Synthetic and structure-activity relationship studies of cytotoxic marine natural products, aplyronine A and swinhoeisterol A

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List of abbreviations and acronyms

[α]	specific rotation
Å	angstrom(s)
Ac	acetyl
ApA	aplyronine A
aq.	aqueous
Bn	benzyl
BI	*N*-methylbenzoimidazole
br	broad
Bu	butyl
BRB80	Brinkley Rassembly Buffer 80
brsm	based on recovered starting material
BT	benzothiazole
Bz	benzoyl
B3LYP	3-parameter hybrid Becke's exchange /Lee–Yang–Parr correlation functional
c	concentration
calcd.	calculated
CAN	ammonium cerium(Ⅳ) nitrate
cAMP	cyclic adenosine monophosphate
cat.	catalyst
conc.	concentrated
CBB	Coomassie brilliant blue
CBS	Corey–Baksi–Shibata
cm^{-1}	wave number(s)
°C	degrees Celsius
D	dextro-rotatory
D	doublet; day(s)
Da	dalton(s)
DEAD	diethyl azodicarboxylate
DIBAL	diisobutylaluminum hydride
DMAP	*N*,*N*-dimethyl-4-aminopyridine
DCC	dicyclohexyl carbodiimide
DCE	1,2-dichloroethane
decomp.	decomposition
DFT	density functional theory
dist.	distilled
DMAPP	dimethylallyl diphosphate
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dppp	1,3-bis(dipfenylphosphino)propane
DPTC	*O*,*O*'-di-2-pyridyl thiocarbonate
d.r.	diastereomeric ratio
E	entgegen
EC_{50}	effective concentration 50%
EDTA	ethylenediaminetetraacetic acid
EE	ethoxyethyl
eq.	equivalent
Et	ethyl
ESI	electrospray ionization
F-actin	fibrous actin
FPP	farnesyl diphosphate
g	gram(s)
G-actin	globular actin
GFPP	geranylfarnesyl diphosphate
GGPP	gerangeylgeranyl diphosphate
GPP	geranyl diphosphate
h	hour(s)
HG-Ⅱ	Hoveyda–Grubbs second catalyst
HPLC	high performance liquid chromatograp- hy
HRMS	high resolution mass spectroscopy
HWE	Horner–Wadsworth–Emmons
Hz	hertz
i	iso
IC_{50}	inhibitory concentration 50%
IPP	isopentenyl diphosphate
IR	infrared spectroscopy
k	kilo
KSA	ketene silyl acetal
L	liter(s)
L	levo-rotatory
LDA	lithium diisopropylamide
LHMDS	lithium *bis*(trimethylsilyl)amide
L-selectride	lithium tri-*sec*-butylborohydride
2,6-lutidine	2,6-dimethylpyridine
M	molar; mega
m	multiplet; milli
μ	micro
Me	methyl
min	minute(s)
MNBA	2-methyl-6-nitrobenzoic anhydride
mol	mole(s)
MOM	methoxymethyl
m.p.	melting point
MS	mass spectrometry
Ms	methansulfonyl

MTM	methylthiomethyl
MTPA	α-methoxy-α-(trifluoromethyl)phenylacetyl
MTT	3-(4,5-di-methylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
MyB	mycalolide B
MW	microwave
m/*z*	mass-to-charge ratio
n	nano
n	normal
NaHMDS	sodium *bis*(trimetylsilyl)amide
N.D.	not detected
NHK	Nozaki–Hiyama–Kishi
NMP	*N*-methylpyrrolidone
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
N.R.	no reaction
o	ortho
OSQCY	2,3-oxidosqualene cyclase
%	percent
p	pico
Pa	pascal
PAGE	polyacrylamide gel electrophoresis
PDB	protein data bank
Ph	phenyl
PIDA	phenyliodine diacetate
Piv	pivaloyl
PMB	*para*-methoxybenzyl
PPA	poly phosphoric acid
PPI	protein-protein interaction
ppm	pert(s) per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
proton sponge	1,8- *bis*(dimethylamino)naphthalene
PT	phenyltetrazole
PTLC	preparative thin-layer chromatography
Py.	pyridine
q	quartet
quant.	quantitative
R	rectus (right)
rac	racemic
ref.	reference
R_f	retention factor
rpm	rotation per minute
r.t.	room temperature
s	singlet
S	sinister (left)
sat.	saturated
SDS	sodium dodecyl sulfate
sec	secondary
SEE	silyl enol ether
S_N2	bimolecular nucleophilic substitution
S_NAr	nucleophilic aromatic substitution
sp.	species
SwA	swinholide A
t	triplet
t	*tert* = tertiary
TBAF	tetra-*n*-butylammmonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBS	*tert*-butyldimethylsilyl
T/C	test/control
TCBC	2,4,6-trichlorobenzoic chloride
temp.	temperature
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic acid anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TOF	time of flight
TS	transition state
Z	zussamen

Chapter 1. General introduction

1-1. Natural product chemistry

In nature, organisms live with diverse life forms. Natural products are produced and metabolized in nature. Some natural products show physiological activity to protect the organisms that produces them, from predators. Our hominid ancestors who were suffering from diseases, chewed tree parts that they had never seen before, for pain relief. For example, in the Neolithic Age, opium (morphine) and cumin (cuminaldehyde) were used as medicinal ingredients by some people (Figure 1-1).[1] When mankind used medicinal herbs for the treatment of diseases and wounds in ancient time, they started to have relations with natural products. Thus, everyone was said to be a discovery researcher in the past.

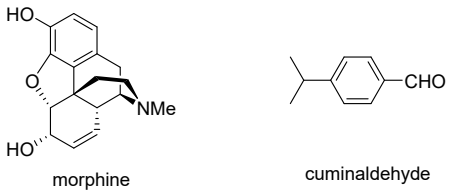


Figure 1-1. Structures of morphine and cuminaldehyde

Natural product chemistry involves isolation, structure determination, organic synthesis, and elucidation of the mode of action of naturally occurring compounds. Terrestrial organisms have been the main sources of natural products that have novel physiological properties. Numerous antibiotics such as penicillin G and avermectin,[2] found from soil bacteria, are used as therapeutic agents (Figure 1-2). However, it is becoming increasingly difficult to obtain novel bioactive compounds from terrestrial organisms. The oceans of the world occupy 70% of the Earth's surface, and they are habitats for more than one million species of living things. Also, since marine organisms live in different environments from terrestrial ones, they have different metabolic systems. Given these facts, researchers of natural products looked to the oceans as a source of new biologically active compounds.

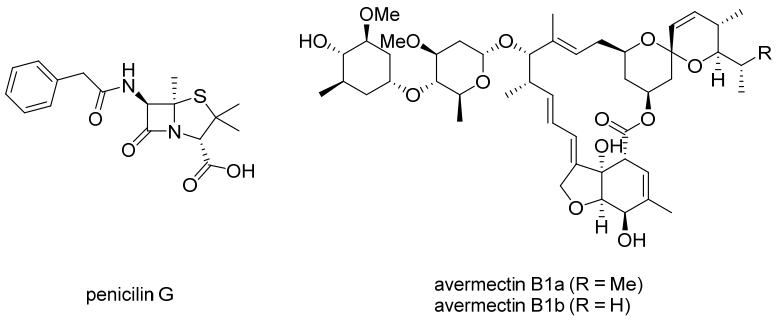


Figure 1-2. Structure of penicilin G and avermectin

Although so many compounds were isolated and many of them have biological activities, they were not utilized fully. Of all the drugs, about 50% are related to natural products.[3] Various drug discovery theories and medicinal modalities have been developed, but new ones have been hard to find in recent years. Natural products that are generated in the process of life are beyond human knowledge, and they should be utilized more.

1-2. Cancer and drug discovery

In the universe, the total number of compounds that may become medicines is said to be 3×10^{62} according to a chemist.[1] Even if we carry out 1000 experiments per second in order to find an effective drug, it is impossible to synthesize such a vast number of compounds before the sun burns out. That's how much drug discovery is difficult. Fortunately, as mentioned above, natural resources have been used as therapeutic agents from around the world. Through the vast experiences that involved actual administration to patients from ancient times, we have gained knowledge about pharmacological effects. This knowledge of ethnic medicine has been transmitted all over the world for generations and has contributed to the development of traditional drugs. Additionally, information garnered from the use of folk medicines continues to serve as a valuable resource for modern drug discovery.

As for anticancer drugs, some of them are famous drugs such as paclitaxel,[4] vinblastine,[5] camptothecin,[6] and doxorubicin[7] (Figure 1-3). Despite such many efforts, the cure rate of cancer has not yet improved dramatically. Cancer is the main cause of death in aging advanced countries. According to WHO, about ten million people were predicted to die of cancer in 2018.[8] In Japan, the number of deaths from cancer per year is three hundred seventy thousand.[9] In the United States, research funds of one hundred twenty trillion yen were spent in the past, but the number of deaths from cancer is increasing, and even now, cancer eradication is regarded as one of the most important issues in the scientific field.

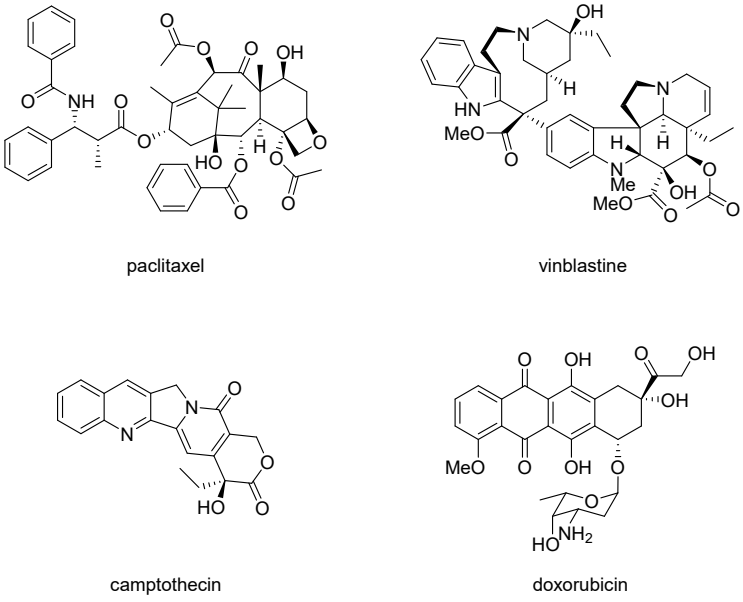
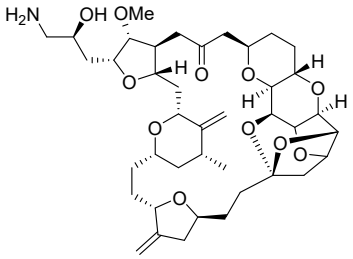


Figure 1-3. Structures of paclitaxel, vinblastine, camptothecin, and doxorubicin

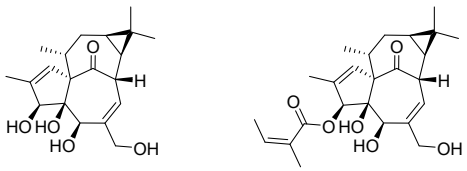
Less than a decade ago, eribulin from Eisai Co., Ltd. was approved and launched in the United States for the first time in 2010 (Figure 1-4). Eribulin is an anticancer drug that was developed based on halichondrin B,[10] a marine natural product isolated from a sponge. Halichondrin B has a complex structure and its total synthesis required many synthetic steps, as established by the Kishi group.[11] As a result, structure-activity relationship studies on halichondrin B became possible, and this led to the discovery of eribulin, the right-half part of halichondrin B responsible for biological activity. The industrial total synthesis of eribulin was achieved in 62 steps.



eribulin

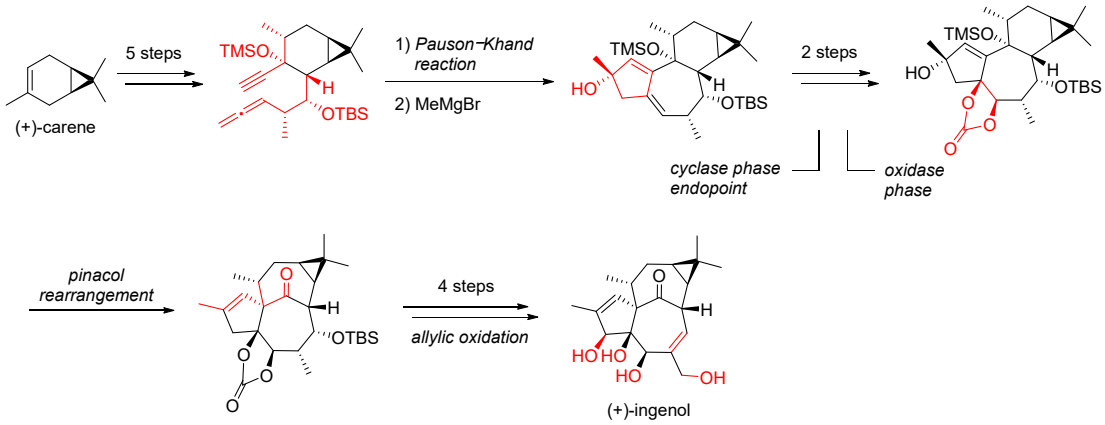
Figure 1-4. A structure of eribulin

In 2013, the Baran group completed a total synthesis of (+)-ingenol (Figure 1-5).[12,13] Ingenol was isolated from *Euphorbia ingens*. Its structure was showing a unique *in,out*-bicyclo[4.4.1]undecane core. Ingenol esters possess important anticancer activity, and indeed the angelate [Picato (LEO pharma A/S)] was approved by the Food and Drug Administration as a first-in-class treatment for actinic keratosis in 2012. The required amount for chemotherapy is currently being provided by extraction from plants, the amount of which is 1.1 mg/kg. In order to be able to supply on a large scale, numerous plants are needed. In addition, chemical solutions were required to conduct a more detailed structure-activity relationship. Ingenol with its complex structure has historically been a good research target for synthetic chemists. Total synthesis of ingenol has been reported three times, and in each case an elegant idea was used for skeleton construction. However, all total synthesis were laborious (37~45 steps).[14,15,16] A synthetic route that is tedious is impractical (＞ 20 steps). Thus, a 14-step route by the Baran group can allow a chemical supply of ingenol. The Baran group adopted the unique idea of a 2-phase (cyclase and oxidase) approach. Natural products are biosynthesized by undergoing oxidase pathway after skeletal construction by cyclase pathway. It is an idea that a short process will be realized even in the artificial synthetic route by imitating biogenesis. They started from inexpensive (+)-carene (~ $10/mol) with a bulky dimethylcyclopropyl group as a foothold for stereochemical control (Scheme 1-1). After 5 steps, Pauson−Khand reaction was carried out to construct a tiglinane skeleton. It was transformed into the ingenane skeleton by pinacol rearrangement, and then total synthesis was achieved through allylic oxidation using selenium. Various analogs are being synthesized using this synthetic route for structure-activity relationship studies.



(+)-ingenol (+)-ingenol 3-angelate (picato)

Figure 1-5. Structures of ingenol and ingenol 3-angelate



Scheme 1-1. Total synthesis of (+)-ingenol by the Baran group

Most drugs are developed by synthetic organic chemistry. Synthetic organic chemistry is a powerful tool to create even unknown compounds not existing in nature. In the material civilization in which we live, synthetic organic chemistry has made a great contribution from the point of material supply. It was also through synthetic organic chemistry that synthesis of unknown compounds became possible. Synthetic organic chemistry has two fields: reaction development and synthesis of target compounds. The two fields are not independent of each other, indeed they have contributed to the development of each other. Ultimately, it is desirable that target compounds are synthesized from simple compounds as starting materials in a short process, inexpensively, safely, and without waste. However, at present, the level of organic synthesis is by no means satisfactory.

The author decided to carry out synthetic studies of cytotoxic marine natural compound, in order to make them a foothold for development of novel anticancer lead compounds like eribulin. This thesis details two research themes: aplyronine A and swinhoeisterol A as target compounds.

References

[1] Donald R. K.; Ogi, O. In *The Drug hunter*, Arcade Publishing, New York, 2017.

[2] Burg, R. W.; Miller, B. M.; Baker, E. E.; Birnbaum, J.; Currie, S. A.; Hartman, R.; Kong, Yu-L.; Monaghan, R. L.; Olson, G.; Putter, I.; Tunac, J. B.; Wallick, H.; Stapley, E. O.; Ōiwa, R.; Ōmura, S. *Antimicrob. Agents Chemother.* **1979**, *15*, 361.

[3] Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2016**, *79*, 629.

[4] Wani, M. C.; Taylor, L. T.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *97*, 2325.

[5] (a) Noble, R. L.; Beer, C. T.; Cutts, J. H. *Ann. N. Y. Acad. Sci.* **1958**, *76*, 882. (b) Svoboda, G. H. *Lloydia* **1961**, *24*, 173.

[6] (a) Wall, M. E.; Wani, M. C.; Cook, C. E.; Palmer, K. H.; McPhail, A. T.; Sim, G. A. *J. Am. Chem. Soc.* **1966**, *88*, 3888. (b) Wall, M. E.; Wani, M. C. *J. Ethnopharmacol*. **1996**, *51*, 239.

[7] Arcamone, F.; Cassinelli, G.; Grein, A.; Orezzi, P.; Pol, C.; Spalla, C. *Biotechnol. Bioeng*. **1969**, *11*, 1101.

[8] World Cancer Report 2019, International Agency for Research on Cancer, World Health Organization

[9] Cancer Registry and Statistics, Cancer Information Service, National Cancer Center, Japan.

[10] Hirata, Y.; Uemura, D. *Pure Appl. Chem.* **1986**, *58*, 701.

[11] (a) Wang, Y.; Hadgood, G. J.; Christ, W. J.; Kishi, Y.; Littlefield, B. A.; Yu, J. *M. Bioorg. Med. Chem. Lett.* **2000**, *10*, 1029. (b) Kim, D. S.; Dong, C. G.; Kim, J. T.; Guo, H.; Huang, J.; Tiseni, P. S.; Kishi, Y. *J. Am. Chem. Soc.* **2009**, *131*, 15636.

[12] Isolation; Hecker, E. *Cancer Res.* **1968**, *28*, 2338.

[13] Total synthesis by the Baran group; (a) Jϕrgensen, L.; Mckerrall, S. J.; Kuttruff, C. A.; Ungeheur, F.; Felding, J.; Baran, P. S. *Science* **2013**, *341*, 878. (b) Mckerrall, S.; Jϕrgensen, L.; Kuttruff, C. A.; Felix U.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 5799.

[14] Winkler, J. D.; Rouse, M. B.; Greaney, M. F.; Harrison, S. J.; Jeon, Y. T. *J. Am. Chem. Soc.* **2002**, *124*, 9727.

[15] Tanino, K.; Onuki, K.; Asano, K.; Miyashita, M.; Nakamura, T.; Takahashi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **2003**, *125*, 1398.

[16] Nichel, A.; Murayama, T.; Tang, H.; Murphy, P. D.; Greene, B.; Yusuff, N.; Wood, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 16300.

Chapter 2. Structure-activity relationship study of aplyronine A by hybridization with swinholide A

2-1. Introduction

2-1-1. Protein-protein interaction and aplyronine A

Protein-protein interactions (PPIs) play major roles in the signal transduction system that are in charge of life phenomena. Their induction and inhibition influence the life phenomena such as proliferation, differentiation, and aging due to collapse or the modulations of biological reactions. The relationship between PPI defects and various diseases has been clarified, thus, PPIs are attracting as the drug targets in post-genomic era.

Rapamycin[1,2] is a natural product that induces PPIs (Figure 2-1). Rapamycin binds to the intracellular receptor protein FKBP12 to form a complex. The rapamycin–FKBP12 complex forms a protein heterodimer by binding to the FKBP12–rapamycin-binding site (FRB) in FKBP12–rapamycin-associated protein (FRAP) and inhibits the bioresponse of the interleukin-2 receptor. Since this inhibition shows immunosuppressive activity, rapamycin is used as an immunosuppressant in organ transplantation.

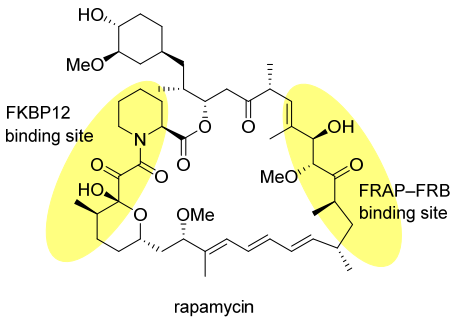


Figure 2-1. Rapamycin

Aplyronine A (**1**),[3,4,5] a 24-membered macrolide, is also one of the PPI inducers in marine natural products isolated from the sea hare *Aplysia kurodai* (Figure 2-2). Aplyronine A (**1**) shows cell growth inhibitory activity against HeLa S3 (IC_{50} = 0.01 nM) and powerful antitumor activity against mouse P388 lymphoma tumor models (T/C = 545%) (Table 2-1).[6,7] The mode of action is shown to form a 1:1:1 heterotrimeric complex with actin and tubulin, and inhibits tubulin polymerization.[8]

The mode of action was investigated as followings. In 2006, the crystal structure of actin–aplyronine A complex was revealed. At that time, the trimethylserine group at C7 is projected at the outer side (Figure 2-3).[9] Meanwhile, aplyronine C (**2**), a natural aplyronine derivative lacking trimethylserine group, shows as high actin-depolymerizing activity as aplyronine A (**1**), and has 1000-fold weaker cytotoxicity than aplyronine A (**1**).[10,11] From these results, the trimethylserine group of aplyronine A (**1**) was suggested to interact with another protein except actin. In addition, side chain analog **4** of aplyronine A has actin-depolymerizing activity but no cytotoxicity,[12,13] and macrolactone analog **3** doesn't have both actin-depolymerizing activity and cytotoxicity (Figure 2-4).[9,14] It is supposed that the side chain part is very important to express actin-depolymerizing activity and the entire compound structure including trimethylserine group at C7 is very important to express powerful cytotoxicity. Finally, our group made sure that the second target protein is tubulin with photoaffinity biotin probe of aplyronine A (**1**).[15] Aplyronine A (**1**) that possesses the unprecedented mode of action is expected to be a novel type of antitumor drug candidate.

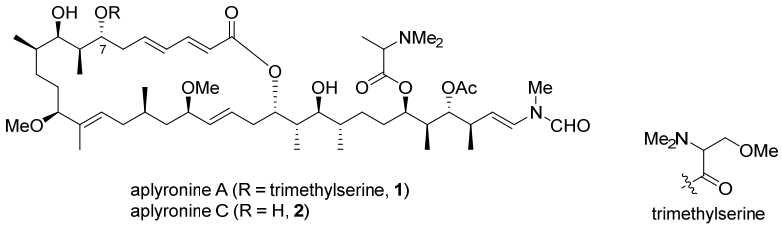


Figure 2-2. Structures of aplyronines A (**1**) and C (**2**)

Table 2-1. Cytotoxicity and actin-depolymerizing activity of aplyronine A and its analogs.

conpound	cytotoxicity against HeLa S3 cells IC_{50} (ng / mL)	actin-depolymerizing activity EC_{50} (μM) [a]
aplyronine A (**1**)	0.011	31
aplyronine C (**2**)	16.1	32
macrolactone analog **3**	2100	inactive
side chain analog **4**	>10000	330

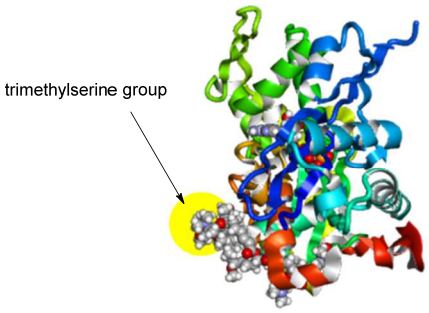


Figure 2-3. A structure of aplyronine A–actin complex (PDB, 1WUA)

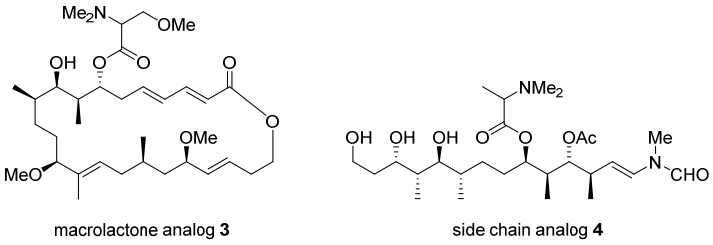


Figure 2-4. Artificial analogs.

2-1-2. Actin, a cytoskeletal protein, and marine natural products targeting actin

There are three types of cytoskeletal proteins: microtubules, medium diameter fibers, and microfilaments. Actin constitutes microfilaments and is known as the most abundant protein in eukaryotic cells. Actin takes two forms of G-actin as a monomer and F-actin as a polymer. G-actin is a globular protein with a diameter of 5 nm consisting of four subdomains. ATP interacts with the cleft between subdomains 2 and 4.[16] When the concentration of G-actin reaches the critical concentration (> 100 nM) under physiological conditions, G-actin starts to polymerize and becomes double-stranded helical F-actin. Repetition of polymerization and depolymerization regulates various life phenomena such as retention of cell shape, cell movement, cytokinesis, and muscle contraction.

Cytotoxic compounds targeting actin are isolated from marine organisms. Swinholide A (**5**),[17] which is a dimeric macrolide with a 44-membered ring, was isolated from the Okinawan sponge *Theonella swinhoei* (Figure 2-5). Swinholide A has cytotoxicity against murine leukemia L1210 cell (IC_{50} = 0.03 μg/mL) and human oral epidermoid carcinoma KB cell (IC_{50} = 0.04 μg/mL).[17b,18] Swinholide A depolymerizes F-actin, and its two side chain parts that are actin binding sites bind at the same time to the hydrophobic cleft between subdomains 1 and 3 of G-actin to form a 1:2 complex with G-actin (K_d = ~50 nM for each side chain).[19,20] Misakinolide A (**6**),[21,22] a natural derivative of swinholide A is cytotoxic against L1210 cells (IC_{50} = 0.035 μg/mL) and has been found to exhibit antitumor activity against P388 leukemia model mice (T/C = 140%) as with aplyronine A.[18] Misakinolide A (**6**) have no cleavage activity against F-actin due to binding to its barbed end.[23] Also, Mycalolide B (**7**)[24] is a macrolide with trisoxazole structure isolated from the marine sponge *Mycale sp.* in Gokasho Bay and exhibits antibacterial activity and cytotoxicity against B16 melanoma cells (IC_{50} = 0.5–1.0 ng/mL). Mycalolide B shows actin-depolymerizing activity (K_d = 13–20 nM) by forming a 1: 1 complex with G-actin.[25]

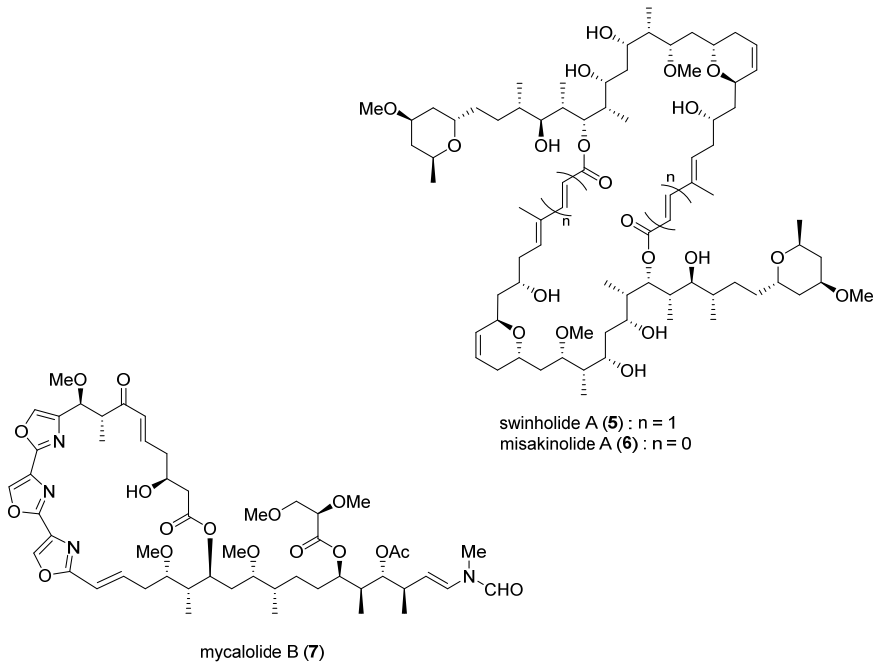
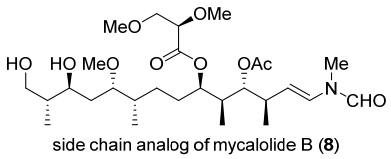


Figure 2-5. Structures of swinholide (**5**), misakinolide (**6**) and mycalolide B (**7**)

2-1-3. Previous studies

In previous studies, the side chain moiety of aplyronine A (**1**) proved to be crucial for actin-depolymerizing activity.[10,12,26] Artificial analog **4** showed relatively potent actin-depolymerizing activity (EC_{50} = 7.9 μM) as shown in Table 2-2. On the other hand, mycalolide B (**7**), which possesses a similar side chain to that of aplyronine A (**1**), has a stronger interaction with actin (K_d = 13–20 nM)[24,25] than aplyronine A (**1**) (K_d = 100 nM) (Figure 2-6).[8] The Kigoshi group synthesized and biologically evaluated the artificial analog **8**, which only consist of the side chain moiety of mycalolide B (**7**), revealing its stronger actin-depolymerizing activity (EC_{50} = 2.7 μM) than analog **4**. [13]



side chain analog of mycalolide B (**8**)

Figure 2-6. Side chain analog of mycalolide B

Table 2-2. Biological activities of aplyronine A and mycalolide B and their side chain analogs

compound	cytotoxicity against HeLa S3 cells IC_{50} (ng / mL)	actin depolymerizing activity EC_{50} (μM)
aplyronine A (**1**)	0.011	1.6
mycalolide B (**7**)	3.5	n.d.
side chain analog **4**	>10000	7.9
side chain analog **8**	>10000	2.7

Reasoning that reinforcement of the actin-depolymerizing activity led to the higher cytotoxicity, aplyronine A–mycalolide B hybrid compound **9** was designed and synthesized, and its cytotoxic activity against HeLa S3 and actin-depolymerizing activity were evaluated (Figure 2-7).[27] As results, aplyronine A–mycalolide B hybrid compound **9** retained potent actin-depolymerizing activity (EC_{50} = 1.0 μM), however its cytotoxicity against HeLa S3 was considerably reduced (IC_{50} = 12 nM) compared to that of aplyronine A (**1**) (IC_{50} = 0.010 nM). It was recognized that the differences in methyl group at the C24 and stereochemistry of substitution at the C25 between aplyronine A (**1**) and aplyronine A–mycalolide B hybrid compound **9** significantly influenced their cytotoxicities. This consideration was supported by a comparison of the X-ray crystallographic structures between the actin–aplyronine A complex and an actin–kabiramide C (mycalolide B-related compound, **10**) complex (Figure 2-8).

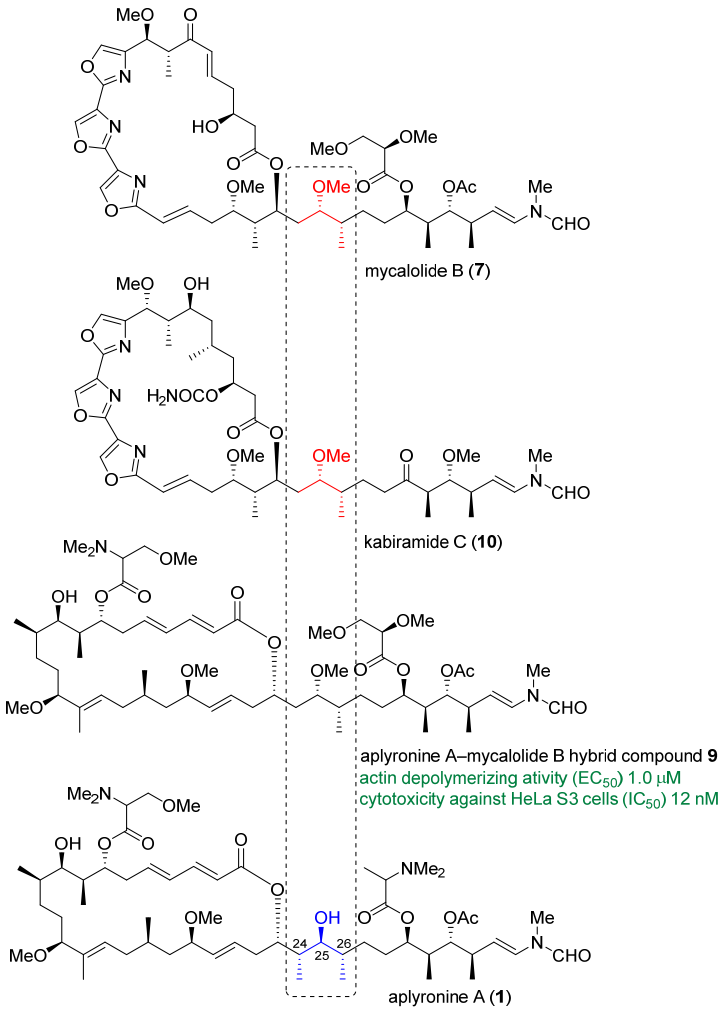


Figure 2-7. The differences in the pattern and stereochemistry of substitution at C24–C26

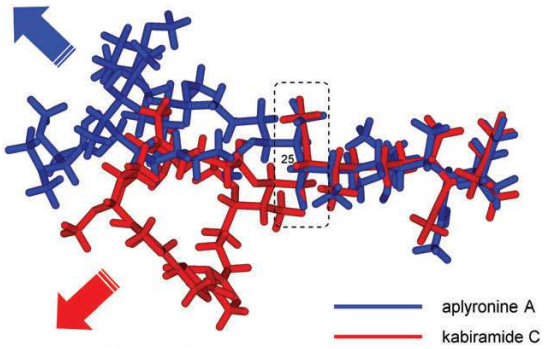


Figure 2-8. Superimposing conformations of actin–aplyronine A and –kabiramide C complexes

2-1-4. Swinholide A and aplyronine A–swinholide A hybrid compound

As mentioned above, swinholide A (**5**) shows strong cytotoxicity against various human cancer cells and actin-depolymerizing activity (Figure 2-9). K_d value of swinholide A (**5**) is almost the same as that of aplyronine A (**1**) in complex with actin. Rayment *et al.* reported the X-ray crystallographic analysis of an actin–swinholide A (**5**) complex, revealing that the side chain moiety of swinholide A (**5**) interacted with actin in the same way as that of aplyronine A (**1**). Superimposed conformations of actin–aplyronine A and –kabiramide C (**10**) or –swinholide A complexes based on X-ray analyses are shown in Figure 2-8 and 2-10. The differences in configuration at C25 and the degree of substitution at C24 between aplyronine A and kabiramide C causes a change in the conformational relationship between the macrolactone and the side chain part. On the other hand, because the stereochemistry of C25 and the degree of substitution at the C24–C26 are same between aplyronine A (**1**) and swinholide A (**5**), the macrolactone part of swinholide A would correspond well with those of aplyronine A on their actin complexes. Hence, we designed aplyronineA–swinholide A hybrid **11**. For the reason that the stereochemistry and the degree of substitution at C24–C26 of swinholide A (**5**) are coincident with those of aplyronine A (**1**), the author expected that the conformation of the aplyronine A–swinholide A hybrid **11** would be similar to that of aplyronine A (**1**).

