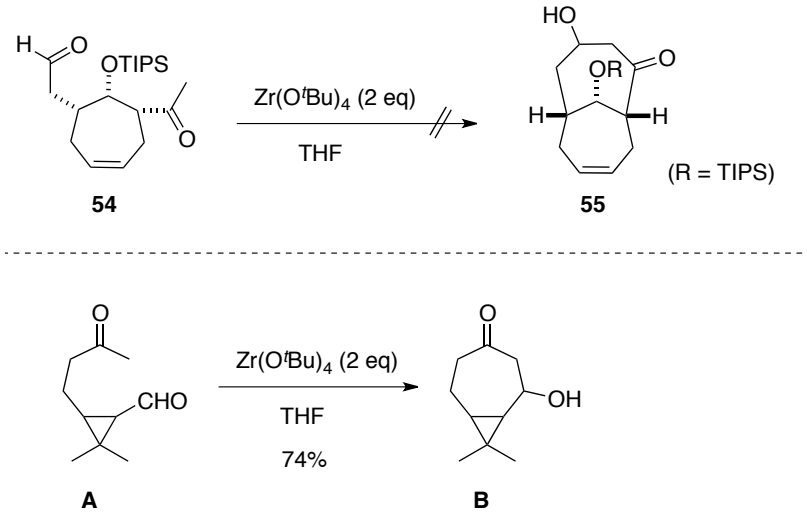
Scheme 23

Diene **51** was reacted with *m*CPBA under mild conditions so as to achieve chemoselective oxidation of the tri-substituted alkene moiety, resulting in formation of epoxide **53** in 64% yield along with 13% recovery of diene **51** (Scheme 24). Oxidative cleavage of epoxide **53** promoted by H_5IO_6 afforded ketoaldehyde **54** which was subjected to intramolecular aldol reactions.



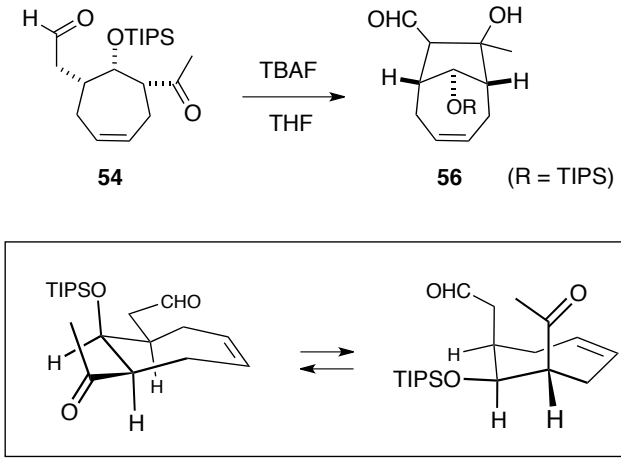
Scheme 24

Shibasaki *et al.*[23] reported the intramolecular aldol reaction of ketoaldehyde **A** mediated by zirconium(IV) *tert*-butoxide which effects selective deprotonation of the methyl ketone moiety to give ketol **B** in 74% yield (Scheme 25). Treatment of ketoaldehyde **54** with zirconium(IV) *tert*-butoxide, however, failed to give the desired product **55**.



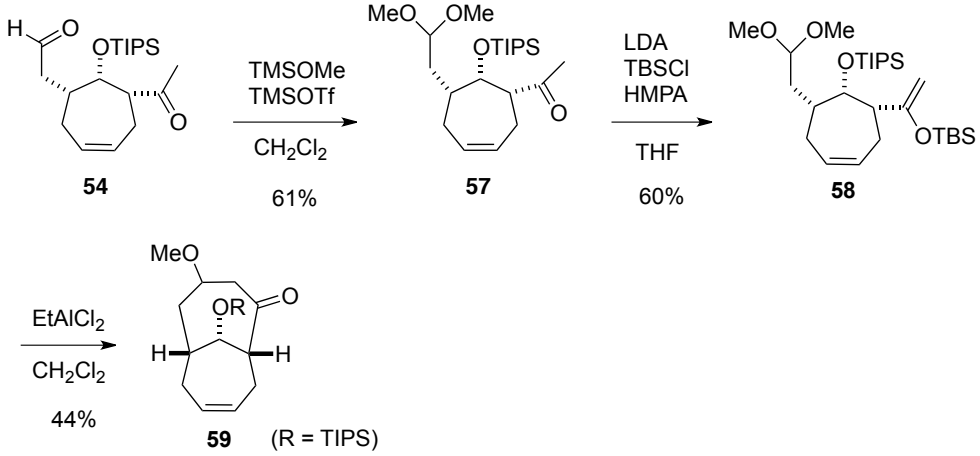
Scheme 25

The result suggested that conformation of the cycloheptane ring may be rigid in which both the ketone and the aldehyde side chains are directed to *pseudo*-equatorial positions. However, treatment of ketoaldehyde **54** with tetrabutylammonium fluoride (TBAF) led to formation of hydroxyaldehyde **56**, indicating that conformation of the cycloheptane ring can flip easily (Scheme 26).



Scheme 26

Preferential formation of an enolate at the aldehyde side chain of **54** led the author to employ the Mukaiyama aldol reaction of the corresponding acetal as shown in Scheme 27. Selective protection of the aldehyde moiety of **57** was achieved by treatment with methoxytrimethylsilane (TMSOMe) and trimethylsilyl triflate (TMSOTf) according to the Noyori's protocol.[24] The resulting acetal **57** was reacted with LDA and TBSCl in the presence of HMPA to afford enol silyl ether **58**. The intramolecular Mukaiyama aldol reaction of **58** was achieved by using ethylaluminum dichloride, giving rise to the desired bicyclic ketone **59**, albeit in low yield.

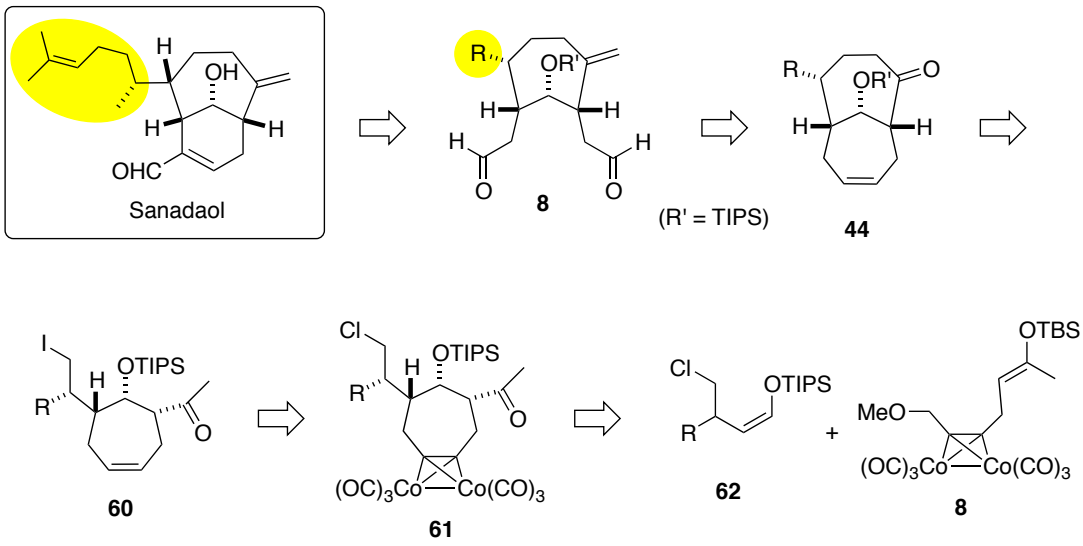


Scheme 27

While construction of the bicyclo[4.4.1]undecane skeleton was achieved, the multi-step transformation involving oxidative cleavage of alkene **51** and acetalization of aldehyde **54** seems to be unsuitable for the total synthesis of Sanadaol. Thus, the author decided to change the synthetic strategy for construction the bicyclo[4.4.1]undecane skeleton.

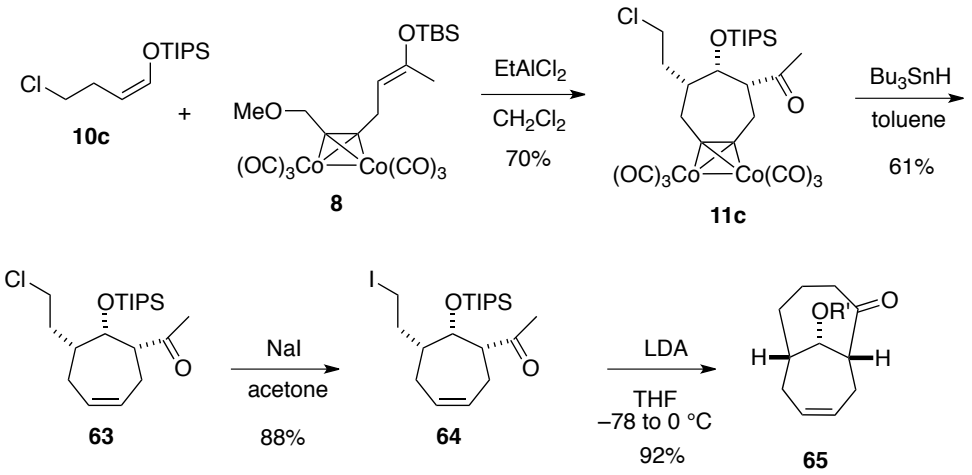
The Third Synthetic Strategy

The new synthetic strategy is based on intramolecular alkylation of iodoketone **60** (Scheme 28). Since decomplexation of a cobalt complex mediated by tributyltin hydride was expected to induce reductive cleavage of the terminal C-I bond, iodoketone **60** is to be prepared from chloroketone **61** through reductive decomplexation and halogen exchange.



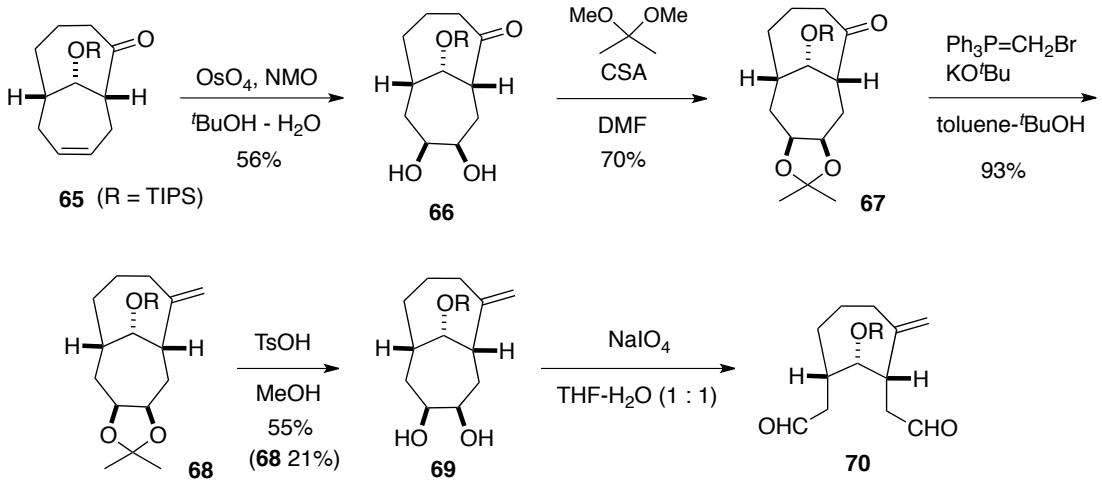
Scheme 28

As was described in Chapter 1, a terminal chloro group of enol silyl ether **10c** does not prevent the [5+2] cycloaddition reaction with five-carbon unit **8** (Scheme 29). In order to establish a method for constructing the bicyclo[4.3.1]decane skeleton, the author planed to use the cycloadduct **11c** as a model compound of **61**. On heating with tributyltin hydride, cobalt complex **11c** underwent decomplexation to afford cycloheptene **63** without removal of the chloro group. After halogen-exchange by a conventional method, the resulting iodoketone **64** was subjected to the intramolecular alkylation reaction. Treatment of **64** with LDA in THF at –78 °C followed by warming up to 0 °C effected the desired cyclization reaction to afford bicyclic ketone **65** in good yield.



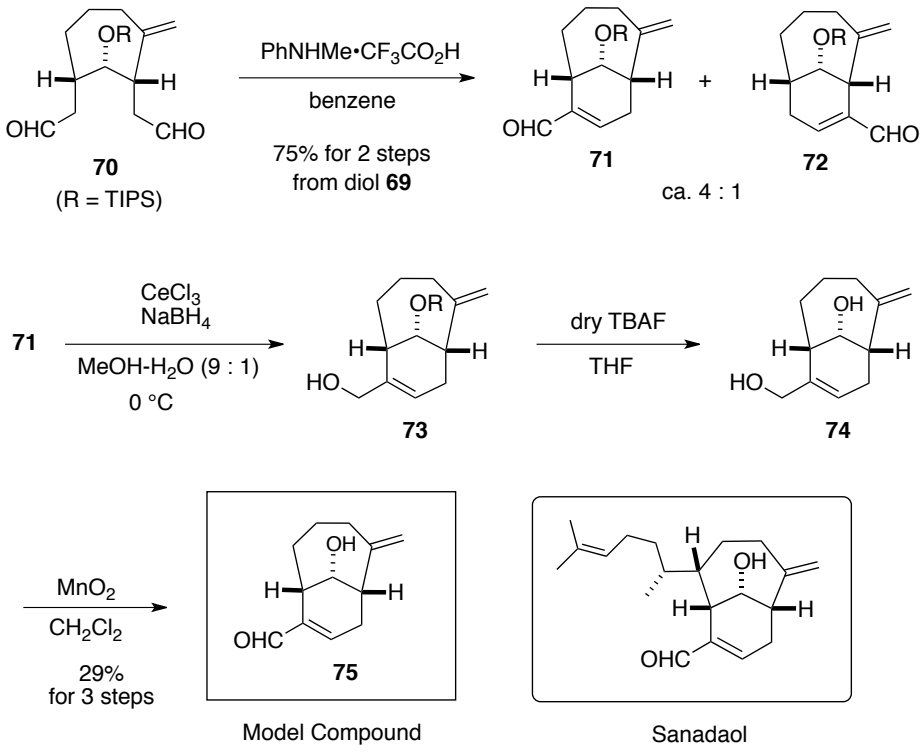
Scheme 29

With the key intermediate **65** in hand, the stage was set for conversion of the bicyclo[4.4.1]undecane skeleton to the bicyclic system of Sanadaol. Oxidation of alkene **65** with Osmium(VIII) oxide and NMO afforded diol **66** in 56% yield (Scheme 30). Attempted transformation of the carbonyl group into a methylene group through the Wittig reaction of **66** resulted in formation of a complex mixture. On the other hand, the corresponding acetonide **67** underwent the Wittig reaction to afford alkene **68** in moderate yield. After removal of the acetonide group under an acidic condition, the resulting diol **69** was subjected to the oxidative cleavage reaction by $NaIO_4$ to afford dialdehyde **70**.



Scheme 30

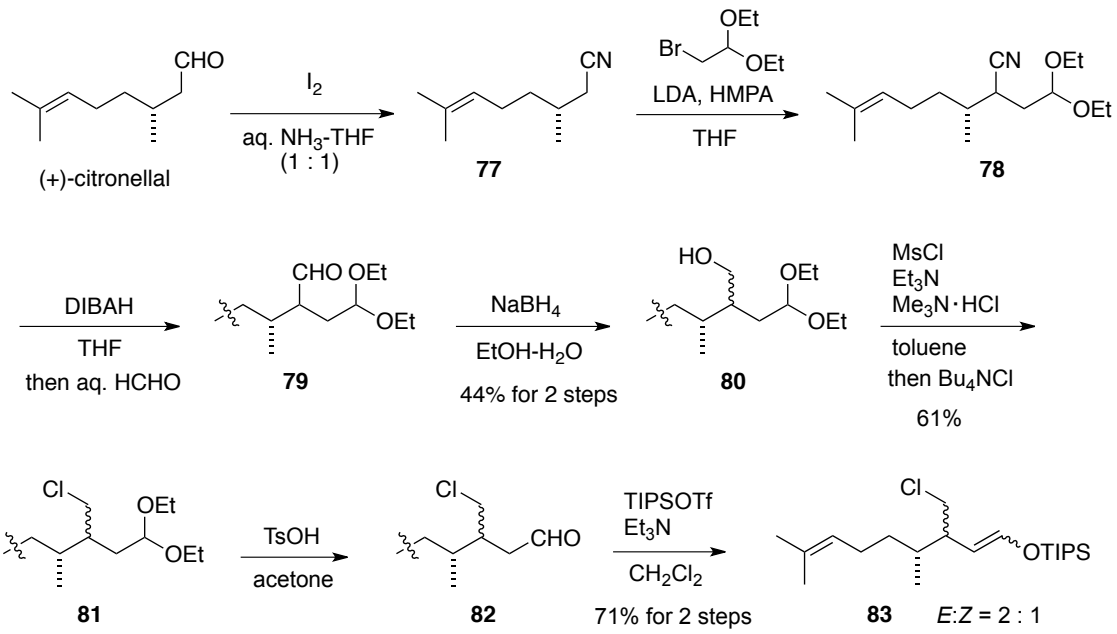
The intramolecular aldol condensation of **70** was performed by heating with *N*-methylanilinium trifluoroacetate in benzene, giving rise to a 4:1 mixture of unsaturated aldehydes **71** and **72**. The Luche reduction of aldehyde **71** afforded allyl alcohol **73** that was treated with TBAF under anhydrous conditions. Finally, the resulting alcohol **74** was re-oxidized by MnO_2, and aldehyde **75** was obtained (Scheme 31).



Scheme 31

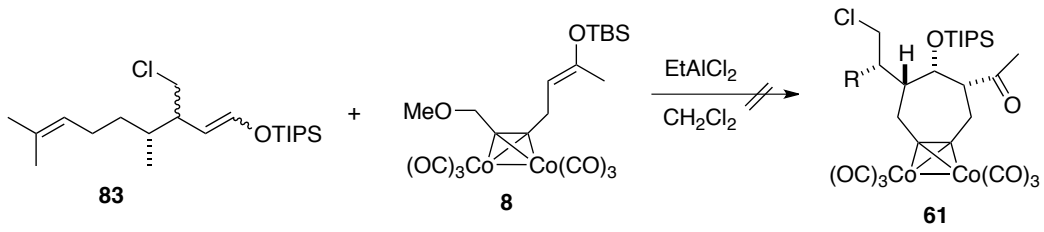
The successful results of the model study led the author to undertake the total synthesis of Sanadaol starting with enol silyl ether **62** having the correct side chain in Scheme 28 (*vide supra*). It is noteworthy that enol silyl ether **62** possesses a common structure with citronellal. Therefore, (+)-citronellal was chosen as the starting material of the asymmetric total synthesis as shown in Scheme 33. Treatment of (+)-citronellal with iodine and aqueous ammonia solution afforded nitrile **77** which was subjected to the alkylation reaction with bromoacetaldehyde diethyl acetal to give nitrile **78**. Nitrile **78** was transformed into alcohol **80** through DIBAH reduction and NaBH4 reduction of the resulting aldehyde **79**. It should be noted that alcohol **80** readily undergoes transacetalization with the terminal diethyl acetal group even under very weak acidic conditions. The chloro group was introduced through mesylation of alcohol **80** by the Tanabe's protocol followed by the S_N2 reaction with tetrabutylammonium chloride in one-pot. After hydrolysis of the acetal group, the resulting

aldehyde **82** was converted to enol silyl ether **83**. The product was a mixture of four stereoisomers consists of diastereomers of the chloromethyl group and the geometrical isomers of the enol silyl ether moiety, the NMR of which indicated the ratio between the E isomers and the Z isomers is about 2:1.



