DISSERTATION

Synthetic Studies on Enfumafungin

（エンフマファンギンの合成研究）

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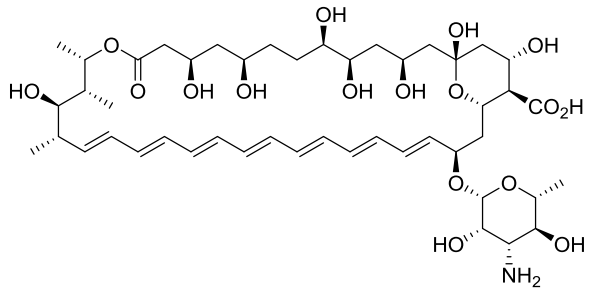
Contents

Introduction

Mycoses are infection diseases, caused by the fact that the fungus to colonize the human or animal. The fungal infections can be classified into two types, namely, superficial fungal infection and invasive fungal infection. The former affects the skin or mucous membranes and it is very general disease, for example, such as ringworm. Since these infections can be treated by antifungal drugs successfully, it is hardly to be severe and is not considered to be a serious problem.[1] On the other hand, the latter is occurred by invasion of fungi to organs and tissues of whole body,[2-4] and it has high fatality rate. Main causes are opportunistic infections of the patients undergoing anticancer chemotherapy or organ transplants and patients with AIDS. The number of patients has been increasing due to the spread of advanced medical and the proceeding of aged society. Moreover, the lack of effective drugs makes it more complex problem. In contrast to that there are a large number of antibacterial antibiotics, the progress in antifungal drug development is relatively slow. The difficulty for the development of novel antifungal drugs is attributed to the eukaryotic nature of fungal cells. It is a challenging task to find an antifungal agent specifically targeting fungal cells without acting on the counterpart of human cells.

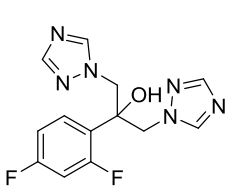
Figure 1 shows some useful drugs, classified by view of mechanism, for antifungal diseases.

Polyene

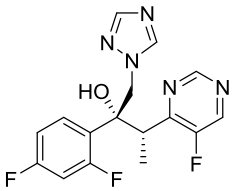


Amphotericin B (1)

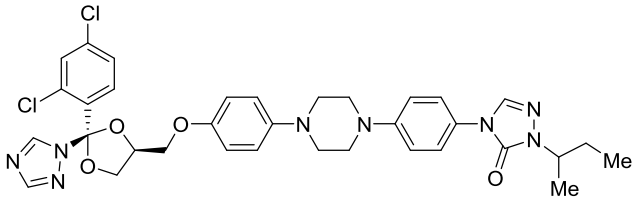
Azoles



Fluconazole (2)

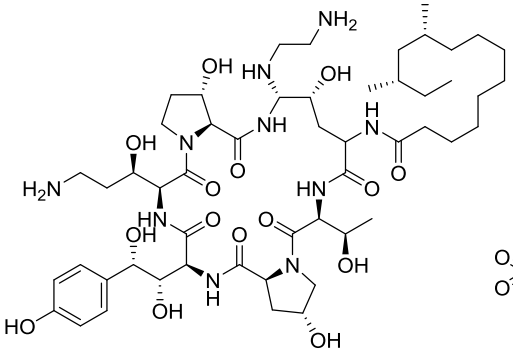


Voriconazole (3)

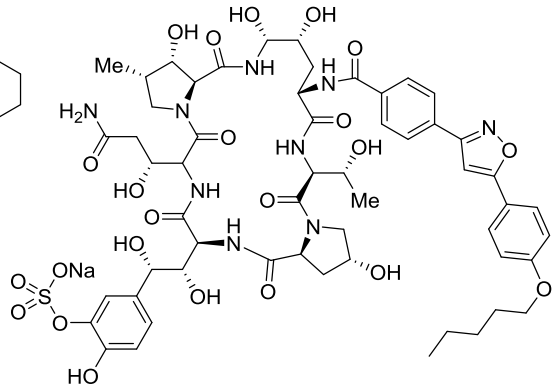


Itraconazole (4)

Echinocandins



Caspofungin (5)



Micafungin (6)

Figure 1. Examples of antifugal drugs

Amphotericin B (**1**) is a polyene macrolide, produced by *Streptomyces nodosus*.[5] It interacts with ergosterol selectively in cell membrane of fungi and forms barrel-stave channels,[6-7] which produced an altered permeability and leakage of vital cytoplasmic components and result in cell death. While

it possesses strong activity and broad spectrum, nephrotoxicity[8] and many other side effects have been reported.[9] Therefore, with a view to reduce side effect of amphotericin B, new formulations[10] and nano particles[11] was elaborated and have been marketed.[12]

Fluconazole (**2**), voriconazol (**3**) and itraconazole (**4**) are representative compounds, classified in azoles of antifungal drugs.[13] These compounds inhibit the lanosterol 14 α-demethylase, a key enzyme in sterol biosynthesis of fungi.[14] They are widely used to antifungal therapy, because of their good activity and low toxicity. However, they are not effective against invasive aspergillosis, and the utility of them is limited due to drug-drug interactions.[15]

Caspofungin (**5**) and micafungin (**6**), belonging to echinocandin group, are new class of antifungal drugs.[16] These compounds are consisted of a complex hexapeptide core whose *N*-terminus is acylated by a long hydrophobic chain. Echinocandins act by specific and noncompetitive inhibitation of β-1,3-glucan synthase, an enzyme that is necessary for synthesis of an essential component of fungal cell wall. Since cell walls are absence in human cells, echinocandins have good selectivity to fungi. Moreover, the echinocandins display fungicidal activity against most *Candida spp*., including strains that are resistant to fluconazole, and they also show fungistatic activity against *Aspergillus spp*. In addition, echinocandins are well tolerated with drug-drug interactions, which makes them to be used preferentially in clinic.[17] On the other hand, there are some drawbacks in utilizing the echinocandins, including the high cost of the semi-synthetic derivatives. The complex structure and large molecular weight of them cause poor solubility and lack of oral absorption.

Thus, some problems are remained to treat antifungal diseases by using these drugs, and new class antifungal drugs to overcome the drawbacks are desired.[18]

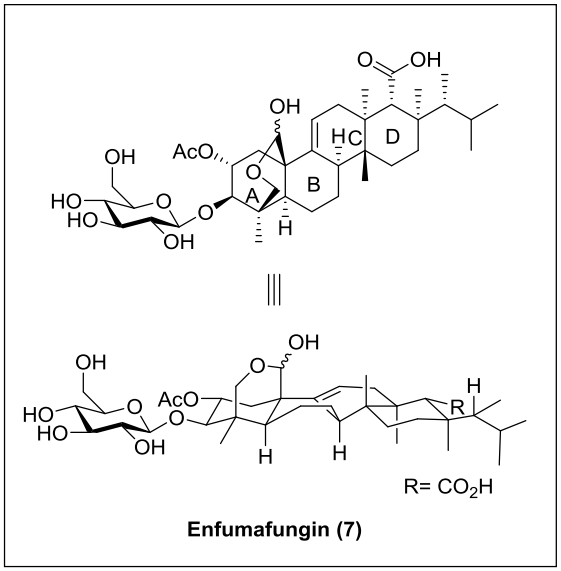
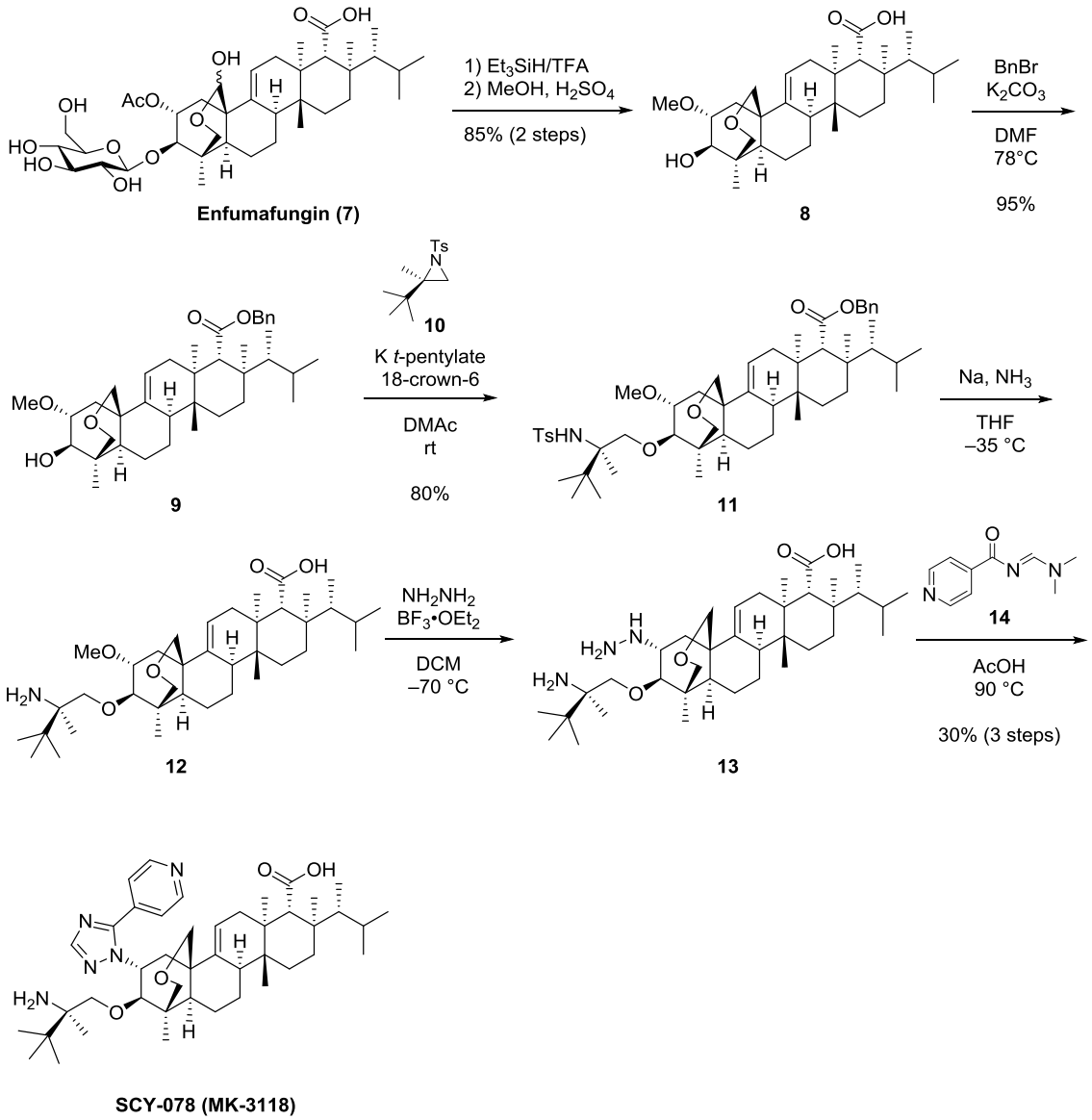


Figure 2. Structure of Enfumafungin

In 2000, Enfumafungin (**7**) was isolated from a fermentation of a *Hormonema* sp., as mixtures of two interconverting hemiacetal forms by Merck's researchers (Fig.2).[19] This compound exhibits potent antifungal activities toward various fungi by inhibiting the β-1,3-gulcane synthase of them.[20] The IC_{50} of the glucan synthesis inhibition in *Candida albicans* is reported as 0.05 μg/mL, that is comparable to that of MIC of 0.2 μg/mL. In addition to the fascinating properties, enfumafungin possesses a complex structure consisting of the tetracyclic carbon skeleton with twelve stereogenic centers five of which are quaternary carbon atoms. Notably, the trans-fused CD ring system possessing two quaternary carbon atoms at the angular positions. The central B ring is in an unusual boat form, due to the two hydrogens at the 1,4-syn positions. Since the structure is quite different from that of known antifungal drugs, enfumafungin is expected to become a lead compound of new structural class of antifungal drugs.

Actually, in the collaboration research with Merck & Co., Inc., Scynexis has developed the semi-synthesized derivative of Enfumafungin, named SCY-078 (former name: MK-3118), as a novel oral and intravenous drug for the treatment of several fungal infections.[21] Scheme 1 shows the synthetic pathway of SCY-078 starting with enfumafungin obtained by fermentation. Reduction of the hemiacetal moiety followed by the treatment with sulfuric acid in methanol afforded carboxylic acid **8**. The stereoselective introduction of the methoxyl group at the C-2 position can be rationalized by assuming the neighboring participation of the cyclic ether moiety. After protection of the carboxyl group as a benzyl ester, the secondary alcohol was reacted with *N*-tosyl aziridine **10** to give ether **11**. Reductive cleavage of the tosyl group followed by substitution of the methoxyl group with hydrazine afforded compound **13** which was subjected to the condensation with amidine **14**,

giving rise to SCY-078 (MK-3118).

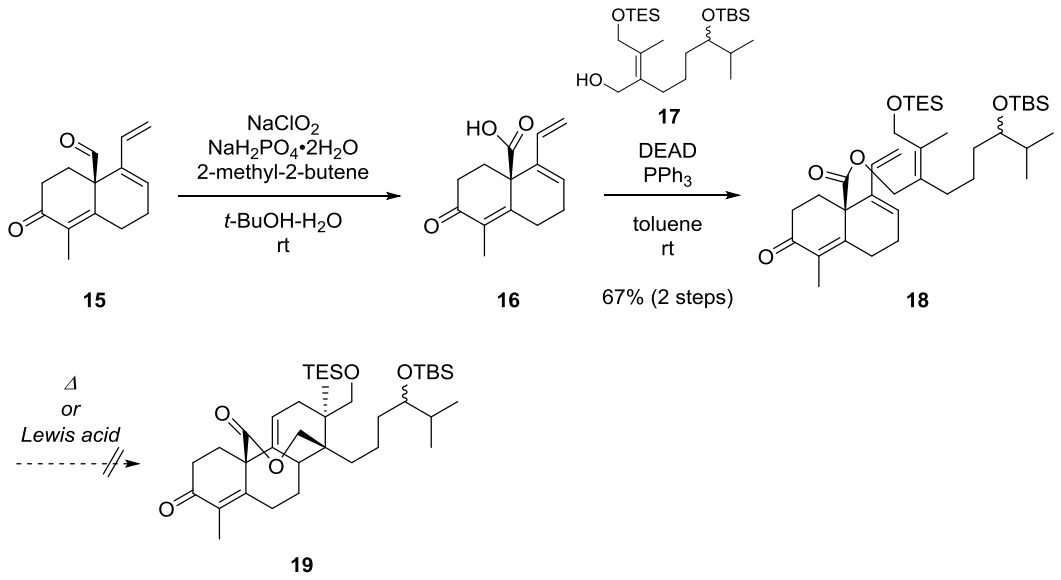


Scheme 1. Semi-synthesis of SCY-078 (MK-3118)

SCY-078 (MK-3118) was found to be a potent β-1,3-glucan synthase inhibitor with a low MIC against *Candida*. *albicans* both in the absence and presence of human serum (0.06 μg/ml and 0.5 μg/ml) and a low MEC against *Aspegillius*. *fumigatus* (<0.03 μg/ml).[22] In addition, this compound has a property of oral absorption (F_{oral}= 34%), and it is currently in Phase II trial.

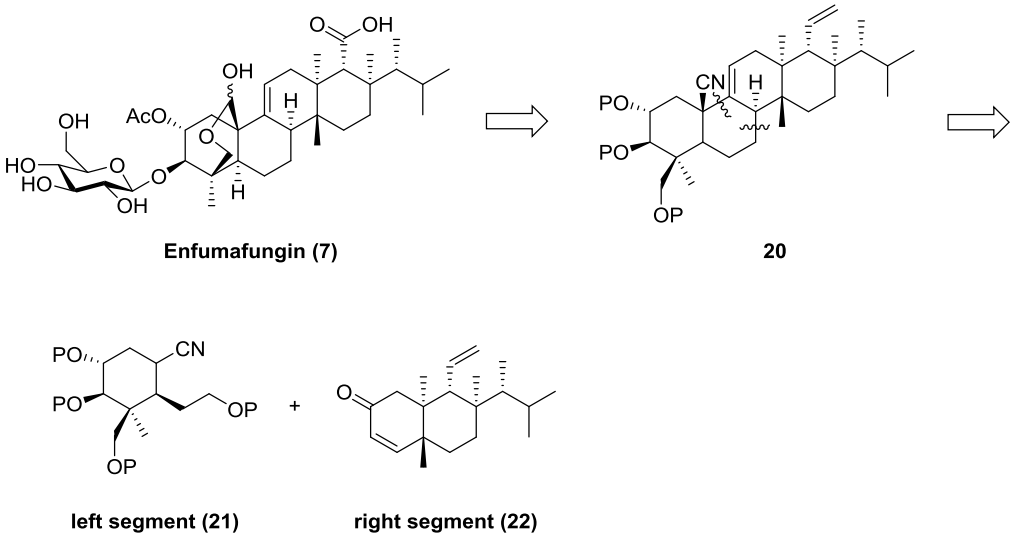
There is no doubt that enfumafungin is a very promising lead compound for treating fungal infections. The synthetic studies on enfumafungin would give important information of the structure activity relationship (SAR), but there are only few reports describing the synthetic

efforts on it. Scheme 2 shows the synthetic study of enfumafungin reported by Lett and co-workers.[23] They planned to employ an intramolecular Diels-Alder (IMDA) reaction to construct the enfumafungin skeleton, and the substrate was prepared through the condensation of carboxylic acid **16** and allyl alcohol **17**. The key IMDA reaction, however, did not occur under various conditions including heating or treating with Lewis acids.



Scheme 2. Synthetic studies on enfumafungin by Lett.

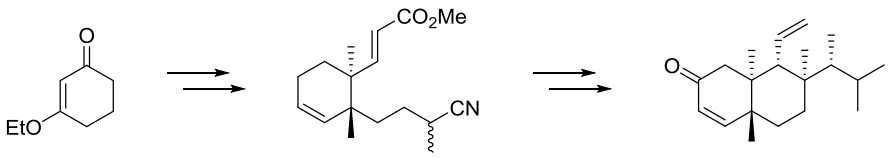
Under these situations, the author planned to develop a new synthetic route of enfumafungin which enables the SAR studies. Scheme 3 shows the retrosynthetic analysis of enfumafungin. Enfumafungin would be derived from tetracyclic compound **20** via functional group transformation and glycosylation. Disconnection of **20** at the C(4a)-C(4b) and C(10b)-C(11) bonds reveals a highly functionalized cyclohexane **21** as the left-hand segment and a bicyclic enone **22** as the right-hand segment. It is noteworthy that the present convergent strategy would be advantageous for providing a variety of analogues of enfumafungin for the SAR studies.



Scheme 3. Retrosynthetic analysis of Enfumafungin

In this dissertation, synthetic studies of enfumafungin based on a convergent strategy will be described. In chapter 1, stereoselective synthesis of the right-hand segment of enfumafungin which possesses the CD ring moiety with contiguous five stereogenic centers is described. In chapter 2, synthetic studies of a model compound that corresponds to the ABC ring system of enfumafungin is described.

Chapter 1



Chapter 2

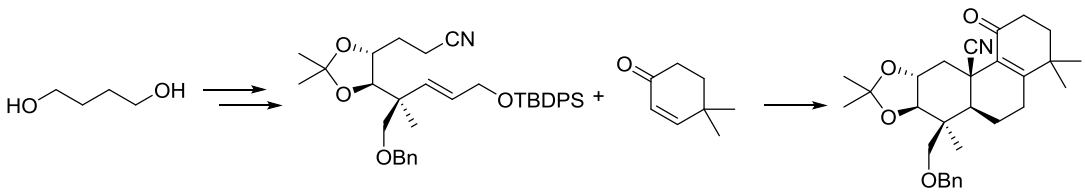


Figure 3.

Chapter 1.
Stereoselective synthesis of the CD ring segment of enfumafungin

1-1. Introduction

To start the synthetic studies on enfumafungin, the author focused on the right-hand segment of the complex molecule (Figure 4). The part has a *trans*-fused decalin skeleton possessing two quaternary carbon atoms at the angular positions and additional three stereogenic centers including another quaternary carbon center. Therefore, construction of the highly substituted decalin skeleton is the most challenging matter, which led the author to synthesize it first.

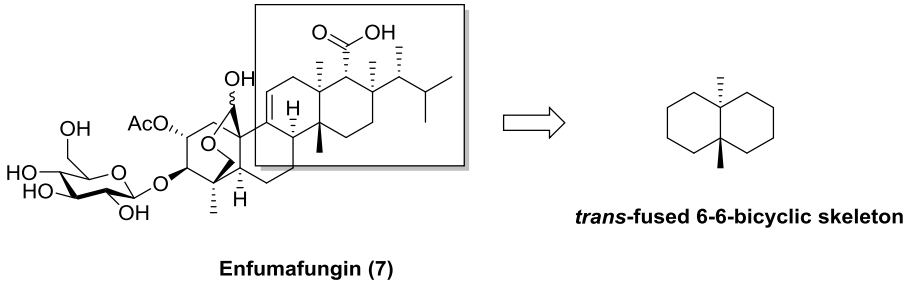
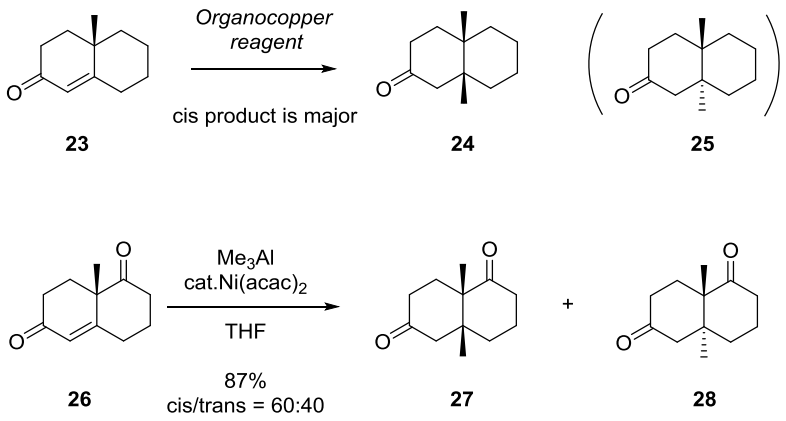


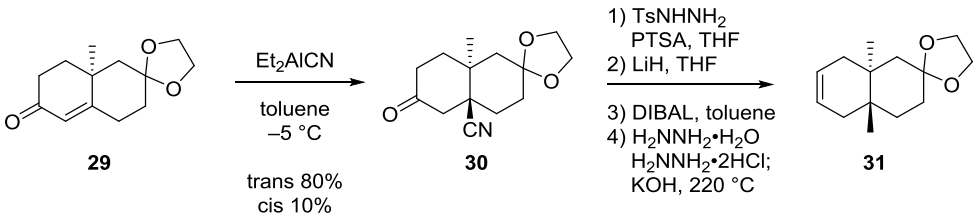
Figure 4. *Trans*-fused decalin skeleton in enfumafungin

Through the document research on this type of compounds, it became clear that there have been few reports describing the stereoselective synthesis of *trans*-decalin skeleton (Scheme 4). For examples, the 1,4-addition reaction of an organocopper reagent to enone **23** produced only *cis*-fused product **24**. On the other hand, Flemming and co-workers reported a *Ni*-catalyzed 1,4-addition reaction of trimethylaluminum to enone **26**,[24] giving rise to a 60:40 mixture of adducts containing the *trans*-isomer **28** as the minor product. The latter reaction is one of the very few examples of the direct introduction of an angular methyl group with a trans configuration.