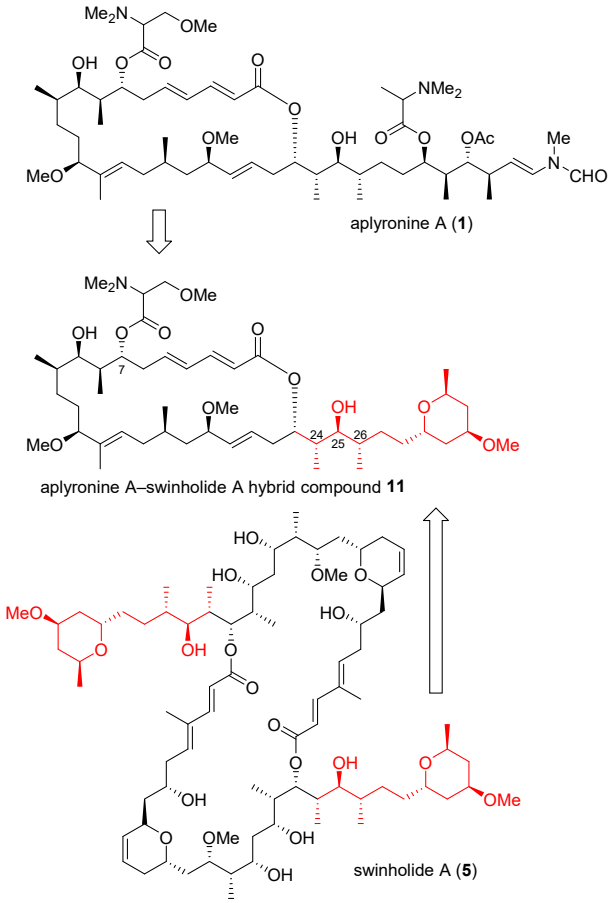


Figure 2-9. Design of aplyronine A–swinholide A hybrid compound

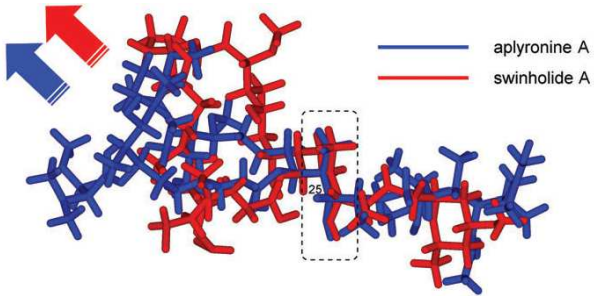
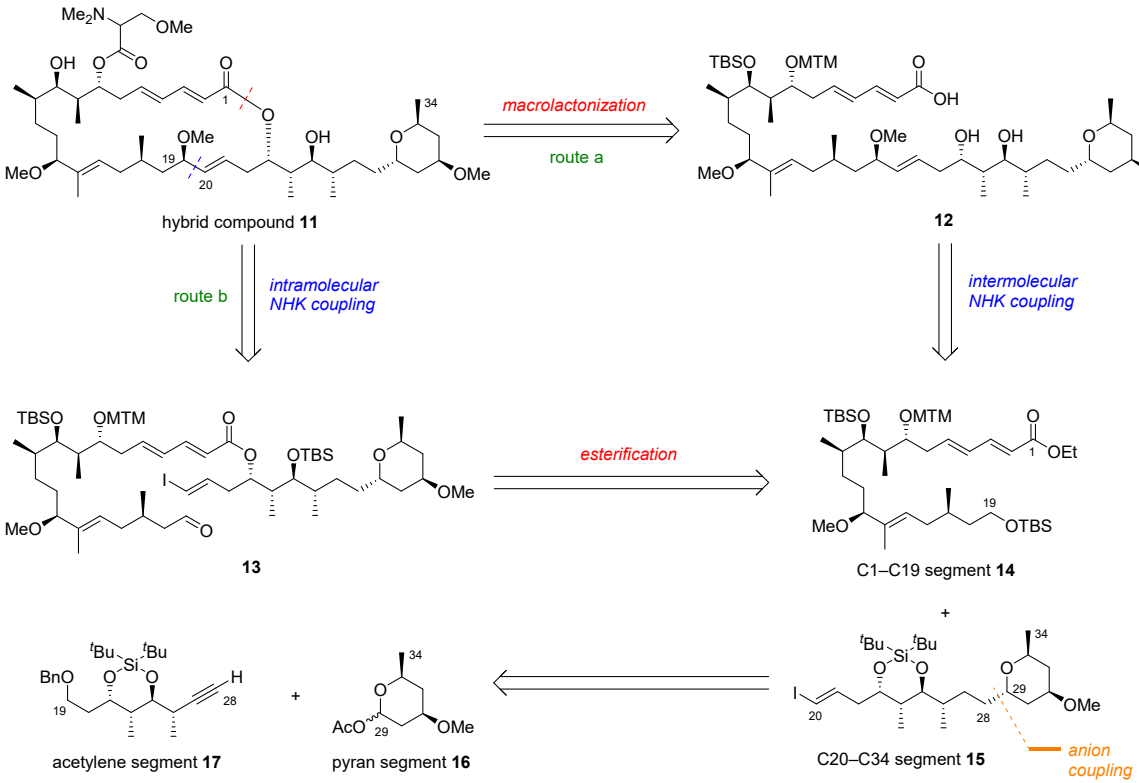


Figure 2-10. Superimposing conformations of actin–aplyronine A and –swinholide A complexes

2-2. Retrosynthetic pathway of aplyronine A–swinholide A hybrid compound

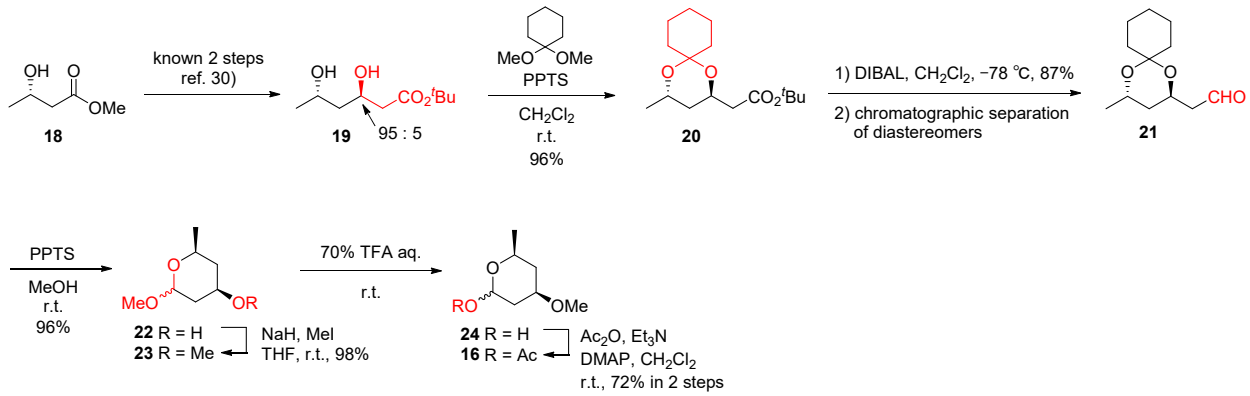
Retrosynthetic pathway of aplyronine A–swinholide A hybrid compound **11** is shown in Scheme 2-1. Thus, we planned the synthesis of hybrid compound **11** based on our second-generation total synthesis of aplyronine A (**1**).[4c] The all carbon framework could be assembled by intermolecular NHK coupling and macrolactonization (path a) or esterification and intramolecular Nozaki–Hiyama–Kishi (NHK) coupling[28] (path b) from C1–C19 segment **14** and C20–C34 segment **15**. C1–C19 segment **14** was the intermediate of aplyronine A (**1**) in the 2nd generation total synthesis.[29] C20–C34 segment **15** is a similar compound as the synthetic intermediate of misakinolide A by Miyashita,[30] and the author followed the Miyashita method with modification. Thus, C20–C34 segment **15** can be constructed by coupling reaction between pyran segment **16** and acetylene segment **17**.



Scheme 2-1. Retrosynthetic pathway

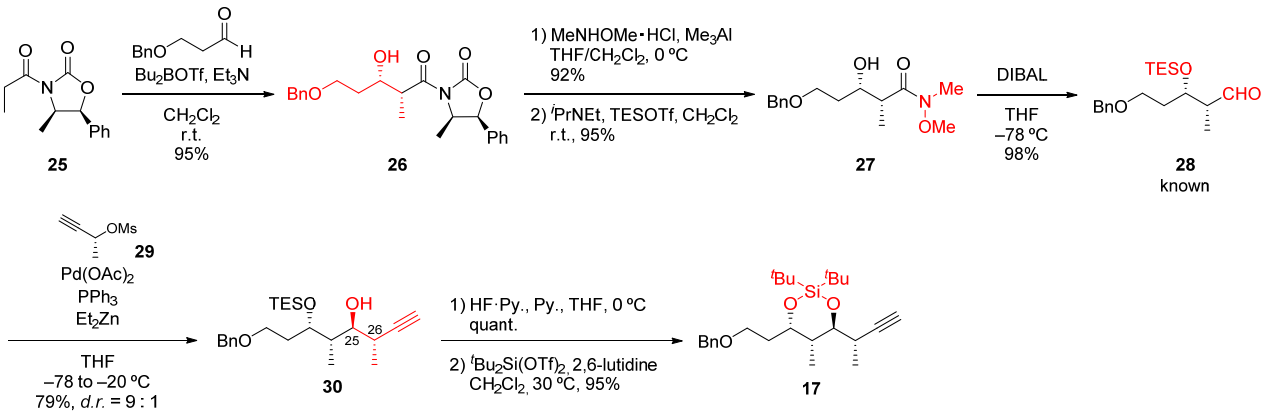
2-3. Synthesis of C20–C34 segment

The known optically active diol **19** was synthesized from commercially available (*S*)-3-hydroxybutanoate (**18**) by using Miyashita reported procedure (Scheme 2-1).[30] Diol **19** was obtained as an inseparable mixture of diastereomers at the newly generated secondary hydroxy group (*d.r.* = 95:5). For separation of the diastereomers, diol **19** was converted to aldehyde **21**. The diastereomers of aldehyde **21** could be separated by silica gel chromatography. Removal of the cyclohexylidene acetal group and cyclization of the resultant diol afforded acetal **22**, which was transformed into methyl ether **23**. Hydrolysis of the methyl acetal in **23** and acetylation of the resultant hemiacetal group in **24** gave pyran segment **16**.



Scheme 2-1. Synthesis of pyran segment **16**

The synthesis of acetylene segment **17** from known aldehyde **28** which was prepared from acyloxazolidinone in 4 steps was examined.[29] For the stereoselective introduction of a secondary hydroxy group at the C25 and a secondary methyl group at the C26, we attempted Marshall asymmetric propargylation.[31] Addition of chiral allenylzinc reagent, generated from mesylate **29**, $Pd(OAc)_2$, PPh_3, and Et_2Zn, to aldehyde **28** gave acetylene **30**, which has four contiguous stereogenic centers. Removal of TES group gave the diol, which was transformed into silylene acetal **17**.

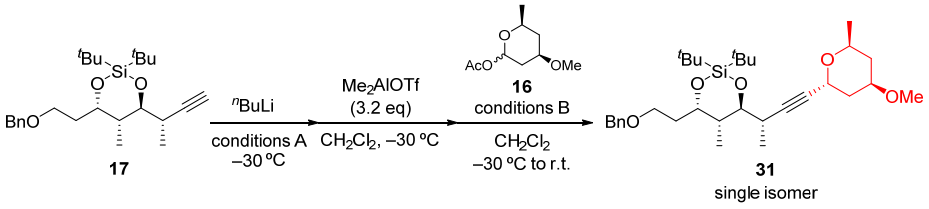


Scheme 2-2. Synthesis of acetylene segment **17**

The coupling reaction between pyran segment **16** and acetylene segment **17** was next examined based on the Miyashita reported conditions (Table 2-1).[30] The coupling reaction using excess pyran segment **16** proceeded in 27% yield (entry 1). We next examined this coupling reaction using excess acetylene segment **17** because **17** was recoverable and **16** was not. As a result, the reaction yield was improved (entries 2 and 3). Next, the solvent at the preparation of the Li-acetylide of **17** was changed. The Li-acetylide, generated in situ from acetylene segment **17** in THF, participated in the coupling reaction to provide the coupling compound **31**

in 66% yield. Finally, increase of the concentration from 0.1 M to 0.3 M improved the yield of **31** to 80%. This reaction proceeded through a more stable chair-like transition state via an oxonium cation, and the stereochemistry in coupling product **31** was determined by the coupling constants between 29-H and 30-H (Figure 2-11).

Table 2-1. Coupling reaction between pyran segment **16** and acetylene segment **17**



entry	conditions A			conditions B		
	17 (equiv)	^{n}BuLi (equiv)	solvent	**16** (equiv)	conc (M)	yield (%)
1	1.0	1.0	CH_2Cl_2	1.4	0.1	27
2	1.4	1.0	CH_2Cl_2	1.0	0.1	42
3	1.4	1.4	CH_2Cl_2	1.0	0.1	55
4	1.4	1.4	THF	1.0	0.1	66
5	1.4	1.4	THF	1.0	0.3	80

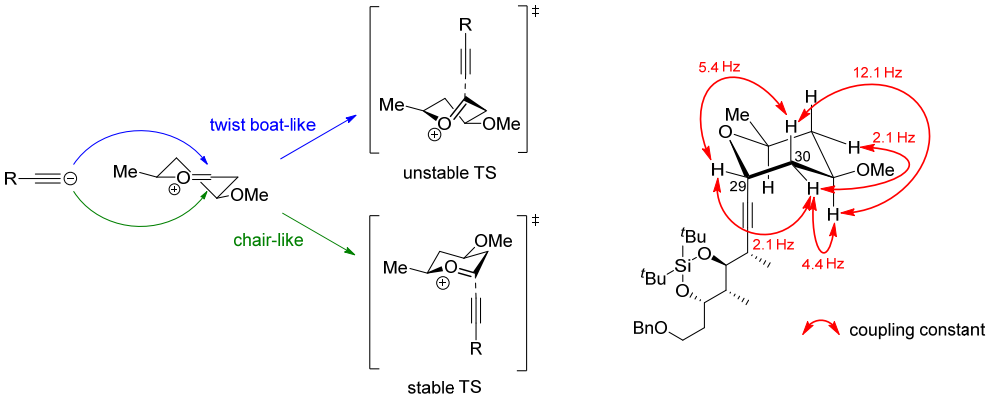
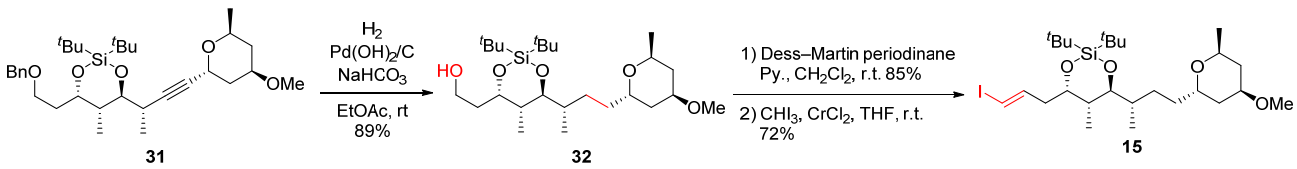


Figure 2-11. Transition states in the coupling reaction to **31** and the coupling constants of **31**

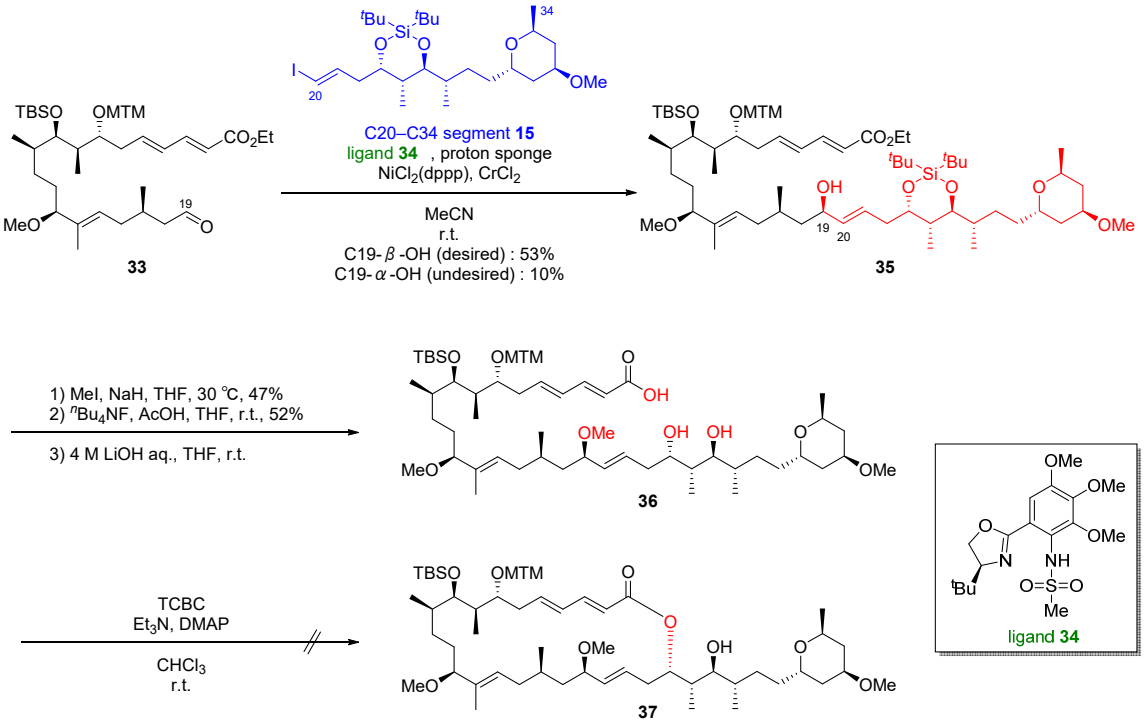
The coupling compound **31** was converted into C20–C34 segment **15** as follows. Hydrogenolysis of the benzyl group and hydrogenation of the triple bond in **31** afforded alcohol **32**,[32] which was oxidized by Dess–Martin periodinane[33] to give an aldehyde. Takai olefination[34] of the aldehyde gave C20–C34 segment **15**.



Scheme 2-3. Synthesis of C20–C34 segment **15**

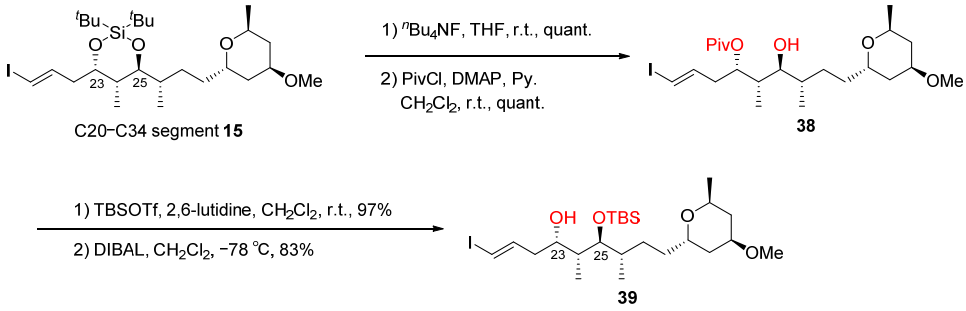
2-4. Synthesis of aplyronine A–swinholide A hybrid compound

Asymmetric NHK coupling reaction with $NiCl_2$(dppp), $CrCl_2$, and ligand **34** between the aldehyde which was derived from C1–C19 segment **14** in 2 steps and C20–C34 segment **15** was conducted. The ligand **34** was developed in our laboratory, and which possesses three electron-donating methoxy groups on the benzene ring, a large ^{t}Bu group on the oxazoline ring, and a small methyl group on the sulfonamide group to improve the reactivity and selectivity.[29] The reaction proceeded with moderate yield. The stereochemistry at C19 was determined by modified Moscher's method.[35] The coupling product was converted to seco acid **36** by methylation, removal of silylene acetal group, and hydrolysis. Unfortunately, seco acid **36** is difficult to handle due to its high polarity, and also following macrolactonization gave no desired macrolactone **37**.



Scheme 2-4. Macrolactonization route

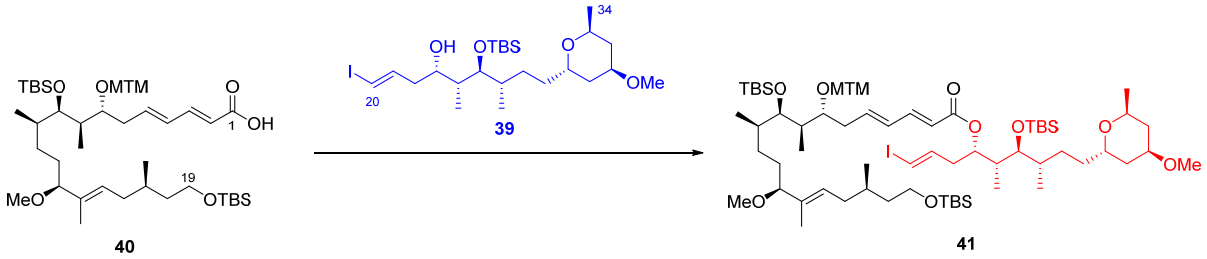
The author planed two synthetic pathways, a macrolactonization route which failed as described above, and an intramolecular NHK coupling route which is shown below. Transformation of protecting group in segment **15** was needed in the intramolecular NHK coupling route. The selective protection of the hydroxy group at C25 in **30** could not be achieved directly. Hence, a circuitous synthetic route to desired monoalcohol was required in the end (Scheme 2-5). Accordingly, the author manipulated the protecting groups in C20–C34 segment **15** to give iodoolefin **39** in four steps: (1) removal of the silylene acetal, (2) regioselective pivalation at 23-*O*, (3) TBS protection of the remaining hydroxy group, (4) reductive removal of the pivaloyl group.



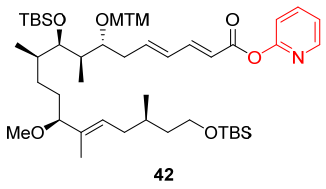
Scheme 2-5. Manipulation of protecting groups in C20–C34 segment **15**

Next, the connection of carboxylic acid **40** synthesized from C1–C19 segment **14** by hydrolysis[29] and iodoolefin **39** was achieved by esterification (Table 2-3). The yields of ester **41** under normal Yamaguchi (entry 1),[36] Shiina (entry 2),[37] and Steglich (entry 3) [38] condition was 55, 49, and 19%, respectively. Under DPTC conditions that were developed by Mukaiyama,[39] carboxylic acid **40** reacted only with pyridone, generated from DPTC, to produce pyridyl ester **42** (entry 4). When toluene was changed to a mixture of THF and toluene, the Yamaguchi condition that gave ester **41** with the best yield.

Table 2-3. Esterification between carboxylic acid **41** and iodoolefin **40**

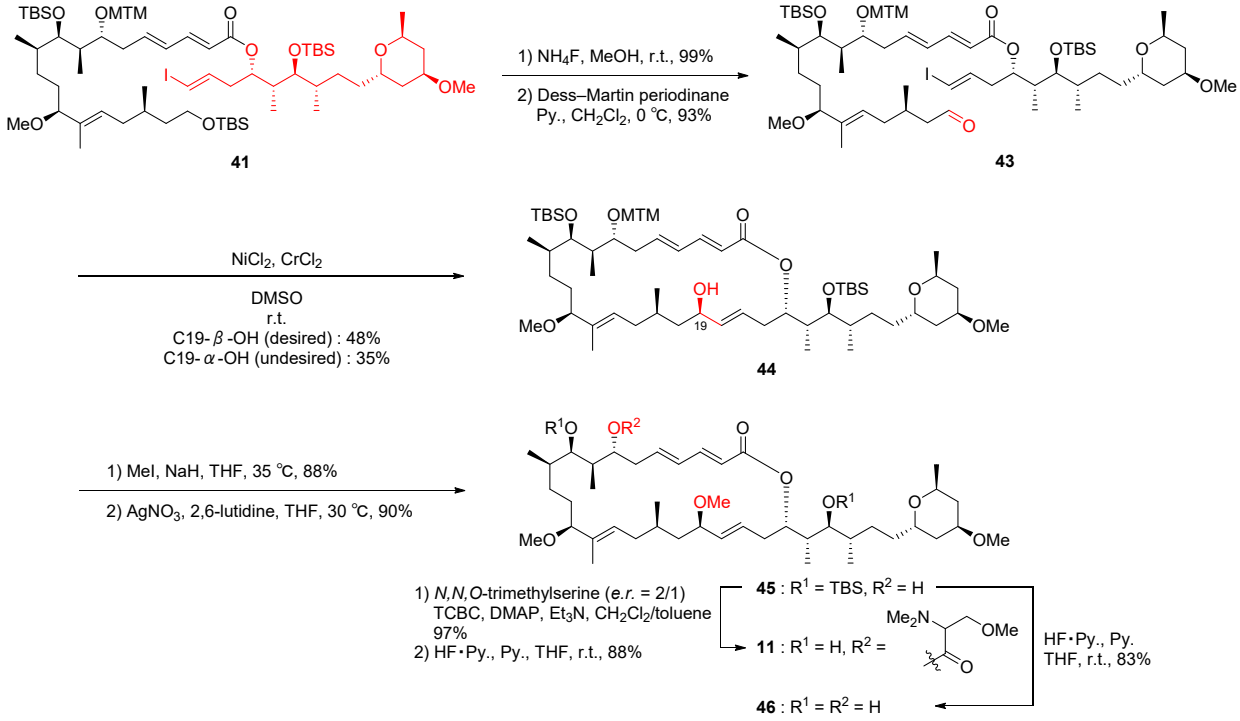


entry	conditions	yield
1	TCBC, Et_3N, DMAP, toluene, r.t.	55%
2	MNBA, Et_3N, DMAP, CH_2Cl_2, r.t.	49%
3	DCC, DMAP, CH_2Cl_2, r.t.	19%
4	DPTC, Et_3N, DMAP, CH_2Cl_2, r.t.	0 % (**42** : 90%)
5	TCBC, Et_3N, DMAP, THF/toluene, r.t.	83%



Removal of the primary TBS group followed by Dess–Martin oxidation produced NHK coupling precursor **43** (Scheme 2-6). Intramolecular NHK coupling of **43** gave the desired macrolide and the C19 diastereomer, which could be separated by silica gel chromatography. The stereochemistry at C19 was confirmed by modified Moscher's method (Figure 2-12).[35] Methylation of the resulting hydroxy group and removal of the MTM group gave alcohol **45**. The *N*,*N*,*O*-trimethylserine ester group with a 1:1 diastereomeric ratio at α-position of trimethylserine was introduced by using a 2:1 enantiomeric mixture of trimethylserine. Finally, removal of two TBS groups afforded aplyrnine A–swinholide A hybrid compound **11**. The synthesis

of hybrid compound **11** was 16-step shorter than the 86-step synthesis of aplyronine A. In addition, to confirm the mode of action of hybrid compound **11**, aplyronine C (a natural aplyronine derivative lacking the trimethylserine ester group) –swinholide A hybrid compound **46**, was synthesized from **45**.



Scheme 2-6. Synthesis of aplyronine A–swinholide A hybrid compound **11** and aplyronine C–swinholide A hybrid compound **46**

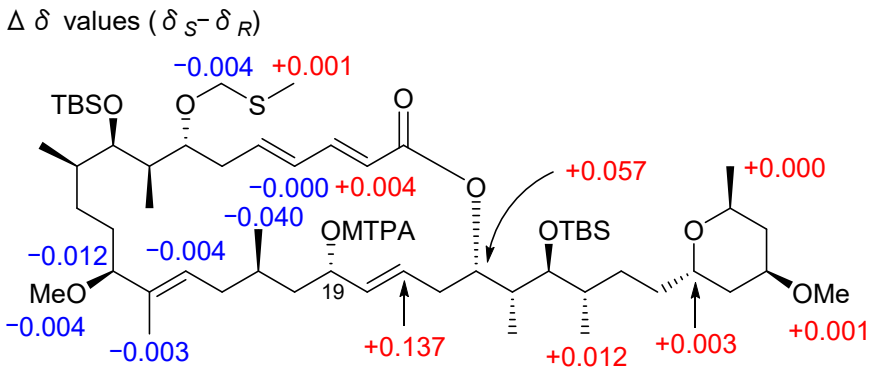


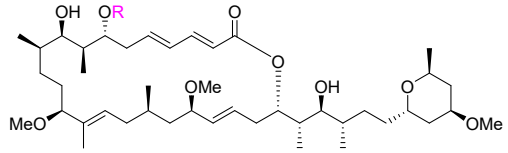
Figure 2-12. Determination of stereochemistry at C19 in **44**

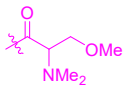
2-5. Biological activities

2-5-1. Cytotoxicity

The cytotoxicities of aplyronines A (**1**), aplyronine A–swinholide A hybrid compound **11**, aplyronine C–swinholide A hybrid compound **46**, and the derivatives **47**-**49** that was synthesized from alcohol **45** by a co-researcher are indicated in Table 2-4. Hybrid compound **11** had strong cytotoxicity, but which was some-what weaker than that of aplyronine A (**1**) presumably due to the simplification of the side chain. On the other hand, hybrid compound **11** was found to have about 10000-fold stronger cytotoxicity than hybrid compound **46**. This fact indicates a similar tendency with aplyronines A and C, where the trimethylserine moiety is very important for cytotoxicity. In addition, the cytotoxicity of **11** was stronger than that of aplyronine A–mycalolide B hybrid compound **9**. Derivatives **47**-**49** was designed with a view to synthesize chemical probes for the elucidation of the binding site with tubulin later and research structure-activity relationship studies of the amino acid moiety in **1** that have never been conducted. Examinations of their cytotoxicities showed that all of them decreased about 1000-fold as compared with hybrid compound **11**. A hydrogen bond between the methoxy group in the trimethylserine and tubulin or a bulky substituent might influence to the cytotoxicity. Chemical probes linked at trimethylserine moiety were supposed to be weaker in activity than hybrid compound **11**.

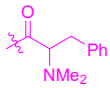
Table 2-4. Cytotoxicities

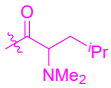


R =  : aplyronine A–swinholide A hybrid compound **11**

R = H : aplyronine C–swinholide A hybrid compound **46**

R =  : dimethylalanine analog **47**

R =  : dimethylphenylalanine analog **48**

R =  : dimethylleucine analog **49**

compound	cytotoxicity against HeLa S3 cells IC_{50} (nM)
ApA (**1**)	0.01
ApC (**2**)	10
ApA−SwA **11**	0.17
ApC−SwA **46**	1500
ApA−MyB **9**	12
dimethylalanine analog **47**	190
dimethylphenylalanine analog **48**	260
dimethylleucine analog **49**	720

2-5-2. Actin-depolymerizing activity

Actin depolymerization activity of synthesized hybrid compound **11** was evaluated in an ultracentrifugation method. In an ultracentrifugation method, each G-actin (monomer) and F-actin (polymer) can be divided into supernatant and precipitate fractions, respectively. Actin in G-buffer is a monomer and was detected in a supernatant fraction (Table 2-5, lane 1). Meanwhile, when $MgCl_2$ was added to the mixture, polymerized actin was detected in a precipitate fraction (lane 2). The purpose of this experiment is whether the addition of aplyronine A (**1**) or hybrid compound **11** to a polymerized actin solution affects the extent of polymerization of actin. In lane 3, actin in the presence of aplyronine A was detected in a supernatant fraction only. In the case of hybrid compound **11**, actin was detected in a supernatant fraction in a dose-dependent manner (lane 4-6). After developing the sample with SDS-PAGE, the bands were stained by CBB. The ratio of G-/F- actin at each sample concentration was obtained by processing the image with Image J, and the EC_{50} value was calculated. Hybrid compound **11** possessed about 10-fold weaker actin-depolymerizing activity than aplyronine A (**1**). Since cytotoxicity of hybrid compound **11** was also about 10-fold weaker than that of aplyronine A (**1**), the result was reasonable.

Table 2-5. Actin-depolymerizing activity.

lane	1	2	3	4	5	6
$MgCl_2$	−	+	+	+	+	+
ApA (**1**, 5 μM)	−	−	+	−	−	−
ApA−SwA (**11**, 5 μM)	−	−	−	+	−	−
ApA−SwA (**11**, 15 μM)	−	−	−	−	+	−
ApA−SwA (**11**, 50 μM)	−	−	−	−	−	+
supernatant						
precipitate						

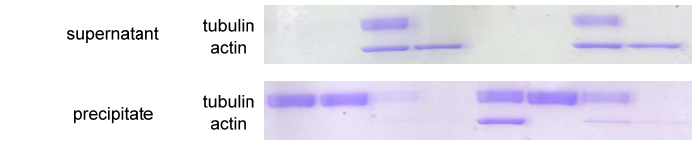
compound	cytotoxicity against HeLa S3 cells IC_{50} (nM)	actin-depolymerizing activity EC_{50} (μM)
ApA (**1**)	0.01	1.3
ApA−SwA **11**	0.17	12.8

2-5-3. Tubulin polymerization inhibitory activity

As hybrid compound **11** retained strong cytotoxicity and actin-depolymerizing activity, the author examined whether it would induce PPI between actin and tubulin. In an ultracentrifugation method, monomer and polymer tubulin are also separated to supernatant and precipitate fractions. Tubulin is polymerized in BRB80 buffer by paclitaxel (Table 2-6, lane 1). Under coexistence of aplyronine A in this solution, tubulin still precipitated (lane 2). In lane 3, when actin was added to the condition of lane 2, actin and most of the tubulin were detected in the supernatant. Actin and tubulin did not interact directly with each other, and polarized proteins were detected (lane 5). These results confirmed that these experiments are suitable for detecting a PPI inducing ability of aplyronine A (**1**) between actin and tubulin, resulting in depolymerization of actin and tubulin. Hybrid compound **11** showed the same result as aplyronine A (**1**) (lanes 6 and 7). Therefore, hybrid compound **11** induces PPI between actin and tubulin just as **1** does, albeit with 10% of the potency of **1**. This results support our hypothesis that aplyronine A (**1**) binds to actin with its side chain moiety and the actin–aplyronine A (**1**) complex interacts with tubulin by using the macrolactone moiety with the trimethylserine to give actin–tubulin–aplyronine A (**1**) complex, resulting in depolymerization of actin and tubulin.