Scheme 33

Although the isomers of **83** could not be separated from each other, the [5+2] cycloaddition reaction with five-carbon unit **8** was examined under the influence of ethylaluminum dichloride. The reaction, however, did not occur even at higher temperature or prolonged reaction period, resulting in decomposition of cobalt complex **8** (Scheme 34).



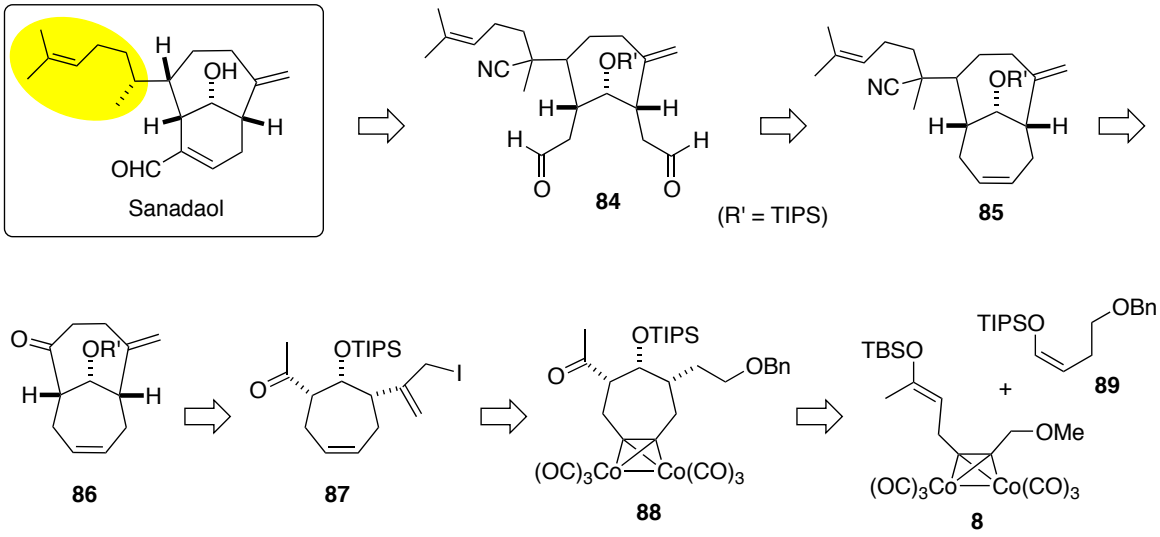
Scheme 34

In often cases, enol silyl ether 68 was recovered in medium yield, indicating that the initial intermolecular addition step suffers from steric hindrance around the enol silyl ether moiety. It is noteworthy that enol silyl ether **34** with bulky isopropyl group underwent the [5+2] cycloaddition reaction with five-carbon unit **8** in Scheme 16 (*vide supra*).

Therefore, the electron-negative chlorine atom of **83** may also affect the reactivity of the enol silyl ether moiety. The problem is to be solved by introducing the bulky side chain after the [5+2] cycloaddition reaction, as shown below.

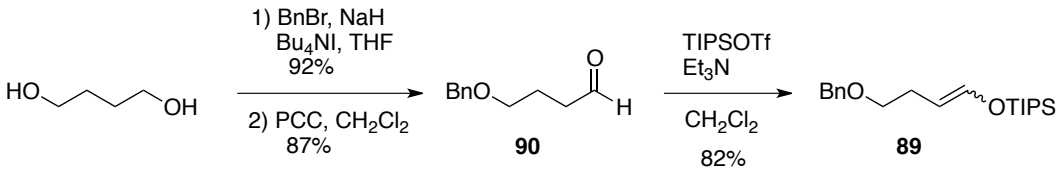
The Fourth Synthetic Strategy

The author designed bicyclic nitrile **85**, which would be derived from ketone **86** possessing a methylene group, as the key intermediate of the total synthesis (Scheme 35). The seven-membered ring of **86** would be formed by intramolecular alkylation of iodoketone **87**. The methylene group of **87** was expected to be introduced after the [5+2] cycloaddition reaction of enol silyl ether **89** with five-carbon unit **8**.



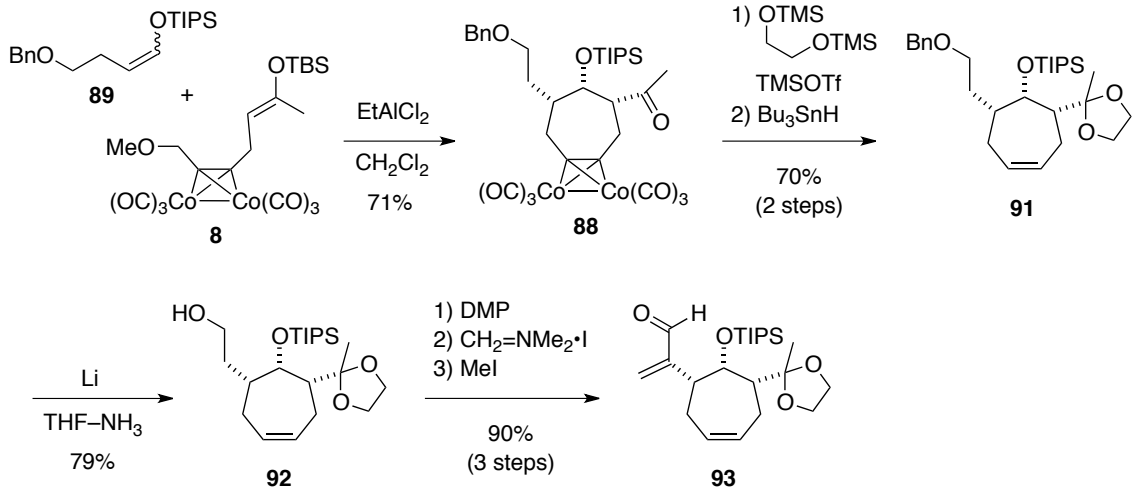
Scheme 35

After mono-benzylation of 1,4-butanediol, the resulting alcohol was converted to enol silyl ether **89** through the PCC oxidation to afford aldehyde **90** followed by treatment with a silyl triflate and triethylamine (Scheme 36).



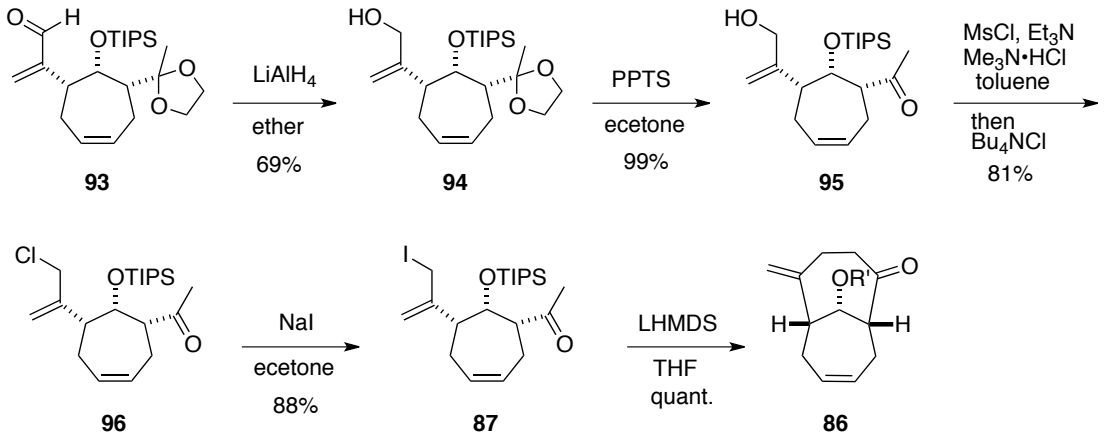
Scheme 36

The intermolecular [5+2] cycloaddition reaction of enol silyl ether **89** and cobalt complex **8** afforded ketone **88** in 71% yield (Scheme 37). Protection of the ketone moiety as an ethylene acetal followed by heating with tributyltin hydride led to formation of cycloheptene **91**. After removal of the benzyl group by Birch reduction, the resulting alcohol **92** was transformed into aldehyde **93** through Dess–Martin oxidation and Mannich reaction of the resulting aldehyde with Eschenmoser's salt.



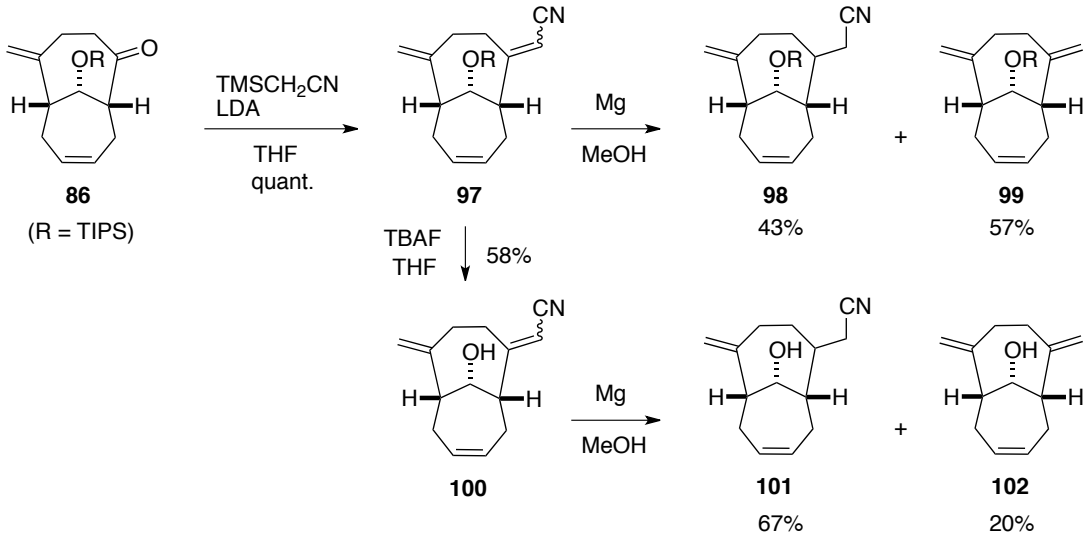
Scheme 37

Reduction of aldehyde **93** and hydrolysis of the acetal group gave allyl alcohol **95** that was converted to allyl iodide **87** in a stepwise manner via chloride **96** (Scheme 38). The intramolecular alkylation reaction of iodide **96** occurred smoothly under the influence of LHMDS at –20 °C, resulting in quantitative formation of the desired ketone **86**. It is noteworthy that the corresponding chloride **96** failed to undergo a cyclization reaction mediated by LHMDS even at 0 °C.



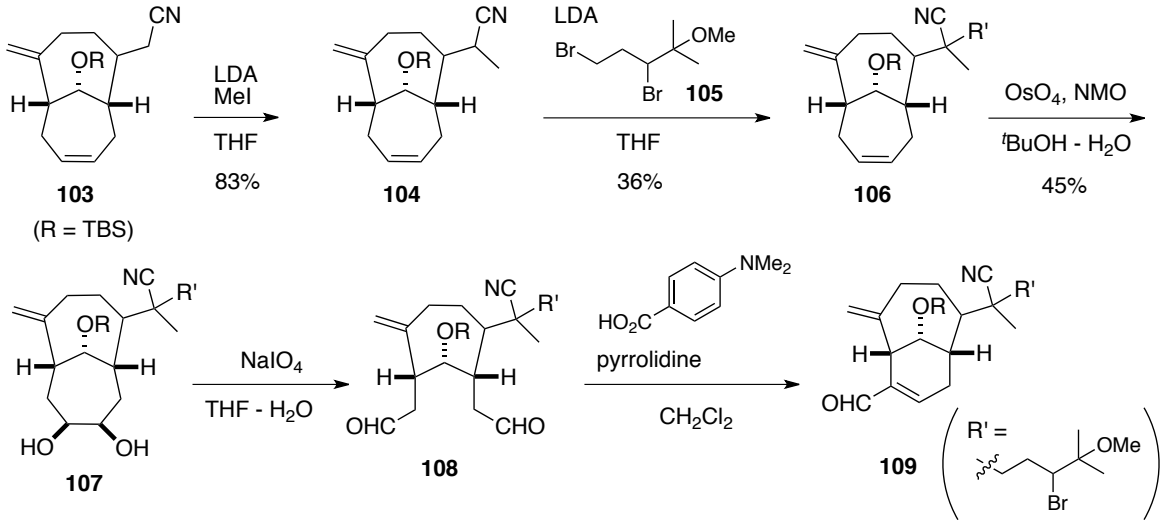
Scheme 38

With the bicyclic ketone **86** in hand, the stage was set for introduction of the side chain of Sanadaol (Scheme 39). Although the Horner-Emmons reaction of ketone **86** with diethyl (cyanomethyl)-phosphonate resulted in recovery of the substrate, the Peterson olefination reaction with (trimethylsilyl)acetonitrile afforded the desired nitrile **97** in quantitative yield. Reduction of unsaturated nitrile **97** with magnesium metal in methanol resulted in formation of a mixture of the desired nitrile **98** along with triene **99** via cleavage of the cyano group. On the other hand, removal of the bulky TIPS group prior to the reduction step led to suppression of the side reaction.



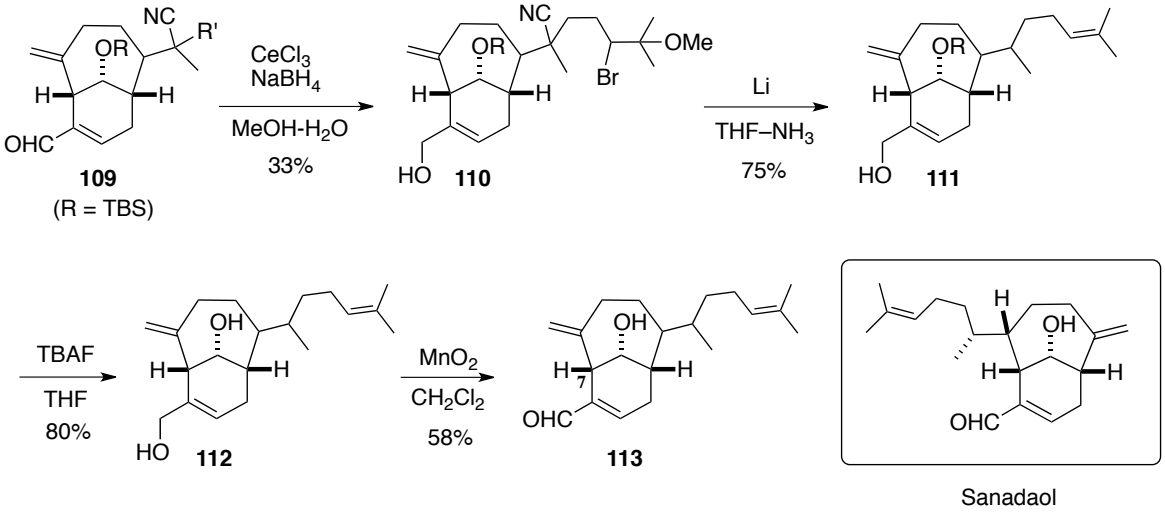
Scheme 39

After protection of the hydroxyl group with a TBS group, nitrile **103** was treated with LDA and methyl iodide to give **104** (Scheme 40). Introduction of the side chain was then achieved by the alkylation reaction with bromide **105** that possesses a β-bromo ether moiety as the masked tri-substituted olefin. Treatment of the resulting diene **106** with a catalytic amount of osmium(VIII) tetroxide and NMO resulted in selective oxidation of the internal olefin moiety, giving rise to diol **107** in 45% yield along with recovery of the starting material in 21%. Oxidative cleavage of diol **107** gave dialdehyde **108** that in turn was subjected to the intramolecular aldol reaction under the Pihko's conditions, leading to regioselective formation of unsaturated aldehyde **109** in moderate yield.



Scheme 40

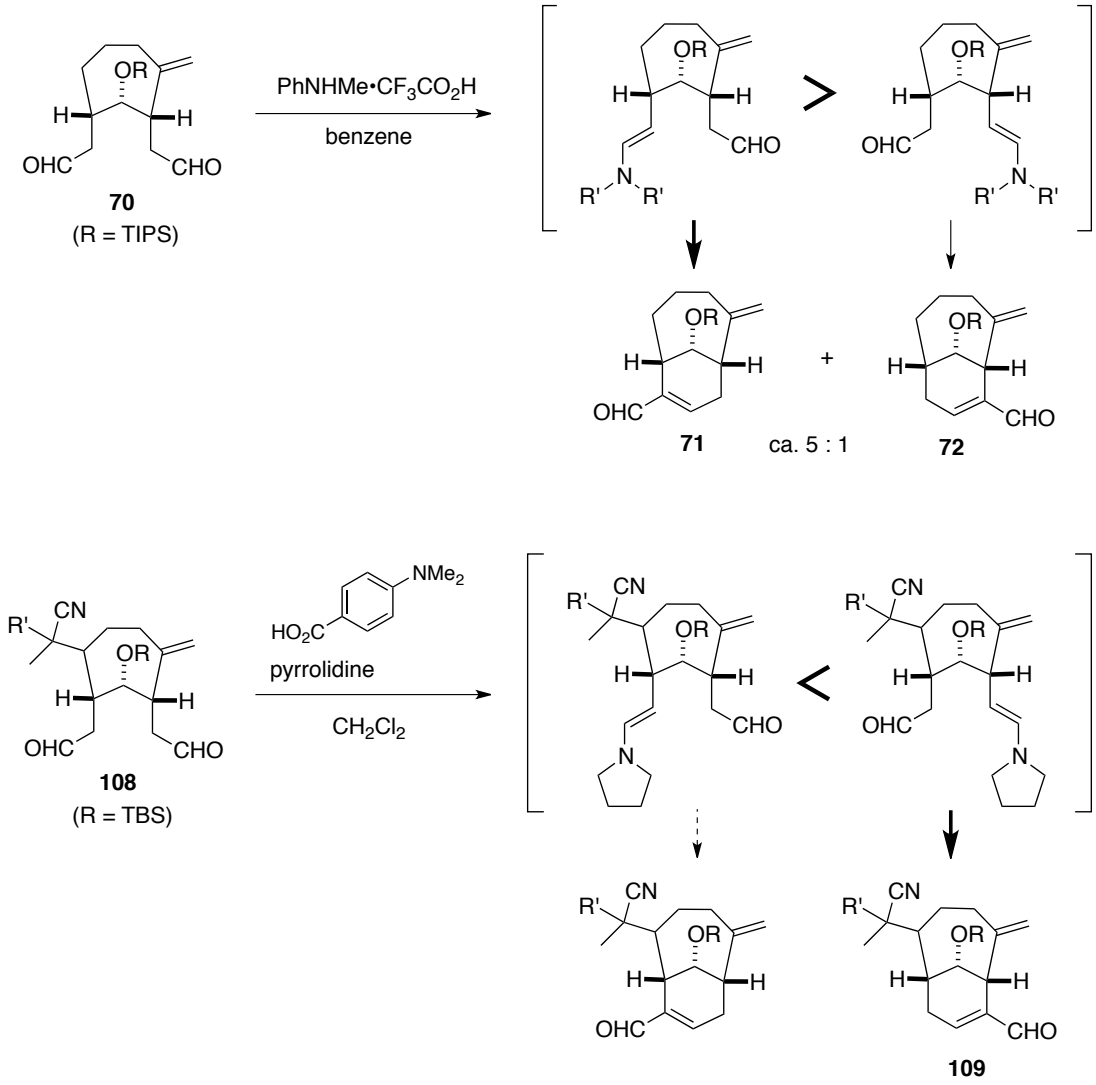
Aldehyde **109** was then transformed into aldehyde **113** through Luche reduction, Birch reduction effecting cleavage of the cyano group and the β-bromo ether moiety, removal of the TBS group, and MnO_2 oxidation (Scheme 41).