Scheme 4. Introduction of an angular methyl group to decalin derivatives by a 1,4-addition reaction

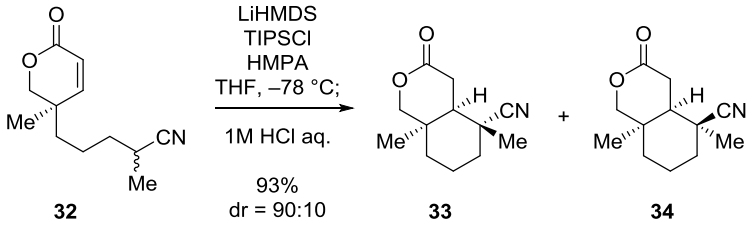
On the other hand, Clercq and co-workers reported an alternative methodology involving stepwise transformations (Scheme 5).[25] Since the Nagata reagent underwent the *trans*-selective conjugate addition reaction with bicyclic enone **29**, the *trans*-decalin derivative **30** was obtained through the transformation of the cyano group into the methyl group. It should be noted that the stereochemistry of the conjugate addition reaction is controlled by the acetal group, because the substrate without the acetal group afforded the *cis*-isomer as a major product.



Scheme 5. Stepwise synthesis of a *trans*-decalin derivative

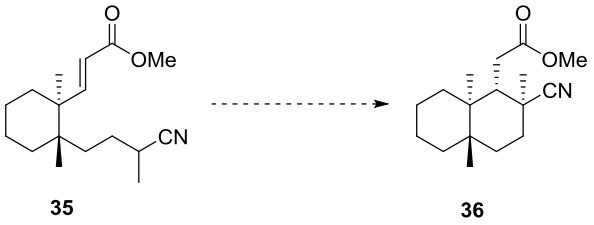
These reports indicate the difficulty in achieving the construction of a *trans*-decalin skeleton with two methyl groups at the angular positions in a stereoselective manner.

On the other hand, the Tanino's group reported the methodology for constructing carbocycles with a quaternary carbon atom by the intramolecular conjugate addition reaction of α,β-unsaturated esters having a nitrile moiety (Scheme 6).[26] This reaction proceeds in a highly stereoselective manner to give a six-membered product possessing two quaternary stereogenic centers.



Scheme 6. Construction of a six-membered ring by an intramolecular conjugate addition reaction

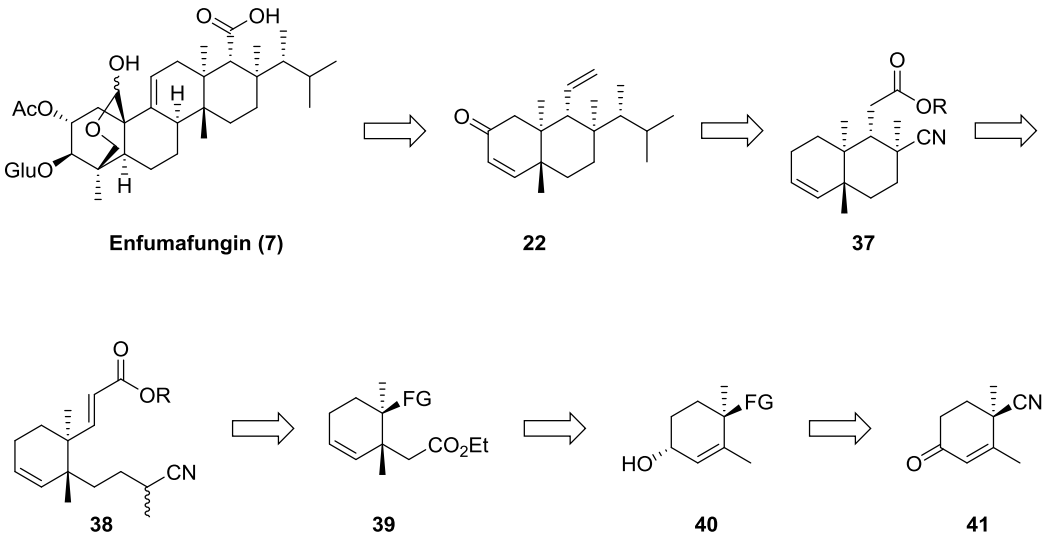
With a view to constructing the desired *trans*-decalin skeleton with appropriate substituents, the author planned the intramolecular conjugate addition reaction of α,β-unsaturated ester **35** possessing a nitrile side chain (Scheme 7).



Scheme 7. Strategy for constructing the *trans*-decalin skeleton by an intramolecular conjugate addition reaction

1-2. Retrosynthetic analysis of the right-hand segment

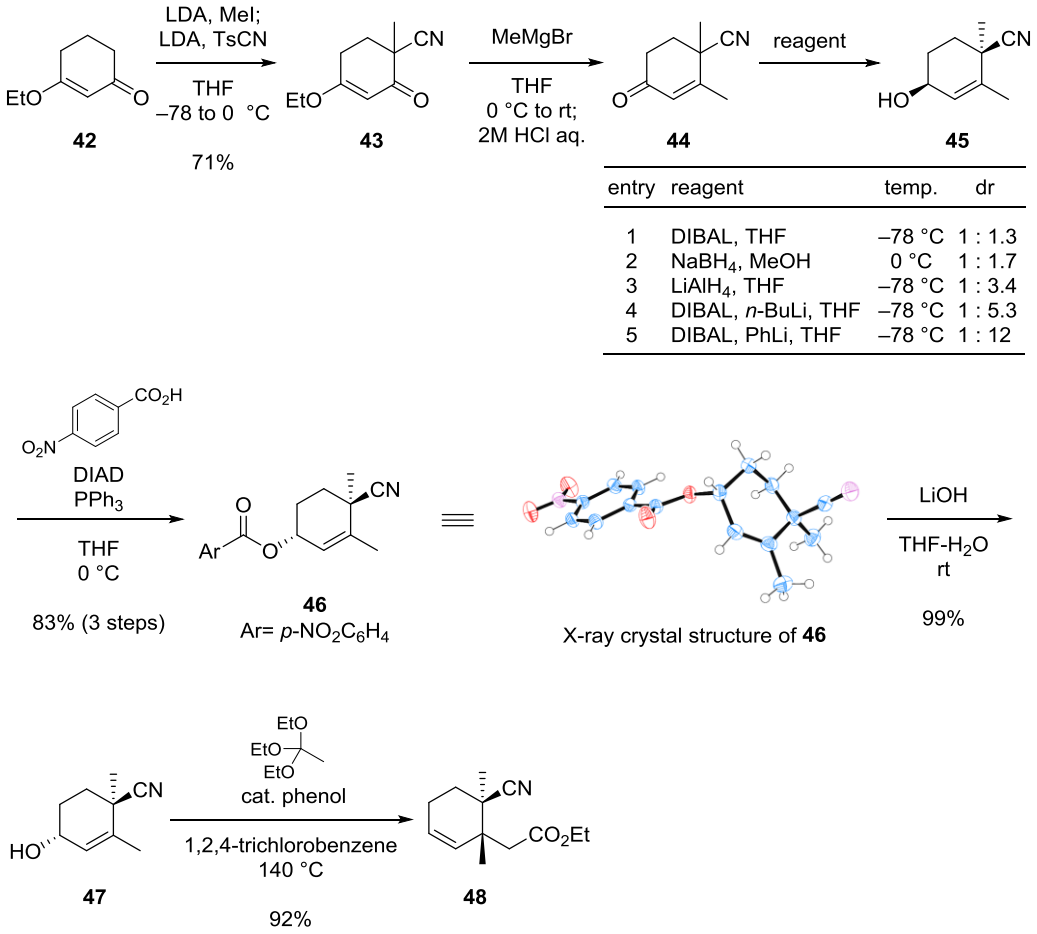
Scheme 8 shows the retrosynthetic analysis of the right-hand segment. From the retrosynthetic perspective, the author envisioned enfumafungin to be obtained from the enone **22** which would arise from ester **37** by allylic oxidation. The *trans*-decalin skeleton of **37** would be constructed by the stereoselective intramolecular conjugate addition reaction of α,β-unsaturated ester **38**. The cyclization precursor **38** is to be synthesized through the elongation of the side chain of **39**. The two contiguous quaternary carbon centers are to be installed by the Johnson-Claisen rearrangement of allyl alcohol **40**, which would be derived from enone **41**. It is noteworthy that the nitrile group of **41** can remain unchanged during the reduction of the ester group of **39**. Based on this strategy, the author undertook the research to synthesize the right-hand segment of enfumafungin.



Scheme 8. Retrosynthetic analysis of the right-hand segment of enfumafungin

1-3. Construction of the *trans*-fused decalin skeleton

The synthesis of the cyclohexene derivative possessing two quaternary carbon atoms was started with commercially available 3-ethoxy-2-cyclohexen-1-one (**42**) (Scheme 9). The one-pot sequence of methylation and cyanation[27] afforded enone **43**, which was subjected to the 1,2-addition reaction with methylmagnesium bromide followed by the treatment with diluted hydrochloric acid. Next, the resulting enone **44** was subjected to reduction with various reagents. The use of diisobutylaluminum hydride or $NaBH_4$ resulted in the formation of alcohols **45** and **47** in low selectivities (entries 1 and 2), and the stereochemistry of the products was unclear at this point. The reaction with $LiAlH_4$ exhibited a slightly higher selectivity (dr=1:3.4, entry 3), and the sterically more demanding reductants were found to give better results (entries 4 and 5). Thus, the combined use of DIBAL and *n*-BuLi[28] afforded a 1:5.3 mixture of **47** and **45**, while the highest selectivity of 1:12 was achieved with the DIBAH-PhLi reagent. The Mitsunobu reaction[29] of the major product **45** with *p*-nitrobenzoic acid, diisopropyl azodicarboxylate, and PPh_3 gave ester **46** the configuration of which was determined by an X-ray crystallographic analysis. The saponification of *p*-nitrobenzoate **46** afforded the desired alcohol **47**. Upon heating with triethyl orthoacetate and a catalytic amount of phenol in 1,2,4-trichlolobenzene at 140 °C, alcohol **47** underwent the Johnson-Claisen rearrangement reaction to afford ester **48** in excellent yield.



entry	reagent	temp.	dr
1	DIBAL, THF	–78 °C	1 : 1.3
2	$NaBH_4$, MeOH	0 °C	1 : 1.7
3	$LiAlH_4$, THF	–78 °C	1 : 3.4
4	DIBAL, *n*-BuLi, THF	–78 °C	1 : 5.3
5	DIBAL, PhLi, THF	–78 °C	1 : 12

Scheme 9. Construction of the contiguous quaternary stereogenic centers

The facial selectivity of reduction of **44** would be explained in Figure 5. The preferential formation of **44** in entries 4 and 5 of table cannot be rationalized by the steric repulsion between the reductant and the allylic methyl group of enone **44**. There are two conformers in which the cyano group is directed to pseudo equatorial (**44-a**) or pseudo axial (**44-b**), and the latter seems to be disfavored by the 1,2-allylic strain between the two methyl groups. Therefore, a transition state involving the equatorial attack of a bulky reductant seems more plausible.

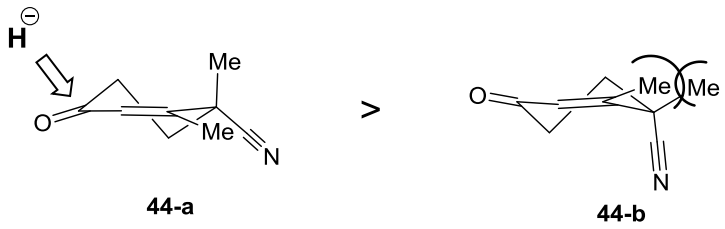
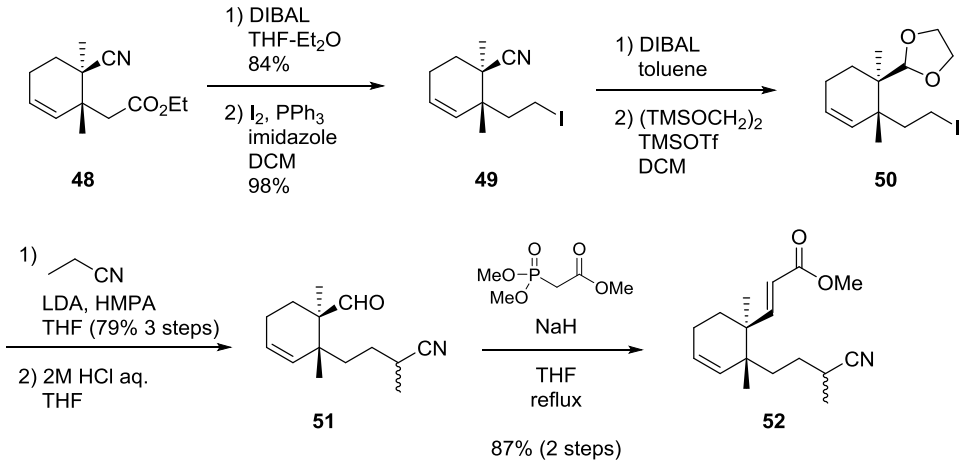


Figure 5. Stereoselectivity of the 1,2-reduction of enone **44**

Elongation of the side chain for preparing the cyclization precursor is shown in scheme 10. Compound **48** was converted to iodide **49** through the chemoselective reduction of the ester moiety, and reduction of the cyano group to aldehyde followed by protection using the Noyori's protocol afforded acetal **50**.[31] The nitrile side chain was constructed by the reaction of iodide **50** with a carbanion generated from propionitrile, and removal of the ethylene acetal group under acidic conditions afforded aldehyde **51**. Finally, the Horner-Wadsworth-Emmons reaction of **51** gave the cyclization precursor **52** for the intramolecular conjugate addition reaction.[32]

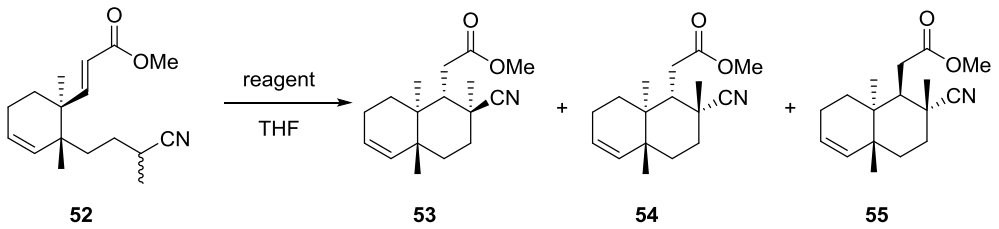


Scheme 10. Synthesis of the cyclization precursor

With the α,β-unsatured ester **52** in hand, the cyclization reactions under basic conditions were explored as shown in Table 1. Firstly, **52** was treated with LiHMDS at −78 to −40 °C (entry 1), and a mixture of cyclized product (**53**, **54**, **55**) was obtained in moderate yields with low selectivity. The stereochemistry of these compounds were determined by the NOESY experiments, the relationship between the protons in which were displayed below. Major product **53** proved to have the configuration that corresponds to the CD ring of enfumafungin. The minor stereoisomer **54** was found to be the epimer of **52** at the nitrile moiety, and another stereoisomer **55** was the epimer of **54** at the ester side chain.

The combined yield and the stereoselectivity of the cyclization reaction were decreased at higher temperature, suggesting that the corresponding ester enolates of the products are not stable. Indeed,

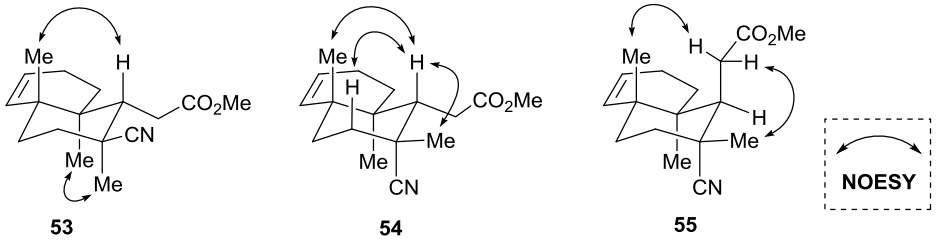
the addition of triisopropylsilyl chloride (TIPSCl), effected improvement in both yield and selectivity of the desired product to 74% yield with the ratio of 16:1.0:1.3. In this case, the crude mixture containing ketene silyl acetals was treated with acetic acid followed by tetrabutylammonium fluoride to afford the corresponding esters. The stereoselectivity was dramatically decreased by the combined use of LiHMDS and HMPA prior to the addition of TIPSCl (entry 3), suggesting that isomer **53** is formed through a transition state in which the nitrogen atom and the carbonyl oxygen are chelating to the lithium ion. This hypothesis is also consistent with that the reaction with NaHMDS or KHMDS led to a decreased formation of isomer **53** (entries 4 and 5).



52 **53** **54** **55**

entry	reagent	temp	yield	**53** : **54** : **55**
1	LiHMDS	–78 to –40 °C	59%	4.4 : 1.0 : 2.0
2*	LiHMDS, TIPSCl; TBAF	0 °C	76%	16 : 1.0 : 1.3
3*	LiHMDS, HMPA, TIPSCl; TBAF	0 °C	84%	1.0 : 1.0 : 2.0
4*	NaHMDS, TIPSCl; TBAF	0 °C	67%	13 : 1.0 : 3.3
5*	KHMDS, TIPSCl; TBAF	0 °C	66%	14 : 1.0 : 9.7

*entries 2-4 were quenched with AcOH-TBAF



53 **54** **55**

Table 1. Intramolecular conjugate addition reactions of cyclization precursor **52**

Figure 6 shows the models of the transition states in the intramolecular cyclization reaction. As was mentioned above, the configuration of the desired isomer **53**, in which the ester side chain and the cyano group occupy the equatorial positions, is consistent with the chelation model **TS-1**. Since **TS-1** involves a 1,3-diaxial repulsion between the two methyl groups, the reactions without the

strong chelation effect of a lithium ion may occur partially through **TS-2** or **TS-3** (entries 3-5 in Table 1). In these cases, the reaction would prefer a linear transition state in which the anion moiety and the enoate moiety are in an antiparallel dipolar arrangement, giving rise to isomer **55**.[33]

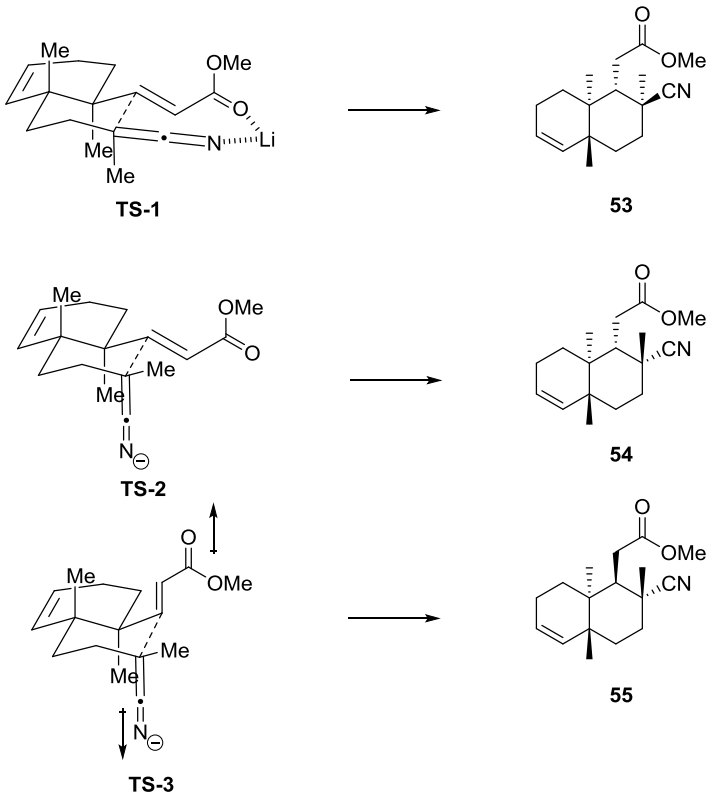
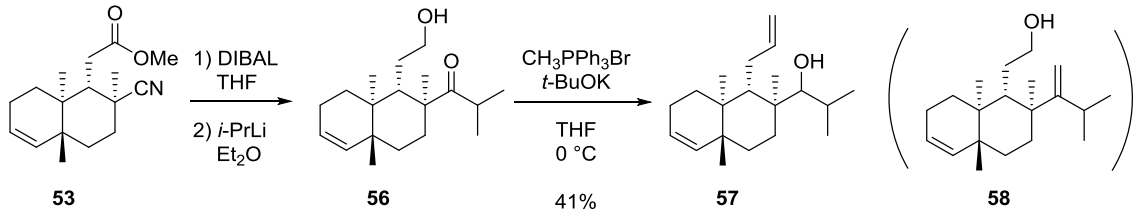


Figure 6. Proposed transition state models of the cyclization reaction of **52**

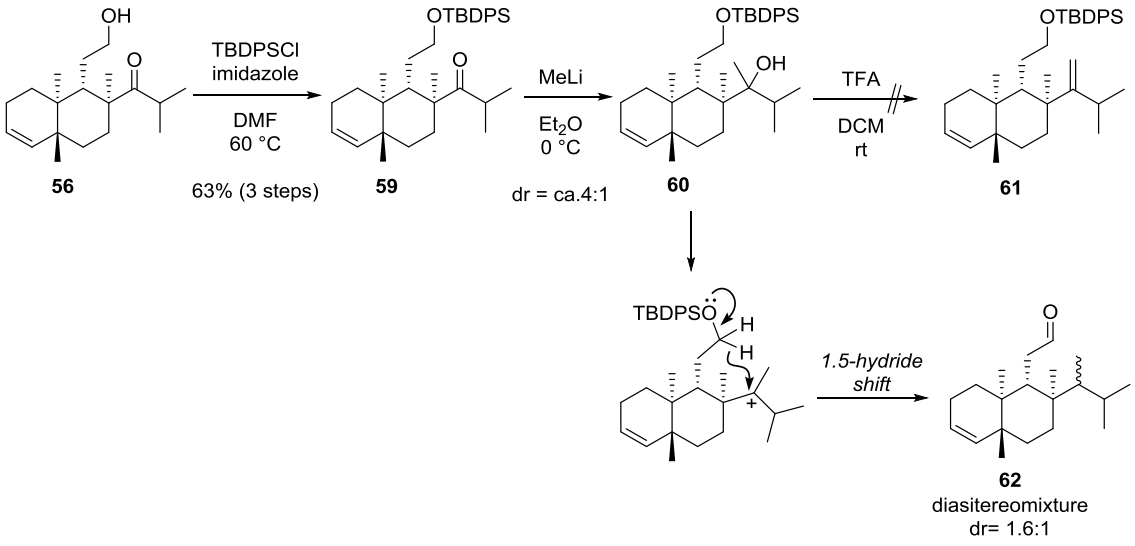
1-4. Stereoselective synthesis of the right-hand segment

With the bicyclic key compound **53** in hand, the author planned the construction of the five carbon side chain by the transformation of the nitrile moiety (Scheme 11). The chemoselective reduction of the ester group followed by the addition reaction with *i*-PrLi afforded keto alcohol **56**. Surprisingly, the reaction of highly hindered ketone **56** with $Ph_3P{=}CH_2$ led to the formation of secondary alcohol **57** instead of the desired product **58**. The result indicates that the ketone moiety underwent the intramolecular oxidation-reduction with the primary alcohol moiety prior to the Wittig reaction.