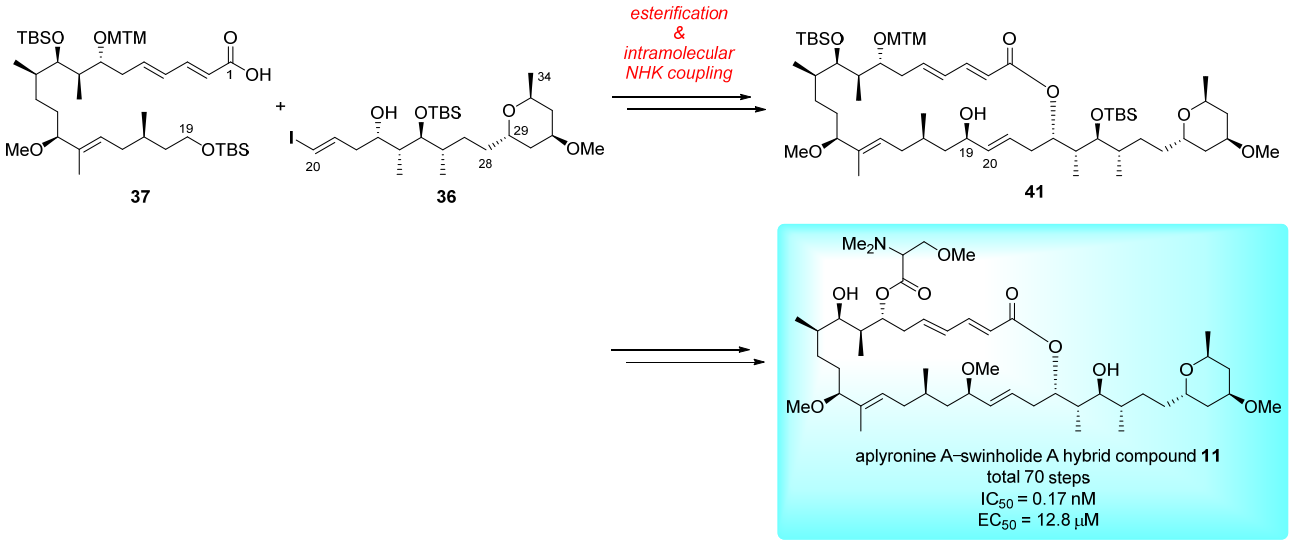
Table 2-6. Tubulin polymerization inhibitory activity.

lane	1	2	3	4	5	6	7	8
tubulin (3 μM)	+	+	+	−	+	+	+	−
actin (3 μM)	−	−	+	+	+	−	+	+
paclitaxel (6 μM)	+	+	+	−	+	+	+	−
ApA (**1**, 10 μM)	−	+	+	+	−	−	−	−
ApA–SwA (**11**, 100 μM)	−	−	−	−	−	+	+	+



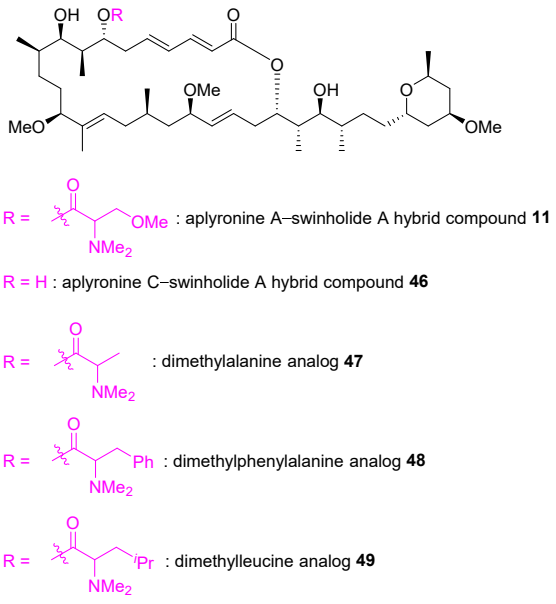
2-6. Summary

Aplyronine A (**1**) is expected to be a novel type of anticancer drug candidate based on the induction of PPI between actin and tubulin. The author planned to develop a lead compound for an anticancer drug based on aplyronine A (**1**) by hybridization with swinholide A (**5**). Aplyronine A–swinholide A hybrid compound **11** was synthesized in 70 steps through esterification and intramolecular NHK coupling (Scheme 2-7). Hybrid compound **11** possesses potent cytotoxicity, and its mode of action was confirmed to be the same as aplyronine A by the actin-depolymerizing activity assay and tubulin polymerization inhibitory activity assay. Also, cytotoxicities of amino acid derivatives **47**-**49** decreased about 1000-fold as compared with hybrid compound **11**.



Scheme 2-7. Summary (1)

Table 2-7. Summary (2)



compound	cytotoxicity against HeLa S3 cells IC_{50} (nM)
ApA (**1**)	0.01
ApC (**2**)	10
ApA–SwA **11**	0.17
ApC–SwA **46**	1500
dimethylalanine analog **47**	190
dimethylphenylalanine analog **48**	260
dimethylleucine analog **49**	720

2-7. Experimental section

2-7-1. General

All moisture-sensitive reactions were performed under an atmosphere of argon or nitrogen, and the starting materials were azeotropically dried with benzene before use. Anhydrous MeOH, MeCN, CH_2Cl_2, THF and DMSO were purchased from Sigma-Aldrich Co., Inc., or Wako Pure Chemical Industries Ltd., and used without further drying. TLC analysis were conducted on E. Merck precoated silica gel 60 F_{254} (0.25 mm layer thickness). Fuji Silysia silica gel BW-820MH (75–200 μm) was used for column chromatography. E. Merck PLC Silica gel 60 F_{254} (0.5 and 2 mm layer thickness) was used for PTLC. Optical rotations were measured with a JASCO DIP-370 polarimeter. Infrared (IR) spectra were recorded on a JASCO FT/IR-4100 instrument and only selected peaks are reported in wavenumbers (cm^{-1}). ^1H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 600, a Bruker AVANCE 500, a Bruker AVANCE 400, and a Bruker DPX 400 spectrometer. The ^1H and ^{13}C chemical shifts (δ) are reported relative to residual $CHCl_3$ ($\delta_H = 7.26$ and $\delta_C = 77.0$), respectively. *J* values are given in Hz. The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. High resolution ESI/TOF mass spectra were recorded on a JEOL AccuTOFCS JMS-T100CS spectrometer.

2-7-2. Cell growth inhibitory assay

Stock cultures of HeLa S3 cells were maintained in Eagle's Minimum Essential Medium containing Earle's Balanced Salts and 10% fetal bovine serum and 1% antibiotic-antimycotic mixed stock solution at 37 °C under 5% CO_2. For the purpose of the experiment, 2×10^4 cells suspended in 100 μL of medium per well were plated in 96-well plate. After 12 h incubation at 37 °C under 5% CO_2 to allow cell attachment, compounds in 100 μL of medium were added to the well at different concentrations and incubated for 96 h under the same conditions. After 3 h of the MTT addition to each well, the medium/MTT mixtures were removed, and the formazan crystals formed were dissolved in 150 uL of DMSO per well. After 30 min, optical absorbance at 540 nm were measured with a microplate reader. The cytotoxic effects of each compound were obtained as IC_{50} values.

2-7-3. *In vitro* actin depolymerizing activity assay

To a solution of actin (3 μM, from rabbit skeletal muscle, Cytoskeleton) in G-buffer (200 μL) was added a 0.12 M solution of $MgCl_2$ (1.6 μL), and the mixture was stirred at 25 °C for 30 min to give F-actin solution. To the solutions of F-actin were added samples in DMSO, and the resulting mixtures were stirred at 25 °C for 30 min and then ultracentrifuged (60000 rpm, 22 °C, 1 h). The supernatants and the precipitates were dissolved in 1 × SDS buffer (30 μL, Sigma) and boiled at 95 °C for 5 min. SDS-PAGE was performed by using a precast 10% polyacrylamide gel (ATTO), and the gels were stained with a Quick-CBB kit (Wako).

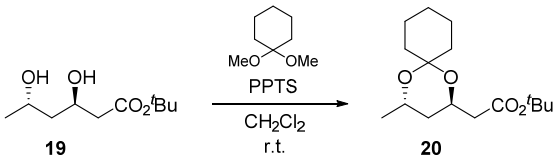
2-7-4. *In vitro* tubulin polymerization inhibitory activity assay

To a solution of actin (6 μM, from rabbit skeletal muscle, Cytoskeleton) in BRB80 (50 μL) were added samples (1 mM or 10 mM in DMSO, 1.0 μL), tubulin in BRB80 (50 μL), H_2O (0.5 μL), and paclitaxel (2 mM in DMSO, 0.3 μL). The resulting mixtures were standed at 37 °C for 30 min and then ultracentrifuged (60000 rpm, 37 °C, 1 h). The supernatants and the precipitates were dissolved in 1 × SDS buffer (20 μL, Sigma)

and boiled at 95 °C for 5 min. SDS-PAGE was performed by using a precast 10% polyacrylamide gel (ATTO), and the gels were stained with a Quick-CBB kit (Wako).
*When the samples were not added, the same amount of the corresponding solution was added.

2-7-5. Synthesis and spectroscopic data of compounds

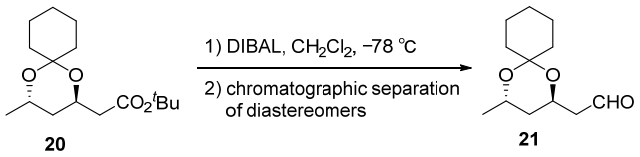
Cyclohexylidene acetal **20**



To a stirred solution of diol **19** (95:5 diastereomeric mixture, 1.11 g, 5.43 mmol) in CH_2Cl_2 (30 mL) were added 1,1-dimethoxycyclohexane (1.34 mL, 8.92 mmol) and PPTS (300 mg, 1.19 mmol) at room temperature. After stirring for 18 h at room temperature, the mixture was diluted with saturated aqueous $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined extracts were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (44 g, hexane–EtOAc 10 : 1) to afford cyclohexylidene acetal **20** (95:5 diastereomeric mixture, 1.48 g, 96%) as a colorless oil.

Major isomer
R_f = 0.27 (hexane : EtOAc = 8 : 1)
$[\alpha]_D^{28}$ +7.0 (*c* 1.11, $CHCl_3$)
IR ($CHCl_3$) 2938, 1721, 1449, 1368, 1157 cm^{-1}
^1H NMR (400 MHz, $CDCl_3$) δ 4.25 (dddd, *J* = 13.5, 8.4, 5.2, 5.2 Hz, 1H), 3.99 (ddq, *J* = 8.1, 6.3, 6.3 Hz, 1H), 2.43 (dd, *J* = 14.9, 8.4 Hz, 1H), 2.34 (dd, *J* = 14.9, 5.2 Hz, 1H), 1.75–1.29 (m, 12H), 1.45 (s, 9H), 1.19 (d, *J* = 6.3 Hz, 3H)
^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 100.4, 80.6, 63.5, 62.3, 42.6, 39.6, 34.6, 34.0, 28.3 (3C), 25.7, 23.2, 23.2, 21.9
HRMS (ESI) *m/z* 307.1895, calcd for $C_{16}H_{28}NaO_4$ $[M+Na]^+$ 307.1885.

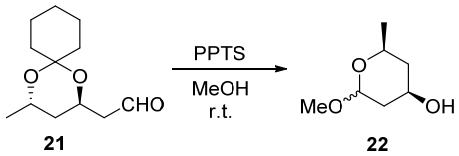
Aldehyde **21**



To a stirred solution of cyclohexylidene acetal **20** (95:5 diastereomeric mixture, 1.72 g, 6.06 mmol) in CH_2Cl_2 (30 mL) was added DIBAL (1.06 M solution in hexane, 6.70 mL, 7.10 mmol) at –78 °C. After stirring for 2 h at same temperature, the mixture was diluted with saturated aqueous Na/K tartrate (10 mL) and stirred at room temperature for 2 h. The resultant mixture was extracted with CH_2Cl_2 (3 × 10 mL). The extracts were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (30 g, hexane–EtOAc 5 : 1) to give a diastereomeric mixture of aldehyde (1.24 g, 96%). Diastereomers were separated by column chromatography on silica gel (20 g, CH_2Cl_2–Et_2O 100 : 1) to afford diastereomerically pure aldehyde **21** (1.11 g, 87%) as a colorless oil.

R_f = 0.23 (hexane : EtOAc = 8 : 1)
$[\alpha]_D^{25}$ +18.0 (*c* 0.423, $CHCl_3$)
IR ($CHCl_3$) 3026, 3003, 2939, 2858, 1725, 1448, 1364, 1129 cm^{-1}
^1H NMR (400 MHz, $CDCl_3$) δ 9.78 (dd, *J* = 2.5, 1.8 Hz, 1H), 4.38 (dddd, *J* = 12.7, 8.8, 4.4, 4.4 Hz, 1H), 4.01 (ddq, *J* = 6.3, 6.3, 6.3 Hz, 1H), 2.61 (ddd, *J* = 16.4, 8.8, 2.5 Hz, 1H), 2.48 (ddd, *J* = 16.4, 4.4, 1.8 Hz, 1H), 1.77–1.30 (m, 12H), 1.21 (d, *J* = 6.3 Hz, 3H)
^{13}C NMR (100 MHz, $CDCl_3$) δ 201.3, 100.6, 62.3, 61.9, 49.4, 39.8, 34.4, 34.0, 25.6, 23.2, 23.1, 21.8
HRMS (ESI) *m/z* 267.1558, calcd for $C_{13}H_{24}NaO_4$ $[M+Na+MeOH]^+$ 267.1572.

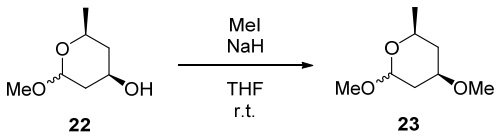
Methyl acetal **22**



To a stirred solution of aldehyde **21** (896 mg, 4.22 mmol) in MeOH (20 mL) was added PPTS (221 mg, 0.878 mmol) at room temperature. After stirring for 31 h at room temperature, the mixture was diluted with saturated aqueous $NaHCO_3$ (10 mL) and extracted with Et_2O (5 × 10 mL). The extracts were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (20 g, hexane–EtOAc 5 : 1) to afford methyl acetal **22** (594 mg, 96%) as a colorless oil.

R_f = 0.15, 0.19 (hexane : EtOAc = 1 : 1)
IR ($CHCl_3$) 3446, 3012, 1385, 1210, 1121 cm^{-1}
^1H NMR (400 MHz, $CDCl_3$) δ 4.84 (d, *J* = 3.4 Hz, 1H) [4.29 (dd, *J* = 9.6, 2.0 Hz, 1H)], 4.09 (m, 1H) [3.81 (m, 1H)], 3.84 (ddq, *J* = 12.6, 2.0, 6.3 Hz, 1H) [3.48 (ddq, *J* = 12.5, 2.0, 6.3 Hz, 1H)], 3.33 (s, 3H) [3.50 (s, 3H)], 2.07 (dddd, *J* = 12.6, 3.7, 2.0, 2.0 Hz, 1H) [2.17 (dddd, *J* = 12.0, 4.7, 2.0, 2.0 Hz, 1H)], 1.96 (dddd, *J* = 12.3, 4.6, 2.0, 2.0 Hz, 1H) [1.92 (dddd, *J* = 12.4, 4.8, 2.0, 2.0 Hz, 1H)], 1.65 (br. s, 1H) [1.61 (br. s, 1H)], 1.49 (ddd, *J* = 12.5, 12.3, 3.4 Hz, 1H) [1.33 (ddd, *J* = 12.4, 11.5, 9.6 Hz, 1H)], 1.23 (ddd, *J* = 12.6, 12.6, 11.8 Hz, 1H) [1.18 (ddd, *J* = 12.5, 12.0, 12.0 Hz, 1H)], 1.22 (d, *J* = 6.3 Hz, 3H) [1.28 (d, *J* = 6.3 Hz, 3H)] (the minor counterparts of doubled signals in the ratio of 1:0.67 are in brackets)
^{13}C NMR (100 MHz, $CDCl_3$) δ 99.2 [101.2], 64.0 [68.2], 63.7 [67.1], 54.5 [56.5], 42.6 [42.4], 39.1 [40.8], 21.4 [21.3] (the minor counterparts of doubled signals in the ratio of 1:0.67 are in brackets)
HRMS (ESI) *m/z* 169.0770, calcd for $C_7H_{14}O_3$ $[M+Na]^+$ 169.0841.

Methyl ether **23**

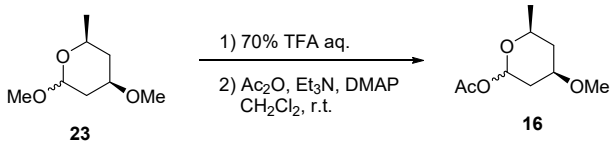


22 **23**

To a stirred solution of methyl acetal **22** (595 mg, 4.07 mmol) in THF (20 mL) was added 60% NaH (267 mg, 6.66 mmol) at room temperature. After 40 min at room temperature, MeI (700 mL, 11.3 mmol) was added to the mixture, and the mixture was stirred at room temperature for 18 h. The resultant mixture was diluted with saturated aqueous NH_4Cl (20 mL) and extracted with Et_2O (3 × 20 mL). The extracts were combined, washed with brine (40 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (20 g, pentane–Et_2O 4 : 1) to afford methyl ether **23** (637 mg, 98%) as a colorless oil.

R_f = 0.45, 0.48 (hexane : EtOAc = 1 : 1)
IR ($CHCl_3$) 3009, 2934, 1449, 1385, 1100 cm^{-1}
^1H NMR (400 MHz, $CDCl_3$) δ 4.84 (d, *J* = 3.5 Hz, 1H) [4.29 (dd, *J* = 9.8, 2.1 Hz, 1H)], 3.82 (ddq, *J* = 12.6, 2.0, 6.3 Hz, 1H) [3.46 (ddq, *J* = 12.3, 2.0, 6.2 Hz, 1H)], 3.62 (dddd, *J* = 11.3, 11.3, 4.6, 4.6 Hz, 1H) [3.42–3.33 (m, 1H)], 3.33 (s, 3H) [3.50 (s, 3H)], 3.32 (s, 3H) [3.35 (s, 3H)], 2.13 (dddd, *J* = 12.7, 4.6, 2.0, 1.7 Hz, 1H) [2.23 (dddd, *J* = 12.0, 4.6, 2.0, 1.9 Hz, 1H)], 2.02 (dddd, *J* = 12.4, 4.6, 1.7, 1.7 Hz, 1H) [1.98 (dddd, *J* = 12.5, 4.6, 2.1, 1.9 Hz, 1H)], 1.43 (ddd, *J* = 12.4, 11.3, 3.5 Hz, 1H) [1.29 (ddd, *J* = 12.5, 11.2, 9.8 Hz, 1H)], 1.20 (d, *J* = 6.3 Hz, 3H) [1.29 (d, *J* = 6.2 Hz, 3H)], 1.15 (ddd, *J* = 12.7, 12.6, 11.3 Hz, 1H) [1.14 (ddd, *J* = 12.3, 12.0, 11.2 Hz, 1H)] (the minor counterparts of doubled signals in the ratio of 1:0.67 are in brackets)
^{13}C NMR (100 MHz, $CDCl_3$) δ 99.4 [101.2], 72.6 [75.4], 64.0 [68.1], 55.5 [56.3], 54.7 [55.5], 39.4 [38.8], 36.0 [37.2], 21.6 [21.3] (the minor counterparts of doubled signals in the ratio of 1:0.67 are in brackets)
HRMS (ESI) *m/z* 183.0987, calcd for $C_8H_{16}O_3$ $[M+Na]^+$ 183.0997.

Acetate **16**

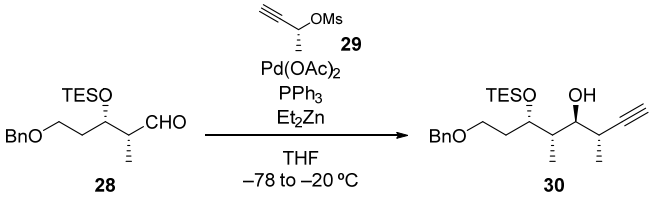


Methyl ether **23** (941 mg, 5.87 mmol) was treated with 70% aqueous TFA (30 mL) at room temperature. After being stirred at room temperature for 2 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ (100 mL) at 0 °C and extracted with $CHCl_3$ (5 × 60 mL). The extracts were combined, washed with brine (50 mL), dried over Na_2SO_4, and filtered. Removal of the solvent afforded crude hemiacetal **24**, which was used for the next reaction without further purification.

To a stirred solution of crude hemiacetal **24** in CH_2Cl_2 (38 mL) were added Et_3N (5.20 mL, 37.3 mmol), Ac_2O (1.10 mL, 11.6 mmol), and DMAP (158 mg, 1.29 mmol) at room temperature. After stirring for 1 h at room temperature, the mixture was diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The extracts were combined, washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (20 g, pentane–Et_2O 4 : 1) to afford acetate **16** (789 mg, 72% in 2 steps) as a colorless oil.

R_f = 0.39, 0.44 (hexane : EtOAc = 1 : 1)
IR ($CHCl_3$) 3010, 1743, 1450, 1375, 1240, 970, 669 cm^{-1}
^1H NMR (400 MHz, $CDCl_3$) δ 6.26 (d, *J* = 3.0 Hz, 1H) [5.64 (dd, *J* = 10.2, 2.3 Hz, 1H)], 3.95 (ddq, *J* = 12.5, 2.2, 6.2 Hz, 1H) [3.60 (ddq, *J* = 11.4, 2.0, 6.2 Hz, 1H)], 3.63 (dddd, *J* = 11.2, 11.2, 4.5, 4.5 Hz, 1H) [3.43 (dddd, *J* = 11.2, 11.2, 4.5, 4.5 Hz, 1H)], 3.34 (s, 3H) [3.34 (s, 3H)], 2.14 (dddd, *J* = 13.2, 4.5, 2.2, 1.9 Hz, 1H) [2.25 (dddd, *J* = 11.9, 4.5, 2.0, 2.0 Hz, 1H)], 2.07 (m, 1H) [1.99 (dddd, *J* = 12.6, 4.5, 2.3, 2.0 Hz, 1H)], 2.06 (s, 3H) [2.10 (s, 3H)], 1.54 (ddd, *J* = 11.2, 10.2, 3.0 Hz, 1H) [1.39 (ddd, *J* = 12.6, 11.2, 10.2 Hz, 1H)], 1.22 (ddd, *J* = 13.2, 12.5, 11.2 Hz, 1H) [1.17 (ddd, *J* = 11.9, 11.4, 11.2 Hz, 1H)], 1.21 (d, *J* = 6.2 Hz, 3H) [1.29 (d, *J* = 6.2 Hz, 3H)] (the minor counterparts of doubled signals in the ratio of 1:0.82 are in brackets)
^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5 [169.3], 93.0 [92.7], 71.9 [74.9], 66.7 [69.3], 55.3 [55.6], 38.8 [38.4], 34.7 [36.1], 21.5 [21.1], 21.2 [21.1] (the minor counterparts of doubled signals in the ratio of 1:0.82 are in brackets)
HRMS (ESI) *m/z* 211.0929, calcd for $C_9H_{16}NaO_4$ $[M+Na]^+$ 211.0946.

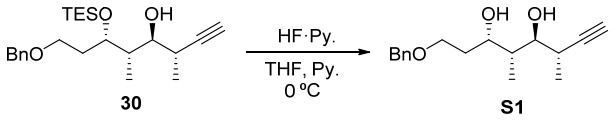
Acetylene **30**



To a stirred solution of $Pd(OAc)_2$ (30.0 mg, 0.134 mmol) in THF (4.0 mL) were added solutions of PPh_3 (183 mg, 0.523 mmol) in THF (2.0 mL), aldehyde **28** (183 mg, 0.523 mmol) in THF (2.0 mL), and mesylate **29** (160 mg, 1.08 mmol) in THF (2.0 mL) at –78 °C. Et_2Zn (1.1 M hexane solution, 1.50 mL, 1.60 mmol) was slowly added to the mixture at –78 °C. After stirring for 5 min at –78 °C, the reaction mixture was warmed to –20 °C and stirred for 15 h. The resultant mixture was diluted with saturated aqueous NH_4Cl (6.0 mL) and extracted Et_2O (3 × 6 mL). The extracts were combined, washed with brine (5.0 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (9.3 g, hexane–EtOAc 20 : 1) to afford acetylene **30** (103 mg, 51%) and diastereomeric mixture of acetylene **30** (57.3 mg, 28%, *d.r.* = 1 : 0.36) as yellow oils, respectively (total; 160 mg, 79%, *d.r.* = 91 : 1).

R_f = 0.48 (hexane : EtOAc = 5 : 1)
$[\alpha]_D^{26}$ –32.5 (*c* 1.00, $CHCl_3$)
IR ($CHCl_3$) 3427, 3307, 3008, 2959, 2877, 2112, 1455, 1110, 1003 cm^{-1}
^1H NMR (600 MHz, $CDCl_3$) δ 7.36–7.27 (m, 5H), 4.52 (d, *J* = 11.8 Hz, 1H), 4.48 (d, *J* = 11.8 Hz, 1H), 4.36 (d, *J* = 2.2 Hz, 1H), 4.03 (dt, *J* = 8.9, 3.2 Hz, 1H), 3.59–3.53 (m, 2H), 3.48 (ddd, *J* = 9.9, 2.3, 2.2 Hz, 1H), 2.58 (ddq, *J* = 2.3, 2.3, 7.1 Hz, 1H), 2.11 (ddq, *J* = 9.9, 8.9, 7.0 Hz, 1H), 2.00 (d, *J* = 2.3 Hz, 1H), 1.89–1.80 (m, 2H), 1.30 (d, *J* = 7.1 Hz, 3H), 0.96 (t, *J* = 7.9 Hz, 9H), 0.81 (d, *J* = 7.0 Hz, 3H), 0.63 (q, *J* = 7.9 Hz, 6H)
^{13}C NMR (151 MHz, $CDCl_3$) δ 138.6, 128.5 (2C), 127.8 (2C), 127.7, 85.2, 76.1, 74.3, 73.1, 70.2, 67.3, 41.6, 31.9, 30.5, 17.8, 13.5, 7.0 (3C), 5.0 (3C)
HRMS (ESI) *m/z* 413.2486, calcd for $C_{23}H_{38}NaO_3Si$ $[M+Na]^+$ 413.2488.

Diol **S1**

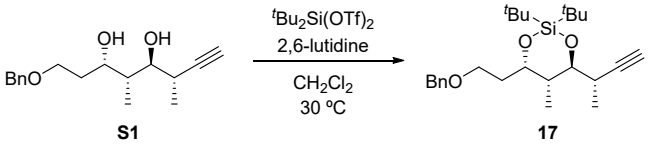


30 **S1**

A solution of acetylene **30** (225 mg, 0.575 mmol) in a 1 : 3 : 5 mixture of HF·Py., Py., and THF (40 mL) was stirred at 0 °C for 3 h. The reaction mixture poured into saturated aqueous $NaHCO_3$ (500 mL) at 0 °C, and extracted with EtOAc (3 × 100 mL). The combined extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3.8 g, hexane–EtOAc 5 : 1 → 2 : 1) to afford diol **S1** (158 mg, quant.) as a colorless oil.

R_f = 0.28 (hexane : EtOAc = 1 : 1)
$[\alpha]_D^{26}$ +1.44 (*c* 1.00, $CHCl_3$)
IR ($CHCl_3$) 3452, 3306, 3010, 2875, 2109, 1454, 1099, 984, 699, 641 cm^{-1}
^1H NMR (600 MHz, $CDCl_3$) δ 7.33–7.28 (m, 5H), 4.53 (s, 2H), 4.16 (m, 1H), 3.76 (ddd, *J* = 9.2, 4.8, 4.8 Hz, 1H), 3.67 (ddd, *J* = 9.2, 9.2, 4.0 Hz, 1H), 3.53 (br. s, 1H), 3.47 (m, 1H), 3.43 (br. s, 1H), 2.63 (ddq, *J* = 2.4, 2.4, 7.1 Hz, 1H), 2.10 (d, *J* = 2.4 Hz, 1H), 2.00–1.92 (m, 2H), 1.63 (dddd, *J* = 8.9, 4.8, 4.0, 2.2 Hz, 1H), 1.28 (d, *J* = 7.1 Hz, 3H), 0.89 (d, *J* = 7.1 Hz, 3H)
^{13}C NMR (151 MHz, $CDCl_3$) δ 138.0, 128.6 (2C), 128.0, 127.8 (2C), 85.1, 76.7, 73.6 (2C), 70.7, 70.0, 40.9, 32.7, 30.6, 18.0, 12.0
HRMS (ESI) *m/z* 299.1602, calcd for $C_{17}H_{24}NaO_3$ $[M+Na]^+$ 299.1623.

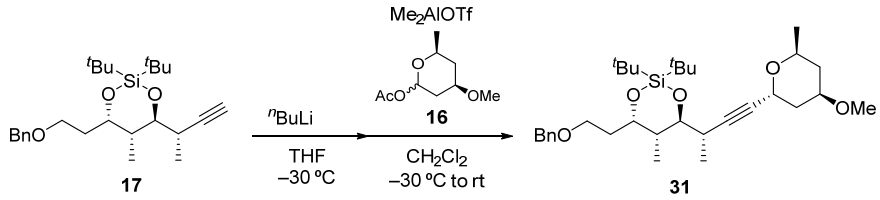
Silylene acetal **17**



To a stirred solution of diol **S1** (21.3 mg, 77.1 mmol) in CH_2Cl_2 (0.40 mL) were added 2,6-lutidine (40.0 mL, 345 mmol) and $^tBu_2Si(OTf)_2$ (50.0 µL, 154 mmol) at room temperature. After stirring for 2 h at 30 °C, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ (1.0 mL) and extracted with EtOAc (3 × 1 mL). The extracts were combined, washed with brine (1.0 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (0.8 g, hexane–EtOAc 8 : 1 → 1 : 1) to afford acetylene segment **17** (30.5 mg, 95%) as a colorless oil.

R_f = 0.65 (hexane : EtOAc = 5 : 1)
$[\alpha]_D^{25}$ –62.8 (*c* 1.00, $CHCl_3$)
IR ($CHCl_3$) 3306, 2964, 2934, 2859, 2109, 1474, 1363, 1149, 1065, 826, 647 cm^{-1}
^1H NMR (600 MHz, $CDCl_3$) δ 7.36–7.27 (m, 5H), 4.55 (s, 2H), 4.16 (ddd, *J* = 11.0, 5.5, 3.0 Hz, 1H), 3.76–3.68 (m, 2H), 3.67 (dd, *J* = 9.8, 2.4 Hz, 1H), 2.57 (ddq, *J* = 2.4, 2.4, 7.0 Hz, 1H), 2.49 (ddq, *J* = 9.8, 5.5, 7.1 Hz, 1H), 2.00 (d, *J* = 2.5 Hz, 1H), 1.83–1.73 (m, 2H), 1.28 (d, *J* = 7.0 Hz, 3H), 1.04 (s, 9H), 0.94 (s, 9H), 0.80 (d, *J* = 7.1 Hz, 3H)
^{13}C NMR (151 MHz, $CDCl_3$) δ 138.8, 128.5 (2C), 127.8 (2C), 127.6, 85.4, 75.3, 73.9, 73.3, 69.8, 68.1, 39.8, 31.3, 30.5, 27.7 (3C), 27.3 (3C), 21.6, 21.0, 17.6, 13.3
HRMS (ESI) *m/z* 439.2665, calcd for $C_{25}H_{40}NaO_3Si$ $[M+Na]^+$ 439.2644.

Coupling compound **31**



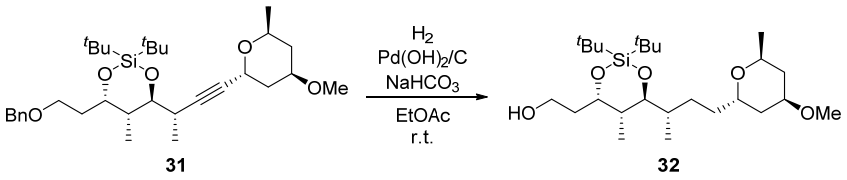
(Preparation of Me_2AlOTf)

To a stirred solution of Me_3Al (1.4 M solution in hexane, 1.72 mL, 2.41 mmol) in CH_2Cl_2 (0.5 mL) was added TfOH (220 mL, 2.49 mmol) in 0 °C. The resultant mixture was stirred at 0 °C for 30 min to afford 1.0 M Me_2AlOTf solution.

To a stirred solution of acetylene segment **17** (372 mg, 0.892 mmol) in THF (0.46 mL) was added ^{n}BuLi (1.6 M hexane solution, 610 mL, 0.976 mmol) at –30 °C. After stirring for 2 h at –30 °C, the above-mentioned 1.0 M Me_2AlOTf solution (2.03 mL, 2.03 mmol) was added to the reaction mixture at –30 °C. After solution of pyran segment **16** (120 mg, 0.637 mmol) in CH_2Cl_2 (0.50 mL) was added, the reaction mixture was stirred at –30 °C for 30 min. The resultant mixture was warmed to room temperature and stirred for 30 min. The reaction mixture was diluted with saturated aqueous Na/K tartrate (5.0 mL) and saturated aqueous $NaHCO_3$ (5.0 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The extracts were combined, washed with brine (5.0 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (10 g, hexane–EtOAc 24 : 1 → 14 : 1) to afford coupling compound **31** (280 mg, 80%) and recovered acetylene segment **17** (126 mg, 34%) as colorless oils, respectively.

R_f = 0.38 (hexane : EtOAc = 1 : 1)
$[\alpha]_D^{26}$ –66.6 (*c* 1.00, $CHCl_3$)
IR ($CHCl_3$) 2971, 2933, 2860, 1473, 1063 cm^{-1}
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36–7.26 (m, 5H), 4.84 (ddd, *J* = 5.4, 2.2, 2.1 Hz, 1H), 4.55 (s, 2H), 4.17 (ddd, *J* = 11.2, 5.6, 2.7 Hz, 1H), 4.00 (ddq, *J* = 12.1, 2.0, 6.2 Hz, 1H), 3.75–3.70 (m, 2H), 3.68 (dd, *J* = 9.8, 2.4 Hz, 1H), 3.64 (dddd, *J* = 12.1, 12.1, 4.4, 4.4 Hz, 1H), 3.33 (s, 3H), 2.62 (ddq, *J* = 2.4, 2.2, 7.0 Hz, 1H), 2.43 (ddq, *J* = 9.8, 5.6, 7.1 Hz, 1H), 2.06 (dddd, *J* = 12.1, 4.4, 2.1, 2.1 Hz, 1H), 2.00 (dddd, *J* = 12.4, 4.4, 2.1, 2.0 Hz, 1H), 1.82–1.72 (m, 2H), 1.56 (ddd, *J* = 12.1. 12.1, 5.4 Hz, 1H), 1.27 (d, *J* = 7.0 Hz, 3H), 1.20 (d, *J* = 6.2 Hz, 3H), 1.10 (ddd, *J* = 12.4, 12.1, 12.1 Hz, 1H), 1.03 (s, 9H), 0.93 (s, 9H), 0.81 (d, *J* = 7.1 Hz, 3H)
^{13}C NMR (151 MHz, $CDCl_3$) δ 138.8, 128.5 (2C), 127.8 (2C), 127.6, 87.8, 79.8, 75.1, 73.8 (2C), 73.3, 68.0, 66.8, 64.8, 55.5, 40.2, 39.8, 36.5, 31.4, 30.7, 27.6 (3C), 27.3 (3C), 21.9, 21.6, 20.9, 17.7, 13.2
HRMS (ESI) *m/z* 567.3491, calcd for $C_{32}H_{52}NaO_4Si$ $[M+Na]^+$ 567.3482.