Scheme 41

The ^{1}H NMR data of **113** was compared with that of the natural product reported, indicating that the synthetic compound is the regioisomer of the natural product. Thus, the C7 proton peak of **113** appeared at low magnetic field that indicates C7 proton is at the double allylic position.

In relation with the result that the intramolecular aldol reaction of dialdehyde **70** in Scheme 30 selectively afforded the regioisomer **71**, the intramolecular aldol reactions of this types of dialdehydes seem to proceed through formation of the enamine intermediate at the less hindered aldehyde moiety (Scheme 42).



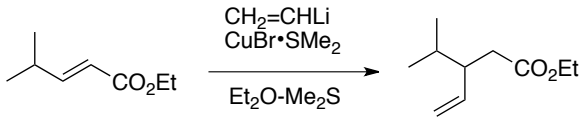
Scheme 42

Conclusion

The author developed the new method for constructing the core bicyclic skeleton of Sanadaol, a naturally occurring compound isolated from *Pachydicton coriaceum* (sanadagusa, in Japanese). The strategy is based on the construction of a seven-membered carbocycle on the basis of a [5+2] cycloaddition reaction of a acetylene dicobalt complex. The resulting cycloadduct possessing an alkyl group, a silyloxy group, and an acetyl group in syn-syn configuration was utilized to construct another seven-membered ring. The bicyclo[4.4.1]undecane skeleton was transformed into a bicyclo[4.3.1]decane core framework of Sanadaol through oxidative cleavage of the cycloheptene moiety followed by regioselective intramolecular aldol condensation. The model compound of Sanadaol without the terpenoid side chain was successfully obtained in 14 steps from commercially available compounds.

Experimental Section

Ethyl 3-isopropyl-4-pentenoate 33

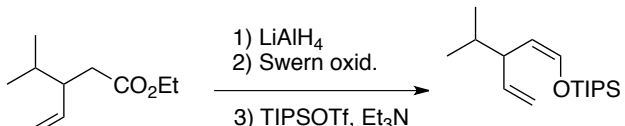


32 51% **33**

To a suspension of $CuBr_2$•Me_2S (8.20 g, 40.0 mmol) in ether (85.0 mL) and Me_2S (58 mL) was added a solution of vinyllithium (prepared from tetravinyltin (5.30 mL, 29 mmol) and ^{B}uLi (29.00 mL, 2.77 M in hexane)) in ether (15 mL) at –78 °C. the reaction mixture were stirred at the same temperature for 1 h, then ether (42 mL) and ester **32** (3.15 mL, 20 mmol) were added. Then the mixture was allowed to warm to –30 °C. Further stirring for 1.5 h, the black solution was quenched with satd. $NaHCO_3$ aq. and NH_3 aq., and extracted with ether, washed with brine, dried over $MgSO_4$. The crude product was purified by silica gel column chromatography to give ester **33** (1.72 g, 10.1 mmol, 50.5%) as a colorless oil.

^{1}H NMR (500MHz, $CDCl_3$) δ 5.63 (ddd, *J* = 14.9, 10.3, 8.6, 1.7 Hz, 1H), 5.01 (dd, *J* = 14.9, 10.3 Hz, 2H), 4.08 (q, *J* = 7.5 Hz, 2H), 2.39 (ddd, *J* = 12.1 (*vic.*), 8.6, 5.2 Hz, 1H), 2.25 (ddd, *J* = 8.6, 5.8, 1.7 Hz, 1H), 1.63 (dq, *J* = 6.9, 5.7Hz, 1H), 1.25 (t, *J* = 7.5 Hz, 3H), 0.88 (d, *J* = 6.9 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H)

3-Isopropyl-1-triisopropylsilyloxy-1,4-pentadiene 34



33 **34**

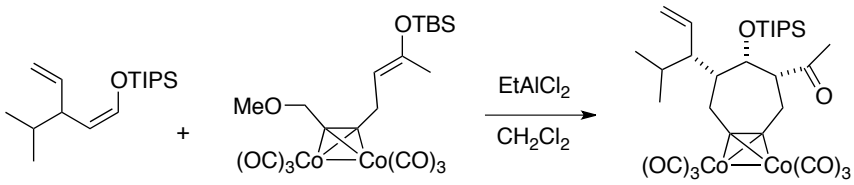
To a solution of ester **33** (1.72 g, 10.1 mmol) in THF (20.0 mL) was added $LiAlH_4$ (0.383 g, 10.1 mmol) at 0 °C. After stirring at 0 °C for 30 min, the reaction mixture was quenched with H_2O and the organic layer was separated. The aqueous layer was extracted with ether, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was used next step without purification.

To a solution of DMSO (2.85 mL, 40.4 mmol) in CH_2Cl_2 (10 mL) was added oxalyl chloride (1.75 mL, 20.2 mmol) at –78 °C and the mixture was stirred for 20 min, and a solution of alcohol in CH_2Cl_2 (15 mL) was added. After stirring for 1 h at –78 °C, Et_3N (7.00 mL, 50.5 mmol) was added, and stirring at -60 °C. Then the reaction mixture was poured into satd. NH_4Cl aq., and separated. The aqueous layer was extracted with ether. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The crude aldehyde was used next step without purification.

To a solution of crude aldehyde and Et_3N (4.20 mL, 30.3 mmol) in CH_2Cl_2 (20.0 mL) was added TIPSOTf (3.30 mL, 12.1 mmol) at 0 °C. After stirring for 1h, the reaction mixture was quenched with satd. $NaHCO_3$ aq. and extracted three times with hexane. The combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography to give enol silyl ether **34** (1.85 g, 6.54 mmol, 64.8 for 3 steps) as a colorless oil.

^{1}H NMR (500MHz, $CDCl_3$) δ 6.32 (d, *J* = 5.8 Hz, 1H), 5.72 (ddd, *J* = 10.3, 7.5, 2.9 Hz, 1H), 4.94 (dd, *J* = 15.5, 10.3 Hz, 2H), 4.29 (dd, *J* = 6.3, 5.8 Hz, 1H), 3.11 (dd, *J* = 15.5, 6.9 Hz, 1H), 1.60 (ddd, *J* = 6.9, 6.3, 2.9 Hz, 1H), 1.05 (m, 21H), 0.86 (d, *J* = 6.9 Hz, 3H), 0.84 (d, *J* = 6.9 Hz, 3H)

Acetylene dicobalt complex 35

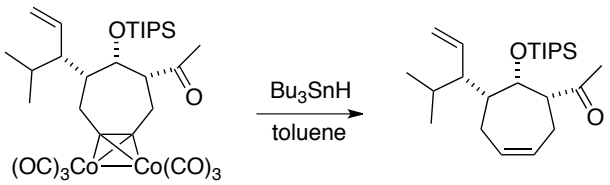


34 **8** **35**

To a solution of enol silyl ether **34** (0.226 g, 0.800 mmol) and dicobalt complex **8** (0.224 g, 0.400 mmol) in CH_2Cl_2 (4.00 mL) was added $EtAlCl_2$ (0.770 mL, 1.04 M in hexane) at 0 °C. After stirring at 0 °C for 20 minutes, the reaction mixture was quenched with satd. NaK tartrate aq. (Roschell's salt aq) and stirred at room temperature vigorously for 1 h under argon atmosphere. Then aqueous layer were extracted three times with ether, washed with brine and dried over $MgSO_4$. The combined organic layers were concentrated *in vacuo*. The crude product was purified by silica gel column chromatography to give cobalt complex **35** (0.0835 g, 0.123 mmol, 30.9%) as a dark-brown oil.

^{1}H NMR (500MHz, $CDCl_3$) δ 5.28 (dt, *J* = 17.2, 10.3 Hz, 1H), 4.92 (dd, *J* = 10.3, 1.7 Hz, 1H), 4.71 (dd, *J* = 17.2, 1.7 Hz, 1H), 4.69 (s, 1H), 3.16 (dd, *J* = 15.5, 12.6 Hz, 1H), 2.90 (dd, *J* = 15.5, 2.9 Hz, 1H), 2.66 (d, *J* = 7.5 Hz, 1H), 2.22 (dd, *J* = 12.6, 2.9 Hz, 1H), 2.00 (s, 3H), 1.76 (ddd, *J* = 14.9, 8.0, 6.9 Hz, 1H), 1.45 (ddd, *J* = 14.9, 8.0, 7.5 Hz, 1H), 0.81 (m, 21H), 0.69 (d, *J* = 6.9 Hz, 3 H), 0.52 (d, *J* = 6.9 Hz,, 3H)

Ketone 36



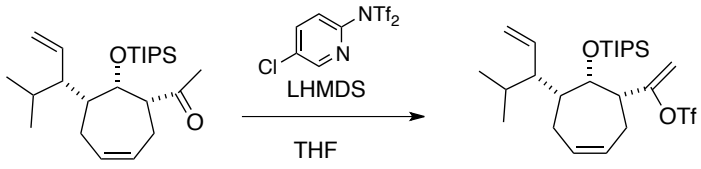
35 **36**

A mixture of cobalt complex **35** (0.127 g, 0.187 mmol) and Bu_3SnH (0.250 mL, 0.935 mmol) in toluene (1.25 mL) was heated at 80 °C at 10 min. After cooling to room temperature, toluene was removed under reduced pressure. The residue was filtered through a pad of silica gel and used without further purification.

To a solution of **36** and the corresponding alcohol (mixture) in CH_2Cl_2 was added Dess-Martin periodinane (0.100 g, 0.136 mmol) at room temperature. After stirring for 1.5h, reaction mixture was quenched with satd. $NaHCO_3$ aq. and $Na_2S_2O_3$ aq. and extracted with ether. The combined organic layers were washed with brine and dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography to give ketone **36** (0.0740g, 100%) as a colorless oil.

^{1}H NMR (500MHz, $CDCl_3$) δ 5.67 (m, 2H), 5.41 (dt, *J* = 17.2, 10.3, 9.7 Hz, 1H), 5.05 (dd, *J* = 9.7, 2.7 Hz, 1H), 4.89 (s, 1H), 4.82 (dd, *J* = 17.2, 2.7 Hz, 1H), 2.69 (t, *J* = 14.3 Hz, 1H), 2.29 (d, *J* = 14.3 Hz, 2H), 2.17 (s, 3H), 2.09 (d, *J* = 11.5 Hz, 1H), 1.99 (ddd, *J* = 10.3, 6.8, 2.9 Hz, 1H), 1.93 (dt, *J* = 10.3, 2.9 Hz, 1H), 1.87 (dd, *J* = 9.7, 6.9 Hz, 2H), 1.38 (dd, *J* = 11.5, 6.9 Hz, 1H), 0.99 (m, 21H), 0.81 (d, *J* = 6.9 Hz, 3H), 0.73 (d, *J* = 6.9 Hz, 3H)

Enol triflate 37



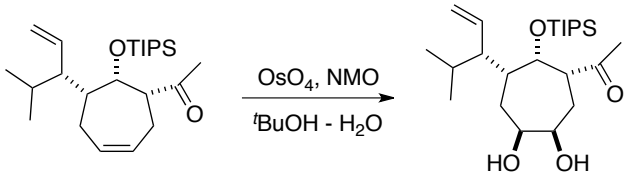
36 **37**

A solution of ketone **36** (0.0801 g, 0.204 mmol)in THF (0.3 mL) was added LHMDS (0.788 mL, 0.5 M solution in THF) at –78 °C. After being stirred for 1 h at the same temperature, a solution of Commins' reagent (0.120 g, 0.306 mmol) in THF (0.3 mL) was added. After being stirred for 40 min at -25 °C, phosphorous buffer (pH 7) was added. The aqueous layer was extracted with hexane, and the combined organic layer were washed with brine, dried over $MgSO_4$ and concentrated. The crude

product was purified by silica gel column chromatography to give enol triflate **37** (0.0535 g, 0.102 mmol, 50.0 %) as a colorless oil.

^{1}H NMR (500MHz, $CDCl_3$) δ 5.79 (ddd, *J* = 10.9, 8.0, 2.9 Hz, 1H), 5.67 (ddd, *J* = 10.9, 8.0, 2.9 Hz, 1H), 5.46 (dt, *J* = 16.1, 6.9 Hz, 1H), 5.22 (d, *J* = 3.5 Hz, 1H), 5.12 (*J* = 12.0, 2.3 Hz, 1H), 5.01 (d, *J* = 2.3 Hz, 1H), 4.88 (dd, *J* = 13.2, 3.5 Hz, 1H), 4.75 (s, 1H), 2.67 (ddd, *J* = 8.5, 6.9, 2.9 Hz, 1H), 2.40 (d, *J* = 12.0 Hz, 2H), 2.03 (ddd, *J* = 13.2, 8.0, 6.9 Hz, 1H), 1.96 (dd, *J* = 12.0, 8.5 Hz 1H), 1.52 (d, *J* = 16.1 Hz, 1H), 1.48 (t, *J* = 12.0 Hz, 1H), 1.10 (m, 21H), 0.88 (d, *J* = 6.9 Hz, 3H), 0.75 (d, *J* = 6.9 Hz, 3H)

Keto diol 39

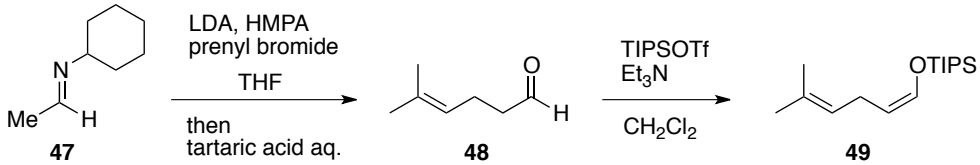


36 **39**

A solution of ketone **36** (54.9 mg, 0.140 mmol) and OsO_4 (0.0540 mL, 0.157 M in ^{t}BuOH) in ^{t}BuOH (0.100 mL) and H_2O (0.190 mL) was added NMO (38.9 mg, 0.332 mmol) at room temperature. After being stirred for 6.5 h at room temperature, the reaction was quenched with $NaHSO_3$ (solid) and $SNaHSO_3$ aq., stirred further 30 min and separated. The aqueous layer was extracted with ether, and the combined organic layer were washed with brine, dried over $MgSO_4$ and concentrated. The crude product was purified to give diol **39** (32.6 mg, 0.0764 mmol, 54.6%) as a white solid.

^{1}H NMR (500MHz, $CDCl_3$) δ 5.41 (dt, *J* = 17.2, 9.8 Hz, 1H), 5.01 (dd, *J* = 10.3, 2.3 Hz, 1H), 4.82 (dd, *J* = 17.2, 2.3 Hz, 1H), 4.72 (s, 1H), 4.16 (t, *J* = 6.9 Hz, 1H), 4.07 (t, *J* = 6.9 Hz, 1H), 2.77 (d, *J* = 6.9, 5.2 Hz, 1H), 2.14 (dq, *J* = 9.2, 6.9 Hz, 2H), 2.10 (s, 3H), 1.94 (dd, *J* = 8.6, 6.3 Hz, 1H), 1.86 (ddd, *J* = 9.2, 6.3, 5.8 Hz, 2H), 1.65 (dt, *J* = 10.3, 8.6 Hz, 1H), 1.53 (ddd, *J* = 9.8, 6.3 , 5.8 Hz, 1H), 0.95 (m, 21H), 0.81 (d, *J* = 6.9 Hz, 3H), 0.74 (d, *J* = 6.9 Hz, 3H)

5-Methyl-1-triisopropylsiloxy-1,4-hexadiene 49



47 **48** **49**

A solution of diisopropylamine (7.00 mL, 50 mmol) and HMPA (8.70 mL, 50 mmol) in THF (50 mL) was added ^{n}BuLi (18.0 mL, 50 mmol, 2.77 M solution in hexane) at –78 °C. After stirring for 10 min at 0 °C, imine **47** (6.26 g, 50 mmol) was added. After stirring for 20 min at 0 °C, the resulting

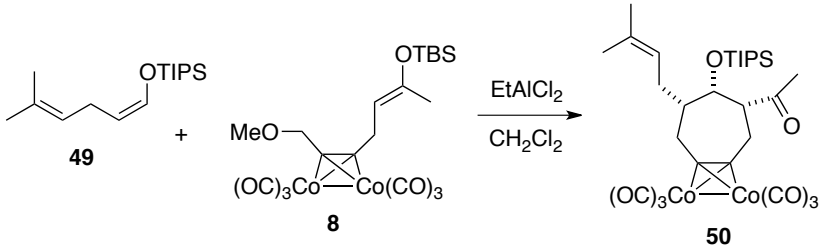
mixture was added *via* cannula to a solution of 1-bromo- 3-methyl-2-butene (5.80 mL, 50 mmol) in THF (30 mL) at -60 °C. The reaction mixture was stirred at -60 °C at 2 h, quenched with 15% aqueous tartaric acid at -15 °C. After stirring for 30 min, the mixture was extracted three times with ether and washed with brine. The combined organic layers were concentrated, and crude product was used next step without purification.

To a solution of crude product **48** and Et_3N (21.0 mL, 150 mmol) in CH_2Cl_2 (100 mL) was added TIPSOTf (16.30 mL, 60 mmol) at 0 °C. After stirring for 1 h, the reaction mixture was quenched with sat. $NaHCO_3$ aq. and extracted three times with ether. The combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography to give enol silyl ether **49** (9.90 g, 36.9 mmol, 74% over two steps) as a colorless oil.