Scheme 11. Attempted Wittig reaction of ketone **56**

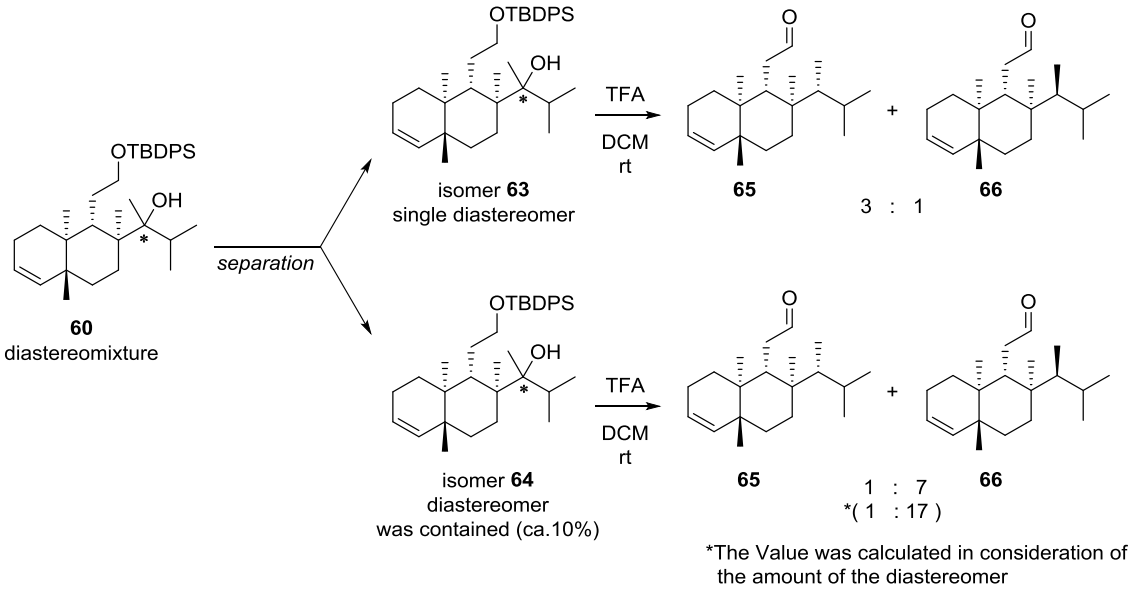
The author planned an alternative route through a dehydration of the corresponding tertiary alcohol under acidic conditions (Scheme 12). After protection of the primary alcohol with TBDPS group, ketone **59** was treated with methyllithium. Although tertiary alcohol **60** was obtained as a 4:1 mixture of epimers, the dehydration reaction mediated by an acid was examined. Treatment of **60** with trifluoroacetic acid, however, afforded aldehyde **62** instead of the desired alkene **61**, indicating that the tertiary carbocation intermediate underwent a 1,5-hydride shift from the α-methylene group of the silyl ether moiety. The unexpected rearrangement reaction opened the door to an alternative pathway for constructing the side chain, while the product was obtained as a 1.6:1 mixture of epimers at the methyl group the configuration of which was unclear at this point.



Scheme 12. 1,5-hydride shift reaction of the tertiary alcohol

Thus, the author investigated the relationship between the stereochemistry of *tert*-alcohol **60** and that of the aldehyde **62** (Scheme 13). The epimeric mixture of *tert*-alcohol **60** was subjected to the

silica gel chromatography, affording the major isomer **63** in pure form and the minor isomer **64** containing 10% of isomer **63**, respectively. Under the influence of TFA, the major isomer **63** afforded a 3:1 mixture of aldehydes **65** and **66**. On the other hand, a 1:7 mixture was obtained from the minor isomer **64** containing 10% of epimer **63**, indicating that the corrected product ratio for pure isomer **64** is to be 1:17.



Scheme 13. Relationship between the stereochemistry of tert-alcohol and that of aldehyde

These results suggested that the 1,5-hydride shift reactions occurred not through an S_N1 reaction of the tertiary carbocation but through an S_N2-like reaction of the protonated form of the substrates **63** and **64**. While the stereochemistry of aldehyde **65** was found to be consistent with that of enfumafungin at the later stage, the configurations of the substrates could not be confirmed at all. Therefore, the author examined the efforts for obtaining information about the transformation of alcohols **63** and **64** into aldehydes **65** and **66** by a calculation method. Thus, the favorable conformations of ketone **59** were optimized by the MOE (Molecular Operating Environment) program, and the conformer depicted in Figure 7 was obtained as the most stable one. The isopropyl group of the ketone moiety is placed at the pseudo-equatorial position, and the addition reaction with MeLi would occur from the opposite face of the bulky TBDPS group, giving rise to alcohol **63** predominantly (Scheme 14).

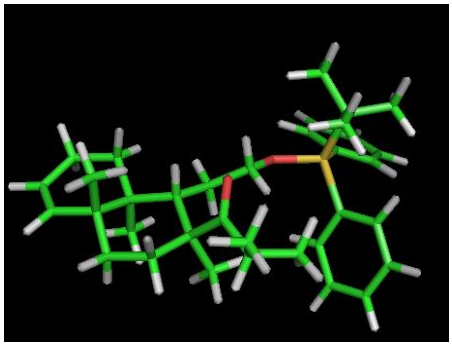
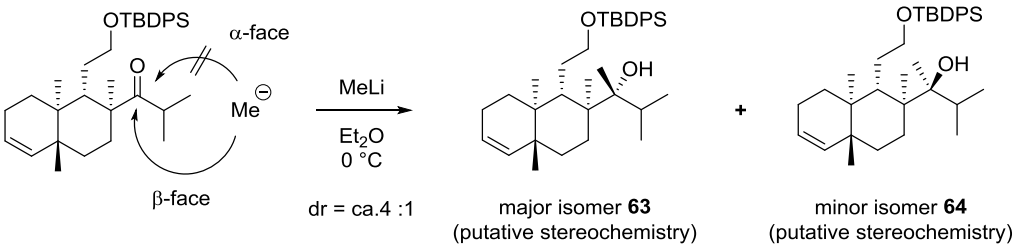


Figure 7. Most stable conformation of **59** calculated by MOE



Scheme 14. Putative stereochemistries of **63** and **64**

With this assumption, the stereochemistry of the 1,5-hydride shift reactions could be explained as follows (Figure 8). After activation of the hydroxyl group of isomer **63** with TFA, the hydride attack occurred from the backside to afford product **65** via the S_N2-type reaction. Since the transition state of the S_N2-type reaction involves the bulky isopropyl group at the pseudo-axial position, the formation of the minor stereoisomer **66** is attributable to the alternative S_N1 reaction in which the carbocation intermediate possesses the isopropyl group at the pseudo-equatorial position. On the other hand, a similar S_N2-type reaction of the isomeric alcohol **64** would proceed more smoothly through the transition state with the isopropyl group at the pseudo-equatorial position, resulting in formation of stereoisomer **66** in high selectivity.

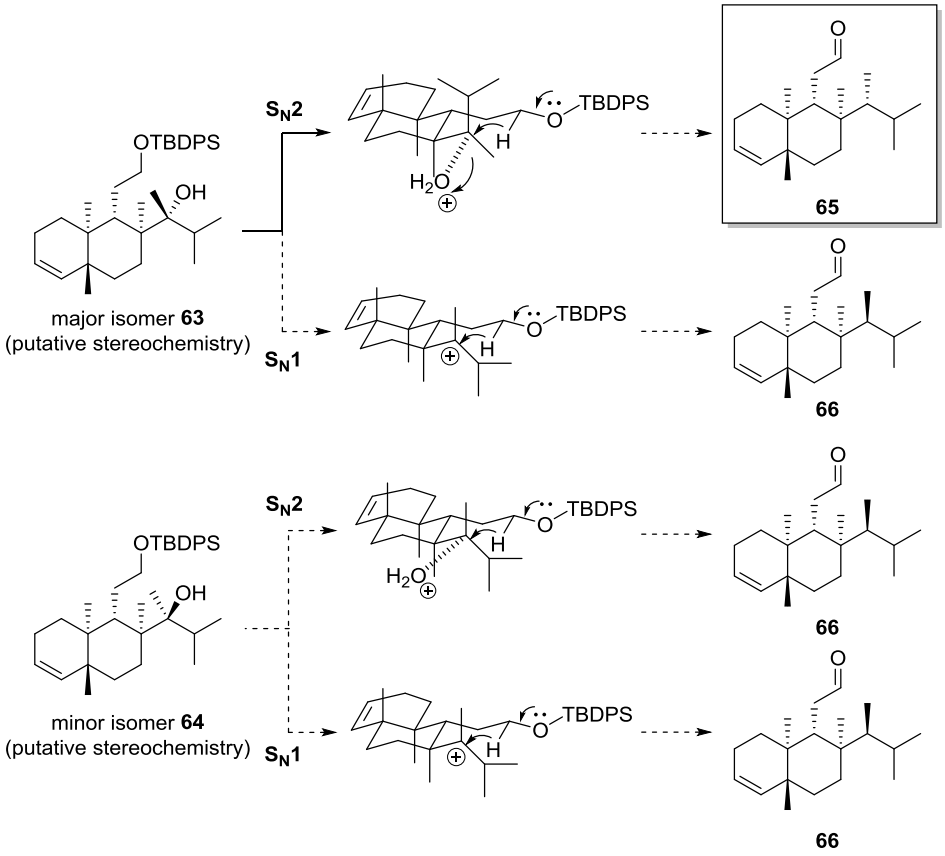
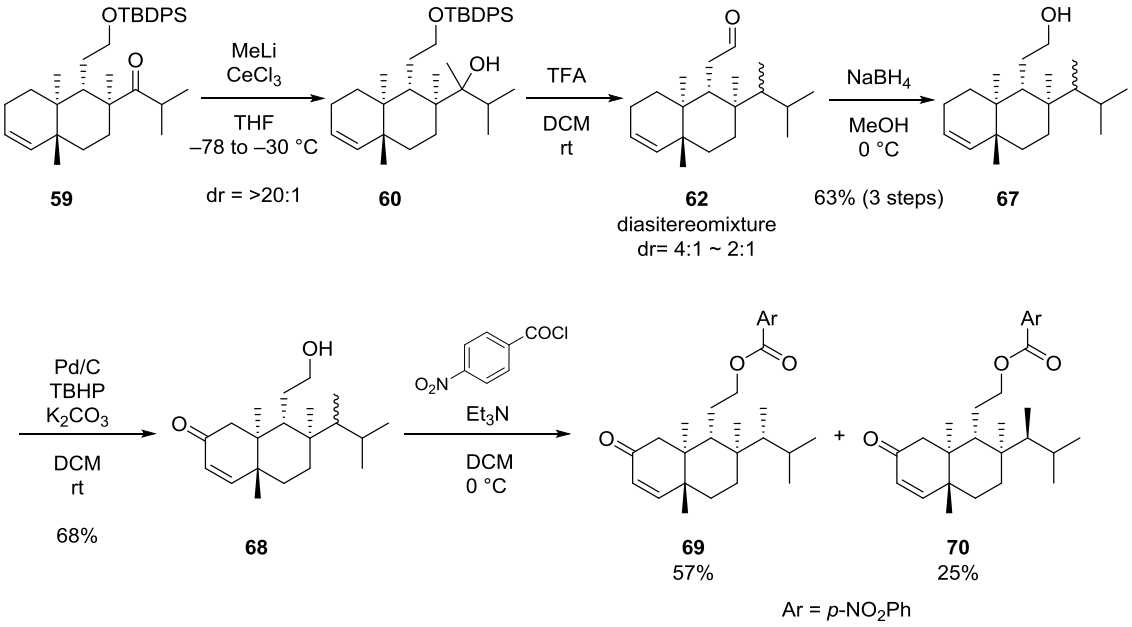


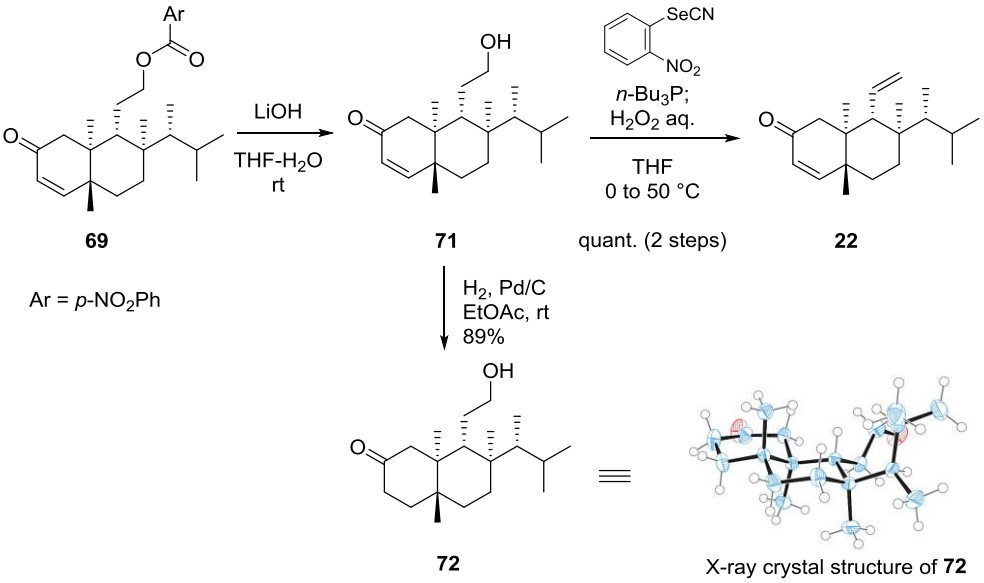
Figure 8. Proposed reaction mechanism of 1,5-hydride shift

These results suggested that the highly stereoselective synthesis of *tert*-alcohol **60** would lead to obtaining the desired aldehyde **65**, the configuration of which was determined at the later stages, in good yield albeit in 3:1 epimeric ratio. Fortunately, the use of a methylcerium reagent instead of methyllithium was found to give *tert*-alcohol **60** as a single diastereomer (Scheme 15).[34] On treatment with TFA, **60** was converted to the aldehyde in moderate ratios varying between 4:1 to 2:1. The epimeric mixture of aldehyde **62** was transformed into *p*-nitrobenzoate **69** through reduction to the corresponding alcohol, the allylic oxidation to enone **68**,[35] followed by benzoylation of the primary alcohol moiety. The epimers at the side chain were separated each from the other by silica gel chromatography at this stage, and the major stereoisomer **69** and the minor isomer **70** were obtained in 57% and 25% isolated yields, respectively.



Scheme 15. Construction of the five-carbon side chain and allylic oxidation

Hydrolysis of *p*-nitrobenzoate **69** to alcohol **71** followed by hydrogenation with Pd/C afforded keto alcohol **72** as a crystalline solid, and the X-ray crystallographic analysis indicated that **72** has a configuration consistent with that of enfumafungin. Finally, alcohol **71** was transformed into diene **22**, which was designed as a key intermediate for the total synthesis of enfumafungin, by using the Grieco-Nishizawa protocol.[36]



Scheme 16. Synthesis of right-hand segment of enfumafungin

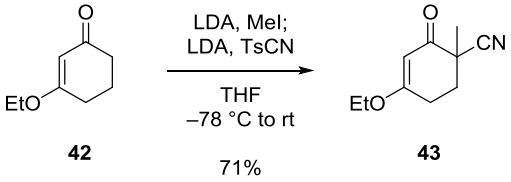
In summary, the author has achieved the stereoselective synthesis of the right-hand segment of enfumafungin. The contiguous two quaternary carbon atoms at the angular positions was constructed through the stereoselective reduction of a cyclohexenone derivative followed by the Johnson-Claisen rearrangement. After the formation of the D ring via a stereoselective intramolecular conjugate addition reaction of a cyano α-unsaturated ester, the 1,2-dimethylprop-1-yl side chain was constructed via an unexpected 1,5-hydride shift reaction. Finally, allylic oxidation of the cyclohexene ring afforded the enone which would act as a bridge for connecting with the left-hand segment of enfumafungin.

Experimental section

General Remarks:

Materials were obtained from commercial suppliers and used without further purification unless otherwise mentioned. All experiments were carried out under positive pressure of dry nitrogen unless otherwise noted. All of the organic solvents used in this study were dried over appropriate drying agents. All melting points were determined on a Yanako micro melting point apparatus. IR spectra were recorded on JASCO FT/IR-4100 spectrophotometer using 5 mm NaCl or CaF_2 plates. Wavelength of maximum absorbance (O max) is quoted in cm^{-1}. ^{1}H-NMR spectra were recorded on Varian Unity INOVA 500 spectrometer (500 MHz) in $CDCl_3$ (δ_H 7.26) with tetramethylsilane as an internal standard. Chemical shifts were reported in part per million (ppm), and signal were expressed as singlet (s), doublet (d), triplet (t), quartet (q), double doublet (dd), double triplet (dt), quartet quarter (qq), double double doublet (ddd), broad singlet (brs), and multiplet (m).^{13}C-NMR spectra were recorded on Varian Unity INOVA 500 spectrometer (125 MHz) in $CDCl_3$ (δ_C 77.0) with tetramethylsilane as an internal standard. Chemical shifts were reported in part per million (ppm). Electro splay ionization mass (ESI-MS) and high resolution mass (HR-MS) spectra were recorded on a Thremo Scientific Exactive at the Instrumental Analysis Division, Equipment Management Center Creative Research Institution, Hokkaido University. Reactions were monitored by tin layer chromatography with Merck Kieselgel 60 F_{254}. The silica gel used for column chromatography was ISCO gold or Yamazen prepacked columns.

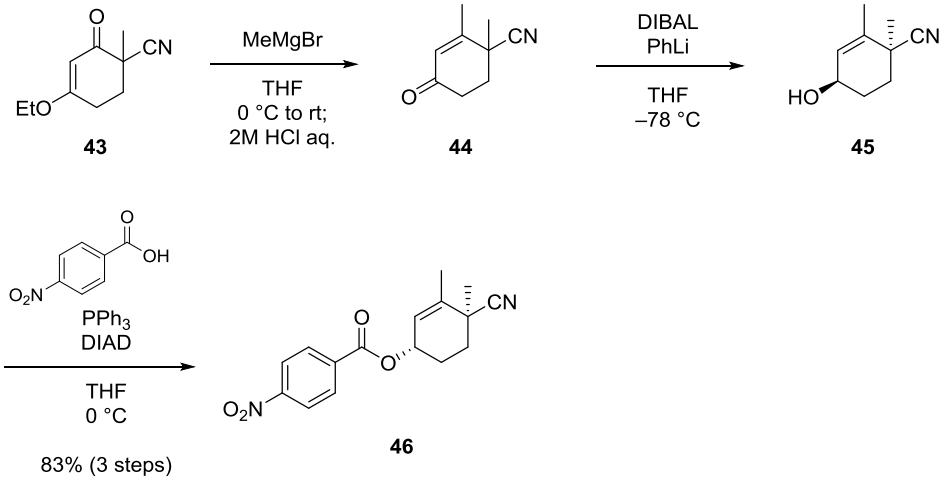
4-ethoxy-1-methyl-2-oxocyclohex-3-ene-1-carbonitrile (43)



42 **43**

To a stirred solution of 3-ethoxy-2-cyclohexen-1-one (**42**) (14.0 g, 100 mmol) in THF (100 mL) was added LDA (1.1 M in THF, 100 mL, 110 mmol) at −78 °C. The resulting bright yellow mixture was warmed up to 0 °C and was stirred for 15 min. The solution was cooled at −78 °C, methyl iodide (6.57 mL, 105 mmol) was added dropwise at that temperature, and the reaction mixture was warmed to 0 °C with stirring over a period of 1 h. The reaction mixture was cooled at −78 °C and was added LDA (1.1 M in THF, 100 mL, 110 mmol). The resulting brown mixture was warmed up to 0 °C and was stirred for 15 min. The solution was cooled at −78 °C, tosyl cyanide (15.1 g, 83 mmol) was added one portion. The reaction mixture was warmed up to 0°C and was stirred for 30 min. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes: EtOAc= 70: 30) to give the compound **43** as a yellow oil (12.7 g, 70.9 mmol, 70.9%): IR (neat): 2985, 2943, 1663, 1596, 1378, 1362, 1316, 1252, 1191, 1038, 1020, 893, 844, 821 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) : 5.38 (s, 1H), 3.96 (q, *J*= 7.0Hz, 2H), 2.79 (ddd, *J*= 18.1, 4.9, 2.5 Hz, 1H), 2.50 (ddd, *J*= 18.1, 5.1, 2.5 Hz, 1H), 2.35 (ddd, *J*= 13.6, 5.1, 2.5 Hz, 1H), 2.03 (ddd, *J*= 13.6, 4.9, 2.5 Hz, 1H), 1.55 (s, 3H), 1.39 (t, *J*= 7.0 Hz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) : 190.65, 177.17, 120.12, 100.22, 65.00, 41.45, 32.44, 26.42, 21.09, 14.00; HRMS (FI+) calcd. for $C_{10}H_{13}NO_2$ $[M]^+$:179.0946, found: 179.0944.

(1S,4S)-4-cyano-3,4-dimethylcyclohex-2-en-1-yl 4-nitrobenzoate (46)

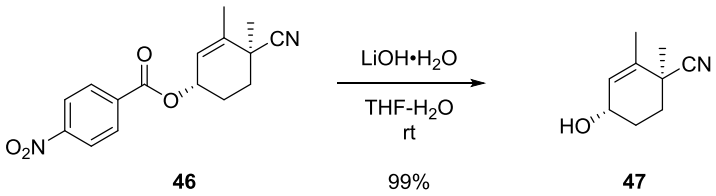


43 **44** **45** **46**

To a stirred solution of compound **43** (9.60 g, 53.6 mmol) in THF was added methyl magnesium bromide (0.92M in THF, 200 ml, 184 mmol,) at 0 °C and was stirred at room temperature. The brown solution was poured into 2M HCl aqueous solution and stirred for 30 min. The aqueous layer was extracted with EtOAc three times. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give the compound **44**. The crude oil was used without further purification in the next step. To a stirred solution of DIBAL (1.0 M in hexane, 70.9 ml, 70.9 mmol) and PhLi (1.6 M in *n*-Bu_2O, 41.2 ml, 70.9 mmol) was added a THF solution of the crude oil of **44** at −78 °C dropwise. The reaction mixture was quenched by slow addition of a saturated solution of sodium potassium tartrate, diluted with EtOAc, and allowed to stir at room temperature to get two separated layers. The aqueous layer was extracted with EtOAc three times. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give the compound **45**. The crude oil was used without further purification in the next step. To a solution of the crude oil, *p*-nitro benzoic acid (10.1 g, 60.8 mmol), and PPh_3 (15.9 g, 60.8 mmol) in THF (200 ml) at 0 °C was added a DIAD (1.9M in toluene, 32.0 ml, 60.8 mmol) dropwise. After stirring for 15 min, the reaction mixture was concentrated in reduce pressure and the residue was purified by flash column chromatography (silica gel, hexanes: $CHCl_3$= 50: 50 to 0: 100) to give the compound **46** as a white solid (13.4 g, 44.6 mmol, 83% for 3 steps).; mp. 118-121 °C; IR (neat):3675, 2363, 2359, 2352, 2345, 2335, 2331, 1719, 1526, 1348, 1270, 1115, 1102, 720 cm^{-1};

^{1}H-NMR (500 MHz, $CDCl_3$): 8.28 (d, *J*= 9.0 Hz, 2H), 8.19 (d, *J*= 9.0 Hz, 2H), 5.83 (d, *J*= 4.2 Hz, 1H), 5.50-5.48 (m, 1H), 2.25-2.15 (m, 2H), 2.08-1.95 (m, 2H), 1.93 (s, 3H), 1.55 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): 164.03, 150.55, 139.32, 135.62, 130.70, 123.88, 123.51, 122.53, 68.33, 35.96, 31.88, 25.07, 24.34, 19.55; HRMS (FD+) calcd. for $C_{16}H_{16}N_2O_4$ $[M]^+$:300.1110, found:300.1119.