Alcohol **32**

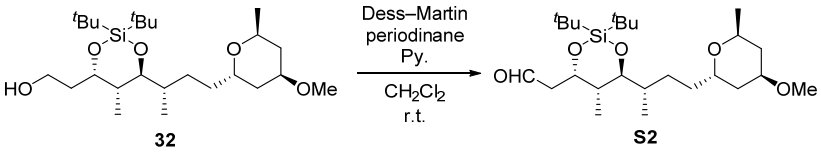


31 **32**

A mixture of coupling compound **31** (179 mg, 0.329 mmol), $NaHCO_3$ (58.6 mg, 0.698 mmol) and 20% $Pd(OH)_2/C$ (wetted with ca. 50% water, 20.5 mg) in EtOAc (4.0 mL) was stirred under hydrogen atmosphere at room temperature for 4 h. The mixture was filtered through a pad of Celite, and the residue was washed with EtOAc. The filtrate and the washings were combined and concentrated. The residual oil was purified by column chromatography on silica gel (3.5 g, hexane–EtOAc 10 : 1 → 5 : 1) to afford alcohol **32** (134 mg, 89%) as a colorless oil.

R_f = 0.20 (hexane : EtOAc = 2 : 1)
$[\alpha]_D^{26}$ –78.0 (*c* 1.00, $CHCl_3$)
IR ($CHCl_3$) 3471, 2963, 2935, 2860, 1474, 1383, 1064, 825, 648 cm^{-1}
^1H NMR (600 MHz, $CDCl_3$) δ 4.26 (ddd, *J* = 11.4, 5.5, 1.8 Hz, 1H), 4.01 (m, 1H), 3.93–3.84 (m, 2H), 3.75 (dd, *J* = 9.2, 2.3 Hz, 1H), 3.69 (ddq, *J* = 10.2, 2.2, 6.2 Hz, 1H), 3.53 (dddd, *J* = 10.3, 10.3, 4.3, 4.3 Hz, 1H), 3.34 (s, 3H), 2.59 (br. s, 1H), 2.26 (m, 1H), 1.98 (dddd, *J* = 12.3, 4.3, 2.2, 2.2 Hz, 1H), 1.91–1.82 (m, 2H), 1.81 (dddd, *J* = 12.3, 4.3, 2.2, 2.2 Hz, 1H), 1.62–1.57 (m, 3H), 1.44–1.29 (m, 2H), 1.23 (m, 1H), 1.19 (d, *J* = 6.2 Hz, 3H), 1.17 (ddd, *J* = 12.3, 10.3, 10.2 Hz, 1H), 1.01 (s, 9H), 1.00 (s, 9H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.77 (d, *J* = 7.1 Hz, 3H)
^{13}C NMR (151 MHz, $CDCl_3$) δ 77.9, 77.5, 73.5, 71.6, 64.7, 62.3, 55.4, 38.9, 38.9, 35.1, 34.9, 32.8, 29.2, 27.8 (3C), 27.5 (3C), 24.1, 21.9, 21.8, 21.1, 16.9, 13.5
HRMS (ESI) *m/z* 481.3348, calcd for $C_{25}H_{50}NaO_5Si$ $[M+Na]^+$ 481.3325.

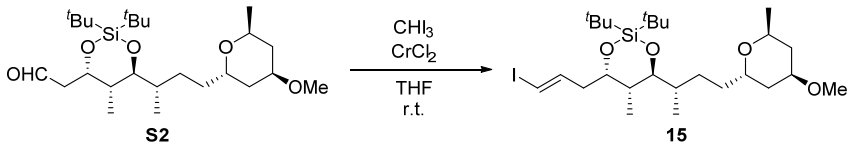
Aldehyde **S2**



To a stirred solution of alcohol **32** (198 mg, 0.434 mmol) in CH_2Cl_2 (2.2 mL) were added pyridine (120 mL, 1.49 mmol) and Dess–Martin periodinane (200 mg, 0.472 mmol) at 0 °C. After stirring for 20 min at room temperature, the mixture was diluted with saturated aqueous $Na_2S_2O_3$ (5.0 mL), saturated aqueous $NaHCO_3$ (5.0 mL), and H_2O (5.0 mL). The resultant mixture was extracted with Et_2O (3 × 5.0 mL). The extracts were combined, washed with brine (1.0 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (24.7 g, hexane–EtOAc 20 : 1 → 19 : 1 → 5 : 1) to afford aldehyde **S2** (167 mg, 85%) as a colorless oil.

R_f = 0.53 (hexane : EtOAc = 2 : 1)
$[\alpha]_D^{24}$ –71.9 (*c* 1.00, $CHCl_3$)
IR ($CHCl_3$) 2963, 2934, 2860, 1726, 1473, 1384, 1128, 1021, 825, 669 cm^{-1}
^1H NMR (600 MHz, $CDCl_3$) δ 9.84 (dd, *J* = 4.0, 1.4 Hz, 1H), 4.69 (ddd, *J* = 11.2, 5.6, 3.2 Hz, 1H), 4.03–3.99 (m, 1H), 3.73 (dd, *J* = 9.7, 1.9 Hz, 1H), 3.69 (ddq, *J* = 10.1, 2.0, 6.3 Hz, 1H), 3.54 (dddd, *J* = 10.1, 10.1, 4.2, 4.2 Hz, 1H), 3.34 (s, 3H), 2.65 (ddd, *J* = 15.2, 11.2, 4.0 Hz, 1H), 2.39 (ddd, *J* = 15.2, 3.2, 1.4 Hz, 1H), 2.36 (ddq, *J* = 9.7, 5.6, 7.1 Hz, 1H), 1.98 (dddd, *J* = 12.5, 4.2, 2.0, 2.0 Hz, 1H), 1.90 (m, 1H), 1.81 (dddd, *J* = 12.9, 4.2, 2.0, 2.0 Hz, 1H), 1.67–1.58 (m, 2H), 1.43–1.32 (m, 2H), 1.23 (m, 1H), 1.20 (d, *J* = 6.3 Hz, 3H), 1.18 (ddd, *J* = 12.5, 10.1, 10.1 Hz, 1H), 1.01 (d, *J* = 6.8 Hz, 3H), 1.00 (s, 9H), 0.97 (s, 9H), 0.74 (d, *J* = 7.1 Hz, 3H)
^{13}C NMR (151 MHz, $CDCl_3$) δ 202.6, 77.2, 73.5, 73.1, 71.4, 64.8, 55.4, 45.8, 38.8, 38.3, 35.2, 34.4, 29.1, 27.6 (3C), 27.3 (3C), 23.7, 21.9, 21.8, 20.9, 16.9, 13.2
HRMS (ESI) *m/z* 479.3172, calcd for $C_{25}H_{48}NaO_5Si$ $[M+Na]^+$ 479.3169.

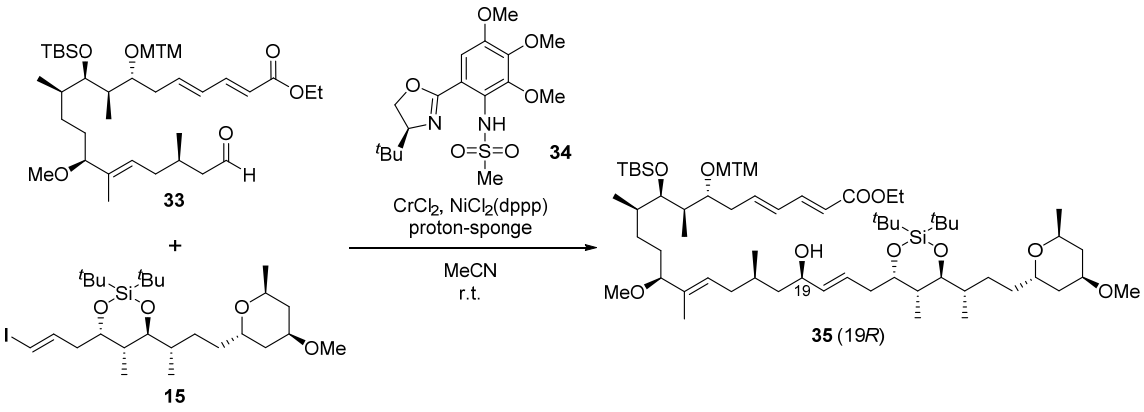
Iodoolefin **15**



THF was degassed by freeze-thawing. To a stirred solution of aldehyde **S2** (167 mg, 0.366 mmol) in THF (6.8 mL) were added $CrCl_2$ (460 mg, 3.74 mmol) and CHI_3 (288 mg, 0.731 mmol) at room temperature in a glove box. After stirring for 2 h at room temperature in a glove box, the resultant mixture was diluted with saturated aqueous $NaHCO_3$ (5.0 mL) and extracted with Et_2O (3 × 5.0 mL). The extracts were combined, washed with brine (1.0 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by PTLC (hexane–EtOAc 2 : 1) to afford iodoolefin **15** (179 mg, 73%) as a white solid.

R_f = 0.18 (hexane : EtOAc = 2 : 1)
m.p. 104–106 °C
$[\alpha]_D^{24}$ –97.5 (*c* 1.00, $CHCl_3$)
IR ($CHCl_3$) 2934, 2859, 2736, 1474, 1384, 1125, 1065, 825, 669 cm^{-1}
^1H NMR (600 MHz, $CDCl_3$) δ 6.70 (ddd, *J* = 14.5, 7.6, 6.5 Hz, 1H), 6.08 (ddd, *J* = 14.5, 1.2, 1.2 Hz, 1H), 4.05 (ddd, *J* = 11.0, 5.3, 2.8 Hz, 1H), 4.01 (m, 1H), 3.72 (dd, *J* = 9.6, 2.1 Hz, 1H), 3.68 (ddq, *J* = 10.2, 2.1, 6.3 Hz, 1H), 3.54 (dddd, *J* = 10.2, 10.2, 4.2, 4.2 Hz, 1H), 3.34 (s, 3H), 2.31 (dddd, *J* = 14.5, 11.0, 6.5, 1.2 Hz, 1H), 2.26 (ddq, *J* = 9.6, 5.3, 7.1 Hz, 1H), 2.17 (dddd, *J* = 14.5, 7.6, 2.8, 1.2 Hz, 1H), 1.98 (dddd, *J* = 12.5, 4.2, 2.1, 2.1 Hz, 1H), 1.89 (m, 1H), 1.81 (dddd, *J* = 12.8, 4.2, 2.1, 2.1 Hz, 1H), 1.62–1.57 (m, 2H), 1.42–1.30 (m, 2H), 1.24 (m, 1H), 1.19 (d, *J* = 6.3 Hz, 3H), 1.17 (ddd, *J* = 12.5, 10.2, 10.2 Hz, 1H), 1.00 (s, 9H), 0.99 (d, *J* = 6.5 Hz, 3H), 0.99 (s, 9H), 0.75 (d, *J* = 7.1 Hz, 3H)
^{13}C NMR (151 MHz, $CDCl_3$) δ 144.6, 77.5, 76.0, 75.8, 73.5, 71.5, 64.7, 55.4, 38.9, 38.7, 38.0, 35.1, 34.6, 29.1, 27.7 (3C), 27.4 (3C), 23.9, 21.9, 21.8, 21.0, 16.9, 13.3
HRMS (ESI) *m/z* 603.2345, calcd for $C_{26}H_{49}INaO_4Si$ $[M+Na]^+$ 603.2342.

Allylic alcohol **35**



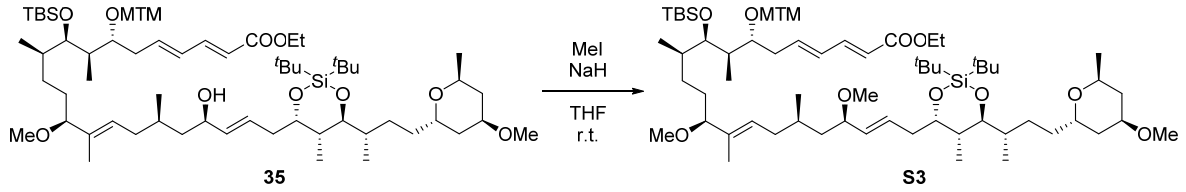
(preparation of a MeCN solution of $CrCl_2$–ligand complex)

MeCN was degassed by freeze-thawing. To a stirred solution of ligand (63.3 mg, 0.164 mmol) in MeCN (0.8 mL) were added $CrCl_2$ (17.2 mg, 0.140 mmol) and proton-sponge® (29.9 mg, 0.140 mmol) at room temperature in a glove box. The mixture was stirred at room temperature for 2 h in a glove box to give a MeCN solution of $CrCl_2$–ligand complex.

The above–mentioned solution of $CrCl_2$–ligand complex was added to a mixture of the aldehyde **33** (14.7 mg, 0.0234 mmol), the iodoorefin **15** (23.8 mg, 0.0404 mmol), and $NiCl_2$(dppp) (2.5 mg, 4.7 μmol) at room temperature in a glove box. After stirring at room temperature for 5 h in a glove box, the mixture was filtered through a pad of florisil with EtOAc, and the filtrate was concentrated. The crude product was purified by PTLC (hexane–Et_2O 1 : 4) to afford desired allylic alcohol **35** (13.3 mg, 53%) as a colorless oil.

R_f = 0.15 (hexane : Et_2O = 1 : 1)
$[\alpha]_D^{24}$ –41.5 (*c* 0.43, $CHCl_3$)
IR ($CHCl_3$) 2958, 2927, 1732, 1494, 1375, 1250, 1045 cm^{-1}
^1H NHR (600 MHz, $CDCl_3$) δ 7.27 (dd, *J* = 15.3, 10.7 Hz, 1H), 6.25 (dd, *J* = 15.2, 10.7 Hz, 1H), 6.17 (ddd, *J* = 15.2, 6.8, 6.0 Hz, 1H), 5.84 (ddd, *J* = 15.4, 7.0, 7.0 Hz, 1H), 5.80 (d, *J* = 15.3 Hz, 1H), 5.51 (dd, *J* = 15.4, 7.4 Hz, 1H), 5.34 (ddd, *J* = 6.5, 6.5, 1.1 Hz, 1H), 4.61 (d, *J* = 11.6 Hz, 1H), 4.59 (d, *J* = 11.6 Hz, 1H), 4.23–4.16 (m, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 4.03–3.99 (m, 2H), 3.75 (dd, *J* = 9.5, 2.0 Hz, 1H), 3.69 (ddq, *J* = 10.2, 2.6, 6.2 Hz, 1H), 3.62 (dd, *J* = 3.5, 3.5 Hz, 1H), 3.56 (ddd, *J* = 6.7, 6.7, 3.6 Hz, 1H), 3.54 (dddd, *J* = 10.2, 10.2, 4.1, 4.1 Hz, 1H), 3.38 (t, *J* = 6.8 Hz, 1H), 3.34 (s, 3H), 3.15 (s, 3H), 2.45 (ddd, *J* = 15.2, 6.0, 3.6 Hz, 1H), 2.32–2.24 (m, 3H), 2.25–2.14 (m, 2H), 2.14 (s, 3H), 1.99 (dddd, *J* = 12.5, 4.1, 2.6, 2.0 Hz, 1H), 1.92–1.82 (m, 3H), 1.82 (dddd, *J* = 12.8, 4.1, 2.0, 1.9 Hz, 1H), 1.69–1.64 (m, 1H), 1.62–1.58 (m, 3H), 1.56–1.51 (m, 3H) , 1.51–1.44 (m, 2H), 1.50 (d, *J* = 1.1 Hz, 3H), 1.42–1.30 (m, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.26–1.21 (m, 1H), 1.20 (d, *J* = 6.2 Hz, 3H), 1.17 (ddd, *J* = 12.5, 10.2, 10.2 Hz, 1H), 1.00 (s, 9H), 1.00 (d, *J* = 7.1 Hz, 3H), 0.99 (s, 9H), 0.90 (d, *J* = 7.1 Hz, 3H), 0.89 (s, 9H), 0.87 (d, *J* = 7.0 Hz, 3H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.76 (d, *J* = 7.0 Hz, 3H), 0.05 (s, 3H), 0.05 (s, 3H) A signal due to a proton (OH) was not observed.
^{13}C NMR (151 MHz, $CDCl_3$) δ 167.4, 144.8, 140.7, 135.3, 135.0, 130.6, 130.2, 127.8, 119.9, 88.3, 79.2, 77.5, 75.9, 75.9, 73.5, 73.4, 71.7, 71.6, 64.7, 60.4, 55.8, 55.4, 44.4, 39.9, 38.9, 37.6, 35.1, 34.9, 34.7, 34.2, 33.7, 32.0, 30.2, 29.9, 29.2, 28.9, 27.7 (3C), 27.5 (3C), 26.3 (3C), 24.0, 21.9, 21.8, 21.0, 20.2, 18.6, 16.9, 15.7, 14.5, 14.4, 13.5, 11.2, 10.6, –3.5, –3.7
HRMS (ESI) *m/z* 1103.7421, calcd for $C_{60}H_{112}NaO_{10}SSi_2$ $[M+Na]^+$ 1103.7412.

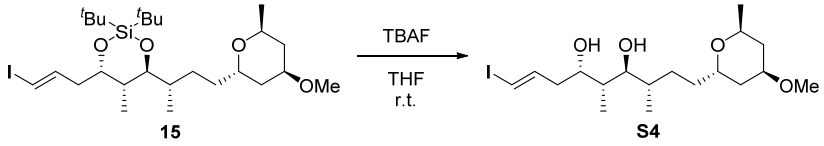
Methyl ether **S3**



To stirred solution of coupling product **35** (3.8 mg, 3.5 μmol) in THF (1.0 mL) were added NaH (60%, 2.2 mg, 5.5 μmol) and MeI (3.4 μL, 5.5 μmol). After stirred for 7 h at room temperature, the reaction mixture was deluted with saturated aqueous NH_4Cl (1.0 mL) and extracted with Et_2O (3 × 1 mL). The extracts were combined, washed with brine (5.0 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (0.8 g, pentane–Et_2O 4 : 1) to afford methyl ether **S3** (1.7 mg, 45%) as a colorless oil.

R_f = 0.52 (hexane : EtOAc = 3 : 1)
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27 (dd, *J* = 15.4, 10.8 Hz, 1H), 6.25 (dd, *J* = 14.9, 10.8 Hz, 1H), 6.17 (ddd, *J* = 14.9, 6.4, 6.4 Hz, 1H), 5.80 (d, *J* = 15.4 Hz, 1H), 5.80 (ddd, *J* = 15.4, 7.4, 7.4 Hz, 1H), 5.33 (dd, *J* = 6.5, 6.5 Hz, 1H), 5.28 (dd, *J* = 15.4, 8.4 Hz, 1H), 4.61 (d, *J* = 11.5 Hz, 1H), 4.58 (d, *J* = 11.5 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 4.05 (ddd, *J* = 10.4, 5.0, 3.2 Hz, 1H), 4.03–3.98 (m, 1H), 3.75 (dd, *J* = 9.4, 2.0 Hz, 1H), 3.69 (ddq, *J* = 10.3, 2.5, 6.2 Hz, 1H), 3.61 (dd, *J* = 3.6, 3.6 Hz, 1H), 3.61–3.52 (m, 2H), 3.54 (dddd, *J* = 10.3, 10.3, 4.3, 4.3 Hz, 1H), 3.37 (t, *J* = 6.8 Hz, 1H), 3.34 (s, 3H), 3.25 (s, 3H), 3.15 (s, 3H), 2.46–2.42 (m, 1H), 2.34–2.20 (m, 4H), 2.14 (s, 3H), 2.14–2.10 (m, 1H), 1.99 (dddd, *J* = 12.5, 4.3, 2.5, 2.3 Hz, 1H), 1.92–1.83 (m, 3H), 1.82 (dddd, *J* = 13.0, 4.3, 2.3, 2.3 Hz, 1H), 1.68–1.57 (m, 5H), 1.52–1.33 (m, 7H), 1.50 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.27–1.22 (m, 1H), 1.20 (d, *J* = 6.2 Hz, 3H), 1.17 (ddd, *J* = 12.5, 10.3, 10.3 Hz, 1H), 1.00 (s, 9H), 0.99 (s, 9H), 0.98 (d, *J* = 7.0 Hz, 3H), 0.89 (s, 9H), 0.89 (d, *J* = 7.0 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.77 (d, *J* = 7.1 Hz, 3H), 0.04 (s, 3H), 0.04 (s, 3H)
HRMS (ESI) *m/z* 1117.7549, calcd for $C_{61}H_{114}NaO_{10}SSi_2$ $[M+Na]^+$ 1117.7569.

Diol **S4**

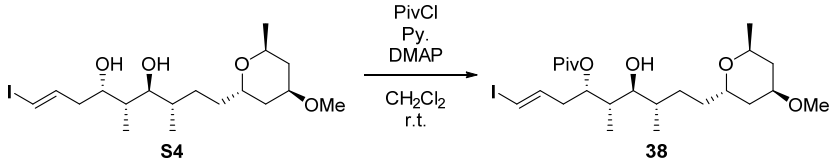


15 **S4**

To a stirred solution of iodoolefin **15** (166 mg, 0.286 mmol) in THF (1.7 mL) was added TBAF (1.0 M solution in THF, 170 mL, 1.70 mmol) at room temperature. After stirring for 1.5 d at room temperature, the reaction mixture was diluted with water and extracted with EtOAc (4 × 3.0 mL). The extracts were combined, washed with brine (5.0 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (5.0 g, hexane–EtOAc 4 : 1 → 3 : 1 → 1 : 1) to afford diol **S4** (125 mg, 99%) as a colorless oil.

R_f = 0.22 (hexane : EtOAc = 1 : 1)
$[\alpha]_D^{22}$ –14.9 (*c* 1.08, $CHCl_3$)
IR ($CHCl_3$) 3482, 3006, 2972, 2944, 1456, 1382, 1153, 1101, 1081, 950, 664 cm^{-1}
^1H NMR (600 MHz, $CDCl_3$) δ 6.55 (ddd, *J* = 14.4, 7.4, 7.0 Hz, 1H), 6.13 (d, *J* = 14.4 Hz, 1H), 4.05–3.96 (m, 2H), 3.72 (dddd, *J* = 12.5, 9.3, 6.2, 3.0 Hz, 1H), 3.53 (ddq, *J* = 8.8, 3.9, 6.3 Hz, 1H), 3.33 (s, 3H), 3.35 (m, 1H), 2.97 (br. s, 1H), 2.31 (ddd, *J* = 14.2, 7.5, 7.4 Hz, 1H), 2.13 (ddd, *J* = 14.2, 7.0, 6.7 Hz, 1H), 1.96 (m, 1H), 1.89–1.74 (m, 3H), 1.70 (m, 1H), 1.66–1.56 (m, 2H), 1.21 (d, *J* = 6.3 Hz, 3H), 1.34–1.18 (m, 2H), 0.97 (d, *J* = 7.1 Hz, 3H), 0.87 (d, *J* = 6.7 Hz, 3H), 0.98–0.85 (m, 1H) A signal due to a proton (OH) was not observed.
^{13}C NMR (151 MHz, $CDCl_3$) δ 143.2, 80.4, 76.9, 73.2, 71.3, 70.6, 65.0, 55.3, 40.9, 38.1, 37.3, 35.3, 34.9, 29.0, 27.7, 21.6, 16.5, 11.4
HRMS (ESI) *m/z* 463.1326, calcd for $C_{18}H_{33}NaIO_4$ $[M+Na]^+$ 463.1321.

Pivalate **38**

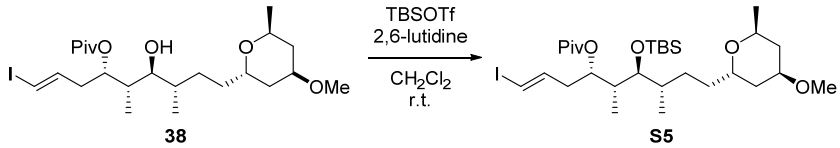


S4 **38**

To a stirred solution of diol **S3** (22.7 mg, 51.5 mmol) in CH_2Cl_2 (0.50 mL) and pyridine (0.25 mL) were added PivCl (12.7 mL, 103 mmol) and DMAP (3.1 mg, 25.8 mmol) at room temperature. After stirring for 5 h at room temperature, the reaction mixture was diluted with water and extracted with CH_2Cl_2 (3 × 2.0 mL). The extracts were combined, washed with brine (3.0 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (0.7 g, hexane–EtOAc 6 : 1 → 4 : 1) to afford pivalate **38** (27.0 mg, quant.) as a colorless oil.

R_f = 0.78 (hexane : EtOAc = 3 : 1)
$[\alpha]_D^{25}$ –8.5 (*c* 0.95, $CHCl_3$)
IR ($CHCl_3$) 3480, 2974, 2943, 1704, 1479, 1384, 1219, 1168, 1101, 1079, 940, 681 cm^{-1}
^1H NMR (600 MHz, $CDCl_3$) δ 6.41 (ddd, *J* = 14.4, 7.7, 6.4 Hz, 1H), 6.12 (d, *J* = 14.4 Hz, 1H), 5.30 (ddd, *J* = 7.4, 4.2, 1.5 Hz, 1H), 3.99 (m, 1H), 3.68 (dddd, *J* = 12.8, 9.4, 6.3, 3.0 Hz, 1H), 3.53 (ddq, *J* = 9.8, 4.7, 6.2 Hz, 1H), 3.33 (s, 3H), 3.04 (br. s, 1H), 2.95 (dd, *J* = 9.5, 2.3 Hz, 1H), 2.48 (ddd, *J* = 15.2, 7.7, 7.4 Hz, 1H), 2.21 (dddd, *J* = 15.2, 6.4, 4.4, 1.5 Hz, 1H), 1.97 (m, 1H), 1.88 (m, 1H), 1.80 (dddd, *J* = 12.8, 4.0, 2.0, 1.8 Hz, 1H), 1.75 (dddd, *J* = 16.2, 7.1, 6.7, 1.8 Hz, 1H), 1.66 (m, 1H), 1.59 (ddd, *J* = 12.8, 10.4, 5.4 Hz, 1H), 1.39 (ddd, *J* = 12.8, 6.7, 3.1 Hz, 1H), 1.22 (d, *J* = 6.2 Hz, 3H), 1.20 (s, 9H), 1.32-1.13 (m, 3H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 6.9 Hz, 3H)
^{13}C NMR (151 MHz, $CDCl_3$) δ 179.6, 141.7, 77.6, 76.5, 73.3, 71.6, 71.4, 64.6, 55.3, 40.0, 39.4, 39.1, 38.6, 34.9, 33.3, 29.2, 27.3 (3C), 24.2, 21.8, 17.7, 9.7
HRMS (ESI) *m/z* 547.1868, calcd for $C_{23}H_{41}NaIO_5$ $[M+Na]^+$ 547.1896.

TBS ether **S5**

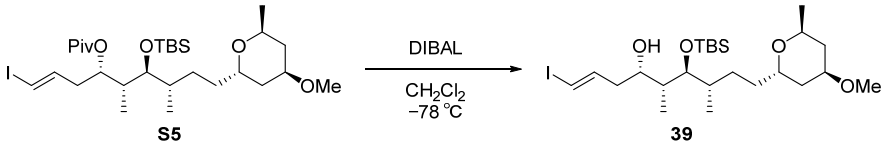


38 **S5**

To a stirred solution of pivalate **38** (145 mg, 0.276 mmol) in CH_2Cl_2 (2.5 mL) were added 2,6-lutidine (130 mL, 1.11 mmol) and TBSOTf (0.13 mL, 0.55 mmol) at room temperature. After stirring for 2 h at room temperature, the reaction mixture was diluted with water and extracted with CH_2Cl_2 (3 × 3 mL). The extracts were combined, washed with brine (5.0 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (4.4 g, hexane–EtOAc 12 : 1 → 9 : 1) to afford TBS ether **S5** (172 mg, 97%) as a colorless oil.

R_f = 0.67 (hexane : EtOAc = 3 : 1)
$[\alpha]_D^{29}$ –20.7 (*c* 2.11, $CHCl_3$)
IR ($CHCl_3$) 2954, 2932, 1717, 1461, 1382, 1256, 1166, 1101, 1081, 945, 680 cm^{-1}
^1H NMR (600 MHz, $CDCl_3$) δ 6.41 (ddd, *J* = 14.5, 7.4, 7.4 Hz, 1H), 6.06 (ddd, *J* = 14.5, 1.0, 1.0 Hz, 1H), 5.02 (ddd, *J* = 6.4, 6.4, 4.2 Hz, 1H), 3.96 (dddd, *J* = 9.6, 4.8, 4.8, 2.6 Hz, 1H), 3.66 (dddd, *J* =13.0, 9.6, 6.4, 3.0 Hz, 1H), 3.51 (ddq, *J* = 9.8, 4.7, 6.1 Hz, 1H), 3.39 (dd, *J* = 6.7, 2.4 Hz, 1H), 3.33 (s, 3H), 2.33 (ddd, *J* = 7.4, 6.4, 1.0 Hz, 2H), 1.97 (m, 1H), 1.86–1.76 (m, 3H), 1.65–1.53 (m, 2H), 1.42 (m, 1H), 1.27–1.13 (m, 3H), 1.19 (d, *J* = 6.1 Hz, 3H), 1.17 (s, 9H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.90 (s, 9H), 0.90 (d, *J* = 6.7 Hz, 3H), 0.06 (s, 3H), 0.04 (s, 3H)
^{13}C NMR (151 MHz, $CDCl_3$) δ 177.7, 141.8, 78.3, 73.3, 72.3, 71.9, 64.6, 55.2, 41.1, 39.8, 39.0, 38.7, 36.2, 34.8, 29.8, 27.5, 27.3, 27.2 (3C), 26.2 (3C), 25.9, 21.7, 18.4, 17.3, 11.4, –3.9, –4.1
HRMS (ESI) *m/z* 661.2742, calcd for $C_{29}H_{55}NaIO_5Si$ $[M+Na]^+$ 661.2761.

Alcohol **39**

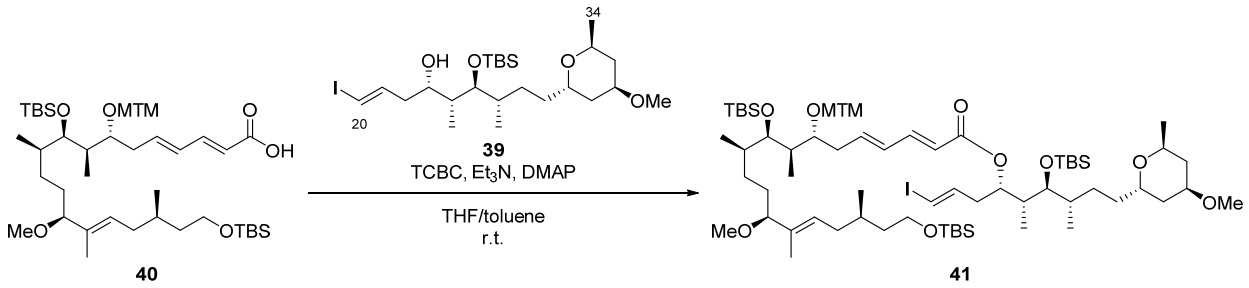


S5 **39**

To a stirred solution of TBS ether **S5** (35.0 mg, 54.8 mmol) in CH_2Cl_2 (1.0 mL) was added solution of DIBAL (1.06 M solution in CH_2Cl_2, 160 mL, 170 mmol) at –78 °C. After stirring for 2 h at –78 °C, the reaction mixture was diluted with saturated aqueous Na/K tartrate (10 mL) and stirred at room temperature for 2 h. The resultant mixture was extracted with CH_2Cl_2 (3 × 2 mL). The extracts were combined, washed with brine (3 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (1.1 g, hexane–EtOAc 9 : 1 → 7 : 1 → 5 : 1) to afford alcohol **39** (25.6 mg, 84%) as a colorless oil.

R_f = 0.51 (hexane : EtOAc = 3 : 1)
$[\alpha]_D^{29}$ –25.5 (*c* 2.13, $CHCl_3$)
IR ($CHCl_3$) 3446, 3005, 2932, 1646, 1463, 1382, 1257, 1154, 1093, 1018, 836, 670 cm^{-1}
^1H NMR (500 MHz, $CDCl_3$) δ 6.52 (ddd, *J* = 14.5, 7.9, 6.8 Hz, 1H), 6.10 (ddd, *J* = 14.5, 1.3, 1.3 Hz, 1H), 4.12 (dd, *J* = 6.9, 6.8 Hz, 1H), 3.96 (m, 1H), 3.70 (dddd, *J* = 12.8, 9.5, 6.4, 3.0 Hz, 1H), 3.57–3.46 (m, 3H), 3.33 (s, 3H), 2.28 (dddd, *J* = 14.2, 7.9, 6.8, 1.3 Hz, 1H), 2.05 (ddd, *J* = 14.2, 6.9, 6.8 Hz, 1H), 1.97 (ddq, *J* = 12.4, 8.5, 2.1 Hz, 1H), 1.87–1.76 (m, 2H), 1.76–1.65 (m, 2H), 1.60 (ddd, *J* = 12.9, 10.0, 5.4 Hz, 1H), 1.52 (m, 1H), 1.29–1.16 (m, 2H), 1.21 (d, *J* = 7.5 Hz, 3H), 1.08 (ddd, *J* = 10.7, 4.1, 2.4 Hz, 1H), 0.98 (d, *J* = 8.5 Hz, 3H), 0.92 (d, *J* = 6.3 Hz, 3H), 0.91 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H)
^{13}C NMR (125 MHz, $CDCl_3$) δ 143.2, 83.1, 76.5, 73.2, 71.6, 70.0, 64.9, 55.3, 41.3, 38.3, 38.1, 36.8, 34.8, 30.2, 29.7, 26.1 (3C), 21.7, 18.2, 15.7, 12.3, –3.9, –4.0
HRMS (ESI) *m/z* 577.2175, calcd for $C_{24}H_{47}NaIO_4Si$ $[M+Na]^+$ 577.2186.