^{1}H NMR (500MHz, $CDCl_3$) δ 6.25 (d, *J* = 5.7 Hz, 1H), 5.11 (dd, *J* = 6.9, 5.7 Hz, 1H), 4.35 (t, *J* = 6.3Hz, 1H), 2.78 (dd, *J* = 6.9, 6.3 Hz, 2H), 1.66 (s, 3H), 1.61 (s, 3H)

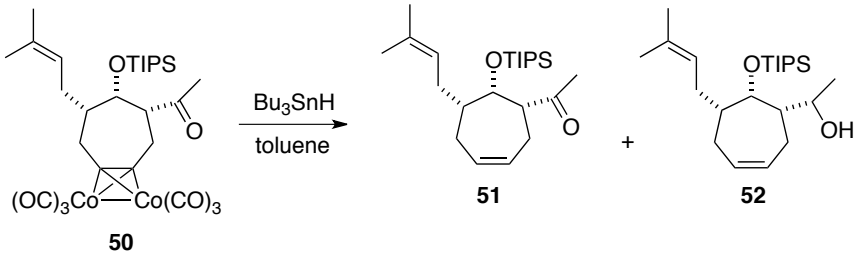
IR (neat) 3040, 2900 – 3100 (br), 2873, 1655, 1462, 1380, 1257, 1180, 1120, 1066, 1032, 877 cm^{-1}

Acetylene dicobalt complex 50



To a solution of enol silyl ether **49** (2.55 g, 9.50 mmol) and dicobalt complex **8** (5.10 g, 9.50 mmol) in CH_2Cl_2 (95.0 mL) was added $EtAlCl_2$ (18.3 mL, 19.0 mmol) at 0 °C. After stirring at 0 °C for 8 minutes, the reaction mixture was quenched with satd. NaK tartrate aq. (Roschell's salt aq.) and stirred at room temperature vigorously for 1 h under argon atmosphere. Then aqueous layer were extracted three times with ether, washed with brine and dried over $MgSO_4$. The combined organic layers were concentrated *in vacuo*. The crude product was purified by silica gel column chromatography to give cobalt complex **50** (3.77 g, 5.69 mmol, 59.8%) as a dark brown oil.

^{1}H NMR (500MHz, $CDCl_3$) δ 5.10 (t, *J* = 7.1 Hz, 1H), 3.72 (s, 1H), 3.41 (dd, *J* = 16.1 Hz, 13.2 Hz, 1H), 3.15 (d, *J* = 16.1 Hz, 1H), 2.94 (dd, *J* = 15.5 Hz, 12.1 Hz, 1H), 2.90 (dd, *J* = 15.5 Hz, 13.2 Hz, 1H), 2.47 (d, *J* = 12.1 Hz, 1H), 2.28 (m, 1H), 2.25 (s, 3H), 2.19 (m, 1H), 1.73 (s, 3H), 1.61 (s, 3H), 1.05 (m, 21 H)



A mixture of cobalt complex **50** (3.77 g, 5.69 mmol) and Bu_3SnH (7.65 mL, 28.5 mmol) in toluene (38.0 mL) was heated at 80 °C at 10 min. After cooling to room temperature, toluene was removed under reduced pressure. The residue was filtered through a pad of silica gel and purified by column chromatography to give **51** (1.27 g, 3.35 mmol, 59.0%) and **52** (0.280 g, 1.2 mmol, 21.7%).

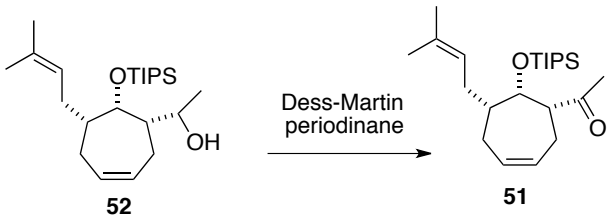
Ketone 51

^{1}H NMR (500MHz, $CDCl_3$) δ 5.75 (ddd, *J* = 10.9, 7.5, 5.2 Hz, 1H), 5.61 (ddd, *J* = 10.9, 5.8, 5.2 Hz, 1H), 4.98 (dd, *J* = 8.1, 6.3 Hz, 1H), 4.51 (s, 1H), 2.60 (dd, *J* = 9.8, 5/2 Hz, 1H), 2.42 (d, *J* = 9.8 Hz, 1H), 2.27 (m, 1H), 2.10 (s, 3H), 1.99 (dt, *J* = 9.2, 8.1 Hz, 1H), 1.94 (t, *J* = 9.2, 1H), 1.73 (ddd, *J* = 8.6, 7.5, 6.3 Hz, 2H), 1.62 (s, 3H), 1.50 (s, 3H), 1.05 s, 21 H)

Alcohol 52

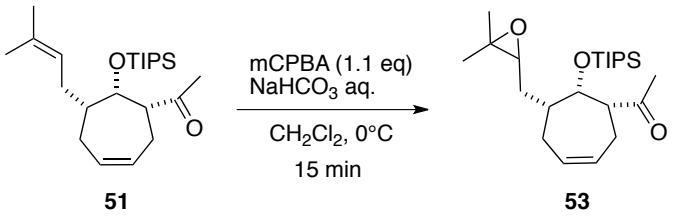
^{1}H NMR (500MHz, $CDCl_3$) δ 5.68 (ddd, *J* = 12.6, 9.1, 5.8 Hz, 2H), 4.92 (ddt, *J* = 9.1, 7.5, 6.3 Hz, 1H), 4.75 (s, 1H), 4.13 (dd, *J* = 7.5 Hz, 4.5 Hz, 1H), 3.96 (ddd, *J* = 6.3, 5.8, 4.5 Hz, 1H), 2.42 (dd, *J* = 13.8, 5.7 Hz, 1H), 2.14 (ddd, *J* = 13.8, 9.1, 8.6 Hz, 2H), 2.07 (dd, *J* = 12.6, 8.6 Hz, 1H), 1.90 (m, 1H), 1.87 (m, 2H), 1.62 (s, 3H), 1.50 (s, 3H), 1.16 (d, *J* = 5.7 Hz, 3H)

Dess-Martin oxidation of 52



To a solution of alcohol **52** (0.280 g, 1.2 mmol) in CH_2Cl_2 was added Dess-Martin periodinane (0.760 g, 1.5 mmol) at room temperature. After stirring for 1.5 h, reaction mixture was quenched with satd. $NaHCO_3$ aq. and $Na_2S_2O_3$ aq. and extracted with ether. The combined organic layers were washed with brine and dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography to give ketone **51** (0.278 g, 1.2 mmol, 100%).

Epoxy ketone 50



51 53

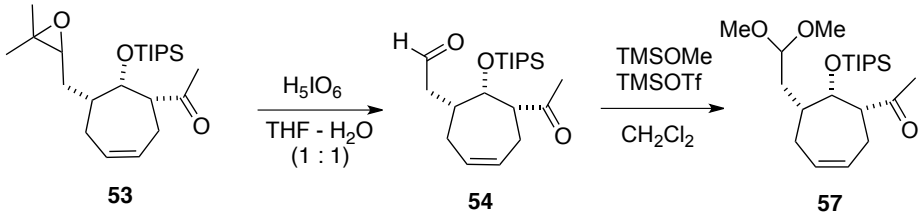
To a solution of ketone **51** (1.14 g, 3.0 mmol) in CH_2Cl_2 (15 mL) was added sat. $NaHCO_3$ aq. and *m*CPBA (0.760 g, 3.3 mmol) at 0 °C. After stirring for 15 min, $NaHCO_3$ (0.5 g) and satd. $Na_2S_2O_3$ aq. The mixture was stirred vigorously for 1 h under argon atmosphere and separated. The aqueous layer was extracted with ether. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography to give epoxide **53** (0.760 g, 1.93 mmol, 64.2%) as a colorless oil.

^{1}H NMR (500MHz, $CDCl_3$) major diastereomer: δ 5.82 (ddd, *J* = 10.9, 5.8, 5.2 Hz, 1H), 5.65 (ddd, *J* = 10.9, 7.5, 5.8 Hz, 1H), 4.48 (s, 1H), 2.66 (t, *J* = 3.5 Hz, 1H), 2.60 (dd, *J* = 6.9 Hz, 1H), 2.55 (d, *J* = 9.7 Hz, 1 H), 2.39 (dd, *J* = 9.2 , 6.9 Hz, 1H), 2.18 (s, 3H), 1.86 (dd, *J* = 6.9, 7.5 Hz, 1H), 1.80 (dd, *J* = 9.7, 9.2 Hz, 1H), 1.55 (ddd, *J* = 7.5, 6.9, 3.5 Hz, 1H), 1.26 (s, 3H), 1.24 (s, 3H), 1.08 (m, 21H)

minor diastereomer : δ5.82 (ddd, *J* = 10.9, 5.8, 5.2 Hz, 1H), 5.65 (ddd, *J* = 10.9, 7.5, 5.8 Hz, 1H), 4.52 (s, 1H), 2.66 (t, *J* = 3.5 Hz, 1H), 2.60 (dd, *J* = 6.9 Hz, 1H), 2.48 (d, *J* = 7.5 Hz, 1H), 2.18 (s, 3H), 1.86 (dd, *J* = 6.9, 7.5 Hz, 1H), 1.80 (dd, *J* = 9.7, 9.2 Hz, 1H), 1.55 (ddd, *J* = 7.5, 6.9, 3.5 Hz, 1H), 1.26 (s, 3H), 1.24 (s, 3H), 1.08 (m, 21H)

IR (neat) ｛2900 – 3000 (br), 2866, 1717, 1462, 1376, 1358, 1243, 1173, 1132, 1098, 1068, 1006, 887, 851, 783 cm^{-1}

Keto acetal 57



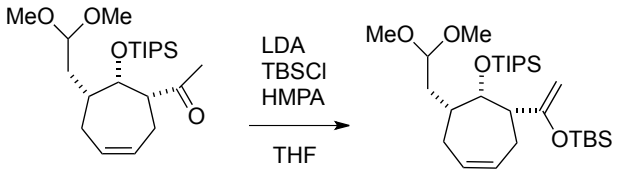
53 54 57

To a solution of epoxide **53** (0.395 g, 1.0 mmol) in dry THF (10 mL) and water (10 mL) was added H_5IO_6 (0.276 g, 1.2 mmol) at room temperature. After stirring for 1.5h at the same temperature, the reaction was quenched with satd. $Na_2S_2O_3$ aq. and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The crude product was used next step without purification.

To a solution of crude product **54** in CH_2Cl_2 (1 mL) was added TMSOMe (0.320 mL, 2.2 mmol) and TMSOTf (20 μl) at –78 °C. After stirring for 1h, the reaction mixture were quenched with satd. $NaHCO_3$ aq. and warmed to room temperature. The aqueous layer was extracted with ether, washed with brine and dried over $MgSO_4$. The organic layer was concentrated and purified by silica gel flush column chromatography to give acetal **57** (0.242 g, 0.606 mmol, 60.6%) as a pale yellow oil.

^{1}H NMR (500MHz, $CDCl_3$) δ 5.77 (ddd, *J* = 10.9, 5.8, 5.2 Hz, 1H), 5.62 (ddd, *J* = 10.9, 5.2, 1.8 Hz, 1H), 4.48 (s, 1H), 4.33 (dd, *J* = 6.3, 4.6 Hz, 1H), 3.24 (s, 3H), 3.20 (s, 3H), 2.57 (ddd, *J* = 10.4, 5.2, 4.6 Hz, 1H), 2.46 (ddd, *J* = 9.8, 3.4, 1.8 Hz, 1H), 2.38 (ddd, *J* = 10.4, 9.8, 5.2 Hz, 1H), 2.20 (s, 3H), 1.98 (ddd, *J* = 15.5, 7.5, 2.3 Hz, 1H), 1.78 (ddd, *J* = 15.5, 7.5, 2.3 Hz, 1H), 1.68 (ddd, *J* = 6.3, 5.8, 3.4 Hz, 2H), 1.00 (m, 21H)

Enol silyl ether 58

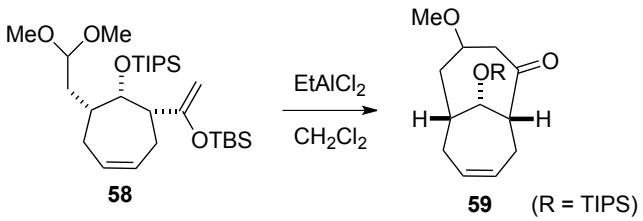


57 **58**

To a solution of ketone **57** (0.449 g, 1.13 mmol), TBSCl (0.364 g, 2.42 mmol) and HMPA (0.780 mL, 410 mmol) in THF (11.5 mL) was added LDA (3.95 mL, 0.5 M solution in THF) at –78 °C . After stirring for 20 min at 0 °C, the reaction mixture was quenched with satd. $NaHCO_3$ aq. and extracted with ether, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo.* The crude product was purified by silica gel column chromatography to enol silyl ether **42** (0.345 g, 0.673 mmol, 59.5%) as a colorless oil.

^{1}H NMR (500MHz, $CDCl_3$) δ 5.58 (dt, *J* = 8.0, 4.0 Hz, 2H), 4.35 (s, 1H), 4.30 (dd, *J* = 6.3, 5.2 Hz, 1H), 3.99 (s, 1H), 3.92 (s, 1H), 3.17 (s, 3H), 3.15 (ddd, *J* = 9.2, 4.0, 2.3 Hz, 1H), 3.13 (s, 3H), 2.47 (ddd, *J* = 12.6, 11.5, 2.3 H, 2H), 1.82 (d, *J* = 11.5 Hz, 1H), 1.76 (ddd, *J* = 9.2, 6.3, 2.9 Hz, 1H), 1.61 (ddd, *J* = 12.6, 6.3, 2.9 Hz, 1H), 1.42 (dd, *J* = 8.0, 6.3 Hz, 1H), 1.40 (s, 9H), 0.93 (m, 21H), 0.01 (s, 3H), -0.03 (s, 3H)

Bicycloketone 59

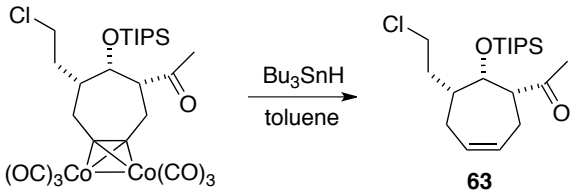


58 **59** (R = TIPS)

To a solution of acetal **58** (0.0256 g, 0.050 mmol) in CH_2Cl_2 (0.5 mL) was added $EtAlCl_2$ (0.0960 mL, 1.04 M in hexane) at –30 °C. After stirring for 20 min, the reaction mixture was quenched with satd. $NaHCO_3$ aq. The aqueous layer was extracted with ether, washed with brine and dried over $MgSO_4$. The crude product was purified by silica gel column chromatography to give ketone **59** (8.1 mg, 0.0220 mmol, 44.2%) as a colorless oil.

^{1}H NMR (500MHz, $CDCl_3$) δ 5.52 (ddd, *J* = 10.3, 5.8, 4.6 Hz, 1H), 5.47 (ddd, *J* = 10.3, 6.3, 5.2 Hz, 1H), 4.15 (dd, *J* = 4.6, 2.9 Hz, 1H), 3.83 (ddd, *J* = 12.6, 4.6 Hz, 1H), 3.21 (s, 3H), 2.85 (dt, *J* = 16.0, 8.0 Hz, 1H), 2.61 (dd, *J* = 12.6, 4.6 Hz, 2H), 2.34 (m, 1H), 2.20 (dt, *J* = 15.5, 8.0 Hz, 1H), 2.06 (ddd, *J* = 15.5, 6.9, 6.3, 5.8 Hz, 1H), 1.95 (dt, *J* = 16.0, 4.6 Hz, 2H), 0.95 (m, 21H).

Chloroketone 63

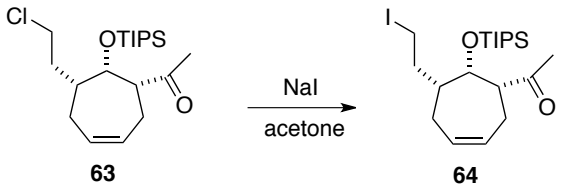


11c **63**

A mixture of cobalt complex **11c** (1.81 g, 3.41 mmol) and Bu_3SnH (2.75 mL, 10.2 mmol) in toluene (23 mL) was heated at 70 °C for 20 min. After cooling to room temperature, toluene was removed under reduced pressure. The residue was filtered through a pad of silica gel and purified by column chromatography to give **63** (770 mg, 2.07 mmol, 61%).

^{1}H NMR (500MHz, $CDCl_3$) δ 5.93-5.89 (m, 1H), 5.71-5.66 (m, 1H), 4.52 (s, 1H), 3.65-3.60 (m, 1H), 3.53-3.48 (m, 1H), 2.62 (s, 2H), 2.43-2.37 (m, 1H), 2.25 (s, 3H), 2.10-2.03 (m, 1H), 1.93-1.84 (m, 3H), 1.72-1.65 (m, 1H), 1.07 (d, *J* = 14.9 Hz, 20H). ^{13}C-NMR (125MHz, $CDCl_3$) δ 209.50, 131.41, 128.86, 76.39, 57.89, 43.43, 41.81, 33.82, 30.08, 26.32, 23.91, 18.39, 13.00.

Iodoketone 64

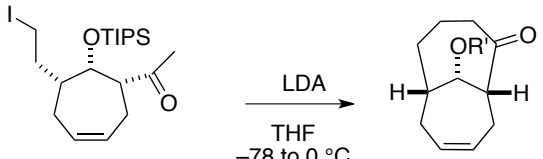


63 **64**

A mixture of ketone **63** (770 mg, 2.07 mmol) and sodium iodide (1.55g, 10.4 mmol) in acetone (4 mL) was heated at 60 °C for 21 h. After dilution with ether, the mixture was filtered through a pad of silica gel and purified by silica gel column chromatography to give **64** (847 mg, 1.82 mmol, 88%).

^{1}H NMR (500MHz, $CDCl_3$) δ 5.93-5.89 (m, 1H), 5.72-5.68 (m, 1H), 4.53 (s, 1H), 3.33-3.28 (m, 1H), 3.15-3.09 (m, 1H), 2.68-2.60 (m, 2H), 2.42-2.36 (m, 1H), 2.25 (s, 3H), 2.08 (dd, *J* = 13.5, 6.7 Hz, 1H), 1.99-1.91 (m, 1H), 1.86-1.77 (m, 2H), 1.73-1.66 (m, 1H), 1.08 (d, *J* = 15.5 Hz, 20H). ^{13}C-NMR (125MHz, $CDCl_3$) δ 209.47, 131.42, 128.84, 75.8, 58.05, 45.59, 34.71, 30.01, 26.19, 23.87, 18.46, 18.45, 13.06, 5.73.

Bicycloketone 65

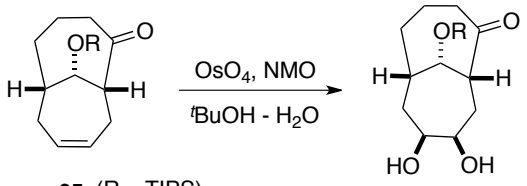


64 **65**

To a solution of ketone **64** (847 mg, 1.82 mmol) in THF (9 mL) was added LDA (2.6 mL, 1.0 M solution in THF) at –78 °C. After stirring for 1 h at 0 °C, the reaction mixture was quenched with satd. $NaHCO_3$ aq. and extracted with ether, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography to afford ketone **65** (567 mg, 1.68 mmol, 92%).