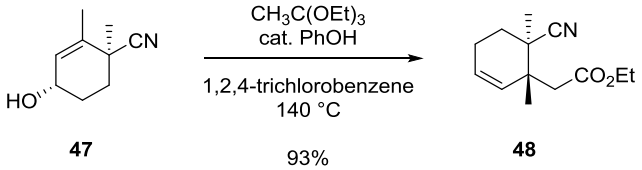
(1S,4S)-4-hydroxy-1,2-dimethylcyclohex-2-ene-1-carbonitrile (47)



46 99% **47**

To a solution of the nitro benzoate **46** (8.50 g, 28.3 mmol) in THF (50 ml)-H_2O (50 ml) was added $LiOH \cdot H_2O$ (3.56 g, 85 mmol) one portion at room temperature. After stirring for 30 min, the aqueous layer was extracted with EtOAc three times. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes: EtOAc= 50: 50) to give the compound **47** as a colorless oil (4.25 g, 28.1 mmol, 99%), IR (neat):3300 (br), 2361, 2231, 1444, 1286, 1125, 1024, 857, 852 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): 5.68 (d, *J*= 2.3 Hz, 1H), 4.26-4.20 (m, 1H), 2.08-1.96 (m, 2H), 1.96-1.88 (m, 1H), 1.86 (s, 3H), 1.82 (brs, 1H), 1.77-1.69 (m, 1H), 1.48 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): 135.81, 128.41, 123.14, 64.06, 35.93, 31.56, 28.02, 24.24, 19.40; HRMS (FI+) calcd. for $C_9H_{13}NO$ $[M]^+$: 151.0997, found: 151.0994.

Ethyl 2-((1R,6R)-6-cyano-1,6-dimethylcyclohex-2-en-1-yl)acetate (48)

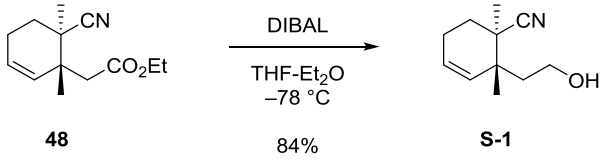


47 93% **48**

The solution of the allyl alcohol **47** (5.3 g, 35.1 mmol), triethyl orthoacetate (32.3 ml, 175 mmol),

and catalytic amounts of PhOH (330 mg, 3.51 mmol) in 1,2,4-trichlorobenzene (100 ml) was heated at 140 °C for 40 h. After being cooled to room temperature, the reaction mixture was purified by flash column chromatography (silica gel, hexanes: EtOAc =100:0 to 60:40) to give the compound **48** as a yellow oil (7.2 g, 32.5 mmol, 93%).; IR (neat): 2981, 2367, 2360, 2354, 2345, 2338, 2334, 2316, 1733, 1457, 1378, 1242, 1159, 1097, 1032 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): 5.80-5.60 (m, 2H), 4.15 (q, *J*= 7.1Hz, 2H), 2.37-2.24 (m, 3H), 2.18-2.05 (m, 1H), 2.05-1.95 (m, 1H), 1.85-1.76 (m, 1H), 1.41 (s, 3H), 1.27 (t, *J*= 7.1 Hz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): 170.93, 131.68, 125.18, 123.32, 60.52, 41.76, 40.06, 38.27, 29.67, 23.70, 22.03, 20.44, 14.14; HRMS (FI+) calcd. for $C_{13}H_{19}NO_2$ $[M]^+$:221.1415, found: 221.1430.

(1R,2R)-2-(2-hydroxyethyl)-1,2-dimethylcyclohex-3-ene-1-carbonitrile (S-1)

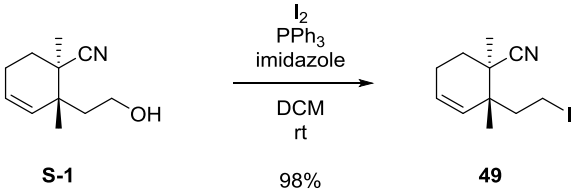


48 84% **S-1**

To a stirred solution of ester **48** (5.3g, 24.0 mmol) in THF (80 ml)-Et_2O (100 ml) at −78 °C was added DIBAL (1.02 M in hexane, 51.7 ml, 52.7 mmol) dropwise. The reaction mixture was slowly warmed up to−30 °C over 2 h and was stirred for 10 h at the same temperature. The reaction mixture was quenched by slow addition of a saturated solution of sodium potassium tartrate, diluted with EtOAc, and allowed to stir at room temperature to get two separated layers. The aqueous layer was extracted with EtOAc three times. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes: EtOAc= 80: 20 to 40: 60) to give the compound **S-1** as a yellow oil. (3.64 g, 20.3 mmol, 84%). IR (neat); 3400 (br), 2947, 2359, 1437, 1220, 1044, 1024, 772 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): 5.69 (dt, *J*= 10.3, 3.7 Hz, 1H), 5.44 (dt, *J*= 10.3, 2.2 Hz, 1H), 3.80-3.70 (m, 2H), 2.36-2.26 (m, 1H), 2.15-2.06 (m, 2H), 1.96-1.88 (m, 1H), 1.87-1.80 (m, 1H), 1.75-1.68 (m, 2H), 1.64-1.58 (m, 2H), 1.34 (s, 3H), 1.27 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): 132.57, 125.34, 123.79, 58.92, 40.15, 39.62, 37.77, 29.41, 23.42, 22.29, 20.33; ; HRMS (FI+) calcd.

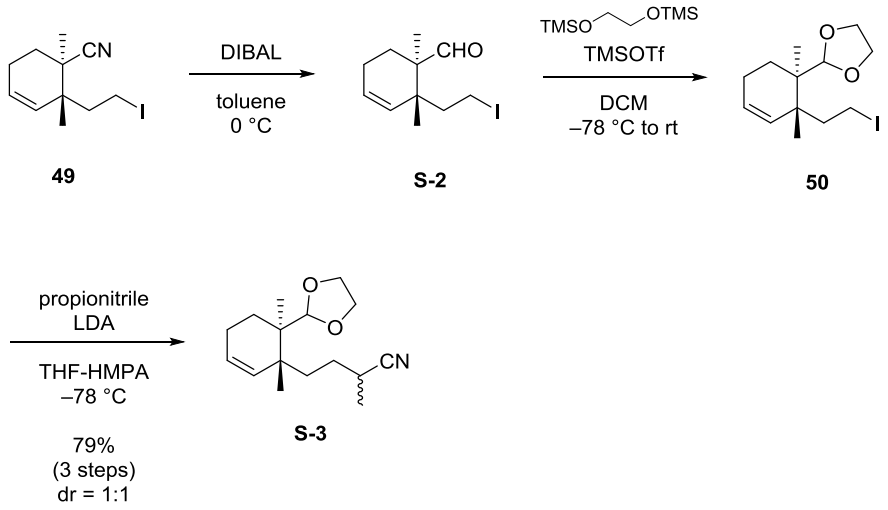
for $C_{11}H_{17}NO$ $[M]^+$: 179.1310, found: 179.1306.

(1R,2R)-2-(2-iodoethyl)-1,2-dimethylcyclohex-3-ene-1-carbonitrile (49)



To a stirred solution of the alcohol **S-1** (1.60 g, 8.93 mmol) in DCM (30 ml) at 0 °C was added imidazole (1.22 g, 17.9 mmol), PPh_3 (3.28 g, 12.5 mmol), I_2 (3.17 g, 12.5 mmol). After 1 h, MeOH (0.145 ml) was added, then the reaction mixture was purified by flash column chromatography (silica gel, hexanes: EtOAc= 90: 10 to 70: 30) to give the compound **49** as a white solid (2.54 g, 8.78 mmol, 98%).; mp 67-71 °C, IR (neat): 3019, 2975, 2951, 2944, 2938, 2930, 2359, 2332, 2232, 1457, 1432, 1377, 1182, 1109 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): 5.74 (dt, *J*= 6.8, 3.5 Hz, 1H), 5.42-5.38 (m, 1H), 3.27-3.17 (m,2H), 2.38-2.25 (m, 1H), 2.18-1.90 (m, 4H), 1.85-1.79 (m, 1H), 1,.34 (s, 3H), 1.26 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): 131.29, 126.25, 123.51, 43.04, 41.01, 39.76, 29.65, 22.61, 22.40, 20.43, -0.53; HRMS (FI+) calcd. for $C_{11}H_{16}NI$ $[M]^+$: 289.0327, found: 289.0312.

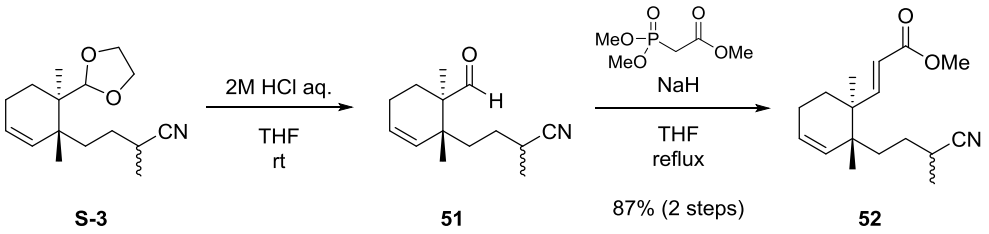
4-((1R,6R)-6-(1,3-dioxolan-2-yl)-1,6-dimethylcyclohex-2-en-1-yl)-2-methylbutanenitrile (S-3)



To a stirred solution of nitrile **49** (3.0 g, 10.4 mmol) in toluene (50 ml) at 0 °C was added DIBAL (1.0 M in hexane, 10.4 ml, 10.4 mmol). After 15 min, the reaction mixture was quenched by 10% tartaric acid aqueous solution. The aqueous layer was extracted with EtOAc three times. The combined organic phases were washed with saturated aqueous solution of $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude oil was used without further purification in the next step. To a stirred solution of the crude aldehyde and 1,2-Bis(trimethylsilyloxy)ethane (4.65 ml, 19.4 mmol) in DCM (50 ml) at −78 °C was added TMSOTf (0.175 ml, 0.969 mmol). The reaction mixture was slowly warmed up to room temperature for overnight. After the reaction mixture was poured into a saturated aqueous solution of $NaHCO_3$, the aqueous layer was extracted with DCM three times. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude oil was used without further purification in the next step. To a solution of propionitrile (3.26 ml, 45.5 mmol) in THF was added LDA (1.1 M in THF-hexane solution, 41.4 ml, 45.5 mmol) at −78 °C. After being stirred for 1 h, the crude in THF (50 ml)-HMPA (8 ml) was added to the reaction mixture at the same temperature. After being stirring for 15 min, the reaction mixture was quenched by saturated aqueous solution of NH_4Cl, and the aqueous layer was extracted with EtOAc three times. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes: EtOAc= 90: 10 to 70: 30) to give the compound **S-3** as a colorless oil (2.16 g, 8.2 mmol, 79% for 3 steps, dr =1:1); IR (neat): 2974, 2951, 2943, 2919, 2915, 2369, 2363, 2360, 2342, 2327, 1718, 1559, 1219, 1087, 772 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): 5.69-5.59 (m, 1H), 5.40-5.33 (m, 1H), 4.78 (s, 0.5H), 4.77 (s, 0.5H), 3.98-3.75 (m, 4H), 2.58-2.48 (m, 1H), 2.05-1.95 (m, 2H), 1.85-1.78 (m, 0.5H), 1.74-1.50 (m, 5H), 1.48-1.40 (m, 0.5H), 1.38 (d, *J*= 7.1 Hz, 1.5H), 1.33 (d, *J*=7.1 Hz, 1.5H), 1.02 (s, 1.5H), 1.00(s, 1.5H), 0.85 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): 133.95, 133.68, 125.33, 125.26, 123.13, 107.14, 107.06, 65.32, 65.29, 64.19, 64.16, 41.51, 41.50, 38.37, 38.34, 34.92, 34.82, 29.06, 29.05, 27.67, 27.61, 26.47, 26.43, 22.19, 22.12, 22.07, 22.04, 18.17, 18.11, 14.34, 14.10 (one signal does not appear due to incidental

overlap); HRMS (FI+) calcd. for $C_{16}H_{25}NO_2$ $[M]^+$: 263.1885, found: 263.1906.

Methyl (E)-3-((1S,2R)-2-(3-cyanobutyl)-1,2-dimethylcyclohex-3-en-1-yl)acrylate (52)



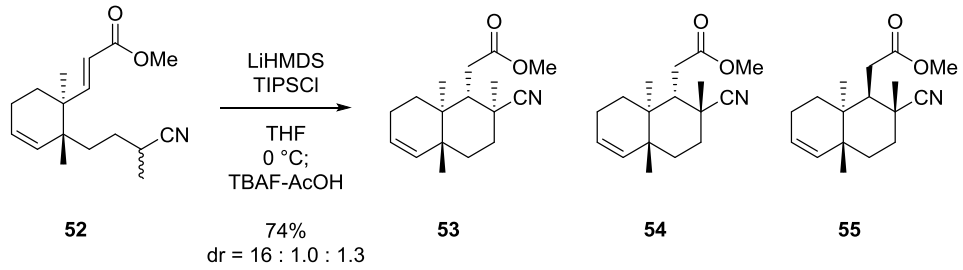
To a solution of acetal **S-3** (419 mg, 1.59 mmol) in THF (5.0 ml), was added 2M HCl aqueous solution (0.795 ml, 1.59 mmol) at room temperature. After being strring for 17 h, the reaction mixture was added a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with EtOAc three times. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude aldehyde was used without further purification in the next step. A suspension of NaH (60% in oil, 301 mg, 7.53 mmol) in THF (30 ml) was added a trimethyl phosphonoacetate (1.21 ml, 8.37 mmol) at 0 °C. After being stirred for 30 min, the crude aldehyde in THF (10 ml) was added to a reaction mixture and the reaction mixture was heated to reflux. After being stirred for 6 h, the reaction mixture was quenched by addition of saturated aqueous solution of NH_4Cl. The aqueous layer was extracted with EtOAc three times. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes: EtOAc= 90: 10 to 70: 30) to give the compound **52** as a colorless oil (380 mg, 1.38 mmol. 87% for 2 steps, dr =1:1); IR (neat): 2973, 2967, 2961, 2951, 1718, 1701, 1653, 1646, 1464, 1457, 1448, 1436, 1300, 1219, 1194, 1174, 1013, 772 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): 7.21 (d, *J*=16.1 Hz, 0.5H), 7.20 (d, *J*=16.1 Hz, 0.5H), 5.83(d, *J*= 16.1 Hz, 0.5H), 5.82 (d, *J*= 16.1 Hz, 0.5H), 5.70-5.64 (m, 1H), 5.45-5.38 (m, 1H), 3.74 (s, 3H), 2.60-2.50 (m, 1H), 2.10-2.00 (m, 2H), 1.70-1.32 (m, 6H), 1.33 (d, *J*= 12Hz, 1.5H), 1.328 (d, *J*= 12 Hz, 1.5 H), 1.07 (s, 1.5H), 1.06 (s, 1.5H), 0.90 (s, 1.5H), 0.89 (s, 1.5H); ^{13}C-NMR (125 MHz, $CDCl_3$): 167.42, 167.41, 155.94, 155.81, 133.57, 133.21, 125.39, 125.32, 122.82, 118.85, 118.84,

118.78, 118.77, 51.42, 41.21, 38.81, 38.79, 35.52, 35.33, 31.10, 30.94, 29.08, 26.38, 26.35, 22.46, 22.38, 22.37, 22.15, 19.38, 19.31, 18.13, 18.10 (two signals does not appear due to incidental overlaps) HRMS (FI+) calcd. for $C_{17}H_{25}NO_2$ $[M]^+$: 275.1885 found: 275.1893.

Methyl 2-((1S,2S,4aR,8aS)-2-cyano-2,4a,8a-trimethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-yl) acetate (53)

Methyl 2-((1S,2R,4aR,8aS)-2-cyano-2,4a,8a-trimethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalen -1-yl) acetate (54)

Methyl2-((1R,2R,4aR,8aS)-2-cyano-2,4a,8a-trimethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalen -1-yl) acetate (55)



To a solution of nitrile **52** (30 mg, 0.109 mmol) in THF was added a TIPSCl (34.6 μl, 0.163 mmol) and LHMDS (1.0M in THF, 218 ml, 0.218 mmol) at 0 °C. After being stirred for 15 min, then,the reaction mixture was quenched by AcOH (31.2 μl) and TBAF (218 μl, 0.218 mmol). The reaction mixture was added H_2O and was extracted with Et_2O three times. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes: EtOAc= 90:10 to 70:30) to give the mixtures of compound **53**, **54** and **55** as a colorless oil (22.2 mg, 0.081 mmol. 74%, dr =16 : 1.0 : 1.3).

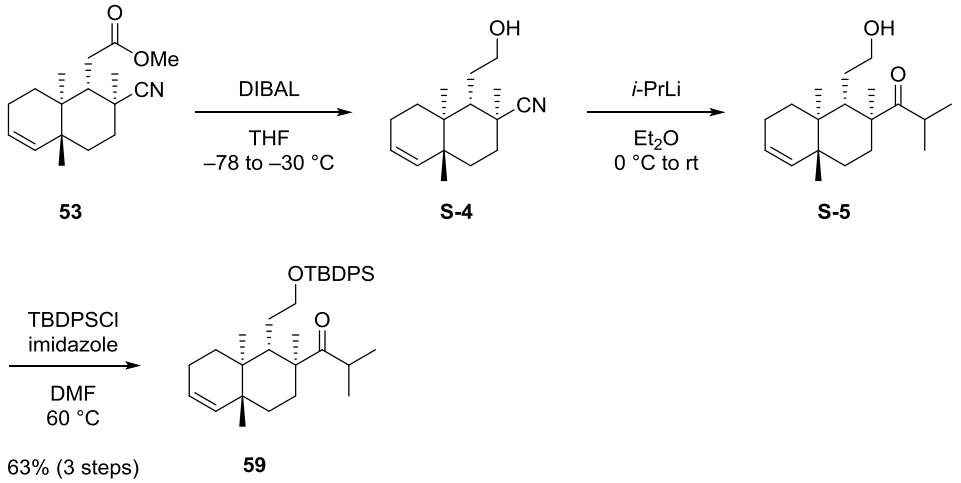
Compound **53**: IR (neat): 2973, 2951, 2919, 2364, 2359, 1735, 1718, 1559, 1436, 1390, 1302, 1219, 1193, 772 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$):5.47-5.44 (m, 2H), 3.72 (s, 3H), 2.78 (dd, *J*= 7.6, 3.6 Hz, 1H), 2.55 (dd, *J*= 16.4, 7.6 Hz, 1H), 2.45 (dd, *J*= 16.4, 3.6 Hz, 1H), 2.38-2.30 (m, 1H), 2.14-2.04 (m, 2H), 1.84-1.74 (m, 2H), 1.60-1.53 (m, 1H), 1.42 (s, 3H), 1.23-1.18 (m, 2H), 1.16 (s,

3H), 0.88 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$):173.30, 136.77, 126.27, 124.65, 52.03, 42.19, 38.71, 37.64, 37.17, 33.07, 32.63, 28.94, 28.29, 23.71, 22.37, 21.86, 16.06. HRMS (FI+) calcd. for $C_{17}H_{25}NO_2$ $[M]^+$: 275.1885, found: 275.1904.