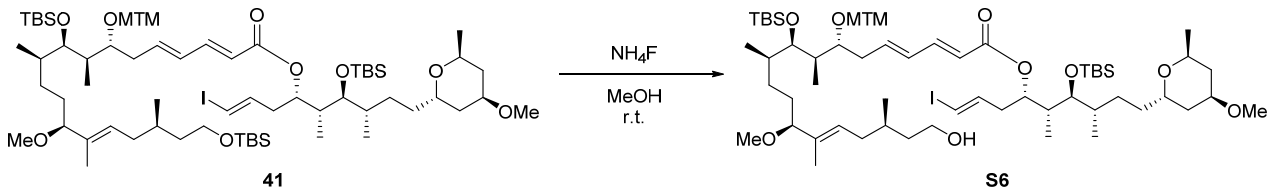
Ester **41**



To a stirred solution of carboxylic acid **40** (86.0 mg, 0.120 mmol) in THF (5.0 mL) were added Et_3N (100 mL, 0.720 mmol) and TCBC (94.0 mL, 0.601 mmol) at 0 °C. After stirring at 0 °C for 5 min, the mixture was allowed to warm to room temperature and stirred for 2 h. Then, a solution of alcohol **39** (92.5 mg, 0.170 mmol) and DMAP (147 mg, 1.20 mmol) in toluene (5.0 mL) was added. The resulting mixture was stirred for 1 h, poured into saturated aqueous $NaHCO_3$ (10 mL), and extracted with EtOAc (3 × 10 mL). The combined extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatography on silica gel (5.4 g, hexane–EtOAc 15 : 1) to afford ester **41** (124.9 mg, 83%) as a pale yellow oil.

R_f = 0.64 (hexane : EtOAc = 3 : 1)
$[\alpha]_D^{24}$ –18.8 (*c* 1.38, $CHCl_3$)
IR ($CHCl_3$) 3000, 2955, 2929, 2857, 1704, 1640, 1463, 1382, 1363, 1256, 1177, 1089, 1038, 1004, 940, 908, 836 cm^{-1}
^1H NMR (500 MHz, $CDCl_3$) δ 7.23 (dd, *J* = 15.4, 10.4 Hz, 1H), 6.46 (ddd, *J* = 14.4, 7.3, 7.2 Hz, 1H), 6.24 (dd, *J* = 14.8, 10.3 Hz, 1H), 6.19 (ddd, *J* = 14.8, 7.1, 7.1 Hz, 1H), 6.09 (d, *J* = 14.4 Hz, 1H), 5.78 (d, *J* = 15.4 Hz, 1H), 5.34 (ddd, *J* = 7.2, 7.2, 1.0 Hz, 1H), 5.11 (dd, *J* = 10.1, 6.3 Hz, 1H), 4.61 (d, *J* = 11.6 Hz, 1H), 4.59 (d, *J* = 11.6 Hz, 1H), 3.96 (m, 1H), 3.75–3.46 (m, 6H), 3.44 (dd, *J* = 6.3, 3.1 Hz, 1H), 3.38 (dd, *J* = 6.9, 6.9 Hz, 1H), 3.33 (s, 3H), 3.15 (s, 3H), 2.49–2.23 (m, 4H), 2.14 (s, 3H), 2.09 (dd, *J* = 14.4, 7.2 Hz, 1H), 1.98 (m, 1H), 1.91–1.76 (m, 4H), 1.72–1.39 (m, 11H), 1.49 (s, 3H), 1.30–1.15 (m, 3H), 1.20 (d, *J* = 6.2 Hz, 3H), 0.96–0.81 (m, 4H), 0.94 (d, *J* = 7.2 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.91 (d, *J* = 5.8 Hz, 3H), 0.889 (s, 9H), 0.888 (s, 9H), 0.885 (s, 9H), 0.84 (d, *J* = 7.1 Hz, 3H), 0.05 (s, 3H), 0.044 (s, 3H), 0.039 (s, 12H)
^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 144.7, 141.7, 140.8, 134.9, 130.4, 128.0, 119.8, 88.2, 79.0, 78.5, 77.3, 75.8, 73.3, 73.2, 72.5, 72.0, 64.6, 61.4, 55.6, 55.3, 40.2, 39.6, 39.52, 39.50, 38.7, 37.5, 36.4, 35.0, 34.8, 33.5, 31.7, 30.2, 29.8, 29.7, 28.6, 27.5, 26.2 (3C), 26.1 (3C), 26.0 (3C), 21.8, 19.7, 18.4, 18.3, 17.2, 15.6, 14.4, 11.5, 11.0, 10.4, –3.7, –3.8, –3.9 (2C), –5.3 (2C)
HRMS (ESI) *m/z* 1273.6816, calcd for $C_{62}H_{119}NaIO_9SSi_3$ $[M+Na]^+$ 1273.6815.

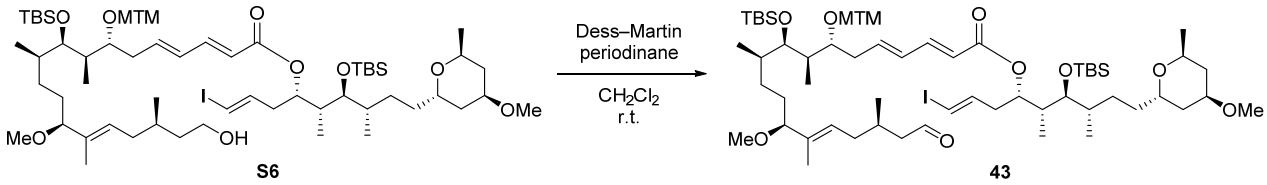
Alcohol **S6**



To a stirred solution of ester **41** (124 mg, 99.8 μmol) in MeOH (6.0 mL) was added NH_4F (370 mg, 9.98 mmol) at room temperature. The mixture was stirred at room temperature for 3.5 d, poured into a mixture of saturated aqueous NH_4Cl (8 mL) and H_2O (8 mL), and extracted with EtOAc (3 × 10 mL). The combined extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatography on silica gel (3.7 g, hexane–EtOAc 4 : 1 → 3 : 1) to afford alcohol **S6** (106 mg, 93%) as a colorless oil.

R_f = 0.30 (hexane : EtOAc = 3 : 1)
$[\alpha]_D^{26}$ –38.3 (*c* 1.17, $CHCl_3$)
IR ($CHCl_3$) 3477, 3004, 2955, 2930, 2857, 1702, 1644, 1616, 1463, 1382, 1362, 1301, 1256, 1176, 1089, 1042, 1003, 955, 941, 854, 837 cm^{-1}
^1H NMR (600 MHz, $CDCl_3$) δ 7.23 (dd, *J* = 15.4, 10.8 Hz, 1H), 6.45 (ddd, *J* = 14.4, 7.2, 7.1 Hz, 1H), 6.24 (dd, *J* = 14.9, 10.8 Hz, 1H), 6.18 (ddd, *J* = 14.9, 7.2, 7.2 Hz, 1H), 6.10 (d, *J* = 14.4 Hz, 1H), 5.78 (d, *J* = 15.4 Hz, 1H), 5.34 (dd, *J* = 7.1, 6.9 Hz, 1H), 5.11 (dd, *J* = 10.1, 6.2 Hz, 1H), 4.61 (d, *J* = 11.4 Hz, 1H), 4.59 (d, *J* = 11.4 Hz, 1H), 3.96 (m, 1H), 3.74–3.63 (m, 3H), 3.61 (dd, *J* = 3.4, 3.4 Hz, 1H), 3.57 (ddd, *J* = 6.4, 6.4, 3.5 Hz, 1H), 3.51 (ddq, *J* = 9.9, 4.8, 6.2 Hz, 1H), 3.43 (dd, *J* = 6.2, 3.0 Hz, 1H), 3.38 (dd, *J* = 6.9, 6.9 Hz, 1H), 3.33 (s, 3H), 3.15 (s, 3H), 2.49–2.26 (m, 4H), 2.14 (s, 3H), 2.10 (ddd, *J* = 14.2, 7.1, 6.9 Hz, 1H), 1.98 (m, 1H), 1.91 (ddd, *J* = 14.2, 7.2, 7.1 Hz, 1H), 1.87–1.76 (m, 4H), 1.74–1.34 (m, 11H), 1.50 (s, 3H), 1.32–1.13 (m, 3H), 1.20 (d, *J* = 6.2 Hz, 3H), 1.00–0.86 (m, 1H), 0.94 (d, *J* = 7.1 Hz, 3H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.89 (s, 18H), 0.84 (d, *J* = 6.9 Hz, 3H), 0.05 (s, 6H), 0.043 (s, 3H), 0.038 (s, 3H)
^{13}C NMR (151 MHz, $CDCl_3$) δ 166.7, 144.8, 141.7, 140.7, 135.1, 130.4, 127.6, 119.8, 88.1, 79.0, 78.5, 77.4, 75.8, 73.30, 73.27, 72.6, 72.0, 64.6, 61.1, 55.7, 55.3, 40.2, 39.7, 39.58, 39.55, 38.7, 37.5, 36.4, 34.9, 34.8, 33.5, 31.7, 30.2, 29.9, 28.6, 27.6, 26.2 (3C), 26.1 (3C), 21.8, 19.7, 18.44, 18.42, 17.2, 15.5, 14.4, 11.5, 11.0, 10.4, –3.7, –3.9, –3.96, –3.98
HRMS (ESI) *m/z* 1159.5940, calcd for $C_{56}H_{105}NaIO_9SSi_2$ $[M+Na]^+$ 1159.5960.

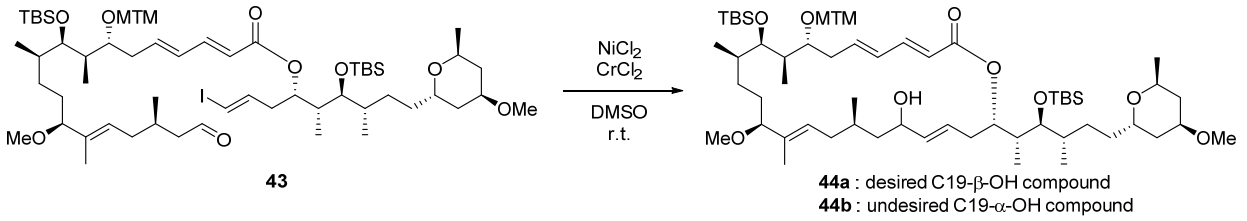
Aldehyde **43**



To a stirred solution of alcohol **S6** (12.1 mg, 10.7 µmol) in CH_2Cl_2 (2.0 mL) was added Dess–Martin periodinane (6.7 mg, 15.8 µmol) at room temperature. The mixture was stirred at room temperature for 1 h, poured into a mixture of saturated aqueous $Na_2S_2O_3$ (2.0 mL), saturated aqueous $NaHCO_3$ (2.0 mL), and H_2O (2.0 mL), and extracted with CH_2Cl_2 (3 × 5 mL). The combined extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatography on silica gel (0.24 g, hexane–EtOAc 7 : 1) to afford aldehyde **43** (11.2 mg, 93%) as a colorless oil.

R_f = 0.64 (hexane : EtOAc = 3 : 1)
$[\alpha]_D^{23}$ –22.3 (*c* 1.27, $CHCl_3$)
IR ($CHCl_3$) 3004, 2955, 2930, 2857, 1718, 1704, 1644, 1463, 1382, 1362, 1301, 1255, 1176, 1136, 1090, 1039, 1003, 954, 940, 854, 837 cm^{-1}
^1H NMR (600 MHz, $CDCl_3$) δ 9.76 (br. t, 1H), 7.23 (dd, *J* = 15.4, 10.7 Hz, 1H), 6.46 (ddd, *J* = 14.3, 7.3, 7.3 Hz, 1H), 6.24 (dd, *J* = 14.9, 10.7 Hz, 1H), 6.18 (ddd, *J* = 14.9, 7.2, 7.2 Hz, 1H), 6.10 (d, *J* = 14.3 Hz, 1H), 5.78 (d, *J* = 15.4 Hz, 1H), 5.33 (dd, *J* = 6.8, 6.8 Hz, 1H), 5.11 (dd, *J* = 10.1, 6.1 Hz, 1H), 4.61 (d, *J* = 11.7 Hz, 1H), 4.59 (d, *J* = 11.7 Hz, 1H), 3.96 (m, 1H), 3.68 (ddd, *J* = 9.5, 6.5, 2.8 Hz, 1H), 3.61 (dd, *J* = 3.4, 3.4 Hz, 1H), 3.57 (ddd, *J* = 6.5, 6.5, 3.3 Hz, 1H), 3.52 (ddq, *J* = 9.9, 4.8, 6.2 Hz, 1H), 3.44 (dd, *J* = 6.1, 3.0 Hz, 1H), 3.38 (dd, *J* = 6.8, 6.8 Hz, 1H), 3.33 (s, 3H), 3.15 (s, 3H), 2.47–2.29 (m, 5H), 2.26 (ddd, *J* = 16.3, 7.8, 2.3 Hz, 1H), 2.13 (m, 1H), 2.14 (s, 3H), 2.02–1.94 (m, 2H), 1.89–1.77 (m, 3H), 1.67–1.37 (m, 9H), 1.50 (s, 3H), 1.26–1.13 (m, 3H), 1.20 (d, *J* = 6.2 Hz, 3H), 1.01–0.80 (m, 1H), 0.98 (d, *J* = 6.5 Hz, 3H), 0.94 (d, *J* = 7.1 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 18H), 0.87 (d, *J* = 7.3 Hz, 3H), 0.84 (d, *J* = 6.9 Hz, 3H), 0.05 (s, 6H), 0.043 (s, 3H), 0.039 (s, 3H)
^{13}C NMR (151 MHz, $CDCl_3$) δ 202.5, 166.6, 144.7, 141.7, 140.7, 136.4, 130.4, 126.3, 119.9, 88.0, 78.9, 78.5, 75.8, 73.30, 73.25, 72.5, 72.0, 64.6, 55.8, 55.3, 50.6, 40.2, 39.6 (2C), 38.7, 37.5, 36.4, 34.8, 34.7, 33.5, 31.8, 29.9, 29.7, 28.7, 28.6, 27.6, 25.2 (3C), 26.1 (3C), 21.8, 20.0, 18.44, 18.43, 17.2, 15.6, 14.4, 11.6, 11.0, 10.5, –3.7, –3.8, –3.96, –3.98
HRMS (ESI) *m/z* 1157.5798, calcd for $C_{56}H_{103}NaIO_9SSi_2$ $[M+Na]^+$ 1157.5804.

Allylic alcohol **44**



43

44a : desired C19-β-OH compound
44b : undesired C19-α-OH compound

DMSO was degassed by freeze-thawing. To a stirred solution of aldehyde **43** (71.6 mg, 63.1 μmol) in DMSO (5.0 mL) were added $CrCl_2$ (77.5 mg, 631 μmol) and $NiCl_2$ (1.6 mg, 12.6 μmol) at room temperature in a glove box. The mixture was stirred at room temperature for 6 h in a glove box, poured into H_2O (15 mL), and extracted with Et_2O (3 × 15 mL). The combined extracts were washed with brine (10 mL), dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography on silica gel (5.0 g, hexane–EtOAc 7 : 1 → 5 : 1 → 2 : 1) to afford **44a** (30.6 mg, 46%) and **44b** (22.6 mg, 35%) as colorless oils, respectively.

Desired coupling compound **44a**

R_f = 0.20 (hexane : EtOAc = 2 : 1)

$[\alpha]_D^{27}$ –8.0 (*c* 1.86, $CHCl_3$)

IR ($CHCl_3$) 3622, 3453, 3006, 2956, 2930, 2858, 1704, 1642, 1463, 1382, 1362, 1302, 1254, 1177, 1138, 1082, 1046, 1003, 970, 909, 875, 857, 837 cm^{-1}

^1H NMR (600 MHz, $CDCl_3$) δ 7.22 (dd, *J* = 15.4, 10.1 Hz, 1H), 6.24–6.26 (m, 2H), 5.82 (d, *J* = 15.3 Hz, 1H), 5.57 (ddd, *J* = 15.0, 10.5, 4.3 Hz, 1H), 5.30–5.20 (m, 2H), 5.05 (m, 1H), 4.59 (d, *J* = 11.6 Hz, 1H), 4.53 (d, *J* = 11.6 Hz, 1H), 4.09 (ddd, *J* = 9.2, 9.2, 4.7 Hz, 1H), 3.96 (m, 1H), 3.67 (dddd, *J* = 13.5, 10.2, 7.0, 3.7 Hz, 1H), 3.60 (m, 1H), 3.52 (m, 2H), 3.43 (dd, *J* = 5.0, 4.1 Hz, 1H), 3.38 (dd, *J* = 10.6, 4.4 Hz, 1H), 3.33 (s, 3H), 3.18 (s, 3H), 2.39 (ddd, *J* = 13.9, 1.9, 1.9 Hz, 1H), 2.33 (m, 1H), 2.25 (ddd, *J* = 13.9, 10.9, 10.9 Hz, 1H), 2.17 (s, 3H), 2.03–1.94 (m, 2H), 1.86–1.76 (m, 3H), 1.75–1.36 (m, 10H), 1.45 (s, 3H), 1.35–1.06 (m, 6H), 1.20 (d, *J* = 6.24 Hz, 3H), 0.98–0.77 (m, 1H), 0.96 (d, *J* = 7.1 Hz, 3H), 0.922 (d, *J* = 6.8 Hz, 3H), 0.916 (d, *J* = 6.8 Hz, 3H), 0.90 (s, 9H), 0.88 (s, 9H), 0.87 (d, *J* = 7.0 Hz, 3H), 0.81 (d, *J* = 6.1 Hz, 3H), 0.12 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H) A signal due to a proton (OH) was not observed.

^{13}C NMR (151 MHz, $CDCl_3$) δ 166.3, 144.4, 140.7, 135.1, 134.2, 130.0, 129.8, 129.5, 120.4, 87.5, 79.1, 77.5, 76.8, 73.3, 72.7, 72.2, 72.1, 64.6, 55.6 (2C), 55.3, 42.7, 38.7, 38.5, 37.5, 36.6, 36.3, 34.8, 32.9, 30.7, 29.9, 29.7, 29.6, 27.9, 26.2 (3C), 26.0 (3C), 22.7, 21.8, 21.0, 20.1, 18.5, 18.3, 17.2, 14.5, 14.2, 12.5, 12.0, 9.8, –3.8, –4.0, –4.3 (2C)

HRMS (ESI) *m/z* 1031.6837, calcd for $C_{56}H_{104}NaO_9SSi_2$ $[M+Na]^+$ 1031.6837

Undesired coupling compound **44b**

R_f = 0.49 (hexane : EtOAc = 2 : 1)

$[\alpha]_D^{27}$ –2.5 (*c* 1.89, $CHCl_3$)

IR ($CHCl_3$) 3453, 2999, 2954, 2930, 2857, 1703, 1641, 1463, 1382, 1362, 1301, 1256, 1178, 1136, 1088, 1038, 1003, 973, 909, 857, 837 cm^{-1}

^1H NMR (600 MHz, $CDCl_3$) δ7.22 (dd, *J* = 15.5, 10.7 Hz, 1H), 6.22 (dd, *J* = 15.0, 10.7 Hz, 1H), 6.14 (ddd, *J* = 15.0, 7.3, 7.3 Hz, 1H), 5.78 (d, *J* = 15.5 Hz, 1H), 5.62 (ddd, *J* = 15.2, 8.7, 4.9 Hz, 1H), 5.50 (dd, *J* = 15.2, 5.0 Hz, 1H), 5.30–5.17 (m, 2H), 4.61–4.55 (m, 2H), 4.16–4.02 (m, 1H), 3.96 (m, 1H), 3.71–3.62 (m, 2H), 3.58–3.47 (m, 2H), 3.46 (dd, *J* = 6.4, 4.8 Hz, 1H), 3.36 (dd, *J* = 9.6, 5.0 Hz, 1H), 3.33 (s, 3H), 3.15 (s, 3H), 2.52–2.23 (m, 3H), 2.17 (s,

3H), 2.15 (m, 1H), 1.97 (m, 1H), 1.87–1.74 (m, 3H), 1.48 (s, 3H), 1.72–1.36 (m, 10H), 1.19 (d, *J* = 6.2 Hz, 3H), 1.31–1.07 (m, 6H), 0.96 (d, *J* = 7.1 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.90 (s, 9H), 0.88 (s, 9H), 0.85 (d, *J* = 6.9 Hz, 3H), 0.81 (d, *J* = 6.6 Hz, 3H), 1.01–0.79 (m, 4H), 0.11 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H) A signal due to a proton (OH) was not observed.

^{13}C NMR (151 MHz, $CDCl_3$) δ 166.7, 144.7, 140.0, 135.9, 134.5, 130.3, 128.2, 125.8, 120.1, 87.9, 78.9, 73.4, 73.3 (2C), 73.1, 72.0, 69.8, 64.6, 55.5, 55.2 (2C), 44.5, 42.3, 38.7, 37.4, 36.5, 34.8, 31.6, 30.9, 29.9, 29.7, 29.5, 27.9, 26.2 (3C), 26.01, 25.96 (3C), 22.6, 21.7, 19.8, 18.4, 18.3, 17.3, 14.5, 14.4, 14.1, 12.4, 12.0, 10.1, –3.8. –4.0, –4.2 (2C)

HRMS (ESI) *m/z* 1031.6809, calcd for $C_{56}H_{104}NaO_9SSi_2$ $[M+Na]^+$ 1031.6837.

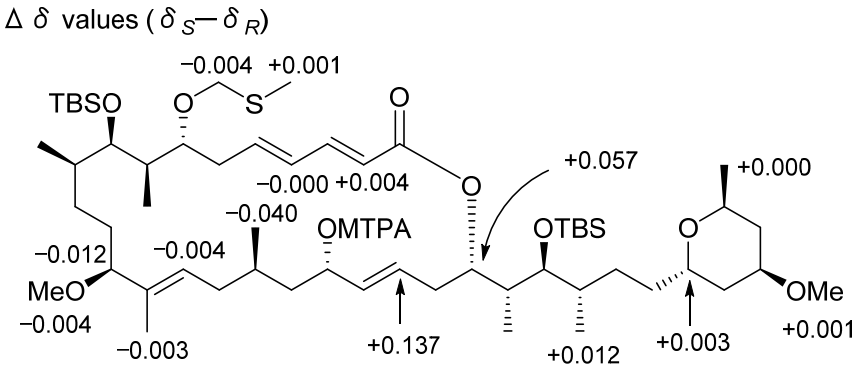
Determination of the absolute configuration at C19 of **44b**

(*S*)-MTPA ester of 44b

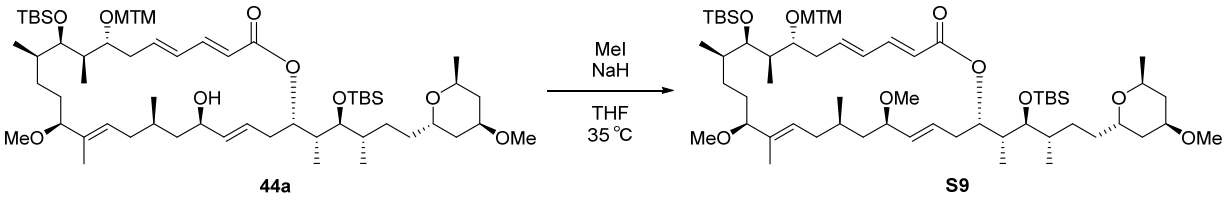
To a stirred solution of alcohol **44b** (2.5 mg, 2.5 μmol) in CH_2Cl_2 (1.0 mL) were added (*R*)-(+)-MTPACl (9.4 μL, 50 μmol) and DMAP (9.1 mg, 75 μmol). The reaction mixture was stirred at room temperature for 2 h, poured into saturated aqueous $NaHCO_3$ (2.0 mL), and extracted with CH_2Cl_2 (3 × 3 mL). The combined extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated. The crude product was purified by PTLC (hexane–EtOAc 9 : 1) to afford (*S*)-MTPA ester of **S7** (2.6 mg, 87%) as a colorless oil.

(*R*)-MTPA ester of 44b

A solution of alcohol **44b** (2.9 mg, 2.9 mmol) in CH_2Cl_2 (1.0 mL) was similarly treated with (*S*)-MTPACl and DMAP to afford (*R*)-MTPA ester of **S8** (2.8 mg, 80%) as a colorless oil. The Δδ values (δ_S–δ_R) for these MTPA esters are described below:



Methyl ether **S9**



44a **S9**

To a stirred solution of **44a** (6.7 mg, 6.64 μmol) in THF (2.0 mL) were added MeI (33.0 μL, 530 μmol) and NaH (60% in mineral oil, 13.3 mg, 332 μmol) at room temperature. The mixture was allowed to warm to 35 °C, and stirring was continued for 9 h. The reaction mixture was poured into saturated aqueous NH_4Cl (2.0 mL) and extracted with EtOAc (3 × 2 mL). The combined extracts were dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography on silica gel (0.2 g, hexane–EtOAc 9 : 1 → 6 : 1) to afford methyl ether **S9** (5.6 mg, 82%) as a colorless oil.

R_f = 0.63 (hexane : EtOAc = 2 : 1)

$[\alpha]_D^{26}$ +38.9 (*c* 1.81, $CHCl_3$)

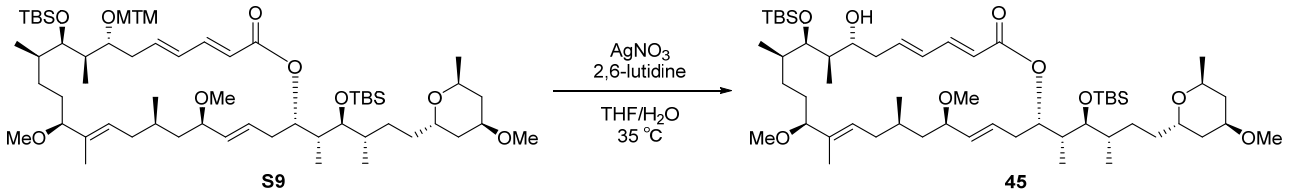
IR ($CHCl_3$) 3003, 2954, 2930, 2857, 2824, 1703, 1645, 1617, 1462, 1379, 1362, 1302, 1257, 1177, 1137, 1081, 1045, 1003, 972, 909, 858, 837 cm^{-1}

^1H NMR (600 MHz, $CDCl_3$) δ 7.22 (dd, *J* = 15.3, 10.2 Hz, 1H), 6.27–6.14 (m, 2H), 5.82 (d, *J* = 15.3 Hz, 1H), 5.55 (ddd, *J* = 15.0, 10.6, 4.2 Hz, 1H), 5.28 (ddd, *J* = 11.1, 4.8, 1.9 Hz, 1H), 5.05 (m, 2H), 4.59 (d, *J* = 11.5 Hz, 1H), 4.53 (d, *J* = 11.5 Hz, 1H), 3.96 (m, 1H), 3.68 (dddd, *J* = 12.9, 9.5, 6.4, 3.0 Hz, 1H), 3.60 (m, 1H), 3.56–3.46 (m, 3H), 3.44 (dd, *J* = 5.3, 4.0 Hz, 1H), 3.38 (dd, *J* = 10.7, 4.4 Hz, 1H), 3.33 (s, 3H), 3.19 (s, 3H), 3.16 (s, 3H), 2.44 (ddd, *J* = 14.0, 1.9, 1.9 Hz, 1H), 2.33 (m, 1H), 2.28 (ddd, *J* = 14.0, 10.8, 10.8 Hz, 1H), 2.16 (s, 3H), 2.02–1.94 (m, 2H), 1.88–1.77 (m, 3H), 1.74–1.38 (m, 10H), 1.44 (s, 3H), 1.35–1.05 (m, 6H), 1.20 (d, *J* = 6.2 Hz, 3H), 1.03–0.71 (m, 1H), 0.96 (d, *J* = 7.1 Hz, 3H), 0.924 (d, *J* = 6.8 Hz, 3H), 0.918 (d, *J* = 7.0 Hz, 3H), 0.90 (s, 9H), 0.88 (s, 9H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.79 (d, *J* = 6.3 Hz, 3H), 0.12 (s, 3H), 0.06 (s, 3H), 0.044 (s, 3H), 0.039 (s, 3H)

^{13}C NMR (151 MHz, $CDCl_3$) δ 166.3, 144.4, 140.6, 134.1, 132.9, 131.3, 130.0, 129.6, 120.4, 87.5, 81.4, 79.0, 77.5, 76.8, 73.3, 72.7, 72.1 (2C), 64.6, 55.6 (2C), 55.3, 42.9, 38.7, 38.5, 37.5, 36.5, 36.3, 34.8, 32.9, 30.6, 29.9, 29.7, 29.5, 27.9, 26.2 (3C), 26.0 (3C), 22.7, 21.8 (2C), 20.1, 18.5, 18.3, 17.2, 14.5, 14.1, 12.4, 12.1, 9.8, –3.8, –4.0, –4.3 (2C)

HRMS (ESI) *m/z* 1045.6997, calcd for $C_{57}H_{106}NaO_9SSi_2$ $[M+Na]^+$ 1045.6994.

Alcohol **45**



To a stirred solution of methyl ether **S9** (17.8 mg, 17.4 μmol) in THF (2.0 mL) and H_2O (0.4 mL) were added 2,6-lutidine (0.40 mL, 3.45 mmol) and $AgNO_3$ (640 mg, 3.77 mmol) at room temperature. After stirring at 30 °C for 19 h in the dark, the reaction mixture was filtered through a pad of Celite®, and the residue was washed with EtOAc (20 mL). The filtrate and the washings were combined, washed and brine (10 mL), dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography on silica gel (0.53 g, hexane–EtOAc 8 : 1 → 6 : 1) to afford alcohol **45** (15.1 mg, 90%) as a colorless oil.

R_f = 0.54 (hexane : EtOAc = 2 : 1

$[\alpha]_D^{27}$ +32.8 (*c* 0.71, $CHCl_3$)

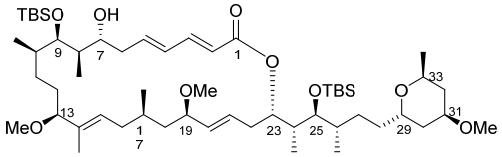
IR ($CHCl_3$) 3449, 3003, 2954, 2930, 2857, 2825, 1704, 1643, 1616, 1463, 1380, 1362, 1302, 1257, 1139, 1083, 1024, 1003, 973, 908, 853, 837 cm^{-1}

^1H NMR (600 MHz, $CDCl_3$) δ 7.23 (dd, *J* = 15.4, 10.4 Hz, 1H), 6.23 (dd, *J* = 15.2, 10.4 Hz, 1H), 6.18 (m, 1H), 5.80 (d, *J* = 15.4 Hz, 1H), 5.52 (ddd, *J* = 14.9, 10.4, 4.3 Hz, 1H), 5.26 (m, 1H), 5.19–5.08 (m, 2H), 3.95 (m, 1H), 3.78 (m, 1H), 3.67 (m, 1H), 3.60 (m, 1H), 3.55–3.47 (m, 2H), 3.45 (dd, *J* = 4.3, 4.3 Hz, 1H), 3.39 (dd, *J* = 9.7, 4.8 Hz, 1H), 3.33 (s, 3H), 3.19 (s, 3H), 3.15 (s, 3H), 2.68 (br. s, 1H), 2.45 (m, 1H), 2.36 (ddd, *J* = 14.3, 5.3, 5.3 Hz, 1H), 2.33–2.23 (m, 2H), 2.05 (ddd, *J* = 6.3, 6.2, 6.2 Hz, 1H), 1.97 (m, 1H), 1.87–1.76 (m, 3H), 1.72–1.36 (m, 9H), 1.45 (s, 3H), 1.36–1.10 (m, 6H), 1.19 (d, *J* = 6.2 Hz, 3H), 0.95 (d, *J* = 7.1 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.91–0.88 (m, 4H), 0.90 (s, 9H), 0.89 (s, 9H), 0.88 (d, *J* = 7.4 Hz, 3H), 0.79 (d, *J* = 6.5 Hz, 3H), 0.12 (s, 3H), 0.08 (s, 3H), 0.062 (s, 3H), 0.059 (s, 3H)

^{13}C NMR (151 MHz, $CDCl_3$) δ 166.5, 144.6, 140.2, 134.0, 133.5, 130.6, 130.5, 129.1, 120.3, 87.7, 82.0, 79.0, 76.8, 74.1, 73.3, 73.0, 72.1, 64.6, 55.7, 55.6, 55.2, 42.9, 42.2, 40.4, 38.7, 38.3, 38.1, 36.6, 35.5, 34.8, 31.6, 30.4, 29.9, 29.7, 27.9, 26.2 (3C), 25.9 (3C), 21.8, 20.2, 18.5, 18.2, 17.3, 16.4, 14.1, 13.3, 12.4, 10.1, –3.8, –4.1, –4.3, –4.4

HRMS (ESI) *m/z* 985.6936, calcd for $C_{55}H_{102}NaO_9Si_2$ $[M+Na]^+$ 985.6960.

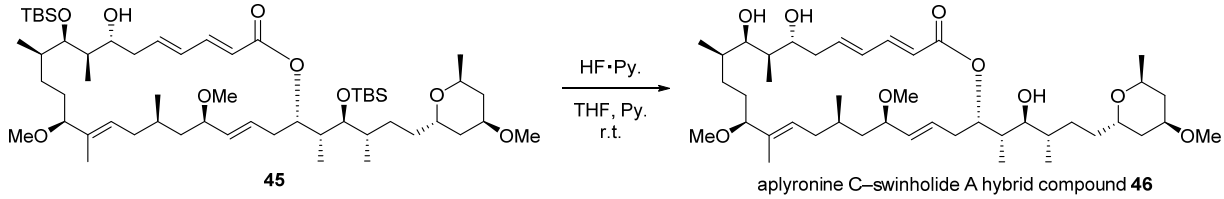
Assignment of ^{1}H NMR spectra of alcohol **45**



2 : 5.80 (d)	10 : 1.72–1.36	19 : 3.55–3.47 (m)	27 : 1.72–1.36, 1.36–1.10
3 : 7.23 (dd)	11 : 1.72–1.36 1.36–1.10	20 : 5.19–5.08 (m)	28 : 1.87–1.76, 1.72–1.36
4 : 6.23 (dd)	12 : 1.72–1.36, 1.36–1.10	21 : 5.52 (ddd)	29 : 3.95 (m)
5 : 6.18 (m)	13 : 3.45 (dd)	22 : 2.36 (ddd), 1.72–1.36	30 : 1.87–1.76, 1.72–1.36
6 : 2.33–2.23 (m)	15 : 5.19–5.08 (m)	23 : 5.26 (m)	31 : 3.55–3.47 (m)
7 : 3.60 (m)	16 : 2.05 (dd), 1.72–1.36	24 : 1.87–1.76	32 : 1.36–1.10
8 : 1.72–1.36	17 : 0.91–0.88	25 : 3.78 (m)	33 : 3.67 (m)
9 : 3.39 (dd)	18 : 1.36–1.10	26 : 1.72–1.36	34 : 1.19 (d)

^{1}H NMR data for alcohol **45** in $CDCl_3$ [carbon number : chemical shift (coupling pattern)]

ApC–ApA hybrid compound **46**



45

aplyronine C–swinholide A hybrid compound **46**

A solution of alcohol **45** (7.8 mg, 8.1 μmol) in a 5 : 3 : 7 mixture of HF·Py., Py., and THF (2.0 mL) was stirred at room temperature for 12 h. The mixture was poured into saturated aqueous $NaHCO_3$ (15 mL) and stirred at 0 °C for 30 min. The resultant mixture was extracted with EtOAc (3 × 8 mL). The combined extracts were washed with brine (15 mL), dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatography on silica gel (0.25 g, hexane–acetone 2 : 1 → 1 : 1) to afford ApC–SwA hybrid compound **46** (5.0 mg, 83%) as a colorless oil.