^{1}H NMR (500MHz, $CDCl_3$) δ 5.82-5.77 (m, 1H), 5.67-5.63 (m, 1H), 4.22 (t, *J* = 4.6 Hz, 1H), 3.03 (td, *J* = 12.6, 2.3 Hz, 1H), 2.87 (td, *J* = 10.9, 5.3 Hz, 1H), 2.77 (q, *J* = 4.2 Hz, 1H), 2.41-2.26 (m, 3H), 2.18-2.05 (m, 3H), 1.80 (q, *J* = 13.9 Hz, 1H), 1.63-1.55 (m, 4H), 1.07 (d, *J* = 5.2 Hz, 18H). ^{13}C-NMR (125MHz, $CDCl_3$) δ 214.58, 130.41, 129.68, 75.40, 56.07, 43.63, 40.14, 28.97, 28.65, 27.25, 19.68, 18.09, 12.19.

Ketodiol 66

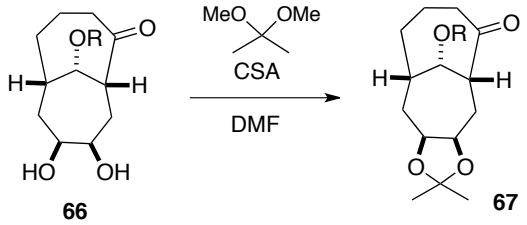


65 (R = TIPS) **66**

A solution of ketone **65** (245 mg, 0.728 mmol) and OsO_4 (22 μL, 0.157 M in *tert*-butanol) in *tert*-butanol (0.49 mL) and water (0.97 mL) was added NMO (170 mg, 1.46 mmol) at room temperature. After being stirred for 8.5 h at room temperature, the reaction was quenched with $NaHSO_3$ (solid) and $NaHSO_3$ aq., stirred further 1 h and separated. The aqueous layer was extracted with ether, and the combined organic layer were washed with brine, dried over $MgSO_4$ and concentrated. The crude product was by silica gel column chromatography to give diol **66** (150 mg, 0.405 mmol, 56%).

^{1}H NMR (500MHz, $CDCl_3$) δ 4.71 (d, *J* = 7.4 Hz, 1H), 4.08 (d, *J* = 8.6 Hz, 1H), 3.92-3.89 (m, 1H), 3.18-3.13 (m, 1H), 2.70 (s, 1H), 2.59-2.52 (m, 1H), 2.47-2.36 (m, 2H), 2.27-2.23 (m, 1H), 1.89-1.83 (m, 1H), 1.78-1.68 (m, 2H), 1.59-1.42 (m, 2H), 1.34-1.22 (m, 4H), 1.09 (d, *J* = 4.0 Hz, 20H) involving peaks due to the minor diastereomer at 4.01 (d, *J* = 7.4 Hz), 3.59 (d, *J* = 11.5 Hz), 2.90 (s), and 2.63 (d, *J* = 16.6 Hz).^{13}C-NMR (125MHz, $CDCl_3$) δ73.28, 71.57, 71.39, 56.10, 42.03, 37.33, 30.85, 28.06, 25.87, 20.35, 18.16, 12.21.

Acetonide 67



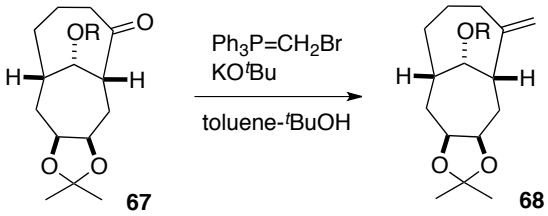
66 **67**

A solution of diol **66** (147 mg, 0.40 mmol), acetone dimethyl acetal (245 μL, 1.99mmol), and 10-camphorsulfonic acid (9.2 mg, 0.04 mmol) in DMF (2.0 mL) was stirred at room temperature. After being stirred for 45 min at room temperature, the reaction was quenched with $NaHCO_3$ aq., and separated. The aqueous layer was extracted with ether, and the combined organic layer were washed with brine, dried over $MgSO_4$ and concentrated. The crude product was purified by silica gel column chromatography to give acetonide **67** (115 mg, 0.28 mmol, 70%).

^{1}H NMR (500MHz, $CDCl_3$) δ: 4.46 (q, *J* = 6.9 Hz, 1H), 4.34 (t, *J* = 4.9 Hz, 1H), 4.28 (td, *J* = 8.2, 3.8 Hz, 1H), 3.06 (td, *J* = 13.6, 2.1 Hz, 1H), 2.92-2.89 (m, 1H), 2.57-2.52 (m, 1H), 2.47 (dd, *J* = 13.7, 6.7 Hz, 1H), 2.36-2.27 (m, 2H), 1.88-1.77 (m, 4H), 1.63-1.54 (m, 2H), 1.46 (s, 3H), 1.30 (s, 3H), 1.06 (d,

J = 4.0 Hz, 21H) involving peaks due to the minor diastereomer at 3.91 (t, *J* = 5.7 Hz), 2.74 (dt, *J* = 20.4, 7.3 Hz), 1.43 (s), and 1.33 (s). ^{13}C-NMR (125MHz, $CDCl_3$) δ 106.75, 74.83, 74.75, 54.57, 44.65, 38.88, 31.68, 29.19, 27.89, 26.67, 23.22, 21.03, 18.16, 18.10, 12.23.

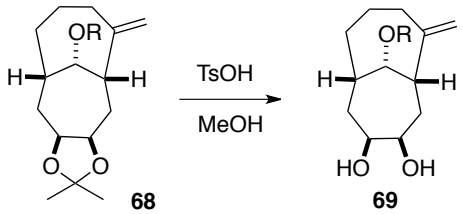
Alkene 68



A mixture of methyltriphenylphosphonium bromide (329 mg, 0.916 mmol), potassium tert-butoxide (102 mg, 0.84 mmol), and ketone **67** (119 mg, 0.280 mmol) in toluene (0.28 mL) and *tert*-butanol (0.28 mL) was stirred at room temperature for 1 h. A sat. NH_4Cl aq. was added, and the mixture was extracted with ether, and the combined organic layer were washed with brine, dried over $MgSO_4$ and concentrated. The crude product was purified by silica gel column chromatography to give olefin **68** (106 mg, 0.259 mmol, 93%).

^{1}H NMR (500MHz, $CDCl_3$) δ 4.88 (s, 1H), 4.76 (s, 1H), 4.53-4.48 (m, 1H), 4.46-4.42 (m, 1H), 4.07 (t, *J* = 5.2 Hz, 1H), 3.13 (s, 1H), 2.76 (t, *J* = 13.5 Hz, 1H), 2.43 (s, 1H), 2.36 (dd, *J* = 13.7, 6.8 Hz, 1H), 2.08-1.99 (m, 2H), 1.96-1.89 (m, 1H), 1.84-1.72 (m, 3H), 1.54 (d, *J* = 14.3 Hz, 1H),1.45 (s, 3H), 1.31 (s, 3H), 1.05 (s, 23H) involving peaks due to the minor diastereomer at 4.64 (s), 4.34-4.28 (m), 3.87 (t, *J* = 5.7 Hz), 2.99-2.93 (m), 2.61-2.51 (m), 1.66-1.62 (m), 1.59 (s), 1.45 (s, 4H), 1.43 (s), 1.34 (s), and 1.31 (s, 3H). ^{13}C-NMR (125MHz, $CDCl_3$) δ 151.70, 112.13, 106.36, 75.02, 74.66, 45.60, 40.44, 37.64, 34.92, 33.34, 28.53, 27.01, 26.14, 23.68, 18.17, 12.38.

Diol 69

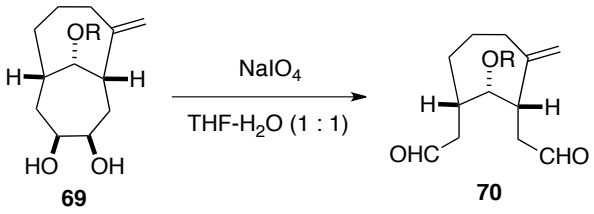


A mixture of acetonide **68** (106 mg, 0.259 mmol) and TsOH•H_2O (24.6 mg, 0.13 mmol) in methanol (1.3 mL) was stirred at room temperature for 2 h. After concentration under reduced pressure, methanol (1.3 mL) was added, and the mixture was stirred at room temperature for additional 1.5 h. The reaction mixture was quenched with satd. $NaHCO_3$ aq. and extracted with ethyl acetate, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo.* The crude product was purified by

silica gel column chromatography to afford diol **69** (52.5 mg, 0.142 mmol, 55%) along with recovery of **68** (23 mg, 0.054 mmol, 21%).

^{1}H NMR (500MHz, $CDCl_3$) δ 4.79 (s, 2H), 4.59 (d, *J* = 6.3 Hz, 1H), 4.08 (d, *J* = 8.0 Hz, 1H), 4.00 (d, *J* = 8.0 Hz, 1H), 2.74 (s, 1H), 2.59 (t, *J* = 12.3 Hz, 1H), 2.45-2.39 (m, 1H), 2.31-2.19 (m, 3H), 1.93 (s, 2H), 1.82-1.74 (m, 3H), 1.70-1.63 (m, 1H), 1.46 (q, *J* = 12.6 Hz, 1H), 1.27-1.23 (m, 1H), 1.07 (s, 21H).). ^{13}C-NMR (125MHz, $CDCl_3$) δ 152.33, 109.72, 75.39, 73.65, 71.49, 46.99, 38.19, 35.50, 33.21, 29.36, 26.76, 26.25, 18.21, 12.30.

Dialdehyde 70

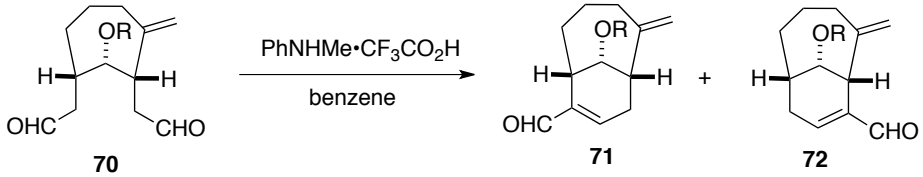


69 **70**

A mixture of diol **69** (52.5 mg, 0.142 mmol) and $NaIO_4$ (36.5 mg, 0.17 mmol) in THF (0.6 mL) and water (0.12 mL) was stirred at room temperature for 75 min. THF (0.1 mL), water (0.05 mL), and $NaIO_4$ (19 mg) was added, and the mixture was stirred at room temperature for additional 4.5 h. The reaction mixture was diluted with water and extracted with ether, dried over $MgSO_4$ and concentrated *in vacuo.* The crude product was used for the next step without purification.

^{1}H NMR (500MHz, $CDCl_3$) δ 9.68 (s, 1H), 9.59 (d, *J* = 2.3 Hz, 1H), 4.93 (s, 1H), 4.76 (s, 1H), 3.53 (dd, *J* = 5.8, 2.4 Hz, 1H), 2.93-2.89 (m, 1H), 2.77-2.63 (m, 2H), 2.52-2.44 (m, 3H), 2.32-2.27 (m, 1H), 2.23-2.18 (m, 1H), 1.91 (t, *J* = 12.6 Hz, 1H), 1.69-1.61 (m, 1H), 1.58-1.46 (m, 2H), 108 (s, 22H).^{13}C-NMR (125MHz, $CDCl_3$) δ 201.75, 201.61, 147.91, 113.67, 79.37, 47.77, 47.28, 39.92, 37.17, 26.53, 24.29, 18,24, 18.23, 13.06.

Enals 71 and 72



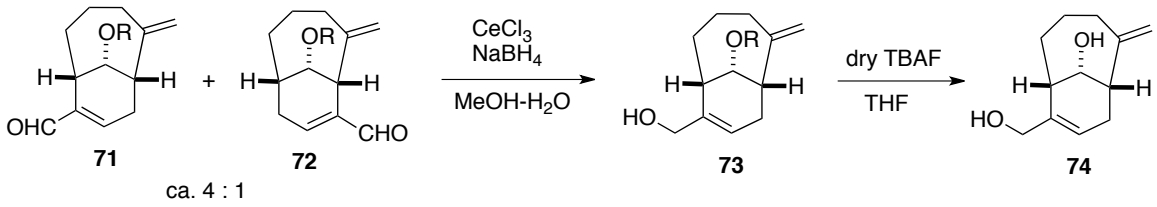
70 (R = TIPS) **71** **72** ca. 4 : 1

A mixture of the crude dialdehyde **70** and TAMA (6.3 mg, 0.029 mmol) in benzene (1.4 mL) was stirred at room temperature for 135 min. The reaction mixture was quenched with satd. $NaHCO_3$ aq. and extracted with ether, dried over $MgSO_4$ and concentrated *in vacuo.* The crude product was purified by silica gel column chromatography to afford a 4:1 mixture of aldehydes **71** and **72** (37.2 mg, 0.107

mmol, 75% from diol **69**).

^{1}H NMR (500MHz, $CDCl_3$) δ 9.42 (s, 1H), 6.75 (s, 1H), 4.83 (s, 1H), 4.76 (s, 1H), 4.10 (t, *J* = 5.4 Hz, 1H), 3.09-3.03 (m, 2H), 2.88-2.80 (m, 1H), 2.59-2.48 (m, 2H), 2.26-2.22 (m, 1H), 2.04-1.98 (m, 1H), 1.78-1.73 (m, 1H), 1.62-1.57 (m, 1H), 1.07 (s, 20H) with peaks due to the minor isomer **72** at 9.40 (s), 5.06 (s), 4.87 (s), 3.76 (d, *J* = 5.7 Hz), 2.70 (dd, *J* = 20.9, 7.7 Hz), and 2.41-2.36 (m).^{13}C-NMR (125MHz, $CDCl_3$) δ 193.34, 154.00, 150.72, 142.76, 113.48, 71.65, 43.61, 37.18, 36.45, 35.51, 24.91, 23.96, 18.13, 12.29 with peaks due to the minor isomer **72** at 192.75, 150.34, 145.06, 142.39, 129.26, 116.36, 71.29, 45.12, 36.99, 36.19, 32.93, 30.79, 21.39, and 12.33.

Diol 74

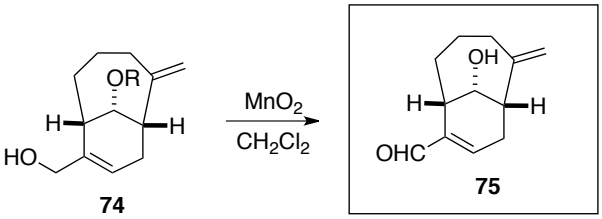


The mixture of aldehydes **71** and **72** (37.2 mg, 0.107 mmol) in methanol (0.39 mL) and water (40 μL) was added $CeCl_3$•$7H_2O$ (199 mg, 0.535 mmol) followed by $NaBH_4$ (20 mg, 0.535 mmol) at 0 °C. After being stirred at room temperature for 2 h, the reaction mixture was diluted with water and extracted with ether, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was used in the next step without purification.

The crude product was stirred with a 1.0 M THF solution of TBAF (0.535 mL, 0.535 mmol) which was pretreated with MS4A. After being stirred at 60 °C for 1.5 h, the reaction mixture was diluted with water, extracted with ethyl acetate, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography to afford diol **74** (21.8 mg, 0.112 mmol, quant.).

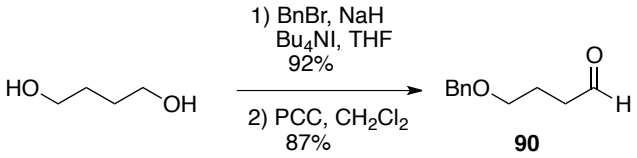
^{1}H NMR (500MHz, $CDCl_3$) δ 5.66 (s, 1H), 4.87 (s, 1H), 4.82 (s, 1H), 4.04 (s, 2H), 3.98 (t, *J* = 4.6 Hz, 1H), 2.85 (t, *J* = 6.0 Hz, 1H), 2.63 (s, 1H), 2.56 (dd, *J* = 17.8, 6.9 Hz, 1H), 2.30 (t, *J* = 6.9 Hz, 2H), 2.22 (d, *J* = 19.5 Hz, 1H), 1.77-1.62 (m, 3H), 1.57-1.51 (m, 1H), 1.46-1.34 (m, 1H) with peaks due to the minor isomer at 5.75 (s), 5.05 (s), 4.97 (s), 3.32 (s), 3.21 (d, *J* = 4.6 Hz), and 2.47 (dd, *J* = 18.0, 6.6 Hz). ^{13}C-NMR (125MHz, $CDCl_3$) δ 149.85, 138.70, 121.99, 115.45, 69.74, 65.36, 44.94, 38.88, 31.86, 31.27, 21.94, 21.91 with peaks due to the minor isomer at 124.25, 117.71, 69.57, 65.81, 35.71, 34.19, 30.76, and 20.19.

Enal 75



The mixture of diol **74** (18.5 mg, 0.095 mmol) and activated MnO_2 (165 mg, 1.9 mmol) in dichloromethane (0.73 mL) was stirred at room temperature for 4.5 h. The mixture was filtered through a pad of celite, and MnO_2 was washed with ethyl acetate. Concentration of the filtrate followed by purification by PTLC afforded 5.3 mg (29%) of enal **75** containing ca.10% of the regioisomer. ^{1}H NMR (500MHz, $CDCl_3$) δ 9.46 (s, 1H), 6.79 (t, *J* = 3.4 Hz, 1H), 4.93 (s, 1H), 4.88 (s, 1H), 3.96-3.93 (m, 1H), 3.09 (s, 1H), 2.99 (t, *J* = 6.0 Hz, 1H), 2.88-2.81 (m, 1H), 2.55 (dd, *J* = 20.9, 4.3 Hz, 1H), 2.36-2.30 (m, 1H), 2.24-2.18 (m, 1H), 1.95 (d, *J* = 8.0 Hz, 1H), 1.81-1.77 (m, 2H), 1.58-1.50 (m, 1H), 1.30-1.20 (m, 2H) with peaks due to the minor isomer at 9.55 (s), 6.96 (s), 5.14 (s), 4.96 (s), 4.05 (s), and 2.71 (dt, *J* = 22.1, 4.7 Hz). ^{13}C-NMR (125MHz, $CDCl_3$) δ 192.89, 149.92, 149.06, 143.06, 116.23, 69.14, 45.10, 35.86, 33.12, 31.92, 22.15, 22.10 with peaks due to the minor isomer at 191.70, 148.74, 141.78, 117.27, 55.29, 45.51, 35.34, 33.92, 32.00, 29.69, and 23.59.