Compound **54**: Mp: 91-94 °C; IR (neat): 3015, 1734, 1459, 1436, 1385, 1304, 1209, 1193, 707 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): 5.50-5.42 (m, 2H), 3.70 (s, 3H), 2.63 (dd, *J* = 17.8, 4.6 Hz, 1H), 2.44 (dd, *J* = 17.8, 4.6Hz, 1H), 2.24 (dd, *J* = 4.6, 4.6 Hz, 1H), 2.14-2.08 (m, 2H), 2.04-1.95 (m, 2H), 1.85-1.75 (m, 1H), 1.54-1.45 (m, 1H), 1.38 (s, 3H), 1.31-1.24 (m, 1H), 1.22-1.16 (m, 1H), 1.12 (s, 3H), 1.07 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$):174.15, 137.02, 125.37, 124.30, 52.04, 43.83, 38.71, 37.68, 35.57, 33.84, 32.65, 30.02, 28.69, 28.46, 23.59, 22.61, 14.49; HRMS (FD+) calcd. for $C_{17}H_{25}NO_2$ $[M]^+$: 275.1885, found:275.1872

Compound **55**: Mp: 125-128°C; IR (neat): 3014, 1736, 1450, 1385, 1364, 1299, 1165, 1073, 989, 708 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): 5.46-5.36 (m, 2H), 3.71 (s, 3H), 2.76-2.58 (m, 2H), 2.24 (dd, *J* = 17.8, 9.2Hz, 1H), 2.20-2.10 (m, 2H), 2.05 (ddd, *J* = 14.0, 14.0, 4.0 Hz, 1H), 1.97-1.85 (m, 2H), 1.68 (ddd, *J* = 14.0, 14.0, 4.0 Hz, 1H), 1.46 (s, 3H), 1.36 (s, 3H), 1.23-1.14 (m, 2H), 0.95 (s, 3H) ; ^{13}C-NMR (125 MHz, $CDCl_3$):174.05, 137.68, 127.64, 123.68, 52.08, 46.32, 38.77, 36.44, 34.17, 32.07, 30.71, 30.27, 29.10, 26.97, 24.77, 23.48, 23.45; HRMS (FI+) calcd. for $C_{17}H_{25}NO_2$ $[M]^+$: 275.1885, found: 275.1884

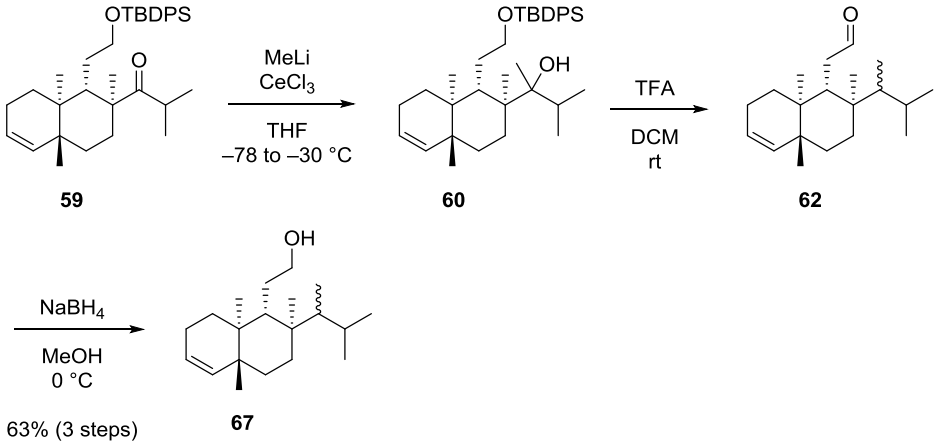
1-((1S,2S,4aR,8aS)-1-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-2,4a,8a-trimethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalen-2-yl)-2-methylpropan-1-one (59)



To a stirred solution of ester **53** (480 mg, 1.74 mmol) in THF (10 ml) at −78 °C was added DIBAL (1.0 M in hexane, 3.83 ml, 3.83 mmol) dropwise. The reaction mixture was warmed up to −30 °C and was stirred for 3 h at same temperature. The reaction mixture was quenched by addition of a saturated aqueous solution of sodium potassium tartrate, diluted with EtOAc, and allowed to stir at room temperature for an additional 2 h to get two separated layers. The aqueous layer was extracted with EtOAc three times. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was used without further purification in the next step. To a stirred solution of the crude alcohol **S-4** in Et_2O (16 ml) at 0 °C was added *i*-PrLi (0.7 M in pentane, 20.5 ml, 14.0 mmol) dropwise. The reaction mixture was warmed up to room temperature and was stirred for 1 h. After cooling to 0 °C , the reaction mixture was quenched by addition of 2M HCl aqueous solution, and the aqueous layer was extracted with EtOAc three times. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was used without further purification in the next step. The crude **S-5** and imidazole (358 mg, 5.26 mmol) were dissolved in DMF (3 mL) and TBDPSCl (676 μl, 2.63 mmol) was added at room temperature. The reaction mixture was heated at 60 °C for 1 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc, washed with saturated aqueous solution of NH_4Cl, water, brine and dried over $MgSO_4$. The residue was purified by flash column chromatography (silica gel, hexanes: EtOAc= 90: 10) to give the compound **59** as a white amorphous (589 mg, 1.10

mmol, 63% for 3 steps).; IR (neat):2981, 2970, 2964, 2936, 2931, 2365, 2361, 2357, 2343, 2337, 2333, 1699, 1696, 1686, 1464, 1457, 1428, 1382, 1111, 998, 755 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$):7.70-7.62 (m, 4H), 7.45-7.32 (m, 6H), 5,43-5.35 (brs, 2H), 3.65 (dt, *J* =10.4, 5.9 Hz, 1H), 3.48 (dt, *J*=10.4, 5.9 Hz, 1H),3.04 (qq, *J*= 6.6, 6.6 Hz, 1H), 1.92-1.88 (m, 3H), 1.86-1.68 (m, 2H), 1.60-1.50 (m,1H), 1.42-1.34 (m, 1H), 1.30-1.10 (m, 5H, including 1.54, s, 3H), 1.08-0.92 (m. 20H, including (1.03, s, 9H), 0.99 (d, *J*= 6.6 Hz, 3H), 0.95 (d, *J*= 6.6 Hz, 3H), (0.94 s, 3H)), 0.84 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): 219.82, 137.77, 135.63, 135.58, 134.24, 134.09, 129.42, 129.40, 127.51, 127.46, 124.37, 65.08, 53.54, 38.39, 38.15, 37.62, 34.17, 32.16, 31.42, 29.53, 29.05, 26.90, 23.74, 22.76, 20.42, 20.30, 19.10, 18.75, 16.26, HRMS (FD+) calcd. for $C_{35}H_{51}O_2Si$ $[M+H]^+$: 531.3659, found: 531.3658.

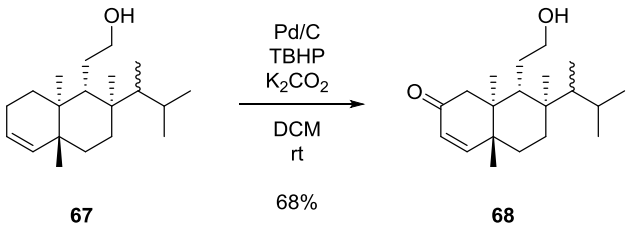
2-((1R,2R,4aR,8aS)-2,4a,8a-trimethyl-2-(3-methylbutan-2-yl)-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-yl)ethan-1-ol (67)



A suspension of $CeCl_3$ (1.65 g, 6.59 mmol, prepared from $CeCl_3 \cdot 7H_2O$) in THF (30 ml) was added MeLi (1.0 M in Et_2O, 6.59 ml, 6.59 mmol) at −78 °C. The reaction mixture was stirred at same temperature for 1 h and a solution of ketone **59** (700 mg, 1.32 mmol) in THF (10 ml) was added and slowly warmed up to −30 °C. After stirring for 30 min, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was used

without further purification in the next step. The crude **60** was dissolved in DCM (10 ml) at room temperature and added TFA (0.748 ml, 9.71 mmol). After stirring for 15 min, the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$, and extracted with EtOAc. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was used without further purification in the next step. The crude **62** was dissolved in MeOH (5 ml) and was added $NaBH_4$ (73.5 mg, 1.94 mmol) one portion. After stirring for 15 min, the reaction mixture was quenched with H_2O, and extracted with EtOAc. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes: EtOAc= 90:10 to 70:30) to give the compound **67** as a colorless oil (244 mg, 0.834 mmol, dr= 2:1、63% for 3 steps).;IR (neat): 3382, 2954, 2884, 1457, 1388, 1040, 757, 705 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$):5.50-5.38 (m, 2H), 3.64-3.52 (m, 2H), 2.20-1.95 (m, 3H), 1.85-1.65 (m, 3H), 1.60-1.30 (m, 6H), 1.20-1.08 (m, 1H), 1.07-0.70 (m, 19H); ^{13}C-NMR (125 MHz, $CDCl_3$): 138.71, 138.59, 124.28, 124.07, 64.98, 64.86, 45.25, 44.86, 41.58, 41.46, 40.44, 40.18, 39.50, 39.22, 37.83, 37.60, 30.77, 30.40, 30.35, 30.32, 29.78, 29.55, 27.85, 27.63, 26.22, 25.82, 25.48, 25.11, 25.10, 23.72, 22.67, 22.66, 21.64, 21.51, 18.67, 18.31, 17.20, 16.53, 8.37, 7.93; HRMS (FD+) calcd. for $C_{20}H_{36}O$ $[M]^+$: 292.2783, found: 292.2766.

(4aR,7R,8R,8aS)-8-(2-hydroxyethyl)-4a,7,8a-trimethyl-7-(3-methylbutan-2-yl)-4a,5,6,7,8,8a-hexahydronaphthalen-2(1H)-one (68)

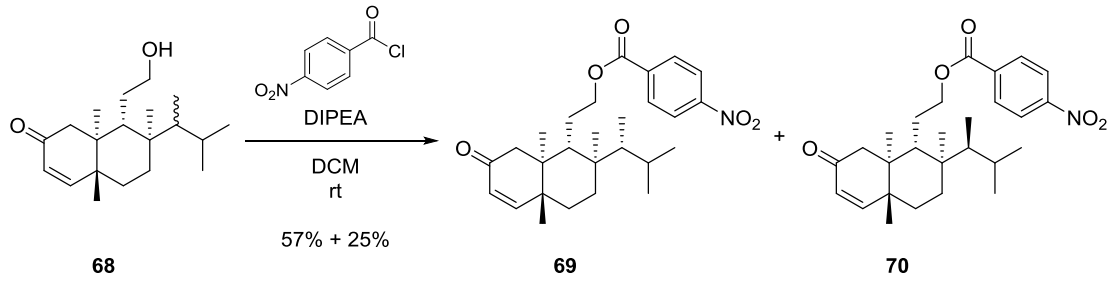


To a solution of compound **67** (244 mg, 0.834 mmol) in DCM (10 ml) was added Pd/C (10% on carbon, 188mg, 0.083 mmol), K_2CO_3 (11.5 mg, 0.083 mmol), TBHP (5M in decane, 0.834 ml, 4.17

mmol) and stirred for 7 h. Additional TBHP (5M in decane, 0.834 ml, 4.17 mmol) was added and stirred for 16 h. Additional TBHP (5M in decane, 0.501 ml, 2.50 mmol), K_2CO_3 (11.5 mg, 0.083 mmol) were added and stirred for 7 h. The reaction mixture was filtrated through a pad of Celite and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes: EtOAc= 60: 40) to give the compound **68** as a colorless oil (174 mg, 0.568 mmol, dr= 2:1, 68%); IR (neat): 3407, 2957, 2359, 1684, 1663, 1472, 1457, 1391, 1373, 1257, 1042, 908, 728 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): 6.75 (d, *J* = 9.8 Hz, 0.67 H), 6.72 (d, *J* = 10 Hz, 0.33 H), 5.86 (d. *J* = 9.8 Hz, 0.67 H), 5.85 (d, *J* = 10 Hz, 0.33 H), 3.64-3.54 (m, 2H), 2.42-2.28 (m, 2H), 2.10-1.91 (m, 2H), 1.89-1.76 (m, 2H), 1.70-1.58 (m, 1H), 1.56-1.38 (m, 2H), 1.35-1.22 (m, 5H), 1.15 (s, 1.8 H), 1.10 (s, 1.2 H) 1.05-0.88 (m, 8H), 0.86-0.74 (m, 4H); ^{13}C-NMR (125 MHz, $CDCl_3$): 200.76, 200.73, 161.08, 160.98, 127.15, 127.01, 64.06, 63.93, 49.22, 48.89, 44.87, 44.53, 42.22, 42.03, 40.77, 40.65, 40.45, 40.20, 39.65, 39.39, 29.47, 29.42, 28.91, 28.67, 27.55, 27.40, 26.24, 25.74, 25.36, 24.96, 22.88, 22.37, 21.22, 21.01, 20.23, 19.39, 18.58, 18.24, 8.28, 7.81; HRMS (FD+) calcd. for $C_{20}H_{35}O_2$ $[M+H]^+$: 307.2624, found: 307.2637.

2-((1R,2R,4aR,8aS)-2,4a,8a-trimethyl-2-((R)-3-methylbutan-2-yl)-7-oxo-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-yl)ethyl 4-nitrobenzoate (69)

2-((1R,2R,4aR,8aS)-2,4a,8a-trimethyl-2-((S)-3-methylbutan-2-yl)-7-oxo-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-yl)ethyl 4-nitrobenzoate (70)



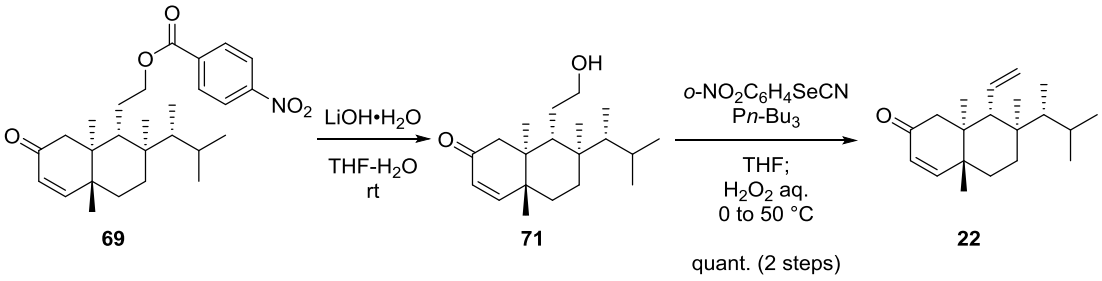
To a solution of compound **68** (170 mg, 0.555 mmol) in DCM (5 ml) was added diisopropylamine (0.194 ml, 1.11 mmol) and *p*-nitro benzoyl chloride (154 mg, 0.832 mmol) at room temperature. The reaction mixture was quenched by H_2O, and the aqueous layer was extracted with EtOAc three

times. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes: EtOAc= 70: 30) to give the compound **69** as a colorless oil (144 mg, 0.316 mmol, 57%) and the compound **70** (63.8 mg, 0.140 mmol, 25%) as a colorless oil.

compound **69**: IR (neat): 3021, 1723, 1668, 1528, 1472, 1465, 1386, 1372, 1271, 1114, 1102, 752, 719 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): 8.30 (d, *J* = 8.8 Hz, 2H), 8.23 (d, *J* = 8.8 Hz, 2H), 6.76 (d, *J* = 10.0 Hz, 1H), 5.88 (d. *J* = 10.0, 1H), 4.41 (dt, *J* = 10.9, 5.7 Hz, 1H), 4.25 (dt, *J* = 10.9, 5.7 Hz, 1H), 2.47 (d, *J* = 17.1 Hz, 1H), 2.39 (d, *J* = 17.1 Hz, 1H), 2.13-2.08 (m, 1H), 2.04-1.78 (m, 4H), 1.76-1.64 (m, 1H), 1.49 (dd, *J* = 7.2, 3.6 Hz, 1H), 1.37-1.22 (m, 5H), 1.16 (s, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.6 Hz, 3 H), 0.94 (s, 3H), 0.82 (d, *J* = 7.1 Hz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): 199.80, 164.43, 160.53, 150.46, 135.51, 130.66, 127.27, 123.46, 66.79, 49.23, 44.85, 42.34, 40.90, 40.45, 40.06, 28.88, 27.39, 26.40, 25.02, 25.01, 22.89, 21.27, 20.19, 18.58, 7.84; HRMS (FD+) calcd. for $C_{27}H_{38}NO_5$ $[M+H]^+$: 456.2742, found: 456.2737.

compound **70**: IR (neat):2988, 2957, 2363, 1723, 1670, 1527, 1349, 1272, 1115, 1103, 720 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): 8.30 (d, *J* = 8.8 Hz, 2H), 8.22 (d, *J* = 8.8 Hz, 2H), 6.73 (d, *J* = 9.8 Hz, 1H), 5.87 (d, *J* = 9.8 Hz, 1H), 4.38 (dt, *J* = 10.1, 6.6 Hz, 1H), 4.28 (dt, *J* = 10.1, 6.6 Hz, 1H), 2.42 (d, *J* = 17.1 Hz, 1H), 2.37 (d, *J* = 17.1 Hz, 1H), 2.10-1.60 (m, 6H), 1.47 (dd, *J* = 7.2, 3.6 Hz, 1H), 1.38-1.20 (m, 5H), 1.14 (s, 3H), 1.03 (s, 3H), 0.93 (d, *J* = 7.1 Hz, 3H), 0.88 (d, *J* = 7.1 Hz, 3H), 0.82 (d, *J* = 7.1 Hz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): 199.78, 164.54, 150.50, 135.56, 130.68, 127.17, 123.49, 66.94, 48.95, 45.07, 42.20, 40.79, 40.23, 40.12, 28.64, 27.60, 25.86, 25.40, 25.09, 22.38, 21.09, 19.39, 18.19, 8.47; HRMS (FD+) calcd. for $C_{27}H_{38}NO_5$ $[M+H]^+$: 456.2742, found: 456.2736.

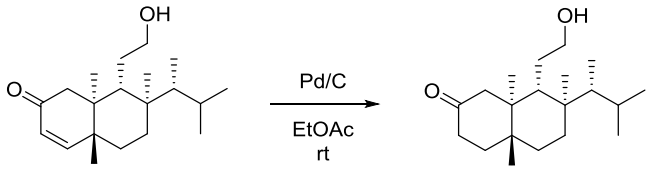
2-((1R,2R,4aR,8aS)-2,4a,8a-trimethyl-2-(3-methylbutan-2-yl)-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-yl)ethan-1-ol (22)



To a solution of the nitro benzoate **69** (150 mg, 0.329 mmol) in THF (1 ml)-H_2O (1 ml) was added $LiOH \cdot H_2O$ (23.7 mg, 0.988 mmol) one portion at room temperature. After stirring for 30 min, the aqueous layer was extracted with EtOAc three times. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was used without further purification in the next step. The crude was dissolved in THF (5 ml) at room temperature and added 1-nitro-2-selenocyanatobenzene (222 mg, 0.979 mmol), *n*-Bu_3P (0.403 ml, 1.631 mmol). After being stirred for 30 min at the same temperature, the reaction mixture was added 30% hydrogen peroxide (0.333 ml, 3.26 mmol) and warmed up to 50 °C. The reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$, added solid of $Na_2S_2O_3$ and extracted with EtOAc three times. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes: EtOAc= 100: 0 to 80: 20) to give the compound **22** as a colorless oil (94mg, 0.329 mmol. 100%). IR (neat):2973, 2363, 2359, 1672, 1457, 1387, 1367, 1240, 1097, 917, 769 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): 6.73 (d, *J* = 9.8 Hz, 1H), 5.85 (d, *J* = 9.8 Hz, 1H), 5.72 (ddd, *J* = 17, 10.3, 10 Hz, 1H), 5.20 (dd, *J* = 10.3, 2.0 Hz, 1H), 4.98 (dd, *J* = 17.0, 2.0 Hz), 2.57 (d, *J* = 10 Hz, 1H), 2.25 (s, 2H), 2.15-2.10 (m, 1H), 1.97 (dt, *J* = 13.6, 4.3 Hz, 1H), 1.86 (dt, *J* = 13.9, 4.4 Hz, 1H), 1.39-1.24 (m, 6H), 1.09 (s, 3H), 1.03 (s, 3H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.86 (d, *J* = 6.6 Hz, 3H), 0.73 (d, *J* = 7.3 Hz, 3H) ; ^{13}C-NMR (125 MHz, $CDCl_3$): 200.86, 159.98, 135.44, 127.74, 119.62, 50.07, 49.46, 45.41, 40.74, 40.33, 40.07, 28.98, 27.55, 26.12, 24.48, 23.20, 21.86, 19.95, 18.66, 7.87, HRMS (FD+) calcd. for $C_{20}H_{32}O$ $[M]^+$: 288.2453, found: 288.2468.

(4aR,7R,8R,8aS)-8-(2-hydroxyethyl)-4a,7,8a-trimethyl-7-((R)-3-methylbutan-2-yl)octahydrona

phthalen-2(1H)-one (72)



71 89% **72**

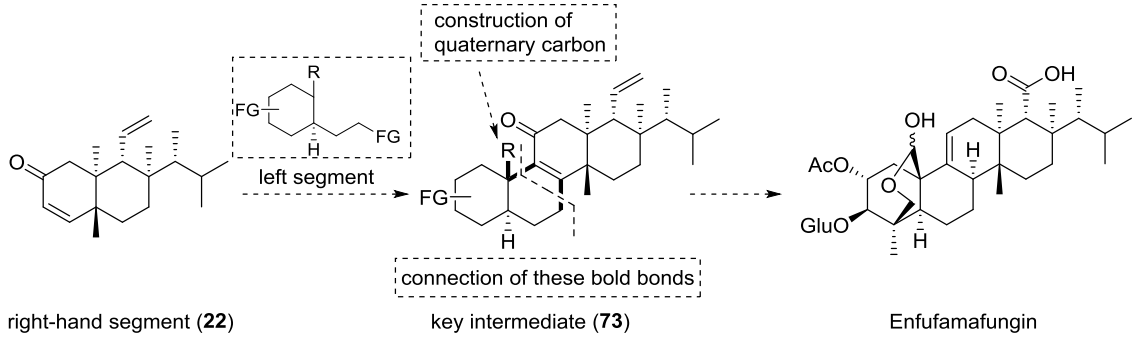
To a solution of compound **71** (21 mg, 0.069 mmol) in EtOAc (1 ml) was added 10% Pd/C (7.0 mg, 3.4 mmol) and hydrogenated at room temperature. After stirring for 30 min at the same temperature, the mixture was purified by flash column chromatography (silica gel, hexanes: EtOAc= 0: 100) to give the compound **72** as a colorless crystal (19 mg, 0.062 mmol, 89%).;mp 123-126 °C; IR (neat): 3300 (br), 2969, 1696, 1457, 1160, 1128, 951 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$):3.60-3.48 (m, 2H), 2.52-2.45 (m, 1H), 2.38-2.32 (m, 1H), 2.23 (d, *J* = 15.2 Hz, 1H), 2.08 (d, *J* = 15.2 Hz, 1H), 2.05-1.96 (m, 1H), 1.88-1.76 (m, 2H), 1.70-1.50 (m, 5H), 1.48-1.38 (m, 3H), 1.24 (dt, *J* = 13.9, 3.4 Hz, 1H), 1.17 (s, 3H), 1.13 (dt, *J* = 13.3, 3.4 Hz, 1H), 0.98 (s, 3H), 0.94 (d, *J* = 7.0 Hz, 3H), 0.92 (d, *J* = 6.4 Hz, 3H), 0.86 (s, 3H), 0.77 (d, *J* = 7.6 Hz, 3H) ; ^{13}C-NMR (125 MHz, $CDCl_3$): 212.91, 64.59, 51.04, 44.58, 42.28, 40.96, 40.09, 37.14, 35.78, 34.42, 31.23, 29.66, 27.39, 26.22, 25.02, 20.86, 19.35, 19.11, 18.74, 7.89 HRMS (FI+) calcd for $C_{20}H_{37}O_2$ $[M+H]^+$:309.2794, found:309.2803.

Chapter 2.

Model studies on a left-hand segment of enfumafungin

2-1. Introduction

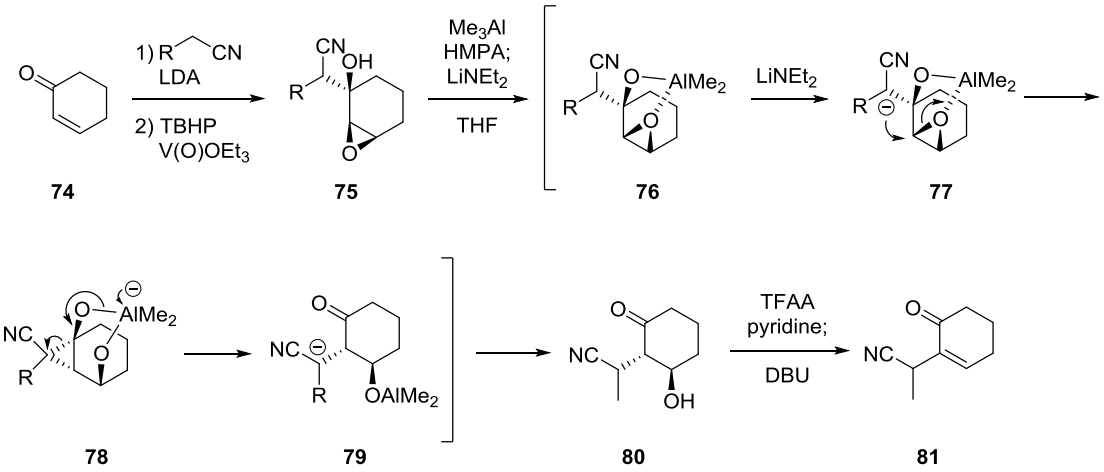
In chapter 1, the synthesis of the right-hand segment of enfumafungin was described. In order to synthesize enfumafungin by a convergent strategy using this segment, there are three serious issues to be resolved. The first is the establishment of a synthetic method for a left-hand segment in a stereoselective manner. The second is the development of an efficient method for connecting the left-hand segment and the right-hand segment. The α,β-enone moiety of the right-hand segment would be utilized for this purpose, while the steric hindrance by the quaternary carbon atom at the γ-position might prevent a carbon-carbon bond formation at the β-position. The last issue is the construction of the quaternary carbon at the angular position of the AB ring system. It was expected that these issues would require the development of new methodologies.