R_f = 0.21 (hexane : acetone = 2 : 1)

$[\alpha]_D^{27}$ +16.5 (*c* 0.44, $CHCl_3$)

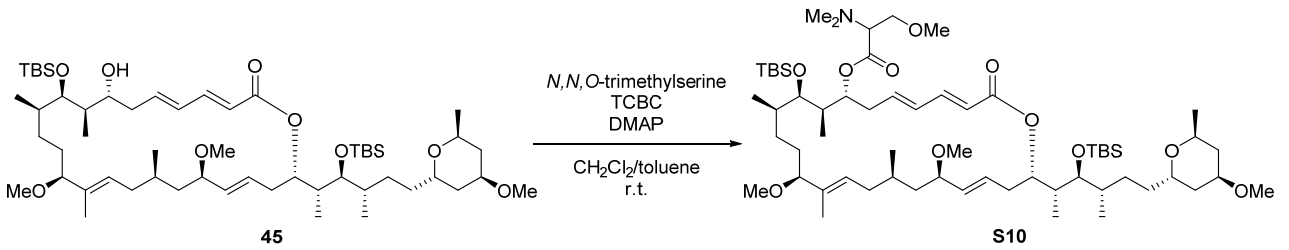
IR ($CHCl_3$) 3445, 3005, 2931, 2875, 2825, 1704, 1685, 1637, 1617, 1457, 1378, 1362, 1261, 1244, 1145, 1099, 1081, 1002, 972, 869 cm^{-1}

^1H NMR (600 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 15.3, 10.6 Hz, 1H), 6.23 (dd, *J* = 15.1, 10.6 Hz, 1H), 6.16 (ddd, *J* = 15.1, 9.8, 5.5 Hz, 1H), 5.85 (d, *J* = 15.3 Hz, 1H), 5.55 (ddd, *J* = 14.9, 10.5, 4.6 Hz, 1H), 5.41 (d, *J* = 10.5 Hz, 1H), 5.15 (dd, *J* = 15.3, 9.0 Hz, 1H), 5.11 (dd, *J* = 7.3, 7.3 Hz, 1H), 4.00 (m, 1H), 3.73 (m, 1H), 3.69 (ddd, *J* = 9.6, 6.5, 2.9 Hz, 1H), 3.64 (dd, *J* = 7.6, 3.7 Hz, 1H), 3.57–3.46 (m, 2H), 3.42 (dd, *J* = 8.5, 6.5 Hz, 1H), 3.33 (s, 3H), 3.23 (d, *J* = 4.8 Hz, 1H), 3.20 (s, 3H), 3.18 (s, 3H), 3.01 (ddd, *J* = 9.6, 6.4, 2.4 Hz, 1H), 2.53 (ddd, *J* = 14.4, 9.8, 7.6 Hz, 1H), 2.50–2.42 (m, 2H), 2.37 (dq, *J* = 9.6, 6.8 Hz, 1H), 2.25 (ddd, *J* = 14.4, 5.5, 3.7 Hz, 1H), 2.20 (m, 1H), 2.03–1.94 (m, 2H), 1.88 (dddd, *J* = 13.5, 9.3, 9.3, 3.8 Hz, 1H), 1.85–1.72 (m, 3H), 1.72–1.55 (m, 5H), 1.52–1.43 (m, 1H), 1.46 (s, 3H), 1.40 (dddd, *J* = 12.7, 7.1, 6.4, 3.4 Hz, 1H), 1.34–1.17 (m, 5H), 1.20 (d, *J* = 6.2 Hz, 3H), 1.08 (m, 1H), 1.04 (d, *J* = 7.0 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.88 (d, *J* = 6.9 Hz, 3H), 0.76 (d, *J* = 5.7 Hz, 3H). Two signals due to a proton (OH) were not observed.

^{13}C NMR (151 MHz, $CDCl_3$) δ 168.0, 145.1, 140.7, 134.7, 133.1, 131.1, 130.4, 128.9, 119.6, 87.2, 81.3, 76.4, 75.4, 74.8, 73.3, 73.1, 71.5, 64.7, 55.7, 55.6, 55.2, 41.4, 40.1, 38.6, 38.14, 38.09, 36.6, 36.2, 35.7, 35.0, 33.2, 29.7, 29.5, 29.3, 26.3, 24.2, 21.8, 19.6, 17.6, 15.5, 11.9, 10.04, 10.02

HRMS (ESI) *m/z* 757.5216, calcd for $C_{43}H_{74}NaO_9$ $[M+Na]^+$ 757.5231.

Trimethylserine ester **S10**



To a stirred solution of alcohol **45** (8.3 mg, 8.6 µmol), *L*-*N*,*N*,*O*-trimethylserine (21.1 mg, 14.3 µmol), and *D*-*N*,*N*,*O*-trimethylserine (10.6 mg, 7.18 µmol) in CH_2Cl_2 (2.0 mL) and toluene (2.0 mL) were added Et_3N (66.0 µL, 474 µmol), TCBC (53.8 µL, 345 µmol), and DMAP (26.3 mg, 215 µmol) at room temperature. After stirring at room temperature for 1 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ (3.0 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined extracts were washed with brine (5.0 mL), dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatography on silica gel (0.50 g, hexane–EtOAc 1 : 1 → 2 : 3) to afford trimethylserine ester **S10** (*S*/*R* = 1/1 as to the trimethylserine part) (9.1 mg, 97%) as a colorless oil.

R_f = 0.11 (hexane : EtOAc = 2 : 1)

$[\alpha]_D^{27}$ +13.9 (*c* 0.83, $CHCl_3$)

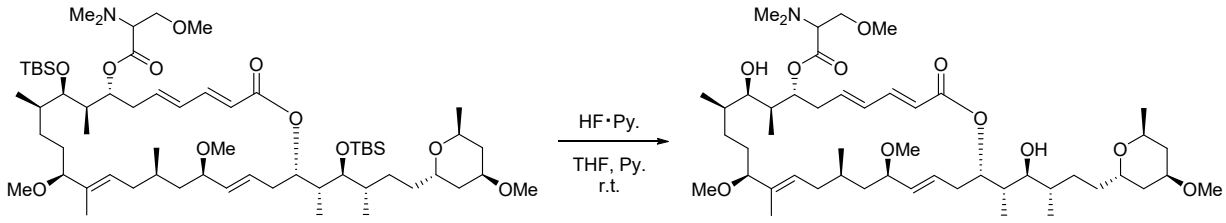
IR ($CHCl_3$) 3000, 2930, 2857, 2827, 1705, 1646, 1617, 1463, 1382, 1361, 1303, 1256, 1175, 1100, 1086, 1036, 1002, 971, 858, 838 cm^{-1}

^1H NMR (600 MHz, $CDCl_3$) δ 7.18 (dd, *J* = 15.3, 11.0 Hz, 1H), 6.21 (dd, *J* = 14.7, 11.0 Hz, 1H), 6.08 (ddd, *J* = 14.7, 7.4, 7.4 Hz, 1H), 5.822 [5.818] (d, *J* = 15.3 Hz, 1H), 5.54 (ddd, *J* = 15.0, 10.5, 4.3 Hz, 1H), 5.27 (ddd, *J* = 11.0, 2.4, 2.4 Hz, 1H), 5.16–4.98 (m, 2H), 4.83 (m, 1H), 3.95 (m, 1H), 3.68 (dddd, *J* = 12.8, 9.5, 6.4, 3.0 Hz, 1H), 3.64–3.60 (m, 2H), 3.56–3.46 (m, 2H), 3.46–3.41 (m, 2H), 3.41–3.34 (m, 2H), 3.36 [3.35] (s, 3H), 3.33 (s, 3H), 3.187 [3.188] (s, 3H), 3.163 [3.162] (s, 3H), 2.55–2.34 (m, 3H), 2.40 (s, 6H), 2.28 (m, 1H), 2.08–1.88 (m, 3H), 1.88–1.77 (m, 3H), 1.77–1.37 (m, 8H), 1.47 (s, 3H), 1.37–1.11 (m, 6H), 1.19 (d, *J* = 6.2 Hz, 3H), 1.09–0.85 (m, 1H), 0.96 (d, *J* = 6.5 Hz, 3H), 0.95 (d, *J* = 6.0 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.773 (d, *J* = 6.2 Hz, 3H), 0.769 (d, *J* = 6.1 Hz, 3H), 0.12 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H) (the counterparts of doubled signals in the ratio of about 1:1 are in brackets)

^{13}C NMR (151 MHz, $CDCl_3$) δ 170.2, 166.16 [166.14], 144.0 [143.9], 138.9, 134.5, 133.1, 131.0, 130.9, 129.3 [129.2], 121.0 [120.9], 87.62 [87.57], 81.3, 79.07 [79.04], 75.3, 73.3, 72.9, 72.0, 71.4 [71.3], 67.4, 67.2, 64.7, 59.13 [59.08], 55.61 [55.60], 55.3 (2C), 42.81 [42.77], 42.3, 42.2 (2C), 41.1, 38.7, 38.5 [38.4], 36.6, 36.1, 34.8, 32.8, 29.9, 29.7, 29.6, 28.0, 26.2 (3C), 26.0 (3C), 21.8, 20.1, 18.5, 18.3, 17.21, 17.19, 14.8, 12.4, 11.84, 11.76, 9.8, –3.8, –4.1, –4.2, –4.3 (the counterparts of doubled signals in the ratio of about 1:1 are in brackets)

HRMS (ESI) *m/z* 1114.7725, calcd for $C_{61}H_{113}NO_{11}Si_2$ $[M+H]^+$ 1114.7750.

ApA–SwA hybrid compound **11**



S10 aplyronine A–swinholide A hybrid compound **11**

A solution of trimethylserine ester **S10** (8.6 mg, 7.9 μmol) in a 5 : 3 : 7 mixture of HF·Py., Py., and THF (2.0 mL) was stirred at room temperature for 12 h. The mixture was poured into saturated aqueous $NaHCO_3$ (15 mL) and stirred at 0 °C for 30 min. The resultant mixture was extracted with EtOAc (3 × 8 mL). The combined extracts were washed with brine (15 mL), dried over Na_2SO4, and concentrated. The crude product was purified by column chromatography on silica gel (0.25 g, $CHCl_3$–MeOH 20 : 1) to give ApA–SwA hybrid compound **11** (6.0 mg, 88%) as a colorless oil.

R_f = 0.45 ($CHCl_3$: MeOH = 9 : 1)
$[\alpha]_D^{27}$ +40.3 (*c* 0.55, $CHCl_3$)
IR ($CHCl_3$) 3502, 3003, 2930, 2874, 2829, 1717, 1644, 1618, 1457, 1382, 1299, 1271, 1245, 1174, 1146, 1100, 1039, 1001, 972, 867, 841 cm^{-1}
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24 (dd, *J* = 15.3, 10.8 Hz, 1H), 6.22 (dd, *J* = 15.0, 10.8 Hz, 1H), 6.12 (ddd, *J* = 15.0, 9.5, 5.2 Hz, 1H), 5.90 (d, *J* = 15.3 Hz, 1H), 5.56 (ddd, *J* = 14.9, 10.4, 4.3 Hz, 1H), 5.42 (d, *J* = 11.0 Hz, 1H), 5.11–5.00 (m, 2H), 4.77 (m, 1H), 4.00 (m, 1H), 3.69 (dddd, *J* = 12.9, 9.5, 6.4, 3.0 Hz, 1H), 3.65–3.59 (m, 2H), 3.56–3.45 (m, 3H), 3.43 (ddd, *J* = 10.5, 3.9, 3.9 Hz, 1H), 3.37–3.32 (m, 1H), 3.35 [3.36] (s, 3H), 3.34 (s, 3H), 3.19 (s, 3H), 3.18 (s, 3H), 3.08 (d, *J* = 4.7 Hz, 1H), 3.03 (m, 1H), 2.54–2.44 (m, 2H), 2.38 (s, 6H), 2.23 (ddd, *J* = 14.2, 5.2, 1.8 Hz, 1H), 2.22 (br. s, 1H), 2.02–1.84 (m, 4H), 1.84–1.76 (m, 2H), 1.73–1.53 (m, 6H), 1.49 (d, *J* = 2.8 Hz, 3H), 1.44–1.32 (m, 2H), 1.32–1.05 (m, 7H), 1.20 (d, *J* = 6.2 Hz, 3H), 1.10 (m, 1H), 1.00 (d, *J* = 7.4 Hz, 3H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.98 (d, *J* = 4.6 Hz, 3H), 0.88 (d, *J* = 6.9 Hz, 3H), 0.718 [0.724] (d, *J* = 6.0 Hz, 3H) (the counterparts of doubled signals in the ratio of about 1:1 are in brackets)
^{13}C NMR (151 MHz, $CDCl_3$) δ 170.0 [170.2], 167.6, 144.49 [145.53], 139.48 [139.51], 135.03 [134.99], 132.9, 131.43 [131.41], 130.87 [130.84], 129.15 [129.21], 120.43 [120.38], 86.8 [86.7], 81.6, 77.2, 76.4, 73.3, 72.9, 71.52 [71.46], 70.6, 67.49 [67.46], 64.7, 59.12 [59.14], 55.712, 55.714, 55.6, 55.3, 42.43 [42.40] (2C), 41.3, 40.11, 40.09, 38.6, 37.1, 36.8, 35.0, 33.5, 33.2, 29.8, 29.3, 28.9, 24.2, 21.8, 19.7, 17.6, 15.70, 15.66, 12.1, 12.0, 10.00, 9.98 (the counterparts of doubled signals in the ratio of about 1:1 are in brackets)
HRMS (ESI) *m/z* 886.6003, calcd for $C_{49}H_{85}NO_{11}$ $[M+H]^+$ 886.6020.

lane	1	2	3	4	5	6
$MgCl_2$	–	+	+	+	+	+
ApA (**1**, 5 μM)	–	–	+	–	–	–
ApA–SwA (**11**, 5 μM)	–	–	–	+	–	–
ApA–SwA (**11**, 15 μM)	–	–	–	–	+	–
ApA–SwA (**11**, 50 μM)	–	–	–	–	–	+

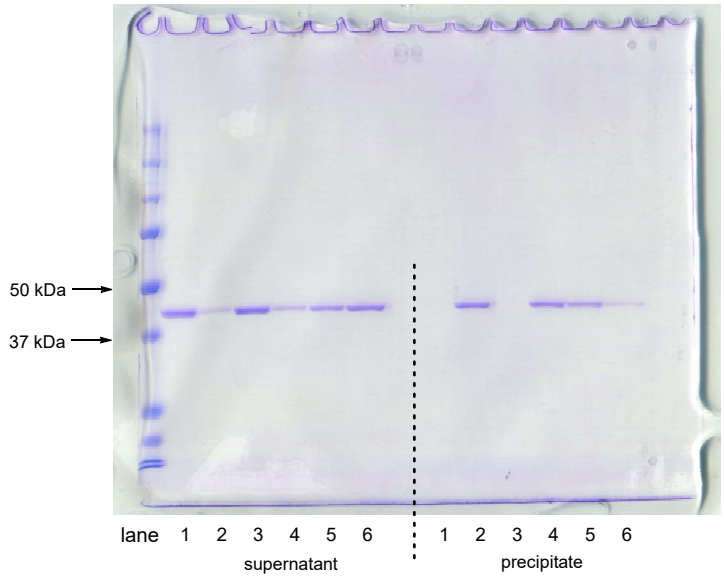


Figure S1. SDS-PAGE of the supernatants and precipitates (Actin depolymerizing activity assay)

Actin was depolymerized in the presence of **1** or **11**, and then precipitated by ultracentrifugation. Actin in the supernatant and the precipitate were analyzed by SDS-PAGE and detected with CBB stain. Polymerized actin was detected in the precipitate fraction.

lane	1	2	3	4	5	6	7	8	9
tubulin (6 μM)	+	+	+	+	–	+	+	+	–
actin (6 μM)	–	–	–	+	+	+	–	+	+
$CaCl_2$ (5 mM)	+	–	–	–	–	–	–	–	–
paclitaxel (2 μM)	–	+	+	+	–	+	+	+	–
1 (10 μM)	–	–	+	+	+	–	–	–	–
11 (100 μM)	–	–	–	–	–	–	+	+	+

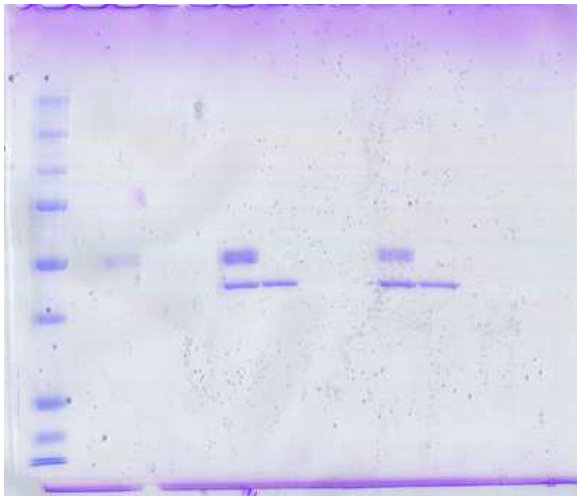


Figure S2. SDS-PAGE of the supernatants (Tubulin polymerization inhibitory activity assay)
Tubulin was polymerized with paclitaxel in the presence of actin and/or **1** or **11**, and then precipitated by ultracentrifugation. Proteins in the supernatant and the precipitate were analyzed by SDS-PAGE and detected with CBB stain. Depolymerized protein was detected in the supernatant fraction.

lane	1	2	3	4	5	6	7	8	9
tubulin (6 μM)	+	+	+	+	–	+	+	+	–
actin (6 μM)	–	–	–	+	+	+	–	+	+
$CaCl_2$ (5 mM)	+	–	–	–	–	–	–	–	–
paclitaxel (2 μM)	–	+	+	+	–	+	+	+	–
1 (10 μM)	–	–	+	+	+	–	–	–	–
11 (100 μM)	–	–	–	–	–	–	+	+	+

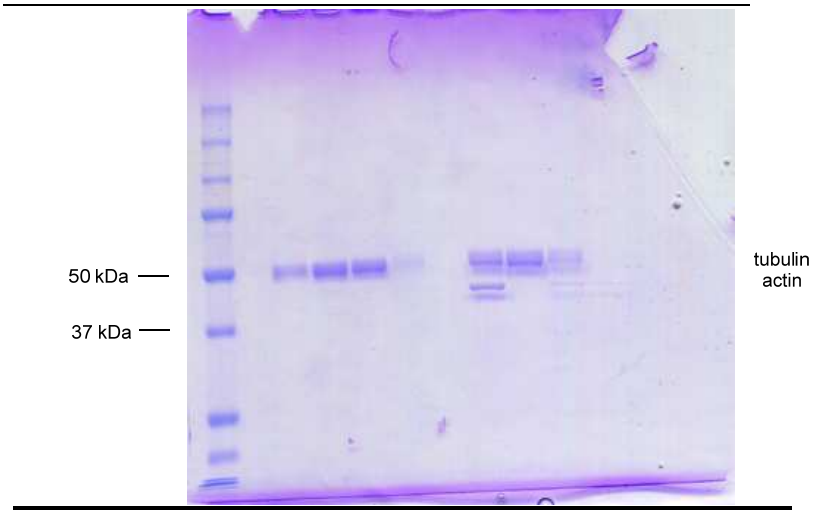


Figure S3. SDS-PAGE of the precipitates (Tubulin polymerization inhibitory activity)
Tubulin was polymerized with paclitaxel in the presence of actin and/or **1** or **11**, and then precipitated by ultracentrifugation. Proteins in the supernatant and the precipitate were analyzed by SDS-PAGE and detected with CBB stain. Polymerized protein was detected in the precipitate fraction.

References

[1] Brown, E. J.; Albers, M. W.; Shin, T. B.; Ichikawa, K.; Keith, C. T.; Lane, W. S.; Schreiber, S. L. *Nature* **1994**, *369*, 756.

[2] Choi, J.; Chen, J.; Schreiber, S. L.; Clardy, J. *Science* **1996**, *273*, 239-242.

[3] Isolation: (a) Yamada, K; Ojika, M.; Ishigaki, T.; Yoshida, Y.; Ekimoto, H.; Arakawa, M. *J. Am. Chem. Soc.* **1993**, *115*, 11020; (b) Ojika, M.; Kigoshi, H.; Ishigaki, T.; Yamada, K. *Tetrahedron Lett.* **1993**, *34*, 8501; (c) Ojika, M.; Kigoshi, H.; Ishigaki, T.; Nisiwaki, M.; Tsukada, I.; Mizuta, K.; Yamada, K. *Tetrahedron Lett.* **1993**, *34*, 8505; (d) Ojika, M.; Kigoshi, H.; Ishigaki, T.; Tsukada, I.; Tsuboi, T.; Ogawa, T.; Yamada, K. *J. Am. Chem. Soc.* **1994**, *116*, 7441.

[4] Total synthesis: (a) Kigoshi, H.; Ojika, M.; Ishigaki, T.; Suenaga, K.; Mutou, T.; Sakakura, A.; Ogawa, T.; Yamada, K. *J. Am. Chem. Soc.* **1994**, *116*, 7443; (b) Kigoshi, H.; Suenaga, K.; Mutou, T.; Ishigaki, T.; Atsumi, T.; Ishikawa, H.; Sakakura, A.; Ogawa, T.; Ojika, M.; Yamada, K. *J. Org. Chem.* **1996**, *61*, 5326; (c) Hayakawa, I.; Saito, K.; Matsumoto, S.; Kobayashi, S.; Taniguchi, A.; Kobayashi, K.; Fujii, Y.; Kaneko, T.; Kigoshi, H. *Org. Biomol. Chem.*, **2017**, *15*, 124; (d) Anzicek, N.; Williams, S.; Housden, M. P.; Paterson, I. *Org. Biomol. Chem.* **2018**, *16*, 1343.

[5] Review: (a) Yamada, K.; Ojika, M.; Kigoshi, H.; Suenaga, K. *Nat. Prod. Rep.* **2009**, *26*, 27; (b) Hayakawa, I.; Kigoshi, H. *Heterocycles* **2015**, *91*, 1137.

[6] Kita, M.; Hirayama, Y.; Sugiyama, M.; Kigoshi, H. *Angew. Chem. Int. Ed.* **2011**, *50*, 9871.

[7] Kita, M.; Kigoshi, H. *Nat. Prod. Rep.* **2015**, *32*, 534.

[8] Saito, S.; Watabe, S.; Ozaki, H.; Kigoshi, H.; Yamada, K.; Fusetani, N.; Karaki, H. *J. Biochem.* **1996**, *120*, 552.

[9] Hirata, K.; Muraoka, S.; Suenaga, K.; Kuroda, T.; Kato, K.; Tanaka, H.; Yamamoto, M.; Tanaka, M.; Yamada, K.; Kigoshi, H. *J. Mol. Biol.* **2006**, *356*, 945.

[10] Suenaga, K.; Kamei, N.; Okugawa, Y.; Takagi, M.; Akao, A.; Kigoshi, H.; Yamada, K. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 269.

[11] Kita, M.; Yoneda, K.; Hirayama, Y.; Yamagishi, K.; Saito, Y.; Sugiyama, Y.; Miwa, Y.; Ohno, O.; Morita, M.; Suenaga, K.; Kigoshi, H. *ChemBioChem* **2012**, *13*, 1754.

[12] Kigoshi, H.; Suenaga, K.; Takagi, M.; Akao, A.; Kanematsu, K.; Kamei, N.; Okugawa, Y.; Yamada, K. *Tetrahedron* **2002**, *58*, 1075.

[13] Suenaga, K.; Kimura, T.; Kuroda, T.; Matsui, K.; Miya, S.; Kuribayashi, S.; Sakakura, A.; Kigoshi, H. *Tetrahedron* **2006**, *62*, 8278.

[14] Kigoshi, H.; Suenaga, K.; Mutou, T.; Ishigaki, T.; Atsumi, T.; Ishiwata, H.; Sakakura, A.; Ogawa, T.; Ojika, M.; Yamada, K. *J. Org. Chem.* **1996**, *61*, 5326.

[15] Kita, M.; Hirayama, Y.; Yoneda, K.; Yamagishi, K.; Chinen, T.; Usui, T.; Sumiya, E.; Uesugi, M.; Kigoshi, H. *J. Am. Chem. Soc.* **2013**, *135*, 18089.

[16] Reutzel, R.; Yoshioka, C.; Govindasamy, L.; Yarmola, E. G.; Agbandje–Mckenna, M.; Bubb, M. R.; McKenna, R. *J. Struct. Biol.* **2004**, *146*, 291.

[17] (a) Carmely, S.; Kashman, Y. *Tetrahedron Lett.* **1985**, *26*, 511. (b) Kobayashi, M.; Kawazoe, K.; Okamoto, T.; Sasaki, T.; Kitagawa, I. *Tetrahedron Lett.* **1989**, *30*, 2963. (c) Kitagawa, I.; Kobayashi, M.; katori, T.; Yamashita, M. *J. Am. Chem. Soc.* **1990**, *112*, 3710.

[18] Kobayashi, M.; Kawazoe, K.; Okamoto, T.; Sasaki, T.; Kitagawa, I. *Chem. Pharm. Bull.* **1994**, *42*, 19.

[19] Spector, I.; Braet, F.; Shochet, N. R.; Bubb, M. R. *Microsc. Res. Tech.* **1999**, *47*, 18.

[20] Klenchin, V. A.; King, R.; Tanaka, J.; Marriott, G.; Rayment, I. *Chem. Biol.* **2005**, *12*, 287.

[21] Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K.; Sakai, R.; Higa, T.; Kashman, Y. *Tetrahedron Lett.* **1987**, *28*, 6225.

[22] Tanaka, J.; Higa, T.; Kobayashi, M.; Kitagawa, I. *Chem. Pharm. Bull.* **1990**, *38*, 2967.
[23] Terry, D. R.; Spector, I.; Higa, T.; Bubb, M. R.; *J. Biol. Chem.* **1997**, *272*, 7841.
[24] Fusetani, N.; Yasumuro, K.; Matsunaga, S.; Hashimoto, K. *Tetrahedron Lett.* **1989**, *30*, 2809.
[25] Saito, S.; Watabe, S.; Ozeki, H.; Fusetani, N.; Karaki, H. *J. Biol. Chem.* **1994**, *269*, 29710.
[26] Ohno, O.; Morita, M.; Kitamura, T.; Teruya, T.; Yoneda, K.; Kita, M.; Kigoshi, H.; Suenaga, K. *Bioorg. Med. Chem. Lett*. **2013**, *23*, 1467.
[27] Kobayashi, K.; Fujii, Y.; Hirayama, Y.; Kobayashi, S.; Hayakawa, I.; Kigoshi, H. *Org. Lett.* **2012**, *14*, 1290.
[28] (a) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644.; (b) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048.
[29] Kobayashi, K.; Fujii, Y.; Hayakawa, I.; Kigoshi, H. *Org. Lett.* **2011**, *13*, 900.
[30] Nakamura, R.; Tanino, K.; Miyashita, M. *Org. Lett*. **2005**, *7*, 2929.
[31] (a) Marshall, J. A.; Schaaf, G. M. *J. Org. Chem.* **2001**, *66*, 7825; (b) Marshall, J. A.; Schaaf, G. M. *J. Org. Chem.* **2002**, *67*, 2751.
[32] Pearlman, W. M. *Tetrahedron Lett*. **1967**, *8*, 1663.
[33] Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
[34] Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 5644.
[35] Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
[36] (a) Shiina, I.; Ibuka, R.; Kubota, M. *Chem. Lett.* **2002**, 31, 286.; (b) Shiina, I.; Kubota, M.; Osumi, H.; Hashizume, M. *J. Org. Chem.* **2004**, *69*, 1822.
[37] Neises, B.; Steglich, W. *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 522.
[38] Saitoh, K.; Shiina, I.; Mukaiyama, T. *Chem. Lett.* **1998**, *27*, 679.
[39] Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

Chapter 3. Synthetic studies of swinhoeisterol A, a novel steroid with an unusual carbon skeleton

3-1. Introduction

3-1-1. Steroids and terpenes

Both triterpenes and steroids are compounds biosynthesized from squalene possessing a C30 skeleton. Steroids are basically no different from terpenes, and they are compounds that have very similar structures to each other (Figure 3-1). Steroids and terpenes are formed by head to tail reaction (tail to tail reaction in some cases) of isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP) (Scheme 3-1).[1] Since the reaction with IPP repeatedly occurs and the carbon chain is elongated, the numbers of carbon atoms in the terpenes generated in the process are multiples of the isoprene unit. Steroids were produced by demethylation in the later stage of biosynthesis, where they deviate from this rule.[2] Thus, steroids are classified as another group, because the biosynthetic mechanisms and bioactivities are different from terpenes. Steroids have a common structure in which three chair-like 6-membered ring and one 5-membered ring are connected. The carbon skeleton was biosynthesized through squalene oxide. The ring closure reaction of squalene oxide proceeds at once by a concerted cyclization reaction accompanied with hydride shift and Wagner–Meerwein rearrangement through 2,3-oxidosqualene cyclase (OSQCY). It was classified into three cases of chair-boat-chair-boat type, chair-chair-chair-boat type, and chair-chair-chair-chair-chair type (Scheme 3-2). The chair-boat-chair-boat type reaction only generates steroids, and other 2 types generate various triterpene skeletons.[3] The series of reactions are catalyzed by each different enzyme and proceeds with strict control of stereochemistry. The conversion from linear squalene to tetracyclic compounds is an example of the most complex and artistic chemical reactions organisms perform.

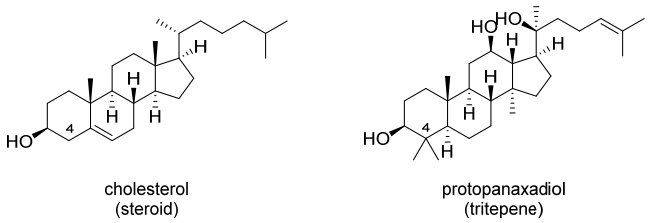
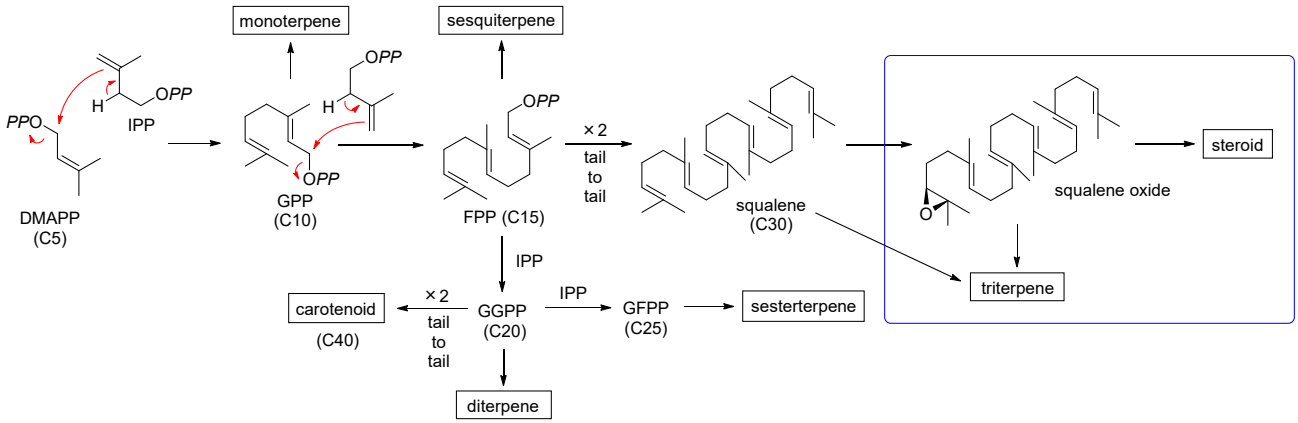
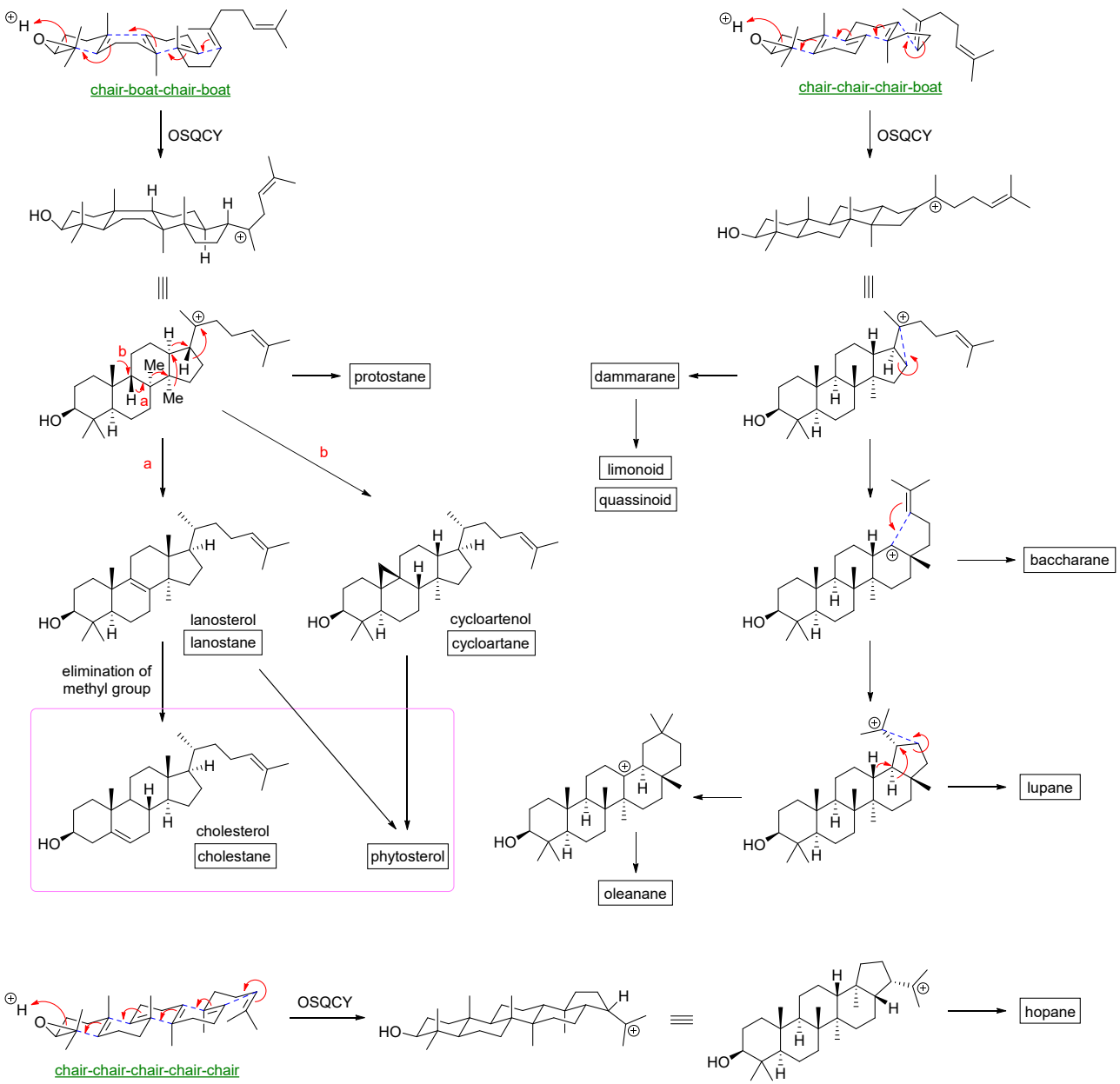


Figure 3-1. Structures of cholesterol and protopanaxadiol.