4-Benzyloxybutanal 90



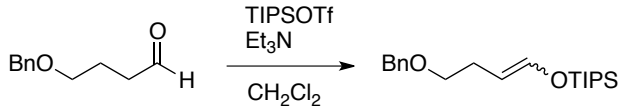
To a suspension of sodium hydride (washed with hexane, 1.44 g, 60.0 mmol) in THF (100 mL) was added 1,4-butanediol **D** (4.43 mL, 50.0 mmol) at 0 ℃. After stirring at room temperature for 1 h, benzyl bromide (5.95 mL, 50.0 mmol) and ^{n}Bu_4NI (0.673 g, 2.50 mmol) was added. After being stirred for 1 h at room temperature, a saturated aqueous NH_4Cl was added. The mixture was separated and the aqueous layer was extracted with ethyl acetate three times. The combined organic layer was dried over $MgSO_4$, and concentrated under reduced pressure. Purification by silica gel column chromatography to give 4-benzyloxy-1-butanol (8.32 g, 46.2 mmol, 92.3%).

^{1}H NMR (500MHz, $CDCl_3$) δ 7.38–7.22 (m, 5H), 4.52 (s, 2H), 3.65 (dd, *J* = 6.3, 5.8 Hz, 2H), 3.52 (dd, *J* = 5.8, 5.7 Hz, 2H), 2.14 (br s, OH), 1.72 (ddd, *J* = 12.6, 6.3, 5.8, 5.7 Hz, 2H), 1.69 (dddd, *J* = 14.3, 12.6, 6.3, 5.8 Hz, 2H) .

To a solution of pyridinium chlorochromate (15.9 g, 73.9 mmol) in CH_2Cl_2 (230 mL) was added a solution of the alcohol (8.32 g, 46.2 mmol) in CH_2Cl_2 (46.0 mL) dropwise over 6 h at room temperature. The mixture was stirred at the same temperature for 12 h and filtrated through a pad of celite. The residue was concentrated under reduced pressure and purified by silica gel column chromatography to give aldehyde **90** (7.12 g, 40.0 mmol, 86.5%).

^{1}H NMR (500MHz, $CDCl_3$) δ 9.79 (s, 1H), 7.38 – 7.24 (m, 5H), 4.49 (s, 2H), 3.51 (t, *J* = 6.3 Hz,2 H), 2.55 (dd, *J* = 6.9, 5.8 Hz, 2H), 1.95 (dddd, *J* = 13.2, 6.9, 6.3, 5.8 Hz, 2H).

Enol silyl ether 89



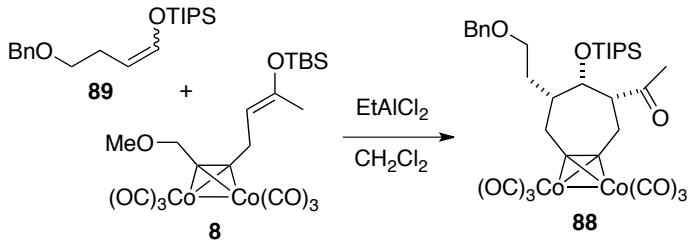
90 **89**

To a solution of aldehyde **90** (7.12 g, 40.0 mmol) and Et_3N (8.36 mL, 60.0 mmol) in CH_2Cl_2 (40 mL) was added TIPSOTf (12.9 mL, 48.0 mmol) at 0 ℃. After stirring for 35 min, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ and extracted three times with ether. The combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography to give **89** (11.7 g, 32.8 mmol, 82.0 % , *E* : *Z* = ca. 1 : 1.2).

^{1}H NMR (500MHz, $CDCl_3$) *E* isomer : δ 7.37 – 7.22 (m, 5H), 6.33 (dt, *J* = 11.5, 1.2 Hz, 1H), 5.01 (dt, *J* =11.5, 7.5 Hz, 1H), 4.50 (s, 2H), 3.44 (t, *J* = 6.9 Hz, 2H), 2.21 (ddd, *J* = 7.5, 6.9, 1.2 Hz, 2H), 1.05 (m, 21H).

Z isomer : δ 7.37 – 7.22 (m, 5H), 6.33 (ddd, *J* = 5.7, 1.8, 1.2 Hz, 1H), 4.52 (s, 2H), 4.45 (ddd, *J* = 6.9, 5.7, 1.8 Hz, 1H), 3.48 (dd, *J* = 7.5, 6.9 Hz, 2H), 2.46 (ddd, *J* = 7.5, 6.9, 1.2 Hz, 2H), 1.05 (m, 21H).

Acetylene dicobalt complex 88

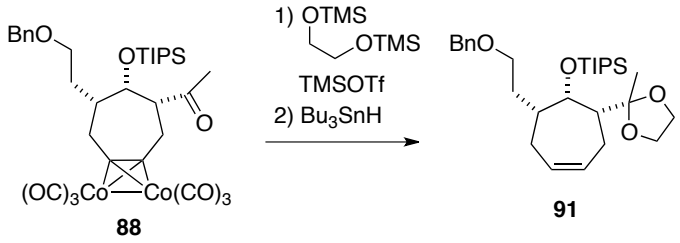


To a solution of $EtAlCl_2$ (1.04 M solution of hexane, 8.9 mL, 9.2 mmol) in CH_2Cl_2 (15 mL) was added a solution of enol silyl ether **89** (3.3 g, 9.2 mmol) and dicobalt complex **8** (2.49 g, 4.60 mmol) in CH_2Cl_2 (15 mL) *via* cannula at 0 ℃. After stirring at 0 ℃ for 9 minutes, the reaction mixture was quenched with a saturated aqueous NaK tartrate (aqueous Roschell's salt) and stirred at room

temperature vigorously for 1 h under argon atmosphere. Then aqueous layer were extracted three times with ether, washed with brine and dried over $MgSO_4$. The combined organic layers were concentrated *in vacuo*. The crude product was purified by silica gel column chromatography to give [5+2] cycloaddition product **88** (2.36 g, 3.26 mmol, 71%) as a dark brown oil.

^{1}H NMR (500MHz, $CDCl_3$) δ 7.34 – 7.26 (m, 5H), 4.72 (s, 1H), 4.52 (s, 2H), 3.60 (dd, *J* = 5.2, 4.0 Hz, 1H), 3.57 (dd, *J* = 12.1, 4.6 Hz, 1H), 3.41 (dd, *J* = 16.1, 12.6 Hz, 1H), 3.14 (dd, *J* = 16.0, 2.9 Hz, 1H), 3.05 (dd, *J* = 16.0, 12.1 Hz, 1H), 2.92 (dd, *J* = 16.0, 3.4 Hz, 1H), 2.50 (dd, *J* = 12.6, 3.4 Hz, 1H), 2.36 (ddd, *J* = 7.5, 4.6, 4.0 Hz, 1H), 2.17 (s, 3H), 1.95 (dd, *J* = 7.5, 6.3 Hz, 1H), 1.78 (dd, *J* = 12.0, 6.3 Hz, 1H), 1.05 (m, 21H).

Acetal 91



To a solution of ketone **88** (4.45 g, 6.15 mmol) in CH_2Cl_2 (6.20 mL) was added ethylenedioxy bis(trimethylsilane) (4.70 mL, 18.5 mmol) followed by trimethylsilyl trifluoromethanesulfonate (0.220 mL, 1.21 mmol) at 0 ℃. After being stirred for 1.5 h, reaction mixture was poured into a saturated $NaHCO_3$ and separated. Then aqueous layer were extracted three times with ether, washed with brine and dried over $MgSO_4$. The combined organic layers were concentrated *in vacuo*. The crude product was purified by silica gel column chromatography to give the corresponding acetal (4.05 g, 5.24 mmol, 85 %).

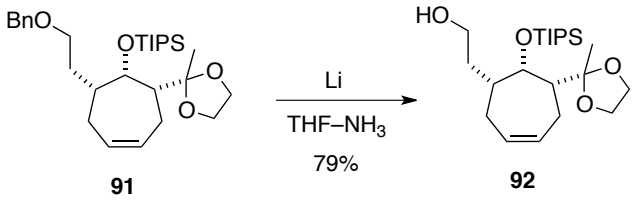
^{1}H NMR (500MHz, $CDCl_3$) δ 7.32 – 7.23 (m, 5H), 4.57 (s, 1H), 4.50 (d, *J* = 2.3 Hz, 2H), 4.00 (s, 1H), 3.92 (dd, *J* = 9.2, 4.0 Hz, 2H), 3.83 (dd, *J* = 5.2, 3.5 Hz, 2H), 3.55 (ddd, *J* = 6.3, 3.5, 2.9 Hz, 2H), 3.15 (dd, *J* = 15.5, 12.0 Hz, 1H), 3.08 (dd, *J* = 6.9, 2.3 Hz, 1H), 3.05 (dd, *J* = 15.5, 12.1 Hz, 1H), 2.85 (dd, *J* = 16.1, 2.9 Hz, 1H), 1.93 (ddd, *J* = 12.0, 6.3, 5.7 Hz, 1H), 1.79 (m, 1H), 1.77 (dd, *J* = 10.9, 5.7 Hz, 2H), 1.30 (s, 3H), 1.05 (m, 21H).

To a solution of the acetal (4.05 g, 5.24 mmol) and Bu_3SnH (6.50 mL, 26.2 mmol) in toluene (35.0 mL) was heated at 75 ℃ for 1 h. After cooling to room temperature, toluene was removed under reduced pressure. The residue was filtered through a pad of silica gel and purified by silica gel column chromatography to give acetal **91** (1.80 g, 3.68 mmol, 70%).

^{1}H NMR (500MHz, $CDCl_3$) δ 7.35 – 7.26 (m, 5H), 5.75 (ddd, *J* = 11.5, 8.0, 3.4 Hz,1H) 5,63 (ddd, *J* = 11.5, 8.0, 3.4 Hz, 1H), 4.51 (s, 1H), 4.51 (d, *J* = 16.7 Hz, 2H), 3.91 (ddd, *J* = 12.0, 9.8, 6.3 Hz, 2H),

3.84 (ddd, *J* = 12.6, 9.8, 6.3 Hz, 2H), 3.50 (dddd, *J* = 14.3, 10.3, 8.0, 6.3 Hz, 2H), 2.53 (dtt, *J* = 13.8, 8.0, 3.5 Hz, 1H), 2.42 (dt, *J* = 13.8, 3.5 Hz, 1H), 2.02 (dd, *J* = 14.9, 9.2 Hz, 1H), 1.81 (ddd, *J* = 14.9, 9.2, 8.0 Hz, 2H), 1.67 (d, *J* = 10.3 Hz, 1H), 1.60 (dd, *J* = 10.3, 8.0 Hz, 2H), 1.30 (s, 3H), 1.05 (m, 21H).

Alcohol 92

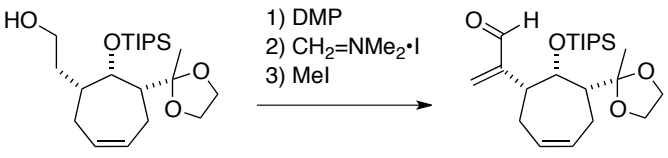


91 **92**

To a solution of lithium wire (washed with hexane, 0.158 g, 22.8 mmol) in liq.NH_3, which was distilled over Na, was added a solution of benzyl ether **91** (1.80 g, 3.68 mmol) in THF (18.5 mL) at –78 ℃. After stirring for 1 h at the same temperature, the mixture was added a saturated aqueous NH_4Cl. The mixture was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography gave alcohol **92** (1.15 g, 2.91 mmol, 79%).

^{1}H NMR (500MHz, $CDCl_3$) δ 5.76 (ddd, *J* = 8.1, 6.3, 3.4 Hz, 1H), 5.65 (ddd, *J* = 11.5, 8.0, 3.5 Hz, 1H), 4.53 (s,1H), 3.91 (m, 4H), 3.70 (ddd, *J* = 15.5, 6.9, 5.2 Hz, 2H), 2.54 (dt, *J* = 14.9, 2.9 Hz, 1H), 2.45 (dt, *J* = 14.9, 2.9 Hz, 1H), 2.03, (dd, *J* = 15.5, 6.3 Hz, 1H), 1.83 (dd, *J* = 15.5, 8.1 Hz, 1H), 1.77 (dd, *J* = 15.5, 8.0 Hz, 1H), 1.68 (d, *J* = 11.5 Hz, 1H), 1.58 (m, 2H), 1.30 (s, 3H), 1.05 (m, 21H).

Aldehyde 93



92 **93**

To a solution of alcohol **92** (1.10 g, 2.76 mmol) in CH_2Cl_2 (13.8 mL) was added Dess-Martin periodinane (1.76 g, 4.14 mmol) at 0 ℃. After stirring at room temperature for 1 h, reaction mixture was quenched with a saturated aqueous $NaHCO_3$ and a saturated aqueous $Na_2S_2O_3$. The aqueous layer was extracted with ether. The combined organic layer was washed with brine and dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was used for the next step without further purification.

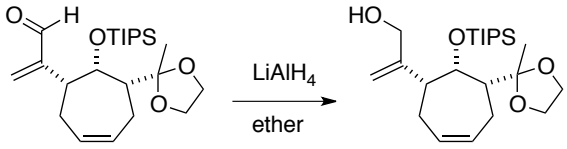
^{1}H NMR (500MHz, $CDCl_3$) δ 9.78 (d, *J* = 2.3 Hz, 1H), 5.78 (ddd, *J* = 11.5, 8.0, 2.9 Hz, 1H), 5.62 (ddd, *J* = 11.5, 8.0, 2.9 Hz, 1H), 4.52 (s, 1H), 3.95 – 3.84 (m, 4H), 2.68 (dd, *J* = 18.4, 5.8 Hz, 1H), 2.49 (ddt, *J* = 14.9, 8.0, 2.3 Hz, 2H), 2.17 (m, 1H), 2.06 (dd, *J* = 16.1, 7.5 Hz, 1H), 1.79 (dd, *J* = 16.1, 5.8 Hz, 2H),1.52 (dd, *J* = 14.9 Hz, 1H), 1.30 (s, 3H), 1.05 (m, 21H).

The mixture of the crude aldehyde and *N,N*-dimethylmethyleneiminium iodide （1.53 g, 8.28 mmol） in dichloroethane (55 mL) was heated at 75 ℃ for 1.5 h. The mixture was poured into a saturated aqueous $NaHCO_3$, and the mixture was separated. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give crude product, which was used for the next step without purification.

The mixture of the crude product and methyl iodide (0.515 mL, 8.28 mmol) in CH_2Cl_2 (55 mL) was heated at 35 ℃. After being stirred for 3 h, the mixture was poured into a saturated aqueous $NaHCO_3$ and separated. The aqueous layer was extracted with CH_2Cl_2 three times. The organic layer was washed with brine and dried over $MgSO_4$. Concentration *in vacuo* followed by purification by silica gel column chromatography gave unsaturated aldehyde **93** (1.01 g, 2.48 mmol, 90 % from **92**).

^{1}H NMR (500MHz, $CDCl_3$) δ 9.56 (s, 1H), 6.23 (s, 1H), 6.09 (s, 1H), 5.81 (ddd, *J* = 8.6, 8.0, 3.5 Hz, 1H), 5.68 (ddd, *J* = 12.0, 8.0, 3.5 Hz, 1H), 4.60 (s, 1H), 3.99 (ddd, *J* = 10.9, 6.9, 2.9 Hz, 2H), 3.90 (ddd, *J* = 12.6, 6.9, 5.7 Hz, 2H), 2.83 (dtt, *J* = 12.0, 8.6, 2.9 Hz, 1H), 2.67 (d, *J* = 12.6 Hz, 1H), 2.53 (ddd, *J* = 12.6, 12.0, 2.9 Hz, 1H), 2.12 (dd, *J* = 13.8, 10.9 Hz, 1H), 1.90 (d, *J* = 13.8 Hz, 1H), 1.85 (dd, *J* = 8.0, 5.7 Hz, 1H), 1.38 (s , 3H), 1.05 (m, 21H).

Alcohol 94



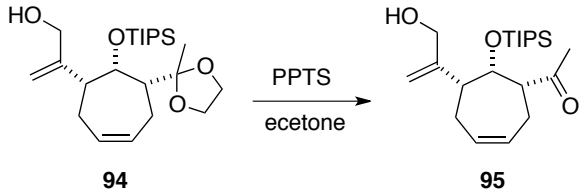
93 **94**

To a suspension of $LiAlH_4$ (71 mg, 1.87 mmol) in ether (1.85 mL) was added aldehyde **93** (763 mg) in ether (1.9 mL) at –40 ℃. After stirring 10 minutes, H_2O (71 μL) was added. The reaction mixture was allowed to warm up at room temperature and treated 4 M aqueous NaOH (71 μL) followed by H_2O (0.213 mL). After being stirred at room temperature for over 3 h, the reaction mixture was filtrated through celite pad and concentrated under reduced pressure. Purification by silica gel column chromatography gave alcohol **94** (526 mg, 1.28 mmol, 69%).

^{1}H NMR (500MHz, $CDCl_3$) δ 5.75 (ddd, *J* = 6.3, 5.2, 3.5 Hz, 1H), 5.68 (ddd, *J* = 8.0, 5.2, 3.5 Hz, 1H), 5.17 (s, 1H), 4.93 (s, 1H), 4.68 (s, 1H), 4.17 (dd, *J* = 8.0, 6.3 Hz, 2H), 3.96 – 3.85 (m, 4H), 2.77 (dtt, *J*

= 14.8, 12.0, 2.9 Hz, 1H), 2.55 (ddt, *J* = 12.6, 12.0, 2.9 Hz, 1H), 2.17 (12.6 Hz, 1H), 2.10 (dd, *J* = 18.9, 7.5 Hz, 1H), 1.98 (dd, *J* = 18.9, 7.5 H z , 1H), 1.74 (dd *J* = 14.8 Hz, 1H), 1.30 (s, 3H), 1.05 (m, 21H).

Ketone 95

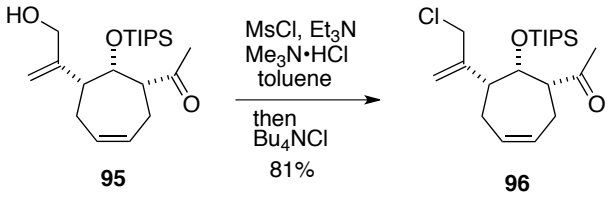


94 **95**

To the mixture of **94** (526 mg, 1.26 mmol) and pyridinium *p*-toluenesulfonate (352 mg, 1.39 mmol) in acetone (6.3 mL) was heated at 65 ℃. After being stirred for 3 h, the reaction mixture was poured into a saturated aqueous $NaHCO_3$ and separated. The aqueous layer was extracted with ethyl acetate and the organic layer was washed with brine and dried over $MgSO_4$. Concentration *in vacuo* followed by purification by silica gel column chromatography gave ketone **95** (457.4 mg, 1.25 mmol, 99%).

^{1}H NMR (500MHz, $CDCl_3$) δ 5.82 (t, *J* = 4.0 Hz, 2H), 5.18 (s, 1H), 4.96 (s, 1H), 4.85 (s, 1H), 4.19 (s, 1H), 4.18 (s, 1H), 2.86 (ddd, *J* = 12.6, 6.3, 4.0 Hz, 2H), 2.42 (d, *J* = 10.9 Hz, 1H), 2.23 (dd, *J* = 10.9, 2.3 Hz, 2H), 2.21 (s, 3H), 1.94 (dd, *J* = 6.3, 2.3 Hz, 1H), 1.05 (m, 21H).