Scheme 17. Convergent strategy for the total synthesis of enfumafungin

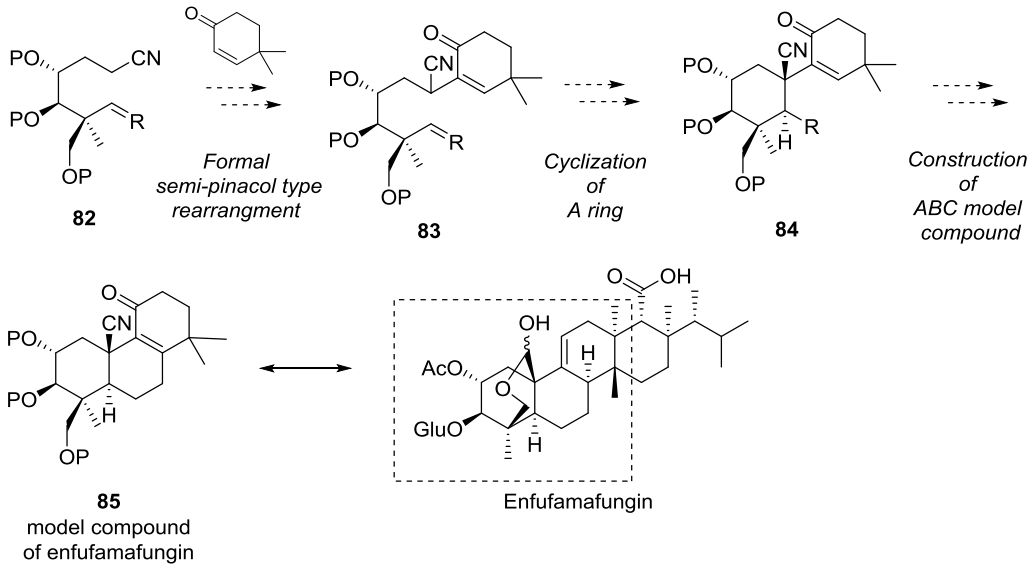
On the other hand, the Tanino's research group, to which the author belongs, recently developed a new formal semi-pinacol rearrangement reaction (scheme 18).[37] Thus, an α,β-enone **74** was reacted with an α-cyano carbanion generated from an alkanenitrile, and the resulting allylic alcohol was subjected to a stereoselective epoxidation reaction catalyzed by a vanadium reagent, giving rise to epoxy alcohol **75**. Successive treatment of **75** with trimethylaluminum and lithium diethylamide resulted in formation of a semi-pinacol rearrangement product **80**. The reaction proceeds through a

stepwise mechanism as follows: (1) the tertiary alcohol reacts with trimethylaluminum to generate the corresponding aluminum alkoxide **76** with evolution of methane, (2) deprotonation of the nitrile moiety by lithium diethylamide gives an α-cyano carbanion which attacks the epoxide moiety to form a cyclopropane intermediate **78**, (3) the resulting cyclopropane undergoes spontaneous cleavage by the electron donation from the aluminum alkoxide moiety. Product **80**, a,β-hydroxy ketone possessing an alkanenitrile side chain at the α-position, can be converted to enone **81** by dehydration mediated by TFFA under basic conditions.



Scheme 18. New formal semi-pinacol rearrangement reaction

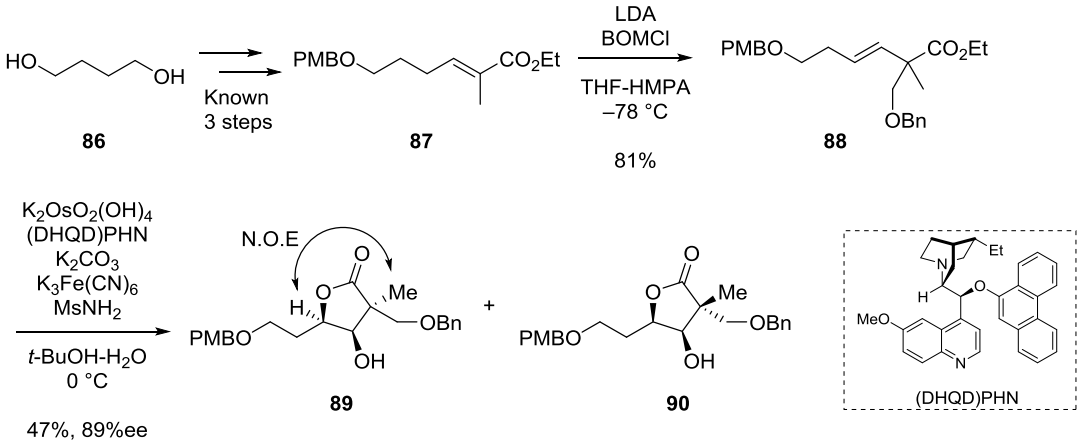
The author planned to use this reaction for connecting the left-hand segment and the right-hand segment, and the synthetic study was initiated starting with 4,4-dimethyl-2-cyclohexen-1-one as a model compound of the right-hand segment. Scheme 19 shows the synthetic strategy toward the model compound of enfumafungin. The A ring precursor **82**, which is prepared as an acyclic compound having the appropriate substituents, would be subjected to the sequence involving the connection with the enone and the formal semi-pinacol rearrangement reaction. The A ring would be constructed by an intramolecular cyclization reaction utilizing the cyano group of **83**, and the B ring is to be formed through intramolecular cyclization at the β-carbon of the C ring enone.



Scheme 19. Model study for constructing the left part of enfumafungin

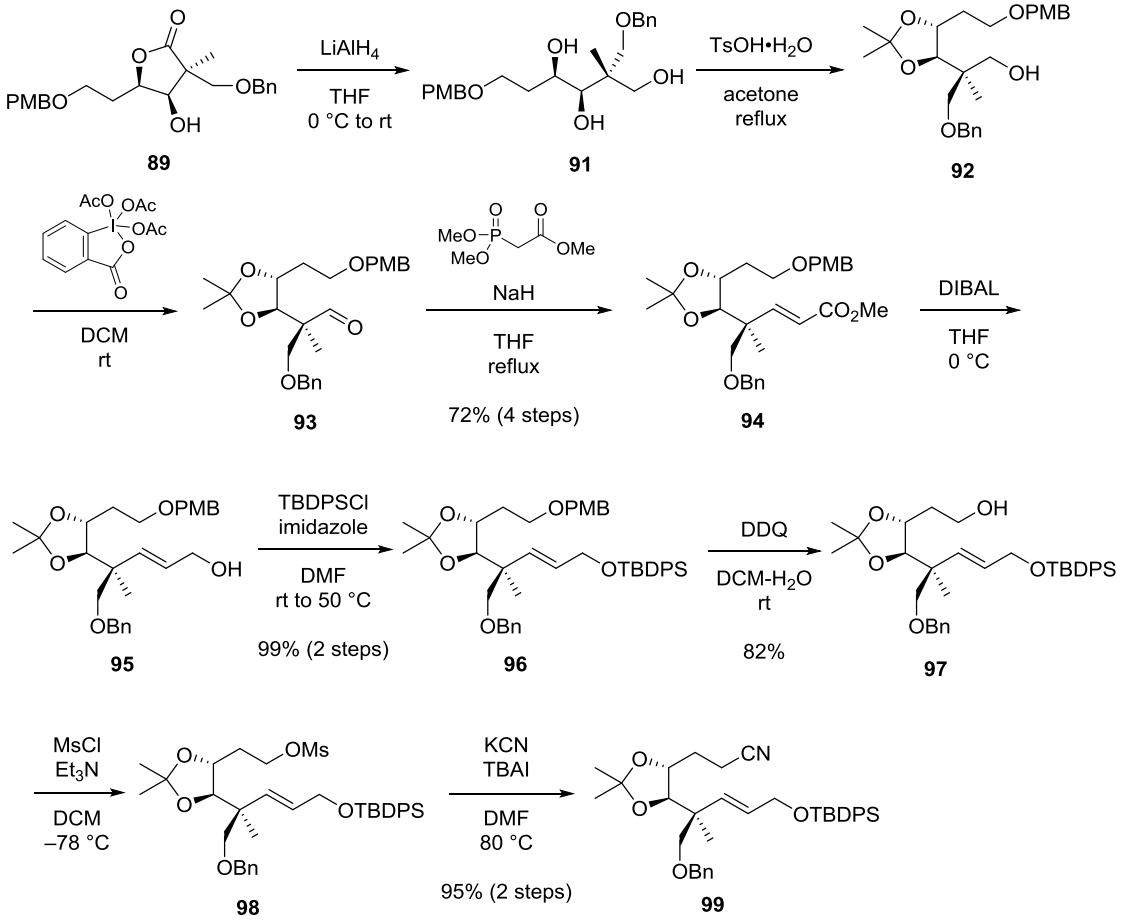
2-2. Stereoselective synthesis of the nitrile derivative

Firstly, the synthesis of a precursor of the A ring, a nitrile derivative having appropriate substituents, was explored. Treatment of α,β-unsaturated ester **87**, which was prepared from 1,4-butanediol (**86**) by a known procedure,[38] with lithium diisopropylamide followed by benzyloxymethyl chloride afforded β,γ-unsaturated ester **88**. The *trans*-alkene was subjected to a Sharpless asymmetric dihydroxylation reaction, during which the 1,2-diol product spontaneously underwent lactonization to give a mixture of lactone **89** and its isomer **90**.[39] Fortunately, these isomers were easily separated each from the other by silica gel column chromatography, and the configuration of the lactones was established by the NOE experiment. It is noteworthy that the sequence based on the resolution of a racemic compound **88** after asymmetric dihydroxylation is advantageous for providing a large amount of optically active intermediate, while the enantiomeric purity of the desired isomer determined by HPLC was 89%ee.



Scheme 20. Preparation of optically active intermediate **89**

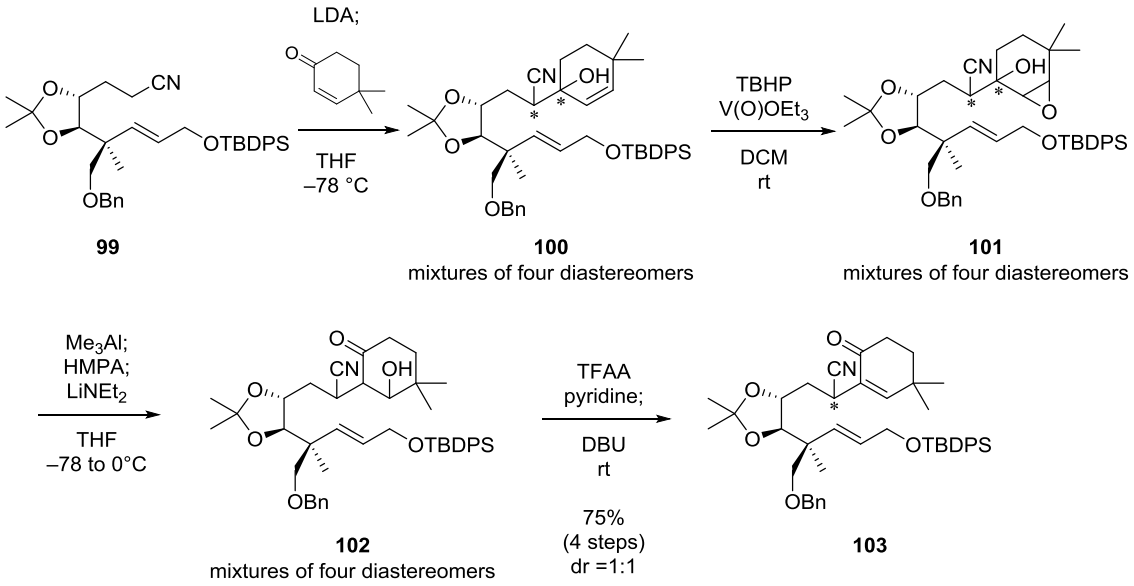
With the desired lactone **89** in hand, elongation of the carbon chain with appropriate functional groups was performed (Scheme 21). Reductive cleavage of the lactone afforded triol **91** which was protected as five-membered acetonide **92** in a regioselective manner. Primary alcohol **92** was converted to allylic alcohol **95** through DMP oxidation, the Horner-Wadsworth-Emmons reaction, and DIBAL reduction. After protection of the alcohol with TBDPS group and removal of the *p*-methoxybenzyl group with DDQ, the resulting alcohol **97** was transformed into nitrile **99** through S_{N2} reaction of mesylate with KCN.



Scheme 21. Stereoselective synthesis of nitrile **99**

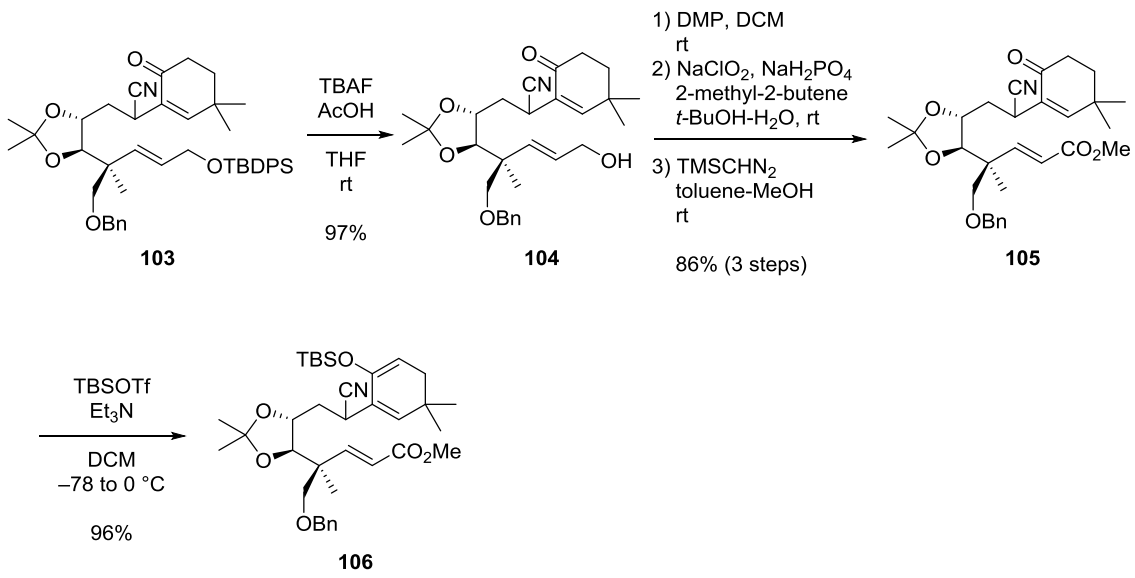
2-3. Construction of the tricyclic skeleton

With the A ring precursor **99** in hand, the stage was set for the introduction of the nitrile side chain to the C ring (Scheme 22). Treatment of nitrile **99** with lithium diisopropylamide afforded the α-cyano carbanion which was reacted with 4,4-dimethyl-2-cyclohexen-1-one to give allylic alcohol **100** as an inseparable mixture of four diastereomers. The mixture was oxidized by TBHP in the presence of a vanadium catalyst, and the resulting epoxy alcohol **101** was successively treated with trimethylaluminum and lithium diethylamide. The formal semi-pinacol rearrangement reaction of **101** occurred smoothly, and the product was subjected to the dehydration reaction by using TFFA under basic conditions. The desired enone **103**, consisting of a 1:1 mixture of epimers at the cyano group, was obtained in 75% overall yield from nitrile **99.**



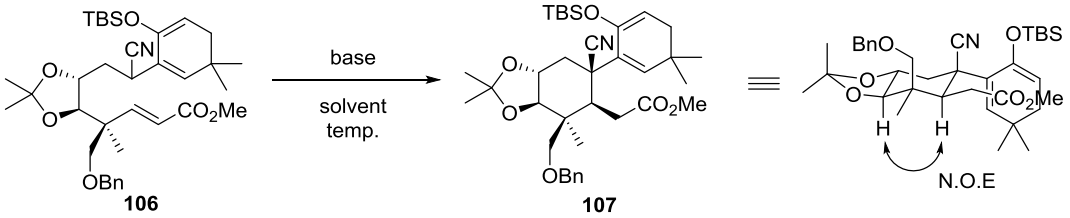
Scheme 22. Synthesis of cyclohexenone via formal semi-pinacol rearrangement reaction

The next issue is the stereoselective construction of the A ring by using the nitrile moiety of the coupling product. The author planned to apply the intramolecular conjugate addition reaction of a nitrile, which has proved to be useful for the stereoselective construction of the D ring. In order to introduce the α,β-unsaturated ester moiety to the substrate, the TBDPS group of silyl ether **103** was removed by tetrabutylammonium fluoride (Scheme 23). Oxidation of the resulting alcohol **104** through Dess-Martin oxidation followed by Pinnick oxidation afforded the corresponding α,β-unsaturated carboxylic acid.[40, 41] After esterification with trimethylsilyl diazomethane,[42] the ketone moiety of **105** was protected as an enol silyl ether by the treatment with *tert*-butyldimethylsilyl trifluoromethanesulfonate.



Scheme 23. Synthesis of the cyclization precursor

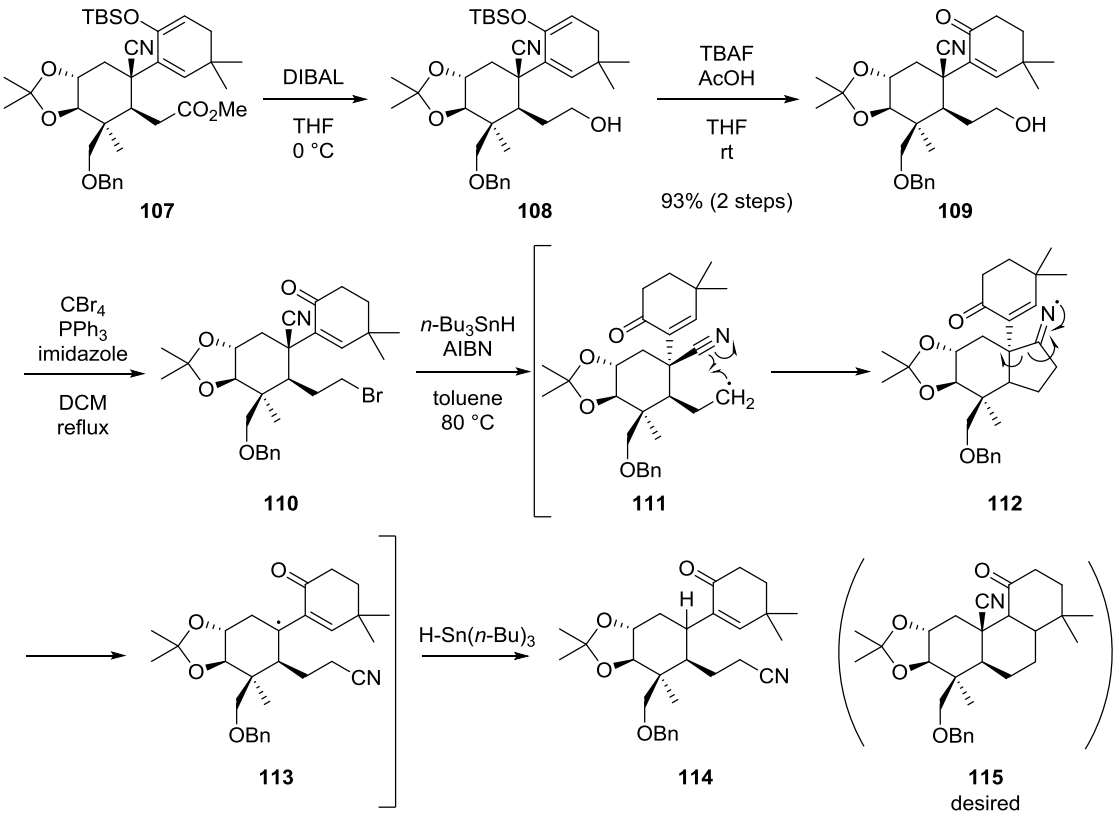
The intramolecular cyclization reaction of nitrile **106** for constructing the A ring was explored (Table 2). Surprisingly, the reaction with a small excess amount of lithium hexamethyldisilazide (LiHMDS) led to recovery of the starting material (entry 1), while a large amount of LiHMDS provided the cyclized product **107**, albeit in 14% yield (entry 2). The combined use of HMPA and TIPSCl as additives also failed to improve the yield of the cyclization reaction (entry 3). On the other hand, DMF was found to be the choice of solvent, resulting in a dramatically improved yield of the desired product **107** as a single isomer. The origin of the remarkable solvent effect is not clear, while DMF may coordinate to the lithium ion of the anionic intermediates. The NOE experiments of **107** indicated the relative stereochemistry of the ester side chain. Although the configuration of the quaternary carbon atom at the nitrile moiety could not be determined from the NOEs, it was supposed that the bulky cyclohexadiene ring would be located at the equatorial position.



entry	reagent	solvent	temp.	yield
1	LiHMDS (1.1 eq)	THF	–78 to 0 °C	SM was recovered (50%)
2	LiHMDS (1.5 eq +0.7 eq)	THF	–78 to 0 °C	14%
3	LiHMDS, HMPA, TIPSCl	THF	–78 to 0 °C	trace
4	LiHMDS (1.4 eq)	DMF	–40 °C	80% single diastereomer

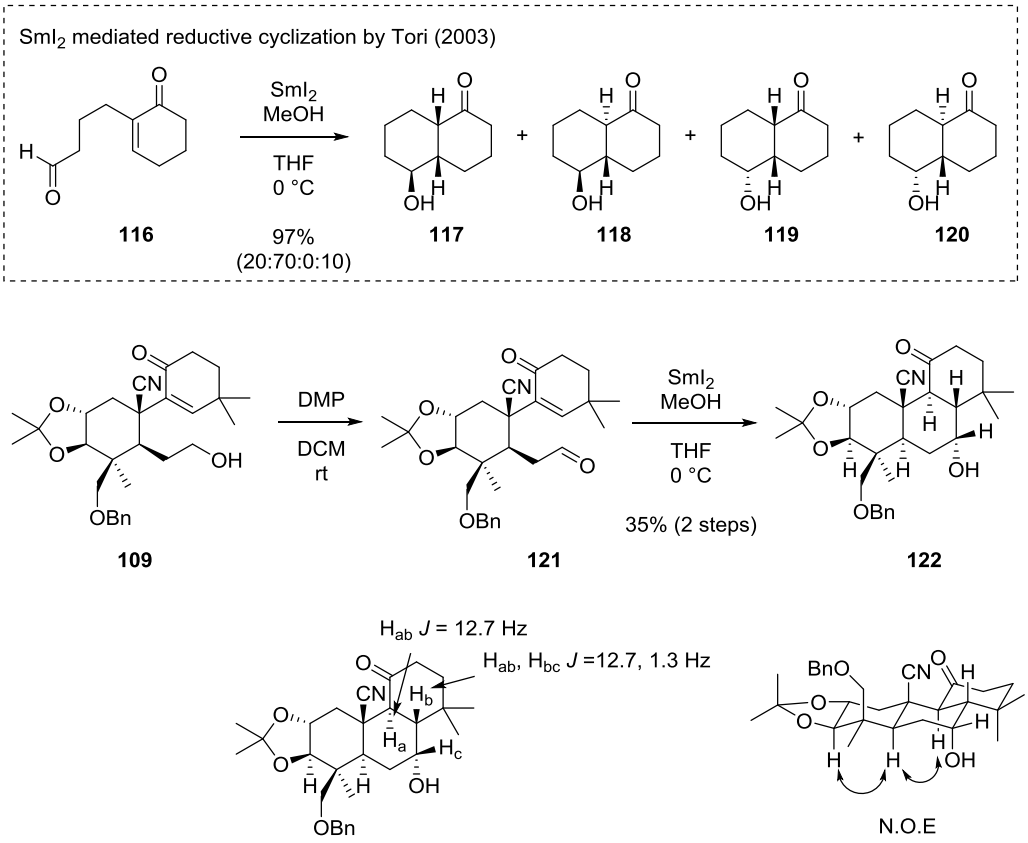
Table 2. Intramolecular conjugate addition reaction of **106** for constructing the A ring

With the intermediate possessing the A ring and the C ring in hand, the stage was set for the construction of the B ring. Initial plan was based on the radical cyclization reaction between the terminal carbon and the cyclohexenone moiety (Scheme 24). Selective reduction of the ester moiety by DIBAL followed by removal of the silyl group afforded enone **109**, and the primary alcohol moiety was converted to the corresponding bromide **110**. Then, construction of the B ring was examined by heating with tributyltin hydride and AIBN. The product, however, was not the desired ketone **115** but enone **114** possessing a cyano group at the terminal position of the side chain. The result indicates that the primary radical generated from the bromide favored the addition with the cyano group rather than the cyclohexene moiety. The resulting imino *N*-radical intermediate would undergo the C-C bond cleavage to form a stable allylic tertiary radical.