Scheme 3-1. Biosynthetic pathway of terpenes and steroids



Scheme 3-2. Biological transformation of squalene oxide

Steroids and steroid derivatives, such as testosterone[4] and cortisol,[5] are used as medicines for hormonal and anti-inflammatory drugs, respectively (Figure 3-2). Therefore, artificial synthetic methods for generating normal steroids are well developed. These steroidal drugs are industrially semi-synthesized from compounds that contain a tetracyclic skeleton, for example, Marker degradation of diosgenin (Scheme 3-3).[6] In small-scale synthesis, steroids are prepared often from Wieland–Miescher ketone, by polyene cyclization, or Diels–Alder reaction (Scheme 3-4).[7,8,9]

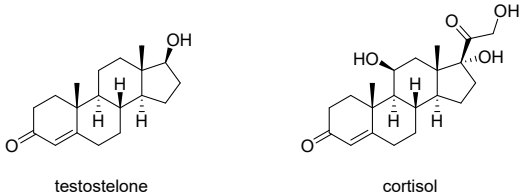
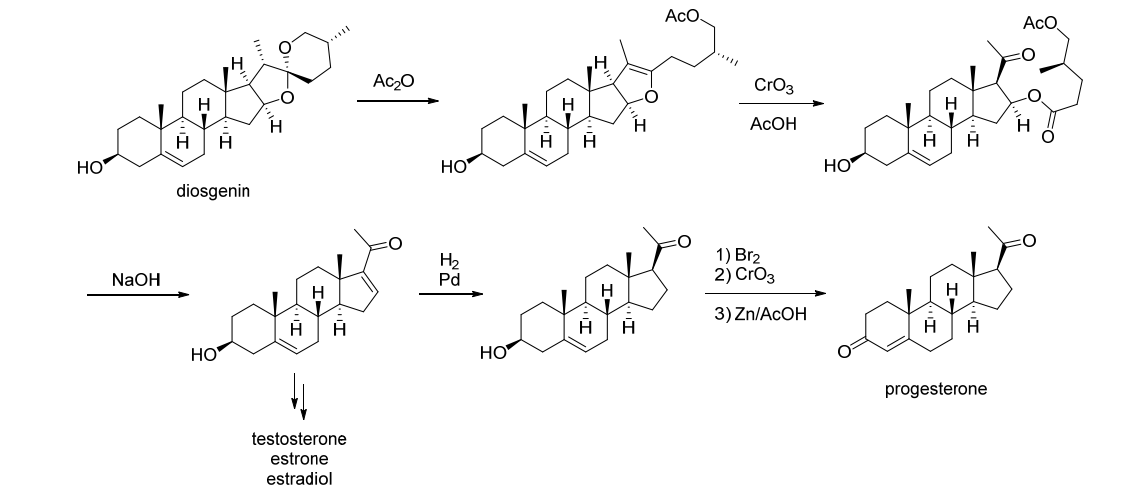
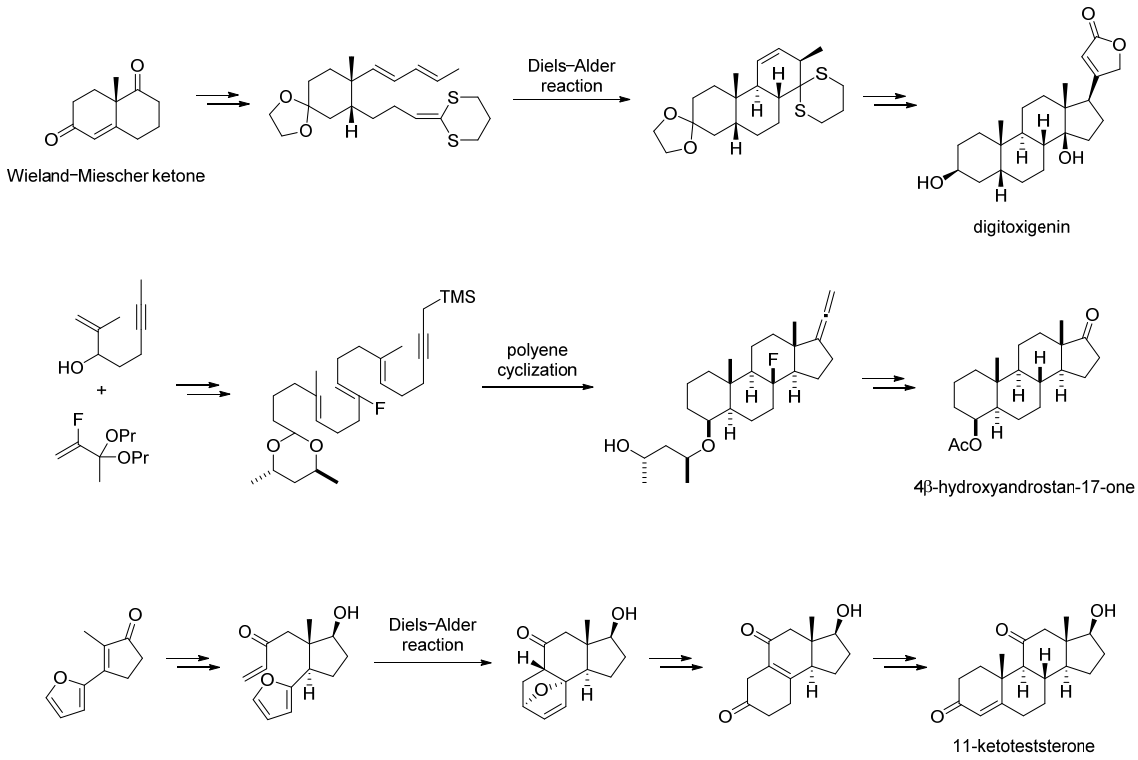


Figure 3-2. Structures of testosterone and cortisol



Scheme 3-3. Marker degradation of diosgenin



Scheme 3-4. Examples of steroid synthesis

Recently, novel steroids having unusual carbon skeletons such as jaborosalactone 10,[10] cortistatin A,[11] cyclocitrinol,[12] and aspafilisine[13] were isolated (Figure 3-3). Some members of the family have unique biological activities: jaborosalactone 10, quinone reductase induction promoting action; cortistatin A, strongest anti-proliferative activity; and cyclocitrinol, cAMP production promoting action. As their novel carbon skeletons are supposed to be biosynthesized after the construction of normal 6/6/6/5 steroidal structure, their biosynthetic pathways are also interesting.

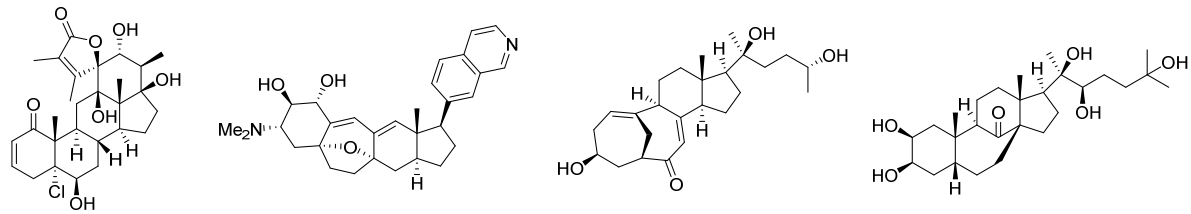
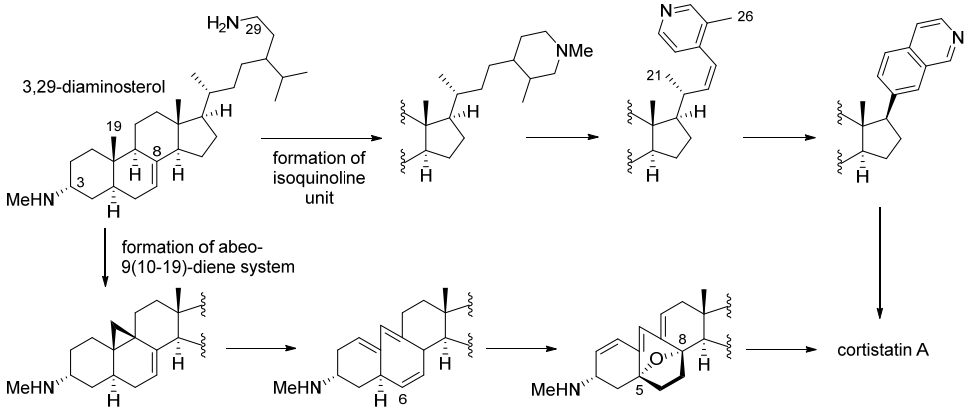


Figure 3-3. Structures of jaborosalactone 10, cortistatin A, cyclocitrinol, and aspafilisine

Cortistatin A is presumed to be biosynthesized from a 3,29-diaminosterol (Scheme 3-5).[14] The abeo-9(10–19)-diene system is formed from a 3,29-diaminosterol through a 9β,19-cyclo system. Then, the 6-ene unit is oxidized to afford a 5,8-oxide ring system. The piperidine-type side chain is formed from cyclization of the 29-amino group. The piperidine unit is dehydrated to afford a 3-methylpyridine unit, which is further converted to an isoquinoline unit by cyclization and demethylation of the C-21 or the C-26 methyl group.



Scheme 3-5. Plausible biogenesis of cortistatin A

Swinhoeisterols A (**50**) and B (**51**) were isolated from the same sp. of the sponge producing swinholide A, *Theonela swinhoei* in 2014 (Figure 3-4).[15] They are novel sterols which possess a 6/6/5/7 ring skeleton. The carbon framework is suggested to result from the rearrangement of normal a 6/6/6/5 steroidal structure by the Zhang group (Scheme 3-6).[13] Oxidative cleavage of the C8–C14 double bond in conicasterol and following deprotonation of H-7 with base generates a nucleophile intermediate, which initiates an intramolecular aldol condensation. An enzyme-catalyzed cleavage of the C13–C14 bond and subsequent rearrangement yields the unprecedented 6/6/5/7 ring system. In 2018, swinhoeisterols C-F (**52-55**)[16] were isolated too. Swinhoeisterol A (**50**) shows a remarkable inhibitory activity against h(p300), a histone acetyltransferase, associated with the manifestation cancer (IC_{50} = 2.9 μM) and cytotoxicity against A549 cells (IC_{50} = 8.6 μM). The author was attracted to both the biological activity and the structure, and started studies toward the total synthesis of swinhoeisterol A (**50**).

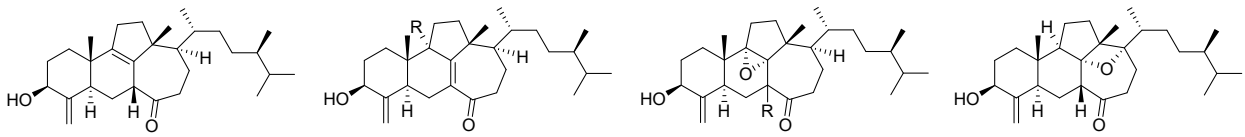
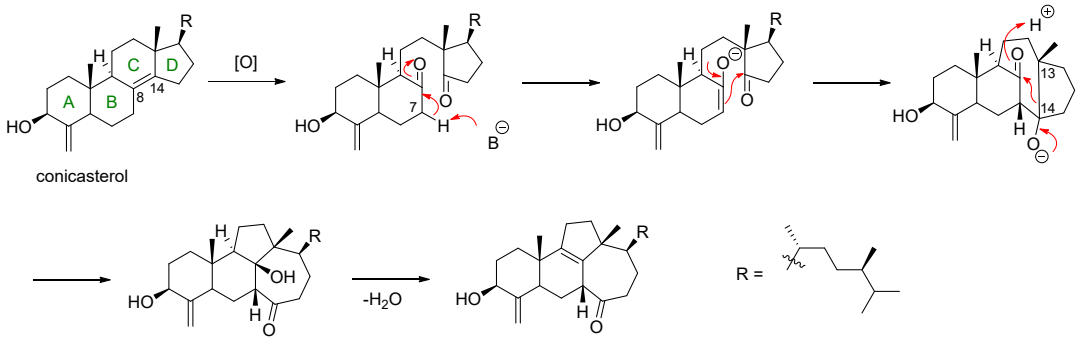


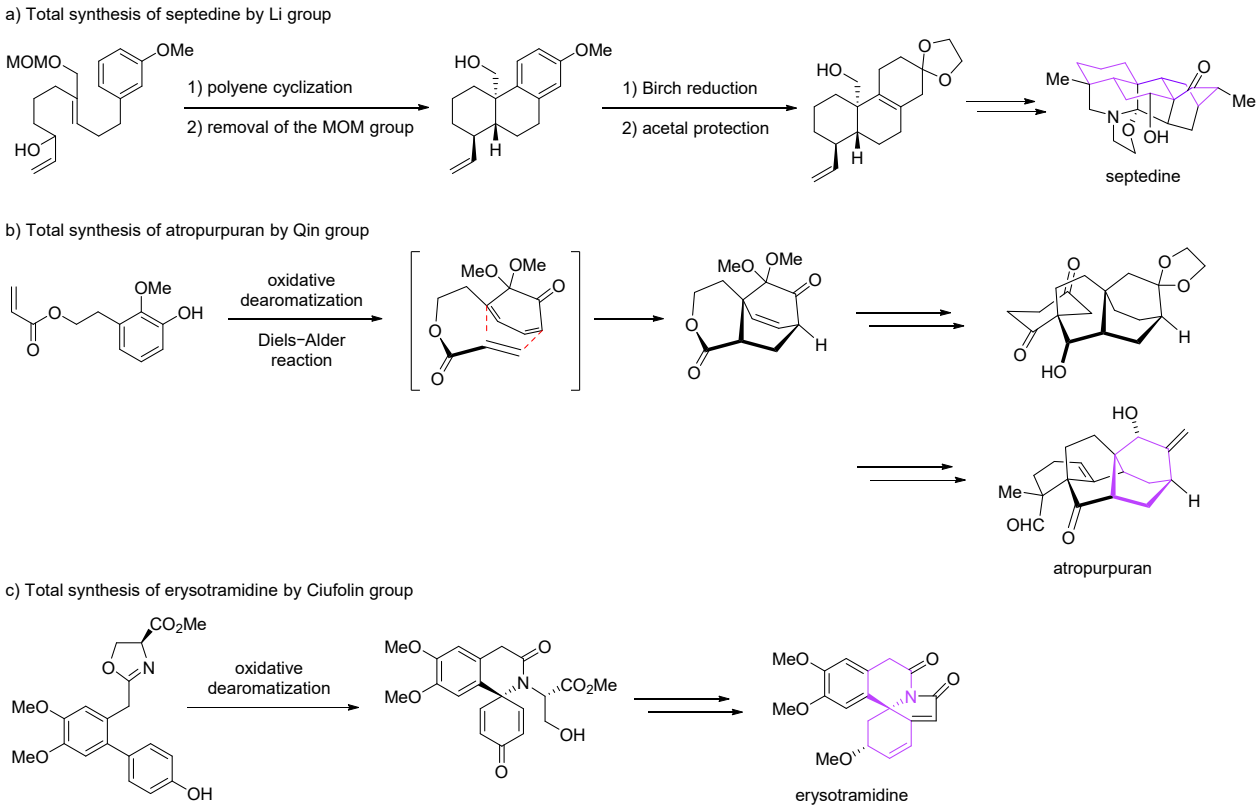
Figure 3-4. Structures of swinhoeisterols A-F (**50**-**55**)



Scheme 3-6. Plausible biosynthetic pathway of swinhoeisterol A (**50**)

3-1-2. Chemistry of benzene

Benzene rings are represented by double bonds and single bonds alternately in the structural formula, but actually, π-electrons are delocalized, so π-electrons do not contribute to a specific bond. When π-electrons are delocalized, the stability is increased compared to the usual double bounds, and its properties are greatly different from that of olefins. The chemistry of benzene provides powerful tools in the synthesis of polycyclic compounds, because it is useful for the synthesis of polycyclic compounds and multisubstituted ring as exemplified in Friedel–Crafts reactions, utilization of benzylic cations, S_NAr reactions and so on, even if the synthetic targets lack benzene rings. The undesired benzene rings should be dearomatized under reductive conditions such as Birch reduction or oxidative conditions with hypervalent iodine or ammonium cerium(IV) nitrate (CAN). The chemistry of benzene has been used in many total syntheses. Li and co-workers synthesized septedine utilizing polyene cyclization following Birch reduction (Scheme 3-7a).[17] Combination of oxidative dearomatization and Diels–Alder reaction give a bicyclo[2.2.2]octane skeleton, and the method was used in the total synthesis of atropurpuran by the Qin group (Scheme 3-7b).[18] Also, oxidative dearomatization of a compound that has a nucleophile in the molecule provides a heterospiro ring (Scheme 3-7c).[19]

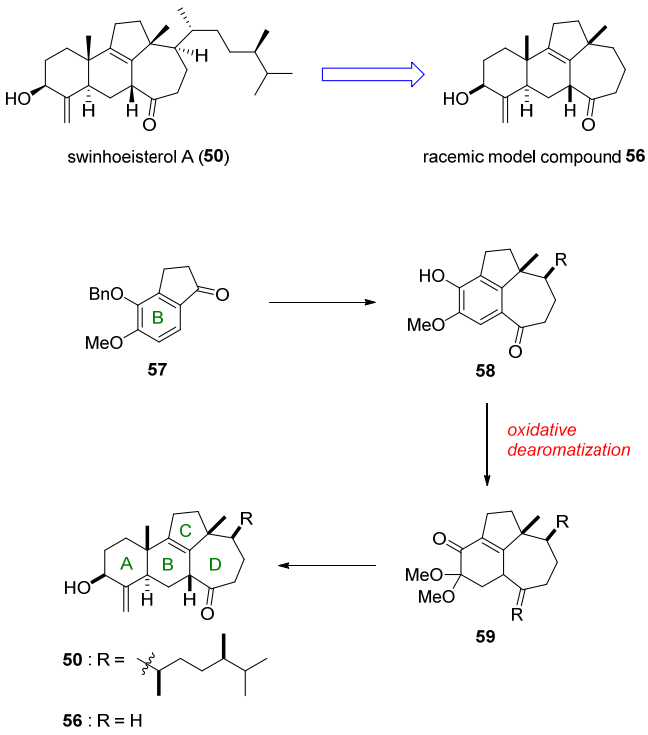


Scheme 3-7. Examples of total synthesis exploiting benzene rings

3-2. Synthetic strategy toward the total synthesis of swinhoeisterol A

In order to study structure-activity relationships, establishment of an efficient synthetic route is essential. Before conducting the synthesis of the natural product, the author focused on a model racemic compound **56** in which the side chain moiety was removed toward the establishment of a synthetic strategy to construct the carbon framework.

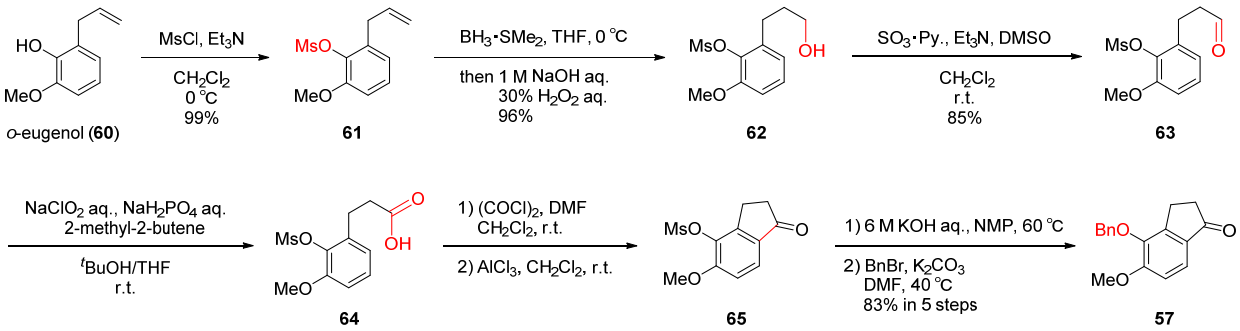
A flexible synthetic route was planned to allow the preparation of various analogs (Scheme 3-8). Benzene ring is used for B ring in model compound **56**, while the CD rings were expected to be efficiently constructed utilizing the chemistry of benzene. It is assumed that the desired tricyclic compound **59** is obtained by dearomatization after CD ring system assembly. Thus, the synthesis was started from indanone **57**. Construction of the A ring at a later stage would lead to model compound **56**. In the case of the natural product, the side chain moiety would be introduced at the stage before the corresponding tricyclic compound. The same route as the model compound is applied to lead to the total synthesis.



Scheme 3-8. Synthetic strategy of swinhoeisterol A (**50**) and the model compound **56**

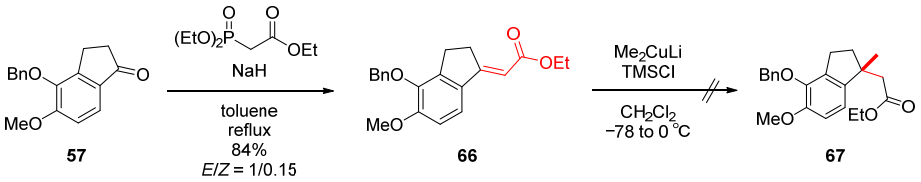
3-3. Synthesis of a model tricyclic compound with BCD rings of swinhoeisterol A

This study began with a synthesis of indanone **57** from commercially available *o*-eugenol (**60**) (scheme 3-9). Mesylation of **60** and hydroboration gave alcohol **62**. After two oxidation steps of alcohol **62**, Friedel–Crafts reaction through an acid chloride afforded indanone mesylate **65**. Because solubility of mesylate **65** was very low, mesylate **65** was transformed into indanone **57**.



Scheme 3-9. Synthesis of indanone

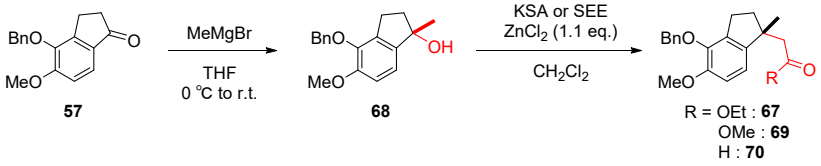
The conjugated ester that was prepared by Horner–Wadsworth–Emmons reaction did not react with Gillman Reagent (Scheme 10).[20,21] So that Michael reaction of a similar compound of **66** was reported, in this case, electron-rich benzene ring was considered to reduce the reactivity.[22]



Scheme 3-10. Michael addition

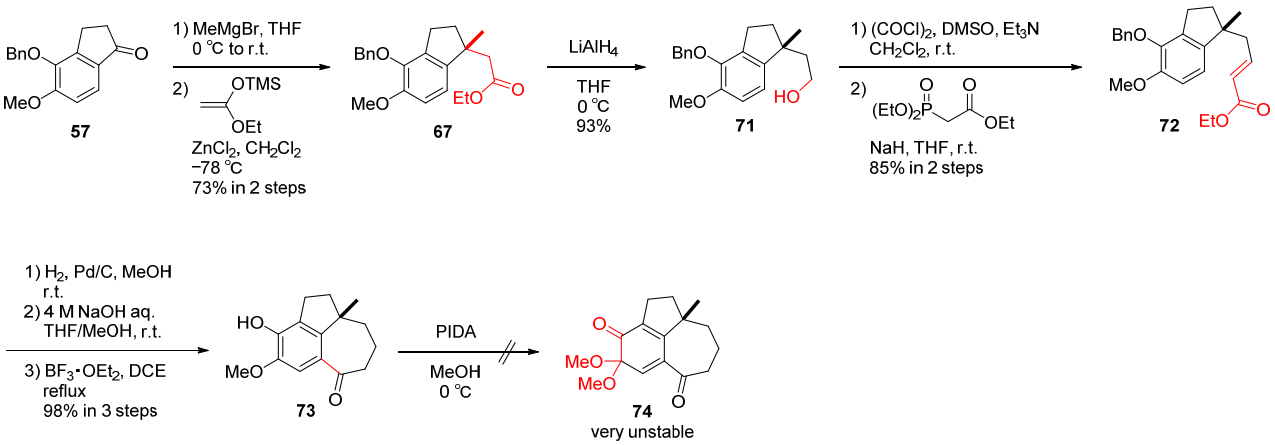
On the other hand, methylation of **57** and substitution of the resultant benzylic tertiary alcohol with ketene silyl acetal (KSA) afforded ester **67** (Table 3-1).[23,24] In entry 1, ketene silyl acetal (KSA) result from EtOAc gave ester **67** in moderate yield. The results of the reaction with ketene *tert*-butyldimethylsilyl methyl acetal (entry 2) or silyl enol ether (SEE) (entry 3) was not better because of dehydration of the starting material and intermolecular Friedel–Crafts reaction. When freshly distilled KSA was used, the desired compound was produced in 73% (entry 4). Because an enantioselective reaction is achievable with a chiral Lewis acid instead of $ZnCl_2$ or a chiral catalyst,[25] the enantioselective preparation of **67** could be carried out.

Table 3-1. Substitution of benzylic tertiary alcohol



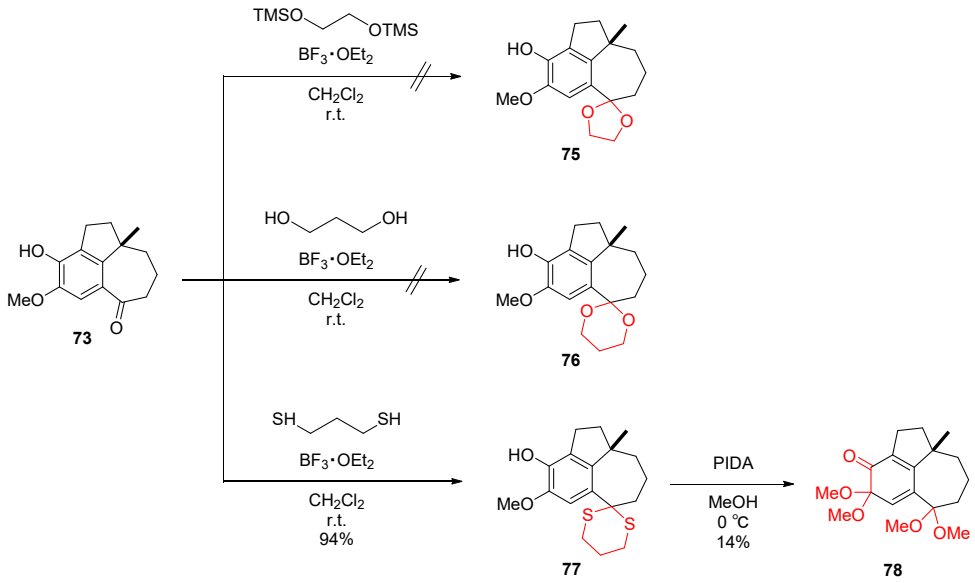
entry	KSA or SEE	temp. (℃)	results (from **57**)
1	 (crude)	−78 to −40	**67** : 58%
2	 (commercially available)	−78 to −40	**69** : N. D.
3	 (commercially available)	−78	**70** : 18%
4	 (dist.)	−40	**67** : 73%

Redox steps on ester **67** that was obtained in this way followed by Horner–Wadsworth–Emmons reaction[20] gave unsaturated ester **72**, which was transformed into tricyclic compound **73** in a 3-step sequence which included Friedel–Crafts reaction (Scheme 3-11). Conditions of PPA or TFA/TFAA was not suitable in this Friedel–Crafts reaction (PPA: 13%, TFA/TFAA: 0 %). Oxidative dearomatization of **73** did not give the desired compound **74** but a complex mixture.



Scheme 3-11. Synthesis of tricyclic compound **73** and the oxidative dearomatization

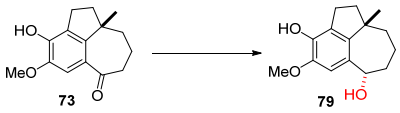
The reaction was considered to fail because the desired compound **74** is so electronically deficient that side reactions might occur, such as Diels–Alder reaction and conjugate addition. Thus, the carbonyl group in **73** should be removed (Scheme 3-12). Acetal protection with either ethylene glycol or propanediol did not proceed.[26] Dithioacetalization and the oxidative dearomatization of **77** proceeded, but the dithioacetal group was transformed into a dimethyl acetal.



Scheme 3-12. Acetalization and dithioacetalization

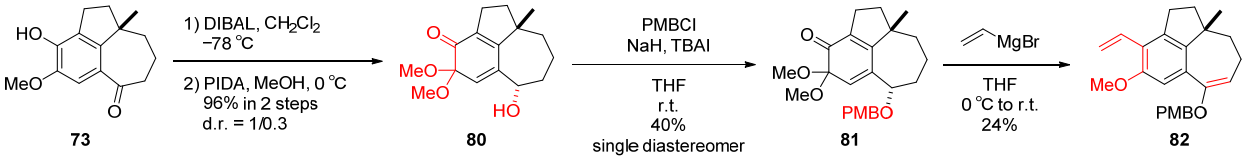
Next, we decided to reduce the carbonyl group (Table 3-2). In entry 1, $NaBH_4$ provided a 1:1 diastereomeric products. In entry 2, the diastereoselectivity was 3:1 in the case of DIBAL. L-selectride, a bulky hydride reagent, did not reduce ketone **73** (entry 3). A borane reduction using 2-Me-CBS-oxazaborolidine[27] gave the alcohol **79** in a good diastereomeric ratio (entry 4).

Table 3-2. Reduction of carbonyl group in **73**

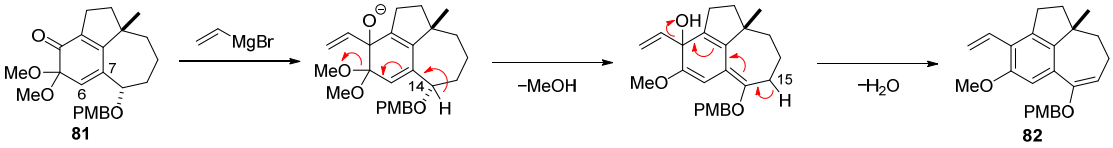


entry	conditions	results
1	$NaBH_4$, MeOH, 0 ℃	quant., d.r. = 1/1
2	DIBAL, CH_2Cl_2, −78 ℃	quant., d.r. = 3/1
3	L-selectride, THF, −78 to 0 ℃	N.R.
4	*rac*-2-Me-CBS, BH_3·SMe_2, THF, −30 ℃	94%, d.r. = 16/1

Alcohol **79**, which was given by reduction of **73** with DIBAL, could be dearomatized with PIDA in MeOH (Scheme 3-13). Corresponding *o*-quinone monoacetal **80** was protected by a PMB group to afford PMB ether **81** in 40% yield as a single diastereomer. The reaction of **81** with vinyl Grignard reagent gave only aromatized compound **82**. The mechanism presumably involved elimination of 14-H as MeOH after addition of Grignard reagent, then the intermediate was aromatized by dehydration (Scheme 3-14).



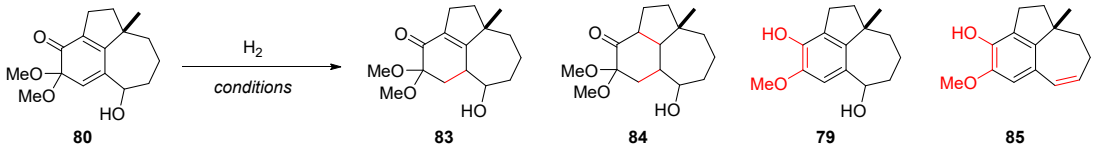
Scheme 3-13. Oxidative dearomatization and the next reaction



Scheme 3-14. Reaction mechanism from **81** to **82**

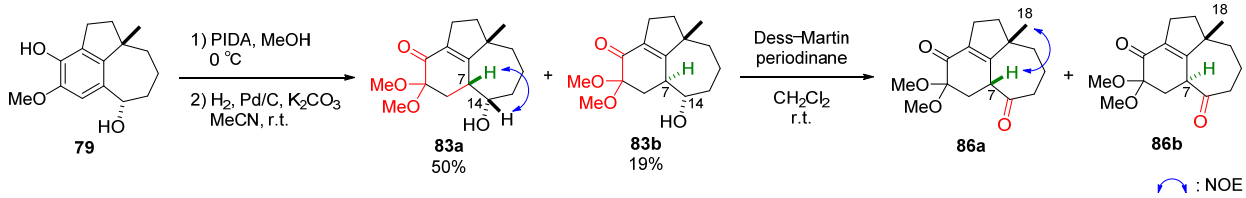
Considering the mechanism, a reduction of $\Delta^{6,7}$ double bond could suppress the production of undesired aromatic compound **82**. Thus, hydrogenation of $\Delta^{6,7}$ double bond was conducted (Table 3-3). A condition of Pd/C in MeOH led to the overreduction (entry 1). Using cationic Crabtree catalyst for regioselective reduction by neighboring group participation of hydroxyl group gave aromatized compounds (entry 2).[28] In entries 3-6, a base that played neutralizing and catalyst poisoning roles was added to the condition of entry 1. K_2CO_3 brought better results (entry 3), and finally, **84** was produced in 80% yield by solvent exchange from EtOAc to MeCN to increase the solubility of K_2CO_3 (entry 6).