Chloride 96

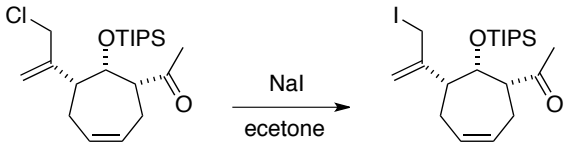


95 **96**

To a solution of alcohol **95** (457 mg, 1.25 mmol), Et_3N (0.70 mL, 5.0 mmol) and $Me_3N \cdot HCl$ (0.119 g, 1.25 mmol) in toluene (6.3 mL) was added methanesulfonyl chloride (0.19 mL, 2.5 mmol) at 0 ℃. After being stirred at 0 ℃ for 20 minutes, Bu_4NCl (0.417 g, 1.50 mmol) was added. The reaction mixture was heated at 80 ℃ for 15 minutes and poured into a saturated $NaHCO_3$. The aqueous layer was extracted with ether. The combined organic layer was washed with saturated brine and dried over $MgSO_4$. Concentration *in vacuo* followed by purification by silica gel column chromatography gave allyl chloride **96** (388 mg, 1.0 mmol, 81%).

^{1}H NMR (500MHz, $CDCl_3$) δ 5.83 (ddd, *J* = 9.7, 6.9, 2.9 Hz, 2H), 5.30 (s, 1H), 5.06 (s, 1H), 4.86 (s, 1H), 4.21 (d, *J* = 12.6 Hz, 1H), 4.12 (d, *J* = 12.6 Hz, 1H), 2.88 (dd, *J* = 12.1, 2.3 Hz, 1H), 2,86 (dd, *J* = 12.1, 2.9 Hz, 1H), 2.43 (d, *J* = 11.5 Hz, 1H), 2.41 (d, *J* = 11.5 Hz, 1H), 2.25 (dd, *J* = 14.9, 9.7 Hz, 1H), 2.32 (s, 3H), 2.22 (dd, *J* = 14.9, 6.9 Hz, 1H). 1.05 (m, 21H).

Iodide 87

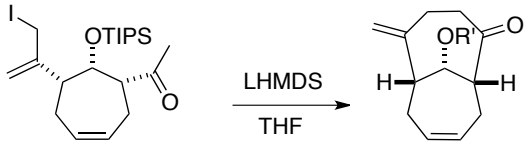


96 **87**

To a solution of chloride **96** (388 mg, 1.01 mmol) in acetone (10 mL) was added NaI (1.51 g, 10.1 mmol). The reaction mixture was heated at 60 ℃ and stirred for 2 h. After cooling to room temperature, the mixture was diluted with ether and filtrated through celite pad and concentrated. Purification by silica gel column chromatography gave allyl iodide **87** (425 mg, 0.89 mmol, 88%).

^{1}H NMR (500MHz, $CDCl_3$) δ 5.84 (ddd, *J* = 11.5, 6.9, 6.3 Hz, 2H), 5.40 (s, 1H), 5.02 (s, 1H), 4.82 (s, 1H), 4.05 (s, 2H), 2.86 (d, *J* = 9.8 Hz, 1H), 2.81 (d, *J* = 9.8 Hz, 1H), 2.45 (t, *J* = 9.8 Hz, 2H), 2.26 (dd, *J* = 14.9, 9.8 Hz, 1H), 2.23 (s, 3H), 1.95 (dd, *J* = 14.9, 6.9, 6.3 Hz, 1H), 1.06 (m, 21H).

Bicyclic ketone 86

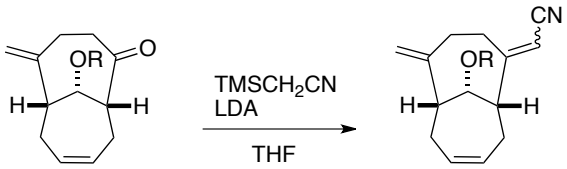


87 **86**

To a solution of iodide **87** (425 mg, 0.89 mmol) in THF (8.9 mL) was added LHMDS (2.96 mL, 0.5 M solution in THF, 1.34 mmol) at -78 ℃. After being stirred for 1.5 h at –30 ℃, a saturated aqueous $NaHCO_3$ was added. The mixture was separated and the aqueous layer was extracted with ether. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel column chromatography gave ketone **86** (311 mg, 0.89 mmol, quant.).

^{1}H NMR (500MHz, $CDCl_3$) δ 5.81 (ddd, *J* = 10.9, 6.3, 1.7 Hz, 1H), 5.74 (ddd, *J* = 10.9, 5.8, 5.2 Hz, 1H), 4.87 (t, *J* = 1.7 Hz, 1H), 4.80 (s, 1H), 4.19 (d, 5.2 Hz, 1H), 3.03 (ddd, *J* = 10.3, 9.2, 5.7 Hz, 2H), 2.85 (ddd, *J* = 9.2, 6.3, 5.7 Hz, 2H), 2.55 (t, *J* = 12.0 Hz, 1H), 2.40 (dd, *J* = 6.9, 5.8 Hz, 1H), 2,38 (dd, *J* = 6.9, 5.8 Hz, 1H), 2.26 (t, *J* = 6.3 Hz, 2H), 2.11 (d, *J* = 10.3 Hz, 1H), 1.05 (m, 21H).

Unsaturated nitrile 97



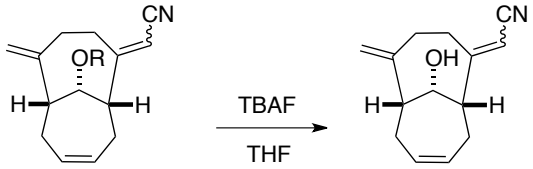
86
(R = TIPS)

97

To a solution of (trimethylsilyl)acetonitrile (0.37 mL, 2.7 mmol) in THF (0.50 mL) was added LDA (3.1 mL, 1 M solution in THF) at –78 ℃. After being stirred at the same temperature for 30 minutes, a solution of ketone **86** (311 mg, 0.89 mmol) in THF (4.0 mL) was added and allowed to warm up at –20 ℃. The mixture was stirred for 1 h at –20 ℃ and added a saturated aqueous NH_4Cl. The mixture was separated and the aqueous layer was extracted with ether. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel column chromatography gave unsaturated nitrile **97** (331 mg, 0.89 mmol, quant.).

^{1}H NMR (500MHz, $CDCl_3$) δ 5.87 (ddd, *J* = 10.3, 4.6, 1.7 Hz, 1H), 5.79 (dddd, *J* = 10.3, 5.8, 4.6, 1.7 Hz, 1H), 5.17 (s, 1H), 4.86 (s, 1H), 4.76 (d, *J* = 1.7 Hz, 1H), 4,15 (dd, *J* = 5.7, 4.6 Hz, 1H), 3.59 (dd, *J* = 11.5, 4.6, 4.0 Hz, 1H), 3.01 (dd, *J* = 9.7, 4.6 Hz, 1H), 2.58 (dd, *J* = 8.6, 6.9 Hz, 2H), 2.53 (11.5, 9.7, 8.1 Hz, 2H), 2.45 (ddd, *J* = 10.3, 8.1, 6.9 Hz, 2H), 2.32 (dt, *J* = 10.3, 5.7 Hz, 2H), 1.05 (m, 21H).

Alcohol 100



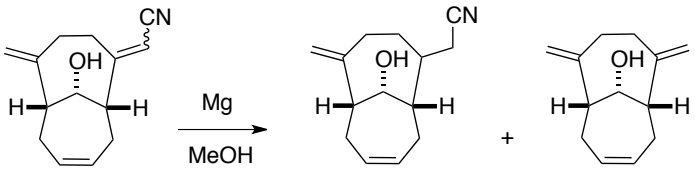
97

100

To unsaturated nitrile **97** (331 mg, 0.89 mmol) was added TBAF (3.1 mL, 1.0 M solution in THF, 3.1 mmol) at room temperature. The mixture was stirred for 30 minutes and poured into water. The mixture was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine and dried over $MgSO_4$, and concentrated under reduced pressure. Purification by silica gel column chromatography gave alcohol **100** (111 mg, 0.516 mmol, 58%).

^{1}H NMR (500MHz, $CDCl_3$) (major diastereomer) δ 5.79 (ddd, *J* = 11.5, 6.9, 5.2 Hz, 1H), 5.70 (ddd, *J* = 9.2, 5.7, 3.5 Hz, 1H), 5.22 (s, 1H), 4.97 (s, 1H), 4.89 (dd, *J* = 8.6, 6.3 Hz, 1H), 3.98 (ddd, *J* = 8.1, 7.5, 4.6 Hz, 1H), 2.99 (dd, *J* = 5.2, 4.6 Hz, 1H), 2.95 (dd, *J* = 5.2, 4.6 Hz, 1H), 2.80 (ddd, *J* = 8.1, 7.5, 6.9 Hz, 2H), 2.55 (ddd, *J* = 8.0, 7.5, 6.9 Hz, 1H), 2.50 (ddd, *J* = 9.2, 6.3, 3.5 Hz, 1H), 2.41 (m, 3H), 1.90 (d, *J* = 8.6 Hz, 1H), 1.05 (m, 21H).

Nitrile 101

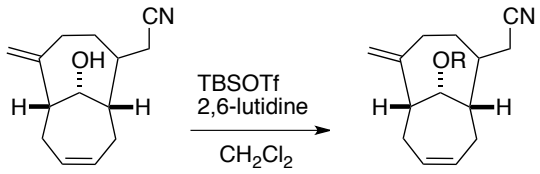


100 **101** **102**

To a solution of unsaturated nitrile **100** (111 mg, 0.516 mmol) in MeOH (5.2 mL) was added activated Mg (0.125 g) at room temperature. After being stirred for 1.5 h, the reaction mixture was filtered through cotton and concentrated. Purification by silica gel column chromatography gave nitrile **101** (75.0 mg, 0.345 mmol, 67 %).

^{1}H NMR (500MHz, $CDCl_3$) δ 5.71 (ddd, *J* = 6.9, 6.3, 1.7 Hz, 2H), 4.91 (s, 1H), 4.85 (t, *J* = 1.7 Hz, 1H), 4.03 (dd, *J* = 4.6, 4.0 Hz, 1H), 2.88 (dd, *J* = 4.6, 4.0 Hz, 1H), 2.51 (dd, *J* = 7.5, 6.9 Hz, 1H), 2.45 (ddd, *J* = 6.3, 5.2, 3.5 Hz, 1H), 2.36 (dd, *J* = 6.3, 2.3 Hz, 2H), 2.32 (dd, *J* = 7.5, 4.6 Hz, 2H), 2.27 (dd, *J* = 10.3, 6.3 Hz, 2H), 2.12 (dd, *J* = 6.3, 3.5 Hz, 1H), 1.91 (d, *J* = 5.7 Hz, 1H), 1.73 (ddd, *J* = 10.3, 6.9, 4.0 Hz, 1H), 1.65 (ddd, *J* = 6.9, 5.3, 2.3 Hz, 1H).

Silyl ether 103

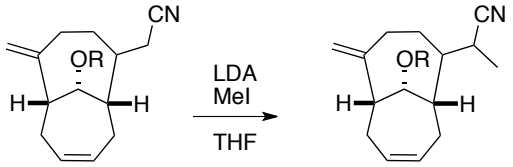


101 **103**
(R = TBS)

To a solution of alcohol **101** (121 mg, 0.55 mmol) and 2,6-lutidine (0.098 mL, 0.83 mmol) in CH_2Cl_2 (5.5 mL) was added *tert*-butyldimethylsilyl triflate (0.154 mL, 0.66 mmol) at 0 ℃. After stirring at the same temperature for 45 min, the mixture was poured into a saturated aqueous $NaHCO_3$. The mixture was separated and the aqueous layer was extracted with ether three times. The combined organic layer was washed with brine and dried over $MgSO_4$, and concentrated under reduced pressure. Purification by silica gel column chromatography gave **103** (152 mg, 0.457 mmol, 83%).

^{1}H NMR (500MHz, $CDCl_3$) δ 5.61 (dddd, *J* = 7.5, 5.8, 5.2, 1.7 Hz, 2H), 4.77 (s, 1H), 4.67 (t, *J* = 1.8 Hz, 1H), 4.00 (dd, *J* = 5.7, 2.9 Hz, 1H), 2.71 (br s, 1H), 2.55 (dd, *J* = 14.3, 7.5 Hz, 1H), 2.43 (dt, *J* = 12.1, 5.2 Hz, 1H), 2.24 (ddd, *J* = 7.5, 5.2, 2.3 Hz, 2H), 2.21 (dd, *J* = 8.6, 4.0 Hz, 2H), 2.21 (m, 3H), 1.93 (dd, *J* = 9.2, 5.8 Hz, 1H), 1.61 (ddd, *J* = 9.2, 4.0, 2.9 Hz, 1H), 1.56 (dt, *J* = 12.1, 2.9 Hz, 1H), 0.91 (s, 9H), 0.3 (s, 3H), 0.0 (s, 3H).

Nitrile 104

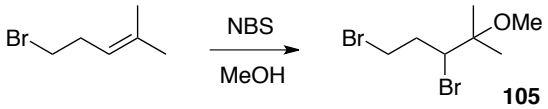


103 (R = TBS) **104**

To a solution of nitrile **103** (48.9 mg, 0.150 mmol) in THF (0.75 mL) was added LDA (0.32 mL, 0.5 M solution in THF, 0.15 mmol) at –78 ℃. After being stirred for 1 h at the same temperature, MeI (19 μl, 0.30 mmol) was added and the mixture was stirred for 1.5 h at –78 ℃. Then a saturated aqueous $NaHCO_3$ was added. The mixture was separated and the aqueous layer was extracted with ether. The combined organic layer was washed with brine and dried over $MgSO_4$, and concentrated under reduced pressure. Purification by silica gel column chromatography gave **104** (43.7 mg, 0.125 mmol, 83%).

^{1}H NMR (500MHz, $CDCl_3$) δ 5.71 (dd, *J* = 5.8, 5.2 Hz, 1H), 5.65 (dd, *J* = 11.5, 5.8 Hz, 1H), 4.85 (s, 1H), 4.74 (s, 1H), 4.05 (dd, *J* = 6.3, 2.9 Hz, 1H), 2.76 (br s, 1H), 2.50 (ddd, *J* = 12.1, 10.3, 2.9 Hz, 2H), 2.47 (dd, *J* = 7.5, 6.9 Hz, 1H), 2.36 (ddd, *J* = 10.9, 6.9, 2.9 Hz, 2H), 2.30 (dd, *J* = 14.9, 11.5 Hz, 2H), 2.17 (dd, *J* = 10.9, 4.6 Hz, 1H), 1.96 (ddd, *J* = 12.1, 10.9, 6.3 Hz, 2H), 1.75 (dd, *J* = 14.9, 2.9 Hz, 1H), 1.32 (d, *J* = 7.5 Hz, 3H), 0.91 (s, 9H), 0.3 (s, 3H), 0.0 (s, 3H).

1,3-Dibromo-4-methoxy-4-methylpentane

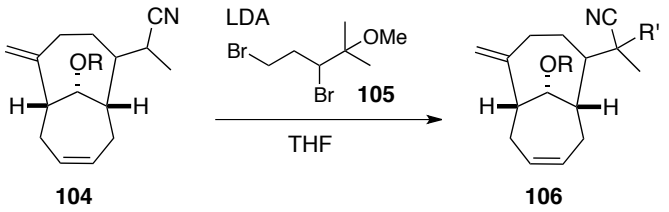


105

To a solution of homoprenyl bromide (0.093 mL, 1.0 mmol) in MeOH (5 mL) was added *N*-bromosuccinimide （214 mg, 1.20 mmol） at room temperature. After being stirred for 1.5 h, the reaction mixture was poured into saturated brine and separated. The aqueous layer was extracted with ether and the organic layer was dried over $MgSO_4$. Concentration *in vacuo* followed by purification by silica gel column chromatography gave bromide **105** (215 mg, 0.786 mmol, 79%).

^{1}H NMR (500MHz, $CDCl_3$) δ 4.23 (dd, *J* = 11.5, 2.3 Hz, 1H), 3.69 (ddd, *J* = 6.3, 5.7, 3.4 Hz, 1H), 3.60 (dt, *J* = 9.2, 4.6 Hz, 1H), 3.21 (s, 3H), 2.46 (dddd, *J* = 10.3, 6.3, 4.6, 2.3 Hz, 1H), 2.23 (dddd, *J* = 10.3, 9.2, 5.7, 3.4 Hz, 1H), 1.38 (s, 3H), 1.30 (s, 3H).

Nitrile 106



104 106

To nitrile **104** (43.7 mg, 0.125 mmol) was added LDA (0.32 mL, 0.5 M solution in THF, 0.15 mmol) at 0 ℃. After being stirred for 1 h at 0 ℃, a solution of bromide **105** (48 mg, 0.15 mmol) in THF (0.30 mL) was added. After being stirred for 1 h, the mixture was poured into a saturated aqueous $NaHCO_3$ and separated. The aqueous layer was extracted with ether followed by the combined organic layer was washed with brine and dried over $MgSO_4$. Concentration *in vacuo* followed by purification by silica gel column chromatography gave nitrile **106** (24.4 mg, 0.045 mmol, 36%).

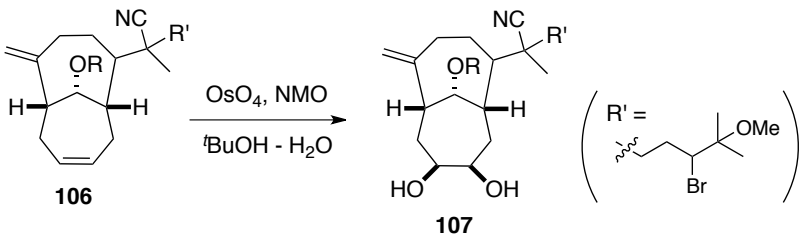
Major diastereomer:

^{1}H NMR (500MHz, $CDCl_3$) δ 5.75 (ddd, *J* = 10.9, 5.8, 5.2 Hz, 1H), 5.65 (ddd, *J* = 10.9, 5.8, 5.2 Hz, 1H), 4.85 (s, 1H), 4.74 (s, 1H), 4.06 (d, *J* = 3.4 Hz, 1H), 3.89 (dd, *J* = 10.3, 1.7 Hz, 1H), 3.23 (s, 3H), 2.75 (br s, 1H), 2.51 (ddd, *J* = 10.9, 5.8, 5.2 Hz, 2H), 2.41 (dd, *J* = 6.9, 4.6 Hz, 2H), 2.27 (dd, *J* = 8.6, 4.6 Hz, 2H), 2.18 (d, *J* = 12.6 Hz, 1H), 2.14 (d, *J* = 12.6 Hz, 1H), 2.02 (ddd, *J* = 12.6, 8.6, 3.4 Hz, 1H), 1.88 (dd, *J* = 10.9, 6.9 Hz, 1H), 1.79 (ddd, *J* = 12.6, 8.6, 3.4 Hz, 2H), 1.35 (s, 3H), 1.32 (s, 3H), 1.30 (s, 3H), 1.26 (m, 2H), 0.91 (s, 9H), 0.3 (s, 3H), 0.0 (s, 3H).