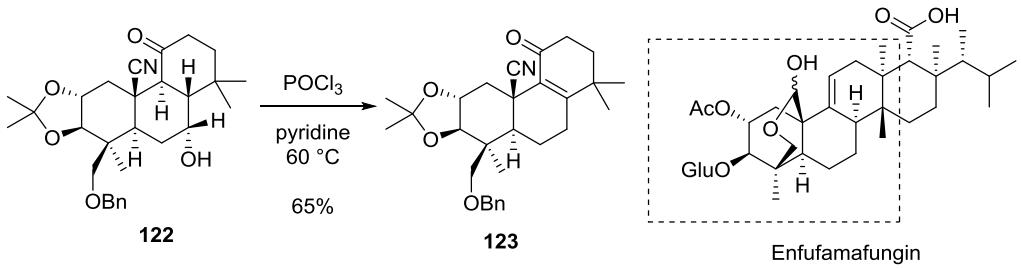
Scheme 24. Attempted radical cyclization reaction of bromide **110**

On the other hand, Tori reported that a cyclohexenone derivative having an aldehyde side chain undergoes intramolecular cyclization reaction promoted by samarium(II) iodide (Scheme 25).[43] The efficient 6-endo cyclization reaction led the author to examine the reaction of aldehyde **121**, which was prepared by the DMP oxidation of alcohol **109**. Upon treatment with samarium(II) iodide, cyclization of **121** occurred to give tricyclic compound **122** in 34% overall yield. The stereochemistry of the product **122** was determined by the NOE experiments and the coupling constants in the proton NMR spectra, in which the large coupling constant (12.7 Hz) observed between H_a and H_b indicated the trans-diaxial relationship of them.



Scheme 25. Construction of the ABC ring system by using SmI_2

Although the stereochemistry of tricyclic compound **122** possessing the *cis*-fused BC ring is not consistent with that of enfumafungin, **122** was found to afford enone **123** by the treatment with phosphoryl chloride in pyridine. The reaction proceeded through dehydration to form a β,γ-unsaturated ketone which isomerized to more stable α,β-unsaturated ketone **123**. These results suggested that the configuration of the angular hydrogen of the BC ring system may be controlled by stereoselective reduction of the α,β-unsaturated ketone moiety.

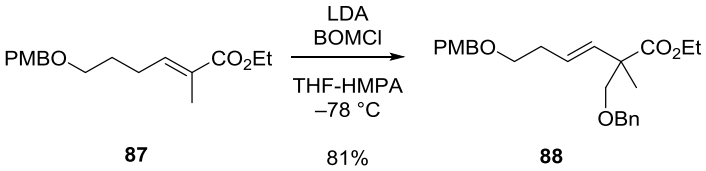


Scheme 26. Dehydration reaction of tricyclic compound **122**

In summary, the author has achieved the stereoselective synthesis of a model compound that corresponds to the left part of enfumafungin. The A ring precursor was synthesized as an acyclic alkanenitrile possessing appropriate substituents thorough the Sharpless asymmetric dihydroxylation reaction. After connection with the C ring segment via a new formal semi-pinacol rearrangement reaction, the A ring was formed by a diastereoselective intramolecular conjugate addition reaction. Finally, the B ring was constructed by a samarium(II) iodide mediated reductive cyclization reaction. The present method for constructing the ABC ring system is to be applied to the total synthesis of enfumafungin.

Experimental section

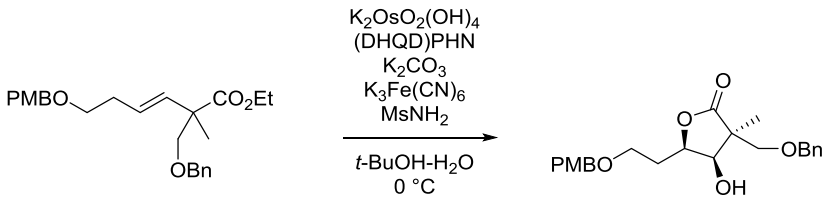
Ethyl (E)-2-((benzyloxy)methyl)-6-((4-methoxybenzyl)oxy)-2-methylhex-3-enoate (88)



87 81% **88**

To a stirred solution of ester **87** (6.17 g, 21.1 mmol) in THF (100 mL) and HMPA (5.51 ml) was added LDA (1.1 M in THF, 28.0 mL, 31.7 mmol) at −78 °C. After stirring for 30 min, BOMCl (5.80 ml, 42.2 mmol) was added dropwise. After stirring for 30 min, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes: EtOAc = 70: 30) to give the compound **88** as a colorless oil (7.08 g, 17.2 mmol, 81%):^{1}H-NMR (500 MHz, $CDCl_3$) : 7.35-7.20 (m, 7H), 6.86 (d, *J*= 8.8 Hz, 2H), 5.64 (d, *J*= 16.0 Hz, 1H), 5.57 (dt, *J*= 16.0, 6.6 Hz, 1H), 4.53 (d, *J*= 12.7 Hz, 1H), 4.51 (d, *J*= 12.7 Hz, 1H), 4.42 (s, 2H), 4.14 (q, *J*= 5.9 Hz, 2H), 3.80 (s, 3H), 3.67 (d, *J*= 8.8 Hz, 1H), 3.44 (t, *J*= 7.0 Hz, 2H), 3.37 (d, *J*= 8.8 Hz, 1H), 2.33 (dt, *J*= 7.0, 6.6 Hz, 2H), 1.34 (s, 3H), 1.23 (t, *J*= 5.9 Hz, 3H).

(3S,4R,5R)-3-((benzyloxy)methyl)-4-hydroxy-5-(2-((4-methoxybenzyl)oxy)ethyl)-3-methyldihydrofuran-2(3H)-one (89)

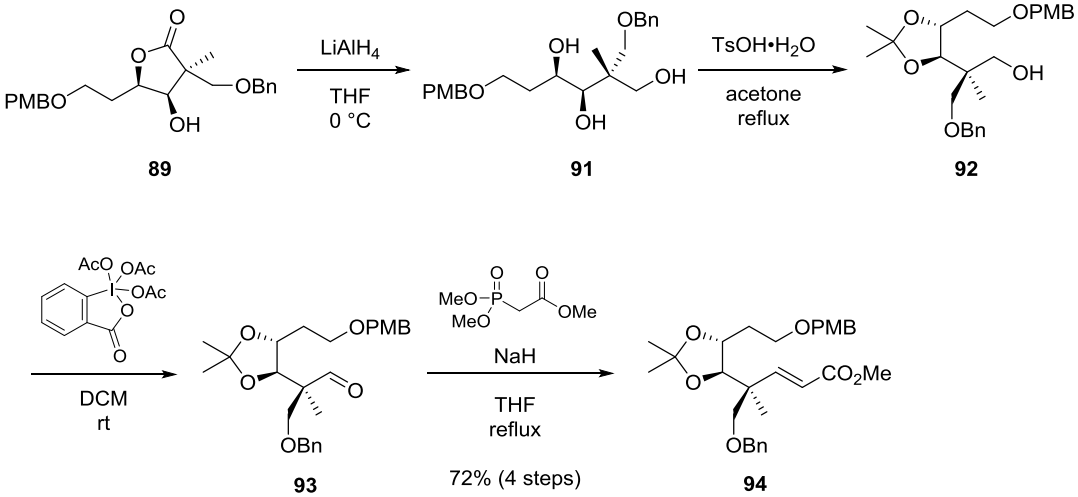


88 47%, 89%ee **89**

To a solution of $K_2OsO_2(OH)_4$ (56.0 mg, 0.153 mmol), (DHQD)PHN (766 mg, 1.53 mmol), K_2CO_3

(21.1 g, 153 mmol), $K_3Fe(CN)_6$ (56.3 g, 153 mmol) and $MsNH_2$ (4.84 g, 50.9 mmol) in *t*-BuOH (350 ml), H_2O (350 ml) was added olefin **88** (21.0 g, 51 mmol) at 0 °C. After stirring for 16 h at same temperature, the reaction was added a solid of $Na_2S_2O_3$ and a saturated aqueous solution of $NaHCO_3$. The reaction mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes: EtOAc = 70: 30) to give the compound **89** as a colorless oil (9.60 g, 24.0 mmol, 47%, 89% ee determined by chiral SFC: Daicel IA, CO_2: MeOH= 90:10, 2 ml/min, minor enantiomer *t*R=12.1 min, major enantiomer *t*R=14.1 min): ^{1}H-NMR (500 MHz, $CDCl_3$): 7.40-7.21 (m, 7H), 6.87 (d, *J*= 8.8 Hz, 2H), 4.64-4.60 (m, 1H), 4.59 (d, *J*= 12.0 Hz, 1H), 4.54 (d, *J*= 12.0 Hz, 1H), 4.48 (d, *J*= 11.0 Hz, 1H), 4.43 (d, *J*= 11.0 Hz, 1H), 4.13-4.08 (m, 1H), 3.86 (d, *J*= 9.5 Hz, 1H), 3.80 (s, 3H), 3.67-3.63 (m, 3H), 3.62-3.55 (m, 1H), 2.15-2.07 (m, 2H), 1.27 (s, 3H).

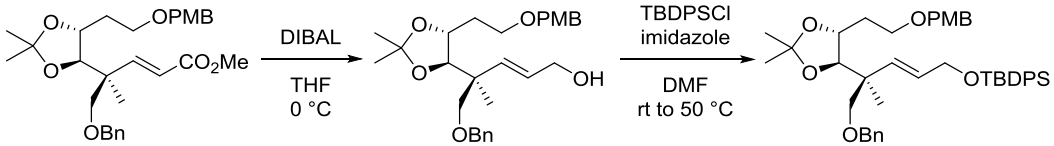
Methyl(S,E)-5-(benzyloxy)-4-((4R,5R)-5-(2-((4-methoxybenzyl)oxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-methylpent-2-enoate (94)



To a suspension of $LiAlH_4$ (1.72 g, 45.3 mmol) in THF (150 ml) was added a solution of lactone **89** (8.74 g, 21.8 mmol) in THF (50 ml) at 0 °C. The reaction was quenched with H_2O (1.72 ml), 15% aqueous solution of NaOH (1.72 ml) and H_2O (5.26 ml). After stirring for overnight, the reaction mixture was filtrated through a pad of Celite. The filtrate was concentrated in vacuo to give **91** as a

colorless oil that was used for next step without purification. Obtained triol was dissolved in acetone (100 ml) and added $TsOH \cdot H_2O$ (395 mg, 2.08 mmol). The reaction mixture was stirred at reflux for 3 h. After being cooled to room temperature, the reaction mixture was added K_2CO_3 and was diluted with Et_2O. After filtrated to remove the precipitate, the filtrate was concentrated in vacuo to give **92** as a colorless oil that was used for next step without purification. To a solution of obtained alcohol in DCM (100 ml) was added Dess-Martin periodinane (8.63 g, 20.3 mmol) and H_2O (0.40 ml, 22.2 mmol). After stirring for 1 h at room temperature, the reaction was quenched with a solid of $Na_2S_2O_3$ and a saturated aqueous solution of $NaHCO_3$. The reaction mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was used without further purification in the next step. A suspension of NaH (60% in oil, 2.22 g, 55.6 mmol) in THF (150 ml) was added trimethyl phosphonoacetate (7.97 ml, 55.6 mmol) at 0 °C. After being stirred for 30 min, a solution of crude aldehyde in THF (50 ml) was added to a reaction mixture and the reaction mixture was heated to reflux. After being stirred for 3.5 h, the reaction was quenched by addition of saturated aqueous solution of NH_4Cl. The aqueous layer was extracted with Et_2O three times. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes: EtOAc= 90: 10 to 70: 30) to give the compound **94** as a colorless oil (7.80 g, 15.6 mmol, 74% for 4 steps): ^{1}H-NMR (500 MHz, $CDCl_3$): 7.38-7.22 (m, 7H), 7.13 (d, *J*= 16.1 Hz, 1H), 6.88 (d, *J*= 8.8 Hz, 2H), 5.92 (d, *J*= 16.1 Hz, 1H), 4.53 (d, *J*= 16.9 Hz, 1H), 4.50 (d, *J*= 16.9 Hz, 1H), 4.44 (s, 2H), 3.93-3.86 (m, 2H), 3.82 (s, 3H), 3.75 (s, 3H), 3.66-3.58 (m, 1H), 3.57-3.53 (m, 1H), 3.51 (d, *J*= 9.0 Hz, 1H), 3.37 (d, *J*= 9.0 Hz, 1H), 1.93-1.87 (m, 1H), 1.85-1.76 (m, 1H), 1.37 (s, 6H), 1.13 (s, 3H).

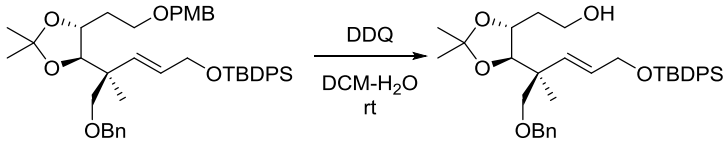
(((S,E)-5-(benzyloxy)-4-((4R,5R)-5-(2-((4-methoxybenzyl)oxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-methylpent-2-en-1-yl)oxy)(tert-butyl)diphenylsilane (96)



94 **95** **96**

To a stirred solution of ester **94** (3.04 g, 6.10 mmol) in THF (50 ml) at −78 °C was added DIBAL (1.0 M in hexane, 14.6 ml, 14.6 mmol) dropwise. After being stirred for 30 min at same temperature, the reaction was quenched by addition of a saturated aqueous solution of sodium potassium tartrate, diluted with EtOAc and allowed to stir at room temperature for an additional 2 h to get two separated layers. The aqueous layer was extracted with EtOAc three times. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was used without further purification in the next step. The crude and imidazole (1.30 g, 19.1 mmol) were dissolved in DMF (10 mL) and TBDPS-Cl (2.46 ml, 9.56 mmol) was added at room temperature. The reaction mixture was heated at 50 °C for 1 h. After cooling to room temperature, the reaction mixture was diluted with Et_2O, washed with water, brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes: EtOAc= 95: 5 to 85: 15) to give the compound **96** as a colorless oil (4.50 g, 6.35 mmol, 99% for 2 steps): ^{1}H-NMR (500 MHz, $CDCl_3$): 7.67 (d, *J*= 7.6 Hz, 4H), 7.44-7.30 (m, 11H), 7.23 (d, *J*= 8.3 Hz, 2H), 6.84 (d, *J*= 8.3 Hz, 2H), 5.89 (d, *J*= 16.4 Hz, 1H), 5.62 (dt, *J*= 16.4, 4.4 Hz, 1H), 4.52 (s, 2H), 4.42 (s, 2H), 4.21 (d, *J*= 4.2 Hz, 2H), 3.95-3.88 (m, 1H), 3.86 (d, *J*= 7.8 Hz, 1H), 3.78 (s, 3H), 3.65-3.58 (m, 1H), 3.57-3.52 (m, 1H), 3.50 (d, *J*= 9.0 Hz, 1H), 3.22 (d, *J*= 9.0 Hz, 1H), 1.94-1.86 (m, 1H), 1.84-1.75 (m, 1H), 1.35 (s, 3H), 1.32 (s, 3H), 1.06 (s, 3H), 1.04 (s, 3H).

2-((4R,5R)-5-((S,E)-1-(benzyloxy)-5-((tert-butyldiphenylsilyl)oxy)-2-methylpent-3-en-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethan-1-ol (97)

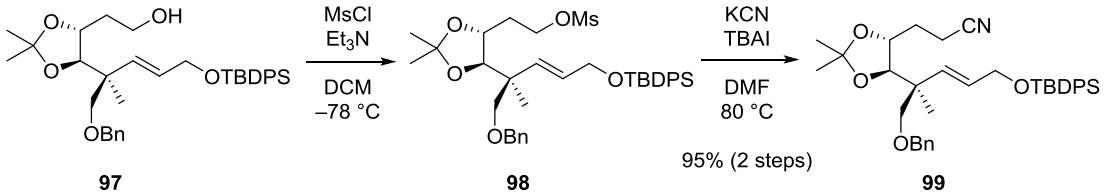


96 **97**

To a solution of ether 00 (4.50 g, 6.35 mmol) in DCM (50 ml), H_2O (15 ml) was added DDQ (2.88

g, 12.7 mmol) at room temperature. After being stirred for 1 h at same temperature, the reaction mixture was quenched with a solid of $Na_2S_2O_3$ and a saturated aqueous solution of $NaHCO_3$. The reaction mixture was extracted with EtOAc. The combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes: EtOAc= 90: 10 to 70: 30) to give the compound **97** as a colorless oil (3.07 g, 5.21 mmol, 82%): ^{1}H-NMR (500 MHz, $CDCl_3$): 7.67 (d, *J*= 7.6 Hz, 4H), 7.45 -7.26 (m, 11H), 5.90 (d, *J*= 16.0 Hz, 1H), 5.63 (dd, *J*= 16.0, 4.6 Hz, 1H), 4.52 (s, 2H), 4.22 (d, *J*= 4.2 Hz, 2H), 4.10-3.98 (m, 1H), 3.87 (d, *J*= 7.8 Hz, 1H), 3.81-3.70 (m, 2H), 3.50 (d, *J*= 9.0 Hz, 1H), 3.24 (d, *J*= 9.0 Hz, 1H), 2.53 (dd, *J*= 7.3, 3.7 Hz, 1H), 1.83-1.74 (m, 2H), 1.38 (s, 3H), 1.33 (s, 3H), 1.05 (brs, 12H).

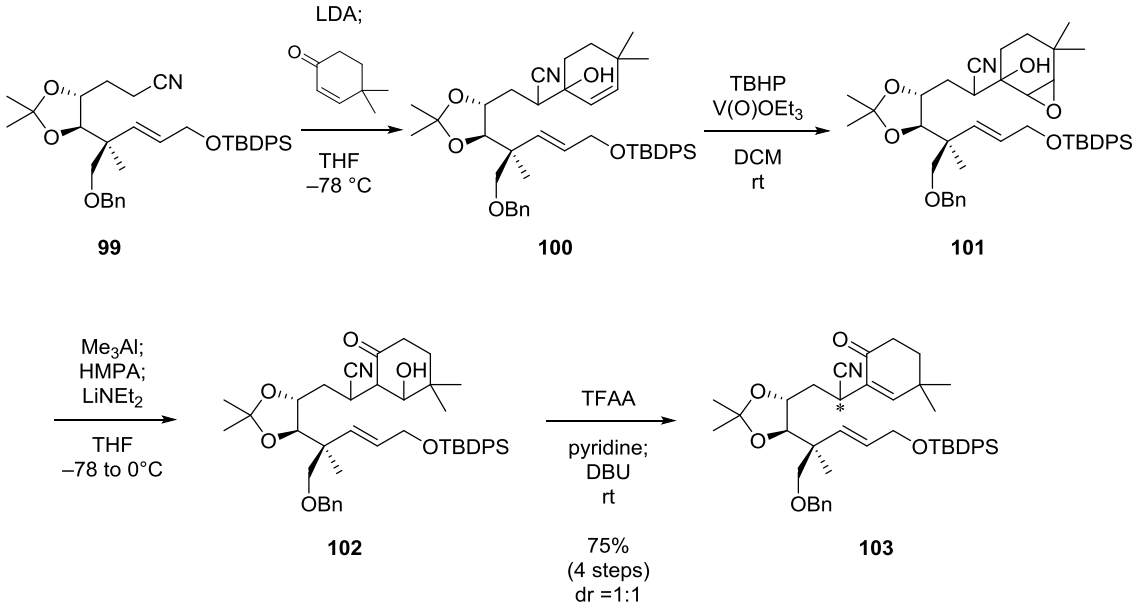
3-((4R,5R)-5-((S,E)-1-(benzyloxy)-5-((tert-butyldiphenylsilyl)oxy)-2-methylpent-3-en-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)propanenitrile (99)



To a solution of alcohol **97** (3.07 g, 5.21 mmol) and triethylamine (1.45 ml, 10.4 mmol) in DCM (25 ml) at −78 °C was added methanesulfonyl chloride (0.487 ml, 6.26 mmol) dropwise. After being stirred for 5 min, the reaction mixture was quenched with H_2O. The reaction mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was used without further purification in the next step. The crude, potassium cyanide (1.03 g, 15.7 mmol) and TBAI (0.194 g, 0.535 mmol) were dissolved in DMF (15 mL) and the reaction mixture was stirred for 6 h at 80 °C. After being cooled to room temperature, the reaction mixture was quenched with H_2O. The reaction mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes: EtOAc= 90: 10 to 80: 20) to give the compound **99** as a colorless oil (2.98 g, 4.98 mmol,

95% for 2 steps): ^{1}H-NMR (500 MHz, $CDCl_3$): 7.66 (d, *J*= 7.3 Hz, 4H), 7.47-7.26 (m, 11H), 5.88 (d, *J*= 16.0 Hz, 1H), 5.64 (dt, *J*= 16.0, 4.5 Hz, 1H), 4.51 (s, 2H), 4.22 (d, *J*= 4.5 Hz, 2H), 3.88-3.80 (m, 2H), 3.48 (d, *J*= 9.0 Hz, 1H), 3.22 (d, *J*= 9.0 Hz, 1H), 2.55-2.49 (m, 1H), 2.41-2.34 (m, 1H), 1.95-1.89 (m, 1H), 1.82-1.77 (m, 1H), 1.35 (s, 3H), 1.33 (s, 3H), 1.05 (s, 12H).