Minor diastereomer:

^{1}H NMR (500MHz, $CDCl_3$) δ 5.75 (ddd, *J* = 10.9, 5.8, 5.2 Hz, 1H), 5.65 (ddd, *J* = 10.9, 5.8, 5.2 Hz, 1H), 4.85 (s, 1H), 4.74 (s, 1H), 4.06 (d, *J* = 3.4 Hz, 1H), 3.82 (d, *J* = 10.9 Hz, 1H), 3.23 (s, 3H), 2.75 (br s, 1H), 2.51 (ddd, *J* = 10.9, 5.8, 5.2 Hz, 2H), 2.41 (dd, *J* = 6.9, 4.6 Hz, 2H), 2.27 (dd, *J* = 8.6, 4.6 Hz, 2H), 2.18 (d, *J* = 12.6 Hz, 1H), 2.14 (d, *J* = 12.6 Hz, 1H), 2.02 (ddd, *J* = 12.6, 8.6, 3.4 Hz, 1H), 1.88 (dd, *J* = 10.9, 6.9 Hz, 1H), 1.79 (ddd, *J* = 12.6, 8.6, 3.4 Hz, 2H), 1.35 (s, 3H), 1.32 (s, 3H), 1.30 (s, 3H), 1.26 (m, 2H), 0.91 (s, 9H), 0.3 (s, 3H), 0.0 (s, 3H).

Diol 107



106 107

To a solution of **106** (24.4 mg, 0.0453 mmol) and OsO_4 (14 μl, 0.159 M in ^{t}BuOH, 2.25 μmol) in ^{t}BuOH (0.03 mL) and H_2O (60 μL) was added NMO (5.3 mg, 0.045 mmol) at room temperature. After

being stirred for 6.5 h at room temperature, the reaction was quenched with $NaHSO_3$ (solid) and a saturated aqueous $NaHSO_3$, stirred further 30 min and separated. The aqueous layer was extracted with ethyl acetate, and the combined organic layer were washed with brine, dried over $MgSO_4$ and concentrated. The crude product was purified to give diol **107** (11.6 mg, 0.020 mmol, 45%) along with starting material **106** (5.1 mg, 0.0095 mmol. 21%).

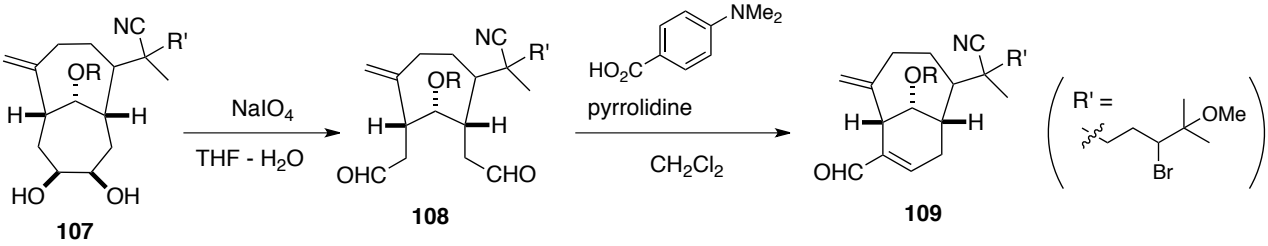
Major diastereomer:

^{1}H NMR (500MHz, $CDCl_3$) δ 4.87 (s, 1H), 4.85 (s, 1H), 4.57 (d, *J* = 7.5 Hz, 1H), 4.17 (d, *J* = 6.9 Hz, 1H), 3.99 (m, 1H), 3.89 (dd, *J* = 10.9, 1.7 Hz, 1H), 3.23 (s, 3H), 2.53 (dd, *J* = 12.0, 9.2 Hz, 2H), 2.43 (dd, *J* = 9.2, 4.1 Hz, 1H), 2.34 (dd, *J* = 7.5, 5.2 Hz, 2H), 2.29 (dd, *J* = 10.9, 2.9 Hz, 1H), 2.15 (d, *J* = 12.6 Hz, 1H), 2.01 (dt, *J* = 14.3, 7.5 Hz, 2H), 1.78 (dt, *J* = 10.9, 2.9 Hz, 2H), 2.15 (d, *J* = 12.6 Hz, 1H), 1.60 (dd, *J* = 10.9, 5.2 Hz, 2H), 1.35 (s, 3H), 1.32 (s, 3H), 1.30 (s, 3H), 1.26 (m, 1H), 0.91 (s, 9H), 0.3 (s, 3H), 0.0 (s, 3H).

Minor diastereomer:

^{1}H NMR (500MHz, $CDCl_3$) δ 4.87 (s, 1H), 4.85 (s, 1H), 4.57 (d, *J* = 7.5 Hz, 1H), 4.17 (d, *J* = 6.9 Hz, 1H), 3.99 (m, 1H), 3.82 (dd, *J* = 10.9, 1.7 Hz, 1H), 3.23 (s, 3H), 2.53 (dd, *J* = 12.0, 9.2 Hz, 2H), 2.43 (dd, *J* = 9.2, 4.1 Hz, 1H), 2.34 (dd, *J* = 7.5, 5.2 Hz, 2H), 2.29 (dd, *J* = 10.9, 2.9 Hz, 1H), 2.15 (d, *J* = 12.6 Hz, 1H), 2.01 (dt, *J* = 14.3, 7.5 Hz, 2H), 1.78 (dt, *J* = 10.9, 2.9 Hz, 2H), 2.15 (d, *J* = 12.6 Hz, 1H), 1.60 (dd, *J* = 10.9, 5.2 Hz, 2H), 1.35 (s, 3H), 1.32 (s, 3H), 1.30 (s, 3H), 1.26 (m, 1H), 0.91 (s, 9H), 0.3 (s, 3H), 0.0 (s, 3H).

Unsaturated aldehyde <u>109</u>



107 **108** **109**

To a solution of diol **107** (11.6 mg, 20.3 μmol) in THF (169 μl) and H_2O (34 μl) was added sodium periodate (6.5 mg, 31 μmol) at room temperature. After being stirred for 1 h at the same temperature, water was added. The aqueous layer was extracted with ether and the organic layer was combined, washed with brine, dried over $MgSO_4$ and concentrated to give crude product dialdehyde **108**, which was used for the next step without purification.

A solution of 4-(dimethylamino)benzoic acid (1.7 mg, 10 μmol) and pyrrolidine (1.0 μl, 12 μmol) in CH_2Cl_2 (51 μl) was heated at 35 ℃. After being stirred for 5 min, a solution of crude aldehyde **108** in CH_2Cl_2 (51 μl) was added. The mixture was heated at 45 ℃ and stirred for 1.5 h. Then poured into a

saturated $NaHCO_3$ and separated. The aqueous layer was extracted with CH_2Cl_2. The organic layer was washed with saturated brine and dried over $MgSO_4$. Concentration *in vacuo* followed by purification by silica gel column chromatography gave unsaturated aldehyde **109** (4.8 mg, 8.7 μmol, 43% from **107**) as a single regioisomer.

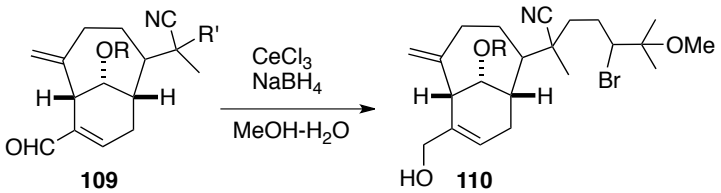
Major diastereomer:

^{1}H NMR (500MHz, $CDCl_3$) δ 9.44 (s, 1H), 6.79 (t, *J* = 3.5 Hz, 1H), 5.02 (s, 1H), 4.95 (d, *J* = 3.5 Hz, 1H), 3.91 (dd, *J* = 9.2, 5.2 Hz, 2H), 3.87 (d, *J* = 10.9 Hz, 1H), 3.56 (br s, 1H), 3.23 (s, 3H), 2.88 (dd, *J* = 15.5, 4.6 Hz, 1H), 2.66 (m, 1H), 2.44 (br s, 1H), 2.32 (dd, *J* = 5.2, 4.0 Hz, 2H), 2.22 (d, *J* = 13.8 Hz, 1H), 2.06 (ddd, *J* = 10.9, 5.8, 5.2 Hz, 2H), 1.73 (ddd, *J* = 13.8, 10.9, 9.8 Hz, 2H), 1.56 (m, 1H), 1.34 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H), 0.91 (s, 9H), 0.3 (s, 3H), 0.0 (s, 3H).

Minor diastereomer:

^{1}H NMR (500MHz, $CDCl_3$) δ 9.44 (s, 1H), 6.79 (t, *J* = 3.5 Hz, 1H), 5.02 (s, 1H), 4.95 (d, *J* = 3.5 Hz, 1H), 3.91 (dd, *J* = 9.2, 5.2 Hz, 2H), 3.81 (d, *J* = 10.9 Hz, 1H), 3.56 (br s, 1H), 3.23 (s, 3H), 2.92 (dd, *J* = 15.5, 4.6 Hz, 1H), 2.61 (m, 1H), 2.44 (br s, 1H), 2.32 (dd, *J* = 5.2, 4.0 Hz, 2H), 2.22 (d, *J* = 13.8 Hz, 1H), 2.06 (ddd, *J* = 10.9, 5.8, 5.2 Hz, 2H), 1.73 (ddd, *J* = 13.8, 10.9, 9.8 Hz, 2H), 1.56 (m, 1H), 1.34 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H), 0.91 (s, 9H), 0.3 (s, 3H), 0.0 (s, 3H).

Allyl alcohol 110



109 (R = TBS) **110**

To a solution of aldehyde **109** (4.8 mg, 8.7 μmol) and cerium(Ⅲ) chloride heptahydrate (32 mg, 87 μmol) in MeOH (90 μl) and water (10 μl) was added sodium borohydride (3.3 mg, 87 μmol) at 0 ℃. The mixture was allowed to warm up at room temperature for 1 h. The reaction mixture was diluted with water and added acetone. Most of organic solvent was removed under reduced pressure and remaining aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated. Purification by silica gel column chromatography gave allyl alcohol **110** (1.4 mg, 2.9 μmol, 33%).

Major diastereomer:

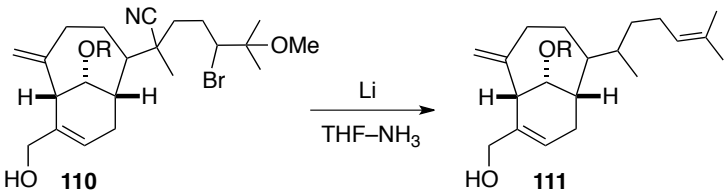
^{1}H NMR (500MHz, $CDCl_3$) δ5.70 (s, 1H), 4.91 (t, *J* = 2.3 Hz, 1H), 4,84 (s, 1H), 4.05 (dd, *J* = 11.5, 6.3 Hz, 1H), 4.02 (s, 2H), 3.88 (d, *J* = 9.2 Hz, 1H), 3.23 (s, 3H), 3.12 (t, *J* = 6.3 Hz, 1H), 2.52 (t, *J* = 11.5 Hz, 2H), 2.39 (dd, *J* = 9.8, 6.3 Hz, 2H), 2.31 (t, *J* = 4.1 Hz, 1H), 2.22 (t, *J* = 13.2 Hz, 2H), 2.02(d, *J* =

10.9 Hz, 1H), 1.96 (dd, *J* = 12.6, 4.1 Hz, 1H), 1.86 (ddd, *J* = 10.9, 5.8, 6.3 Hz, 1H), 1.79 – 1.64 (m, 2H), 1.34 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H), 0.91 (s, 9H), 0.3 (s, 3H), 0.0 (s, 3H).

Minor diastereomer:

^{1}H NMR (500MHz, $CDCl_3$) δ 5.70 (s, 1H), 4.91 (t, *J* = 2.3 Hz, 1H), 4,84 (s, 1H), 4.05 (dd, *J* = 11.5, 6.3 Hz, 1H), 4.02 (s, 2H), 3.82 (d, *J* = 10.9 Hz, 1H), 3.23 (s, 3H), 3.12 (t, *J* = 6.3 Hz, 1H), 2.52 (t, *J* = 11.5 Hz, 2H), 2.39 (dd, *J* = 9.8, 6.3 Hz, 2H), 2.31 (t, *J* = 4.1 Hz, 1H), 2.22 (t, *J* = 13.2 Hz, 2H), 2.02 (d, *J* = 10.9 Hz, 1H), 1.96 (dd, *J* = 12.6, 4.1 Hz, 1H), 1.86 (ddd, *J* = 10.9, 5.8, 6.3 Hz, 1H), 1.79 – 1.64 (m, 2H), 1.34 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H), 0.91 (s, 9H), 0.3 (s, 3H), 0.0 (s, 3H).

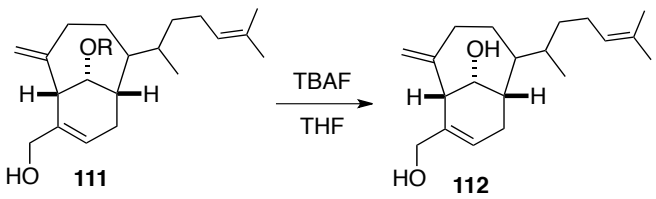
Alcohol 111



To a solution of lithium wire (washed with hexane, 2.0 mg, 290 μmol) in liq.NH_3, which was distilled over Na, was added a solution of allyl alcohol **110** (1.4 mg, 2.9 mmol) in THF (100 μl) at –78 ℃. After stirring for 1 h at the same temperature, the mixture was added a saturated aqueous NH_4Cl. The mixture was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography gave alcohol **111** (0.9 mg, 2.2 μmol, 75%) with a compound whose nitrile group was not eliminated.

^{1}H NMR (500MHz, $CDCl_3$) δ 5.65 (br, s, 1H), 5.08 (t, *J* = 6.9 Hz, 1H), 4.83 (dd, *J* = 4.0, 1.7 Hz, 1H), 4.77 (s, 1H), 4.05 (t, *J* = 5.7 Hz, 1H), 4.01 (s, 2H), 3.08 (dd, *J* = 13.2, 5.7, 5.2 Hz, 1H), 2.37 (dddd, *J* = 9.8, 9.2, 5.8, 5.2 Hz, 1H), 2.27 (dd, *J* = 9.8, 5.2 Hz, 1H), 2.18 (d, *J* = 6.3 Hz, 1H), 2.07 – 1.94 (m, 5H), 1.86 (dd, *J* = 12.6, 6.3 Hz, 1H), 1.68 (s, 3H), 1.59 (s, 3H), 1.54 – 1.28 (m, 4H), 1.09 (m, 3H), 0.91 (s, 9H), 0.3 (s, 3H), 0.0 (s, 3H).

Diol 112

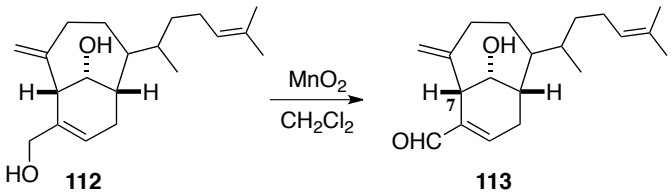


To alcohol **111** (0.9 mg, 2.2 μmol) was added TBAF (100 μl, 1.0 M solution in THF) at room

temperature. The mixture was stirred for 1.5 h at 50 ℃ and poured into water. The mixture was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine and dried over $MgSO_4$, and concentrated under reduced pressure. Purification by silica gel column chromatography gave alcohol **112** (0.5 mg, 1.7 μmol, 80 %).

^{1}H NMR (500MHz, $CDCl_3$) δ 5.71 (br s, 1H), 5.08 (t, *J* = 6.9 Hz, 1H), 5.05 (s, 1H), 4.98 (s, 1H), 4.02 (d, *J* = 12.6 Hz, 1H), 4.00 (d, *J* = 12.6 Hz, 1H), 3.93 (br s, 1H), 3.14 (t, *J* = 1.7 Hz, 1H), 2.39 – 2.15 (m, 6H), 2.00 (br s, 1H), 1.90 (ddd, *J* = 14.9, 9.2, 6.9 Hz, 1H), 1.68 (s, 3H), 1.60 (s, 3H), 1.45 – 1.25 (m, 4H), 1.15 (dddd, *J* = 13.8, 9.8, 6.9, 5.8 Hz, 1H), 0.86 (d, *J* = 6.9 Hz, 3H).

Enal 113



To a solution of **112** (0.5 mg, 1.7 μmol) in CH_2Cl_2 (0.1 mL) was added MnO_2 (17.6 mg, 172 μmol) at room temperature. After being stirred for 40 minutes, the mixture was filtrated through celite pad and concentrated. Purification by preparative thin layer chromatography gave **113** (0.3 mg, 0.99 μmol, 58%).

^{1}H NMR (500MHz, $CDCl_3$) δ 9.45 (s, 1H), 6.85 (t, *J* = 1.7 Hz, 1H), 5.09 (s, 2H), 5.09 (br s, 1H), 3,83 (dd, *J* = 9.2, 4.6 Hz, 1H), 3.54 (s, 1H), 2.60 (ddd, *J* = 16.1, 7.5, 4.0 Hz, 2H), 2.38 (dd, *J* = 10.9, 9.8 Hz, 2H), 2.26 (dd, *J* = 16.1, 11.5 Hz, 1H), 2.17 (s, 1H), 2.02 (dd, *J* = 7.4, 4.0 Hz, 1H), 1.91 (ddd, *J* = 15.5, 7.4, 6.9 Hz, 1H), 1.68 (s, 3H), 1.60 (s, 3H), 1.47 – 1.26 (m, 4H), 1.15 (dddd, *J* = 13.8, 9.2, 5.8, 4.6 Hz, 1H), 0.87 (d, *J* = 6.3 Hz, 3H).

Reference: NMR data of natural product (*Tetrahedron Lett.* **1982**, *23*, 3179–3180.)

^{1}H NMR (270MHz, $CDCl_3$) δ 9.47 (d, *J* = 1.0 Hz, 1H), 6.80 (td, *J* = 3.5, 1.0 Hz, 1H), 5.16 (t, *J* = 7.0 Hz, 1H), 4.90 (td, *J* = 1.0, 1.0 Hz, 2H), 3.78 (ddd, *J* = 9.0, 5.0, 4.3 Hz, 1H), 3.19 (dddd, *J* = 5.0, 1.5, 1.0, 1.0 Hz, 1H), 2.88 (dddt, *J* = 7.0, 4.3, 1.0, 1.0, Hz, 1H), 2.75 (dddd, *J* = 21.0, 7.0, 3.5, 1.5 Hz, 1H), 2.56 (dd, *J* = 21.0, 3.5 Hz, 1H), 2.25 (m, 2H), 2.0, (m, 2H), 1.69 (s, 3H), 1.62 (s, 3H), 1.6 (obscured by Me signals, 1H), 1.6 (obscured by Me signals, 1H), 1.3 (m, 2H), 1.0 (m, 2H), 0.77 (d, *J* = 6.2 Hz, 3H).

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