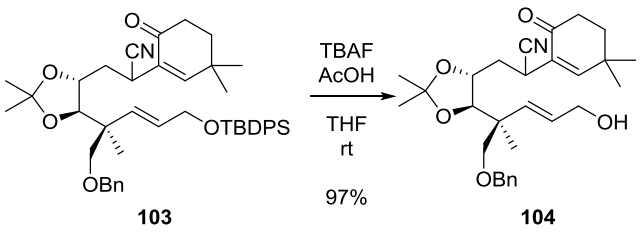
3-((4R,5R)-5-((S,E)-1-(benzyloxy)-5-((tert-butyldiphenylsilyl)oxy)-2-methylpent-3-en-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-(3,3-dimethyl-6-oxocyclohex-1-en-1-yl)-2l3-propanenitrile (103)



To a solution of nitrile **99** (1.74 g, 2.91 mmol) in THF (20 ml) was added LDA (1.0 M in THF, 3.49 mL, 3.49 mmol) at −78 °C. After stirring for 30 min, 4,4-dimethyl cyclohex-2-en-1-one (0.459 ml, 3.49 mmol) was added dropwise. After stirring for 30 min, the reaction was quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was used without further purification in the next step. To a solution of the crude in DCM (20 ml) was added TBHP (1.16 ml, 5.82 mmol) and triethyl orthovanadate (0.026 ml, 0.146 mmol) at room temperature. After stirring for 2 h, the reaction mixture was passed through a pad of silica gel and concentrated in vacuo. The residue was used without further purification in the next step. To a solution of epoxy alcohol in THF (25 ml) was added trimethyl aluminum (2.01 ml, 4.02 mmol) at 0 °C and the

reaction mixture was warmed up to room temperature. After stirring for 30 min at the same temperature, the reaction mixture was added HMPA (1.40 ml, 8.05 mmol) and was cooled to −78 °C. $LiNEt_2$ (10.7 mmol), which was prepared from *n*-BuLi (2.65 M in hexane, 4.05 ml, 10.7 mmol) and diethylamine (1.12 ml, 10.7 mmol) in THF (10 ml), was added to the reaction at same temperature. The mixture was warmed up to room temperature and was stirred for 30 min. After cooling to −78 °C, the reaction was stopped by addition of AcOH (1.53 ml, 26.8 mmol). The mixture was added a saturated aqueous solution of sodium potassium tartrate, diluted with Et_2O, and allowed to stir at room temperature. The aqueous layer was extracted with Et_2O three times. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was used without further purification in the next step. The crude was dissolved in pyridine (25 ml) and was added TFAA (1.13 ml, 8.05 mmol) and DBU (4.04 ml, 26.8 mmol) at room temperature. After stirring for 30 min, the reaction mixture was quenched by H_2O. The reaction mixture was extracted with Et_2O. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes: EtOAc= 90:10 to 70: 30) to give a mixture of diastereomer of compound **103** as a colorless oil (1.58 g, 2.19 mmol, 75% for 4 steps): ^{1}H-NMR (500 MHz, $CDCl_3$): 7.70-7.63 (m, 4H), 7.45-7.25 (m, 11H), 6.82 (s, 0.5H), 6.76 (s, 0.5H), 5.91 (d, *J*= 16.1 Hz, 0.5 H), 5.89 (d, *J*= 16.1 Hz, 0.5H), 5.70-5.62 (m, 1H), 4.56-4.48 (m, 2H), 4.28-4.20 (m, 2H), 4.07 (dd, *J*= 9.9, 4.5 Hz, 0.5H), 4.03-3.96 (m, 0.5H), 3.90-3.82 (m, 1.5 H), 3.79 (dt, *J*= 8.5, 2.9 Hz, 0.5 H), 3.51 (d, *J*= 9.0 Hz, 0.5H), 3.49 (d, *J*= 9.5 Hz, 0.5H), 3.21 (d, *J*= 9.0 Hz, 0.5H), 3.20 (d, *J*= 9.5 Hz, 0.5 H), 2.52-2.42 (m, 2H), 2.05-1.78 (m, 4H), 1.40 (s, 1.5 H), 1.36 (s, 1.5H), 1.34 (s, 1.5H), 1.32 (s, 1.5H), 1.19(s, 1.5H), 1.15 (s, 1.5H), 1.14 (s, 3H), 1.08-1.03 (m, 12H).

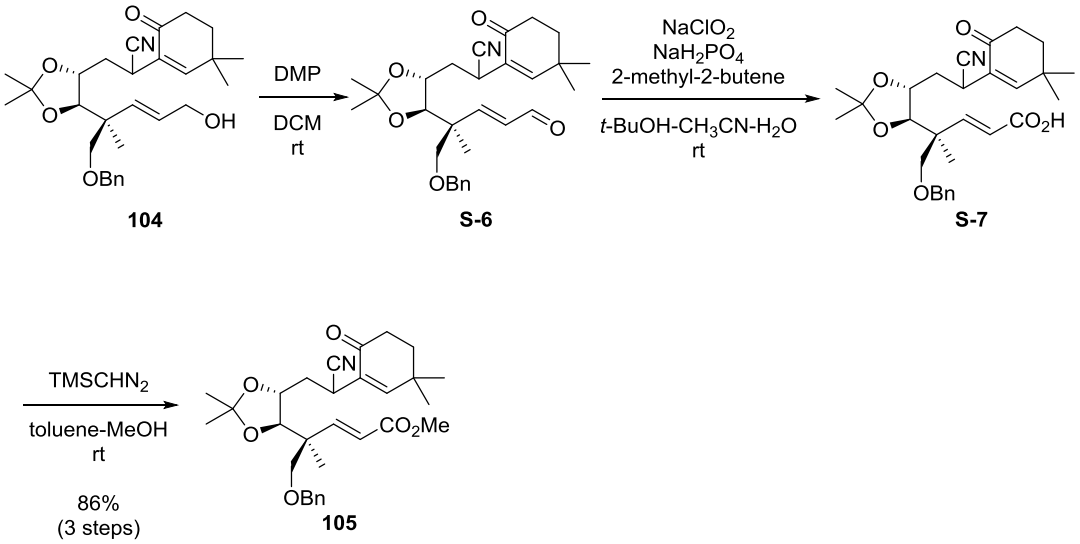
3-((4R,5R)-5-((S,E)-1-(benzyloxy)-5-hydroxy-2-methylpent-3-en-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-(3,3-dimethyl-6-oxocyclohex-1-en-1-yl)propanenitrile (104)



103 **104**

To a solution of silyl ether **103** (1.22 g, 1.69 mmol) in THF (15 ml) was added AcOH (0.145 ml, 2.54 mmol) and TBAF (1.0 M in THF, 2.54 ml, 2.54 mmol) at 0 °C. After being stirred for 4 h at room temperature, the reaction mixture was quenched with brine. The reaction mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes: EtOAc= 90: 10 to 60: 40) to give a mixture of diastereomer of the compound **104** as a colorless oil (793 mg, 1.65 mmol, 97 %):^{1}H-NMR (500 MHz, $CDCl_3$): 7.40-7.28 (m, 5H), 6.81 (s, 0.5H), 6.77 (s, 0.5H), 5.84-5.74 (m, 2H), 4.52-4.48 (m, 2H), 4.17-4.10 (m, 2H), 4.06-3.97 (m, 1H), 3.90-3.75 (m, 1.5H), 3.48 (d, *J*= 9.0 Hz, 0.5H), 3.44 (d, *J*= 9.0 Hz, 0.5H), 3.32 (d, *J*= 9.0 Hz, 0.5 H), 3.28 (d, *J*= 9.0 Hz, 0.5 H), 2.51-2.42 (m, 2H), 1.90-1.80 (m, 2.5H), 1.38 (s, 1.5 H), 1.36 (s, 1.5H), 1.32 (s, 1.5H), 1.322 (s, 1.5H), 1.25 (s, 1.5H), 1.19 (s, 1.5H), 1.17 (s, 1.5H), 1.16 (s, 1.5H), 1.07 (s, 1.5H), 1.05 (s, 1.5H), 0.90-0.80 (m, 2H).

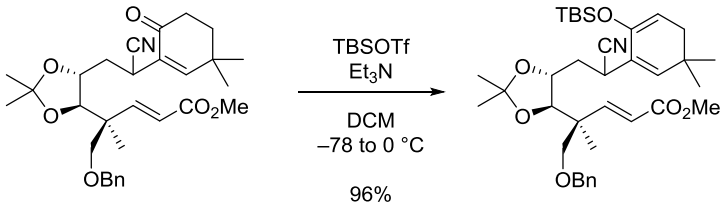
Methyl (4S,E)-5-(benzyloxy)-4-((4R,5R)-5-(2-cyano-2-(3,3-dimethyl-6-oxocyclohex-1-en-1- yl) ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-methylpent-2-enoate (105)



To a solution of alcohol **104** (793 mg, 1.65 mmol) in DCM (16 ml) was added Dess-Martin Periodinane (768 mg, 1.81 mmol) and H_2O (0.036 ml, 1.98 mmol) at room temperature. After stirring for 1 h at same temperature, the reaction was quenched with a solid of $Na_2S_2O_3$ and a saturated aqueous solution of $NaHCO_3$. The reaction mixture was extracted with EtOAc. The combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was used without further purification in the next step. To a solution of crude in *t*-BuOH (15 ml)-CH_3CN (5 ml)-H_2O (5 ml) was added NaH_2PO_4 (790 mg, 6.59 mmol), $NaClO_2$ (298 mg, 3.29 mmol) and 2-methyl-2-butene (1.74 ml, 16.5 mmol) at room temperature. After stirring for 1 h at same temperature, the reaction was quenched with brine. The reaction mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was used without further purification in the next step. To a solution of carboxylic acid in toluene (10 ml)-MeOH (1 ml) was added $TMSCHN_2$ (0.6 M in hexane, 5.49 ml, 3.29 mmol) at room temperature. After stirring for 30 min at same temperature, the reaction mixture was concentrated under vacuum. The residue was purified by flash column chromatography (silica gel, hexanes: EtOAc = 90: 10 to 70: 30) to give a mixture of diastereomer of the compound **105** as a colorless oil (723 mg, 1.42 mmol, 86.2 %): ^{1}H-NMR (500 MHz, $CDCl_3$): 7.36-7.25 (m, 5H), 7.07 (d, *J*= 16.1 Hz, 0.5H), 7.06 (d, *J*= 16.1 Hz, 0.5H), 6.81 (s, 0.5H), 6.75 (s, 0.5H), 5.92 (d, *J*= 16.1 Hz, 0.5 H), 5.90 (d, *J*= 16.1 Hz, 0.5H), 4.52-4.45 (m, 2H), 4.18-3.80 (m, 2.5H), 3.78-3.70 (m, 3.5H), 3.51-3.40 (m, 1H),

3.35-3.28 (m, 1H), 2.50-2.40 (m, 2H), 2.05-1.72 (m, 4H), 1.38 (s, 1.5 H), 1.37 (s, 1.5H), 1.32 (s, 3H), 1.19 (s, 1.5H), 1.18-1.14 (m, 4.5H), 1.09 (s, 1.5H), 1.07 (s, 1.5H).

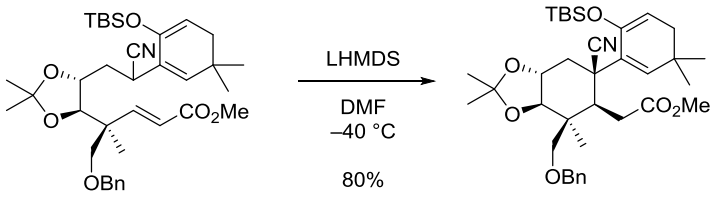
Methyl (4S,E)-5-(benzyloxy)-4-((4R,5R)-5-(2-(6-((tert-butyldimethylsilyl)oxy)-3,3-dimethyl cyclohexa-1,5-dien-1-yl)-2-cyanoethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-methylpent-2-enoate (106)



105 **106**

To a solution of ketone **105** (723 mg, 1.42 mmol) in DCM (16 ml) was added Et_3N (1.75 ml, 12.6 mmol) and TBSOTf (1.16 ml, 5.04 mmol) at −78 °C. After stirring for 1 h at 0 °C, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$.The reaction mixture was extracted with DCM. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes: EtOAc= 95: 5 to 85: 15) to give a mixture of diastereomer of the compound **106** as a colorless oil (758 mg, 1.22 mmol, 96 %): ^{1}H-NMR (500 MHz, $CDCl_3$): 7.36-7.28 (m, 5H), 7.15-7.04 (m, 1H), 5.91 (d, *J*= 16.1 Hz, 0.85H), 5.88 (d, *J*= 16.1 Hz, 0.15H), 5.74 (s, 0.85H), 5.62 (s, 0.15H), 4.85-4.80 (m, 1H), 4.54-4.44 (m, 2H), 4.05-3.80 (m, 3H), 3.74-3.70 (m, 4H), 1.40-0.90 (m, 24H), 0.22-0.17 (m, 6H).

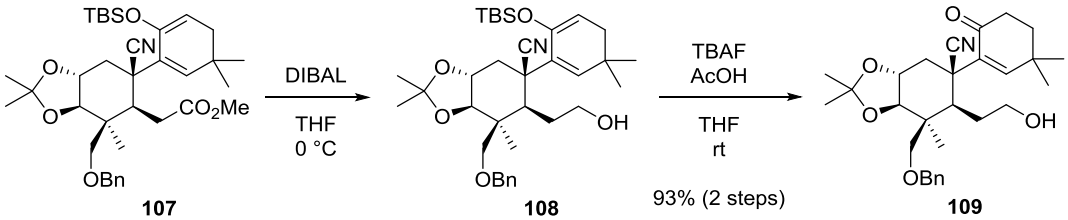
Methyl 2-((3aR,4S,5R,6R,7aR)-4-((benzyloxy)methyl)-6-(6-((tert-butyldimethylsilyl)oxy)-3, 3-dimethylcyclohexa-1,5-dien-1-yl)-6-cyano-2,2,4-trimethylhexahydrobenzo[d][1,3]dioxol- 5-yl) acetate (107)



106 **107**

To a stirred solution of nitrile **106** (700 mg, 1.12 mmol) in DMF (10 mL) was added LHMDS (1.0 M in THF, 1.68 mL, 1.68 mmol) at −40 °C. After stirring for 30 min, the reaction was quenched by AcOH (0.193 ml, 3.37 mmol). The reaction mixture was diluted with H_2O and extracted with EtOAc. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes: EtOAc= 90: 10 to 70: 30) to give the compound **107** as a colorless amorphous (571 mg, 0.915 mmol, 82%): ^{1}H-NMR (500 MHz, $CDCl_3$): 7.35-7.26 (m, 5H), 6.02 (s, 1H), 4.79 (t, *J*= 4.9Hz, 1H), 4.60 (d, *J*= 11.7 Hz, 1H), 4.43 (d, *J*= 11.7 Hz, 1H), 4.28 (d, *J*= 10.0 Hz, 1H), 4.02-3.92 (m, 1H), 3.63 (d, *J*= 10.0 Hz, 1H), 3.56 (s, 3H), 3.41 (d, *J*= 9.8 Hz, 1H), 3.28 (d, *J*= 17.8 Hz, 1H), 3.05-2.95 (m, 1H), 2.85-2.75 (m, 1H), 2.42 (dd, *J*= 17.8, 5.9 Hz, 1H), 2.25-2.18 (m, 1H), 2.02 (dd, *J*= 16.6, 4.9 Hz, 1H), 1.95 (dd, *J*= 16.6, 4.9 Hz, 1H), 1.41 (s, 3H), 1.39 (s, 3H), 1.25 (s, 3H), 1.02 (s, 3H), 1.00 (s, 9H), 0.98 (s, 3H), 0.30 (s, 6H).

2-((3aR,5R,6R,7S,7aR)-5-((l2-azanylidene)-l3-methyl)-7-((benzyloxy)methyl)-6-(2-hydroxyethyl)-2,2,7-trimethylhexahydrobenzo[d][1,3]dioxol-5-yl)-4,4-dimethylcyclohex-2-en-1-one (109)

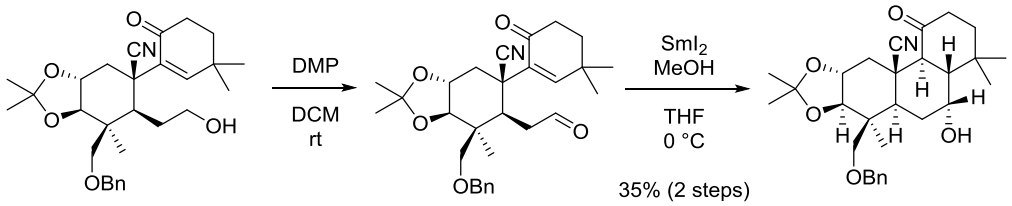


107 **108** **109**

To a stirred solution of ester **107** (364 mg, 0.585 mmol) in THF (10 ml) at 0 °C was added DIBAL (1.0 M in hexane, 2.34 ml, 2.34 mmol) dropwise. After being stirred for 30 min at same temperature, the reaction was quenched by addition of a saturated aqueous solution of sodium potassium tartrate, diluted with EtOAc, and allowed to stir at room temperature for an additional 2 h to get two

separated layers. The aqueous layer was extracted with EtOAc. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was used without further purification in the next step. To a solution of crude in THF (5 ml) was added AcOH (39.0 µl, 0.677 mmol) and TBAF (1.0M in THF, 677 µl, 0.677 mmol) at 0 °C. After being stirred for 5 min at same temperature, the reaction was quenched with H_2O. The reaction mixture was extracted with Et_2O. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes: EtOAc= 90: 10 to 60: 40) to give the compound **109** as a colorless oil (263 mg, 0.546 mmol, 93 % for 2 steps): ^{1}H-NMR (500 MHz, $CDCl_3$): 7.35-7.26 (m, 5H), 7.07 (s, 1H), 4.56 (d, *J*= 12.0 Hz, 1H), 4.48 (d, *J*= 12.0 Hz, 1H), 4.17 (d, *J*= 10.0 Hz, 1H), 4.02-3.95 (m, 1H), 3.64 (d, *J*= 10.0 Hz, 1H), 3.48-3.35 (m, 3H), 2.68 (t, *J*= 12.1 Hz, 1H), 1.84 (t, *J*= 6.8 Hz, 1H), 1.50-1.40 (m, 4H), 1.38 (s, 3H), 1.26 (s, 3H), 1.23 (s, 3H), 1.22 (s, 3H), 1.20-1.18 (m, 1H).

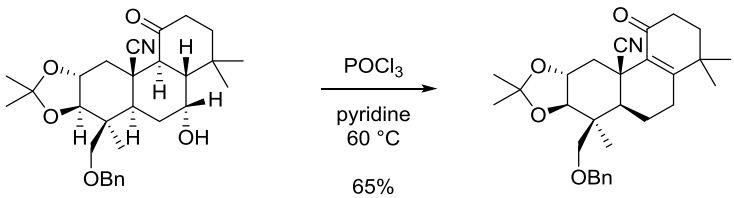
(4aR,5R,6aR,7S,7aR,10aR,11aR,11bS)-7-((benzyloxy)methyl)-5-hydroxy-4,4,7,9,9-pentamethyl-1-oxododecahydrophenanthro[2,3-d][1,3]dioxole-11a(2H)-carbonitrile (122)



To a solution of alcohol **109** (40 mg, 0.083 mmol) in DCM (1.0 ml) was added Dess-Martin periodinane (39 mg, 0.091 mmol). After stirring for 1 h at room temperature, the reaction was quenched with s solid of $Na_2S_2O_3$ and a saturated aqueous solution of $NaHCO_3$. The reaction mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was used without further purification in the next step. To a solution of MeOH (67.7 µl, 1.67 mmol) and samarium(II) iodide (0.1 M in THF, 3.33 ml, 0.334 mmol) was added a solution of crude in THF (1.0 ml) at 0 °C. After being stirred for 15 min at same temperature, the reaction mixture was quenched with a saturated aqueous solution of

$NaHCO_3$. The reaction mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes: EtOAc= 65: 35) to give the compound **122** as a colorless oil (14 mg, 0.029 mmol, 35 % for 2 steps): ^{1}H-NMR (500 MHz, $CDCl_3$): 7.35-7.26 (m, 5H), 4.60 (d, *J*= 12.0 Hz, 1H), 4.42 (d, *J*= 12.0 Hz, 1H), 4.38-4.34 (m, 1H), 4.19 (d, *J*= 10.0 Hz, 1H), 4.05-3.95 (m, 1H), 3.62 (d, *J*= 10.0 Hz, 1H), 3.41 (dd, *J*= 12.2, 3.9 Hz, 1H), 3.17 (d, *J*= 10.0 Hz, 1H), 2.78 (d, *J*= 12.8 Hz, 1H), 2.50 (ddd, *J*= 12.7, 7.3, 3.7 Hz, 1H), 2.35 (dt, *J*= 13.4, 4.2 Hz, 1H), 2.08-2.00 (m, 2H), 1.88 (dd, *J*= 11.2, 3.7 Hz, 1H), 1.74 (dd, *J*= 12.7, 1.3 Hz, 1H), 1.70-1.62 (m, 2H), 1.40 (s, 3H), 1.39 (s, 3H), 1.28 (s, 3H), 1.26-1.20 (m, 4H), 1.13 (d, *J*= 2.7 Hz, 1H), 1.10 (s, 3H).

(6aR,7S,7aR,10aR,11aR)-7-((benzyloxy)methyl)-4,4,7,9,9-pentamethyl-1-oxo-1,3,4,5,6,6a,7,7a,10a,11-decahydrophenanthro[2,3-d][1,3]dioxole-11a(2H)-carbonitrile (123)



122 123

To a solution of alcohol **122** (6.2 mg, 0.013mmol) in pyridine (100 µl) was added $POCl_3$ (12 µl, 0.13 mmol) at room temperature. After stirring for 30 min at 80 °C, the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$. The reaction mixture was extracted with Et_2O, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by preparative thin layer column chromatography (silica gel, hexanes: EtOAc= 85: 15) to give the compound **123** as a colorless oil (3.9 mg, 0.013 mmol, 65%): ^{1}H-NMR (500 MHz, $CDCl_3$): 7.35-7.26 (m, 5H), 4.64 (d, *J*= 11.7 Hz, 1H), 4.41 (d, *J*= 11.7 Hz, 1H), 4.25 (d, *J*= 10.0 Hz, 1H), 4.14-4.09 (m, 1H), 3.68-3.60 (m, 2H), 3.16 (d, *J*= 10.0 Hz, 1H), 2.60-2.40 (m, 3H), 2.30-2.18(m, 2H), 1.88-1.75 (m, 2H), 1.74-1.68 (m, 1H), 1.40 (s, 3H), 1.39 (s, 3H), 1.32 (s, 3H), 1.28-1.18 (m, 2H), 1.16 (s, 3H), 1.14 (s, 3H).

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