Table 3-3. Hydrogenation of **80**

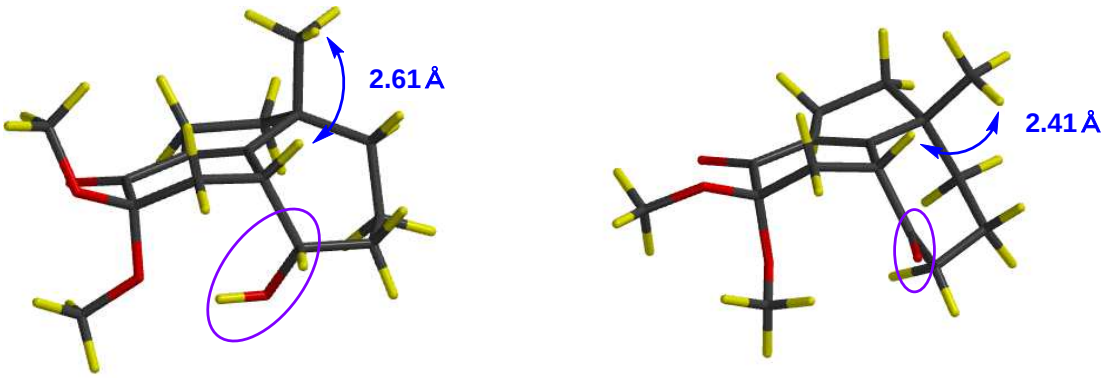


entry	conditions	yields (%)			
		83	**84**	**79**	**85**
1	Pd/C, MeOH, r.t.	0	50	0	0
2	Crabtree cat., DCE, r.t. to 40 ℃	0	0	19	39
3	Pd/C, K_2CO_3, AcOEt, r.t.	55	0	17	0
4	Pd/C, Cs_2CO_3, AcOEt, r.t.	44	0	13	0
5	Pd/C, Et_3N, AcOEt, r.t.	13	0	16	0
6	Pd/C, K_2CO_3, MeCN, r.t.	80	0	0	0

Oxidative dearomatization and hydrogenation was carried out in succession because **80** was unstable (Scheme 3-15). In this way, regioselective hydrogenation of resultant *o*-quinone monoacetal gave α,α-dimethoxy enone **83a** with BCD rings stereoselectivity. The relative configurations of 6/5/7-ring systems **83a** and **83b** were determined by NOE correlations of **83a** and the corresponding diketone **86a**. These results were supported by computational chemistry (Figure 3-5). The DFT calculations for **83a** and **86a** were performed using Spartan 08 at the B3LYP/6-31G* level. The NOE correlation between 7-H and 18-H in the natural compound was observed according to the isolation paper. The distance between 7-H and 18-H in **86a** (2.61 Å) was closer than that in **83a** (2.41 Å).



Scheme 3-15. α,α-dimethoxy enone **83a** with BCD rings

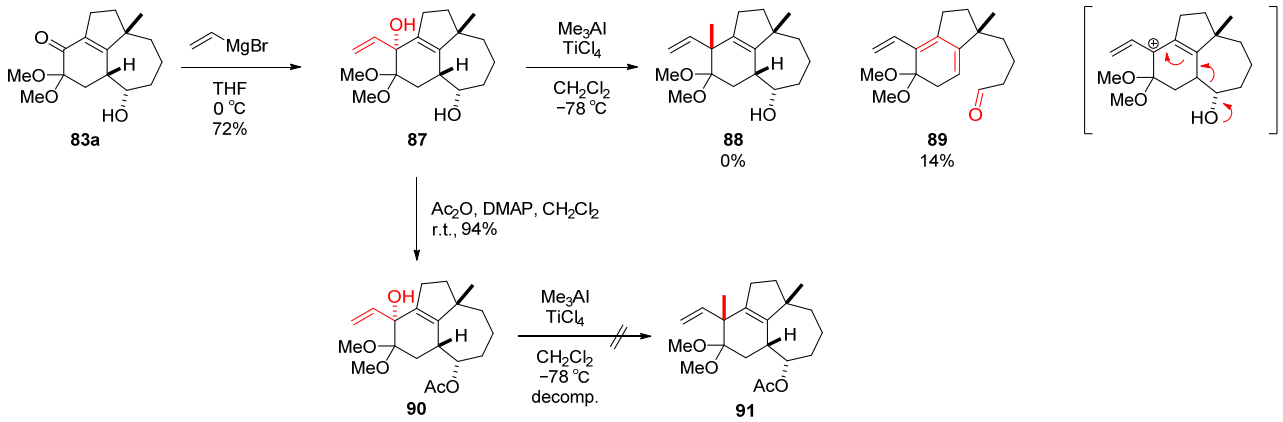


83a **86a**

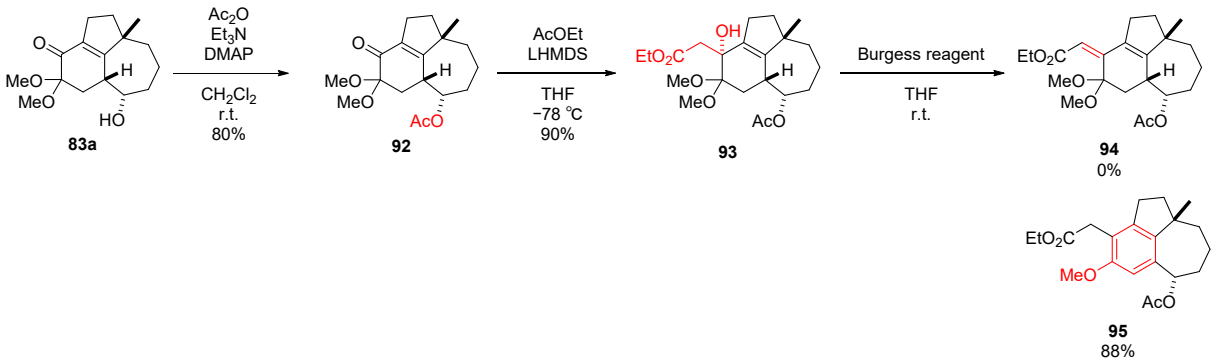
Figure 3-5. Calculated structures of **83a** and **86a** (B3LYP/6-31G*//B3LYP/6-31G*)

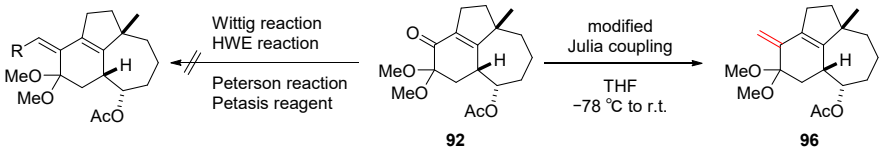
3-4. Attempted construction of the A ring

Transformation of **83a** for the construction of A ring was attempted (Scheme 3-16). Addition of vinyl Grignard reagent proceeded in 72% yield as expected. Methylation of double allylic alcohol **87** was found to result in decomposition, and **89** was detected with low yield, which was produced as a result of Grob type fragmentation. To prevent Grob type fragmentation of **87**, the hydroxyl group was protected to give acetate **90**. However, acetate **90** was decomposed under the conditions of a methylation. The aldol reaction of acetate **92** with the lithium enolate of EtOAc worked well to afford aldol **93**, dehydration of which resulted in aromatization (Scheme 3-17).[29] Exomethylene **96**, a foothold to construct the A ring, was obtained only by modified Julia coupling using BT-sulfone (BI-sulfone: 0%, and PT-sulfone: 11%).[30,31,32,33] Wittig, HWE, Peterson reactions, and Petasis reagent did not allow production of olefins.[20,34,35,36] Acetate **92** seemed to be able to react only with primary nucleophiles. However, subsequent cyclopropanation[37] and hydroboration of **96** did not proceed (Scheme 3-18).



Scheme 3-16. Construction of quaternary carbon

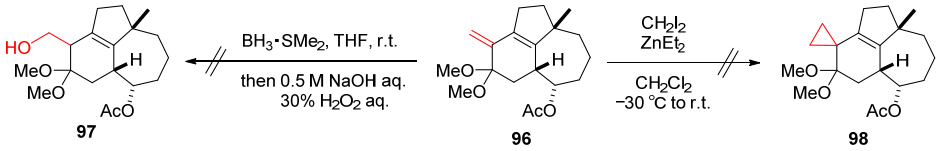




modified Julia coupling condition

conditions	yield
BT-sulfone, NaHMDS	44% (brsm 66%)
BT-sulfone, LHMDS	17% (brsm 41%)
BI-sulfone, NaHMDS	N. R.
PT-sulfone, NaHMDS	11% (brsm 37%)

Scheme 3-17. Olefination



Scheme 3-18. Transformation of exometylene **96**

3-5. Birch reduction

In the previous section, the author mentioned oxidative dearomatization. Next, Birch reduction of **73**, **79** and 8 analogs were examined (Figure 3-6). Each of these results gave reduction of a carbonyl group, recovery of a starting material, or decomposition. Although the substituents and the conditions were changed, the desired compounds were not obtained. It was thought that the substitution number of benzene ring was a problem. There were no reports of Birch reduction with penta-substituted benzenes and a few tetra-substituted benzenes.

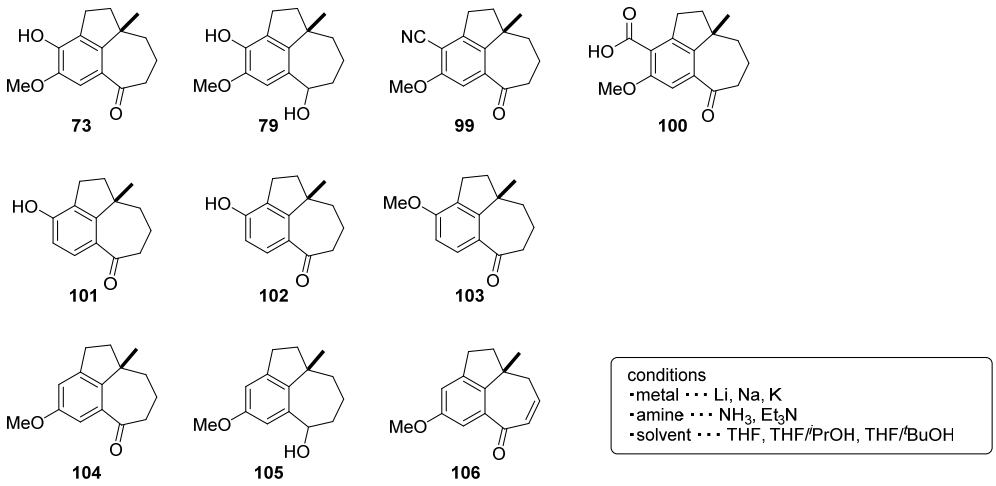
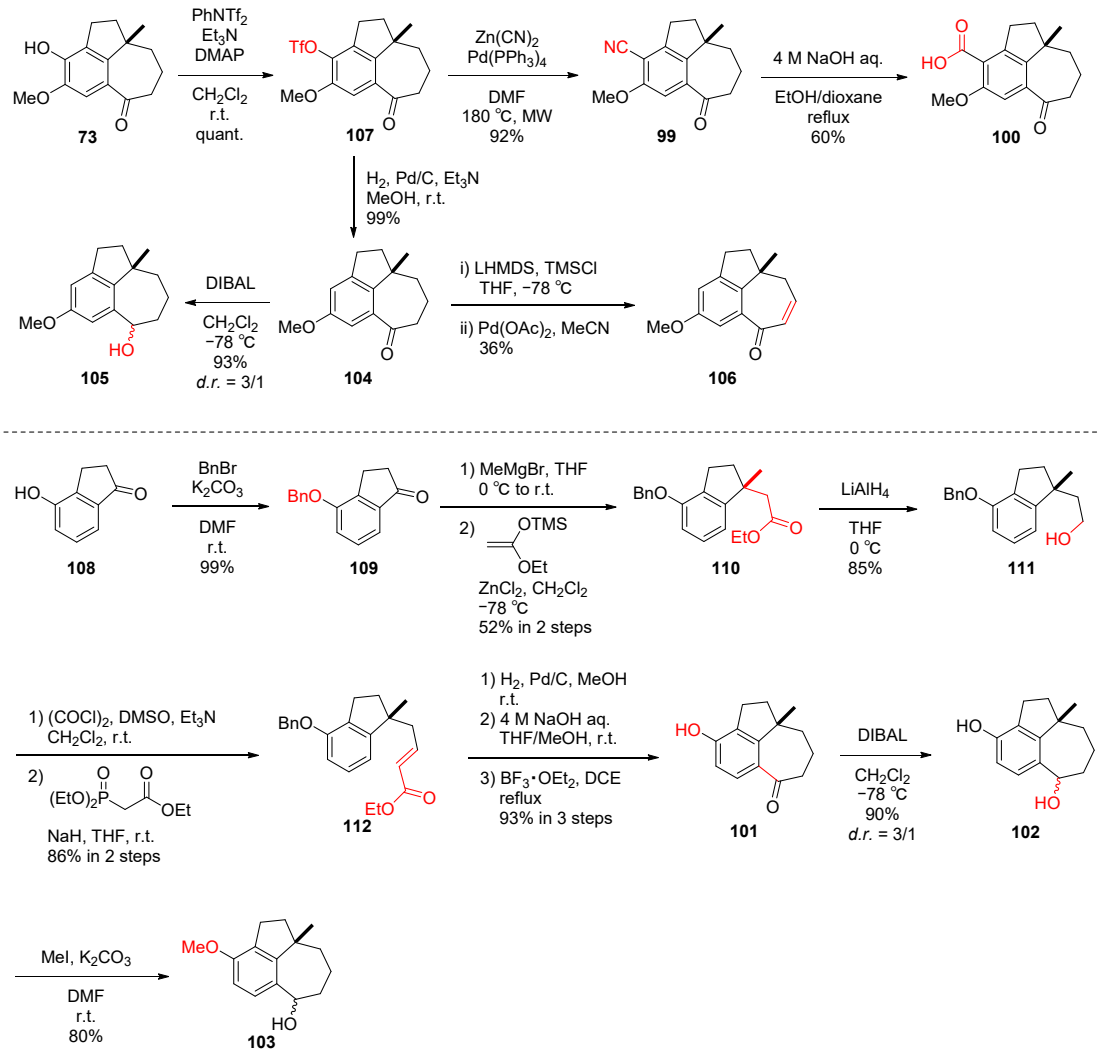


Figure 3-6. Birch reduction

Here, eight analogs were synthesized as below. Compounds **99**, **100**, **104**, **105**, **106** were derived from **73**. Nitrile **99** was prepared by Negishi coupling between triflate **107** and $Zn(CN)_2$,[38] and subsequently hydrolyzed to afford carboxylic acid **100** (Scheme 3-19). Reduced compound **104** was prepared by hydrogenolysis of **107**, and independent reduction of the carbonyl group or Ito–Saegusa oxidation[39] of **104** gave alcohol **105** and enone **106**, respectively. Starting from **109** instead of **57**, tetra-substituted benzene **101** was prepared, which was transformed into tetra-substituted benzenes **102** and **103**. Thus, methylation of **109** and the following substitution with the KSA gave ester **110**. Redox steps on ester **110** that was obtained in this way followed by Horner–Wadsworth–Emmons reaction[20] gave unsaturated ester **112**, which was transformed into tricyclic compound **101** in a 3-step sequence which included Friedel–Crafts reaction.



Scheme 3-19. Synthesis of substrates for Birch reduction

3-6. Synthesis of 6/6/6- and 6/5/6-ring systems

The analogous tricyclic skeletons of **83a** and **83b** prepared by this strategy are included in the natural compounds such as amphilectane-class diterpenes **113** and **114**,[40,41] wickerol A (**115**)[42], and hydropyrene (**116**)[43] as shown in Figure 3-7. The author investigated the applicability of the above strategy for the synthesis of other polycyclic compounds, 6/6/6- and 6/5/6-ring systems.

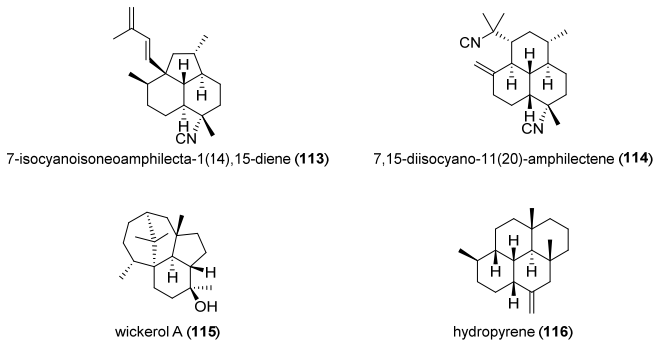
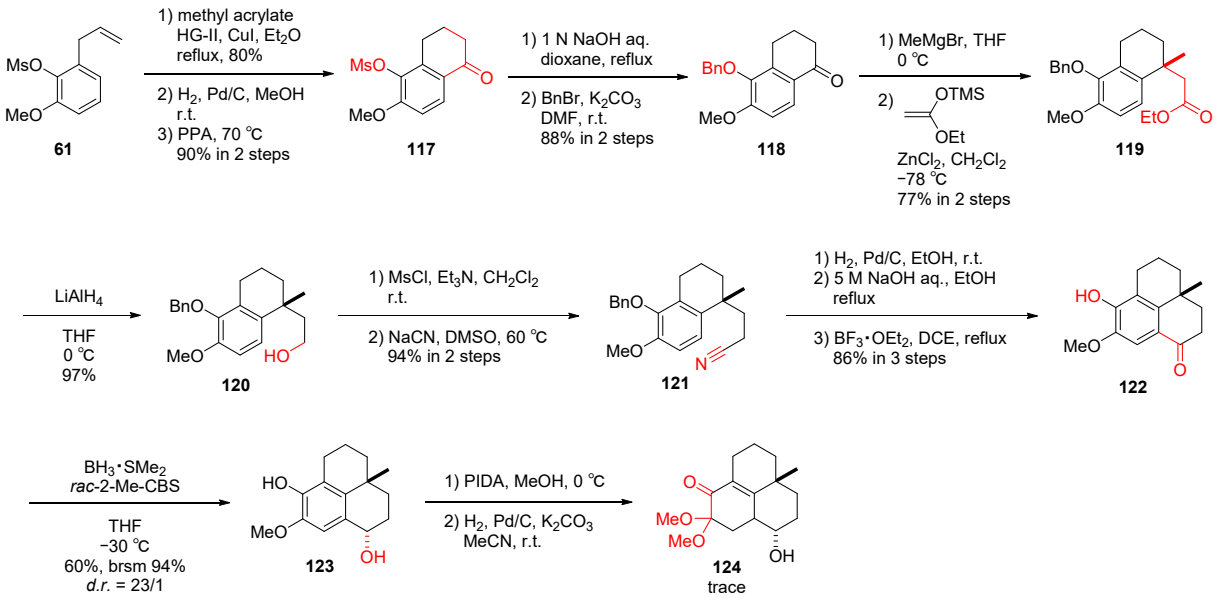


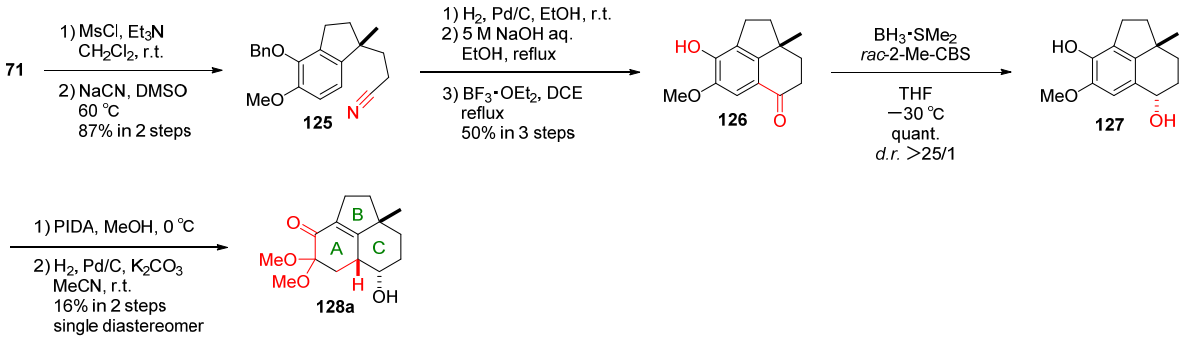
Figure 3-7. Structures of amphilectane-class diterpenes **113** and **114** wickerol A (**115**), and hydropyrene (**116**)

Known tetralone **118**,[44] which was synthesized from *o*-eugenol mesylate **61**, was converted to ester **119**, which was reduced to alcohol **120**. S_N2 reaction with NaCN of the corresponding mesylate provided homologated nitrile **121** (Scheme 3-20). After removal of the benzyl group, hydrolysis and Friedel–Crafts acylation gave the desired 6/6/6-compound **122**. Oxidative dearomatization of **122** failed as with compound **73**. Thus, 6/6/6-compound **122** was reduced by borane and CBS catalyst with good diastereoselectivity. However, oxidative dearomatization gave only a trace amount of the desired compound.



Scheme 3-20. Synthesis of a 6/6/6-ring system compound

Intermediate **71** was converted into nitrile **125** by S_N2 reaction. The same 3-step transformation as in the preparation of **122** afforded 6/5/6-compound **126** in moderate yield (Scheme 3-21). Reduction, dearomatization, and hydrogenation afforded the desired compound as a single diastereomer in 16% yield.



Scheme 3-21. Synthesis of a 6/5/6 system compound

The product **128** has a possibility of four stereoisomers **128a-d** (Figure 3-8), and the correct structure was determined by NMR and DFT calculations comprehensively. Four structures were calculated in CH_2Cl_2 at the B3LYP/6-31G level to reproduce the NMR data in $CDCl_3$. In ^1H NMR spectrum, the coupling of H1-H3 and H1-H5 were observed (5.1 and 13.5 Hz) and that of H1-H7 was not. According to Karplus equation,[45] each dihedral angles were anticipated to be about 50° ($\theta_{(H1\text{-}C2\text{-}C3\text{-}H4)}$), 180° ($\theta_{(H1\text{-}C2\text{-}C3\text{-}H5)}$), and 90° ($\theta_{(H1\text{-}C2\text{-}C6\text{-}H7)}$). The suitable calculated structures to explain these coupling constant values were **128a** and **128d**. Next, coupling constants of axial H8 were observed as 3.4, 13.3, and 13.3 Hz. These facts indicate that the C ring has a chair-like conformation, showing that structure **128a** is correct.

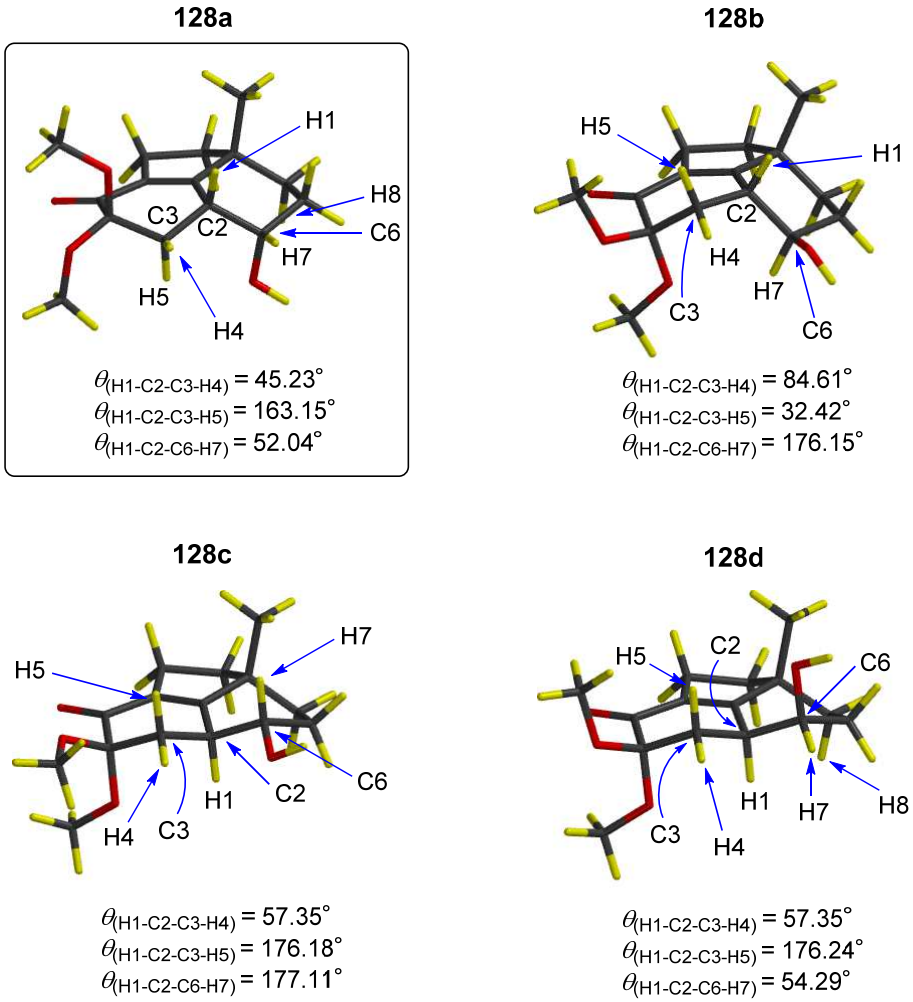
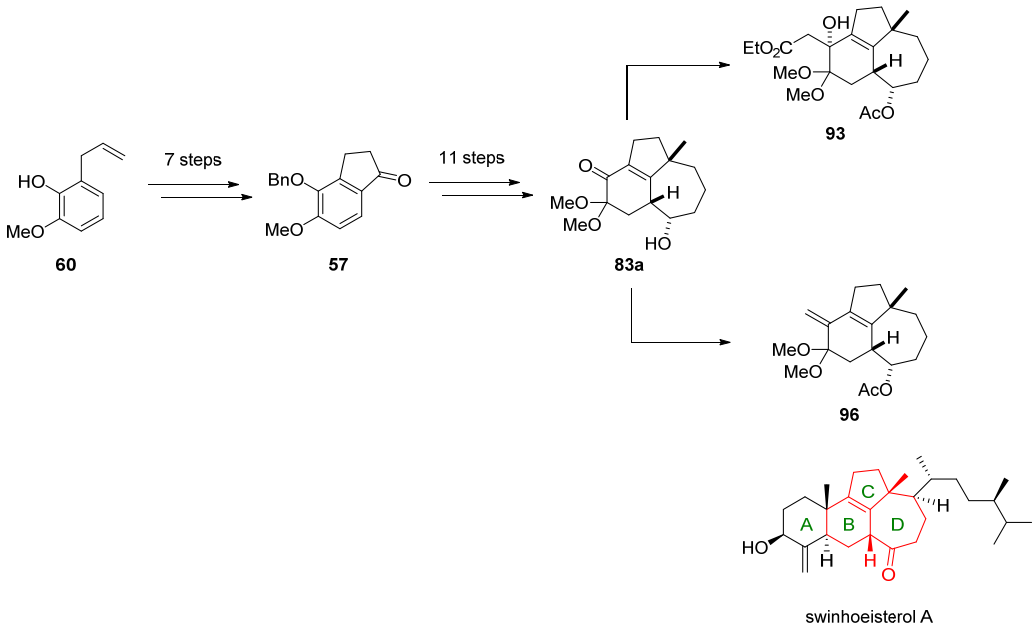


Figure 3-8. Calculated conformation structures of four 6/5/6-ring systems in CH_2Cl_2 (B3LYP/6-31G*//B3LYP/6-31G*)

These experiments indicated that the yields of oxidative dearomatizations of 6/5/7-, 6/6/6-, and 6/5/6-tricyclic systems were much influenced by the ring systems. On TLC, oxidative dearomatization was observed to proceed clearly, therefore, the reason of the low yields of the desired products might be that the unstable *o*-quinone monoacetal decomposed during at the work-up of oxidation step, particularly in the cases of 6/5/6- and 6/6/6-ring systems.

3-7. Summary

The author has achieved the synthesis of two tricyclic compounds **93** and **96**, which corresponds to the BCD ring system of swinhoeisterol A. Swinhoeisterol A is a novel steroid with unusual carbon skeleton, that shows cytotoxicity against A549 cells and H(p300) inhibitory activity. The synthetic strategy, based on the chemistry of benzene, allowed the preparation tricyclic compounds **93** and **96** in 20 steps from *o*-eugenol. Friedel–Crafts acylation and an oxidative dearomatization were the key steps of this synthetic endeavor.



Scheme 3-22. Summary

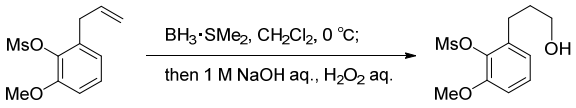
3-7. Experimental section

3-7-1. General

All moisture-sensitive reactions were performed under an atmosphere of argon or nitrogen, and the starting materials were azeotropically dried with benzene before use. Anhydrous MeOH, MeCN, CH_2Cl_2, THF and DMSO were purchased from Sigma-Aldrich Co., Inc., or Wako Pure Chemical Industries Ltd., and used without further drying. TLC analysis were conducted on E. Merck precoated silica gel 60 F_{254} (0.25 mm layer thickness). Fuji Silysia silica gel BW-820MH (75–200 μm) was used for column chromatography. E. Merck PLC Silica gel 60 F_{254} (0.5 and 2 mm layer thickness) was used for PTLC. Infrared (IR) spectra were recorded on a JASCO FT/IR-4100 instrument and only selected peaks are reported in wavenumbers (cm^{-1}). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 600, a Bruker AVANCE 500, a Bruker AVANCE 400, and a Bruker DPX 400 spectrometer. The ^{1}H and ^{13}C chemical shifts (δ) are reported relative to residual $CHCl_3$ (δ_H = 7.26 and δ_C = 77.0), respectively. *J* values are given in Hz. The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. High resolution ESI/TOF mass spectra were recorded on a JEOL AccuTOFCS JMS-T100CS spectrometer.

3-7-2. Synthesis and spectroscopic data of compounds

Alcohol **62**

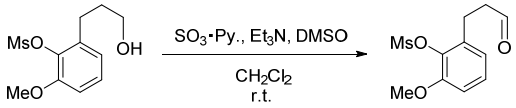


61 **62**

To a stirred solution of mesylate **61** (504 mg, 2.08 mmol) in THF (10.5 mL) was added $BH_3 \cdot SMe_2$ (2.0 M THF, 1.1 mL, 2.20 mmol) at 0 °C. After stirring for 3 h at 0 °C, 1.0 M NaOH aq. (1.4 mL, 1.40 mmol) and 30% H_2O_2 aq. (1.4 mL) were added to the mixture. After stirring for 2 h at 0 °C, The mixture was diluted with saturated aqueous $Na_2S_2O_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (15 g, hexane–EtOAc 7 : 1 → 5 : 1 →3 : 1) to afford alcohol **62** (519 mg, 96%) as a colorless oil:

R_f = 0.40 (hexane : EtOAc = 2 : 1)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (dd, *J* = 8.0, 8.0 Hz, 1H), 6.89 (dd, *J* = 8.0, 1.1 Hz, 1H), 6.84 (dd, *J* = 8.0, 1.1 Hz, 1H), 3.88 (s, 3H), 3.68 (t, *J* = 5.9 Hz, 1H), 3.67 (t, *J* = 5.9 Hz, 1H), 3.36 (s, 3H), 2.85 (t, *J* = 7.7 Hz, 2H), 1.91 (tt, *J* = 7.7, 5.9 Hz, 2H).

Aldehyde **63**

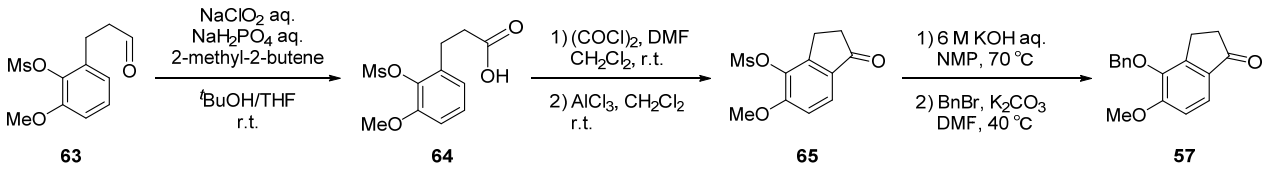


62 **63**

To a stirred solution of alcohol **62** (2.70 g, 10.4 mmol) in CH_2Cl_2 (35 mL) was added SO_3·Py. (4.96 g, 31.2 mmol), Et_3N (5.8 mL, 41.6 mmol), and DMSO (5.9 mL, 75.5 mmol) at 0 °C. After stirring for 1.5 h at room temperature, the mixture was diluted with H_2O (30 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined extracts were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (80 g, hexane–EtOAc 7 : 1 → 5 : 1) to afford aldehyde **63** (2.28 g, 85%) as a colorless oil.

R_f = 0.61 (hexane : EtOAc = 2 : 1)
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (t, *J* = 1.0 Hz, 1H), 7.17 (dd, *J* = 8.0, 8.0 Hz, 1H), 6.85 (d, *J* = 8.0 Hz, 2H), 3.88 (s, 3H), 3.36 (s, 3H), 3.09 (t, *J* = 7.5 Hz, 2H), 2.81 (dt, *J* = 7.5, 1.0 Hz, 2H).

Indanone **57**



To a stirred solution of aldehyde **63** (330 mg, 1.30 mmol) in ^{t}BuOH (13 mL) and THF (8 mL) were added 80% $NaClO_2$ aq. (0.8 mL, 7.08 mmol) and 8.0 M NaH_2PO_4 aq. (12 mL) at room temperature. After stirring for 12 h at the same temperature, the mixture was diluted with Et_2O (20 mL) and extracted with 1.5 M NaOH aq. (3 × 15 mL). The combined extracts were acidified to pH 3 with 3.0 M HCl aq. and extracted with CH_2Cl_2 (3 × 20 mL). The combined extracts were washed with brine (30 mL), dried over Na_2SO_4, and filtered. Removal of the solvent afforded crude carboxylic acid **64**, which was used for the next reaction without further purification.

To a stirred solution of the carboxylic acid **64** in CH_2Cl_2 (7 mL) were added DMF (3 drops) and $(COCl)_2$ (0.2 mL, 2.33 mmol), at 0 ℃. After stirring for 1 h at 0 ℃ and for 1 h at room temperature, the mixture was concentrated. The crude acid chloride was used for the next reaction without further purification.

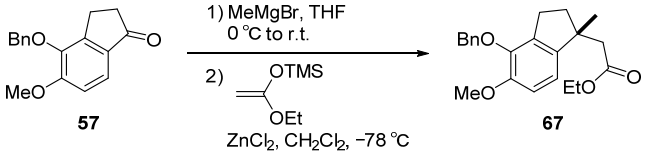
To a stirred solution of the acid chloride in CH_2Cl_2 (7 mL) was added $AlCl_3$ (311 mg, 2.33 mmol) at 0 °C. After stirring for 8 h at room temperature, the mixture was diluted with saturated aqueous $NaHCO_3$ (4 mL) and saturated aqueous Na/K tartrate (4 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were acidified to pH 3 with 3.0 M HCl aq. and extracted with CH_2Cl_2 (3 × 20 mL). The combined extracts were washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated. The crude product was partially purified by column chromatography on silica gel (10 g, $CHCl_3$–MeOH 9 : 1). The resultant indanone **65** was used for the next reaction without further purification.

To a stirred solution of the indanone **65** in NMP (10 mL) was added 6.0 M KOH aq. (1.0 mL, 6.00 mmol) at room temperature. After stirring for 40 min at 70 ℃, the mixture was acidified to pH 3 with 3.0 M HCl aq. and extracted with EtOAc (3 × 8 mL). The combined extracts were washed with brine (10 mL), dried over Na_2SO_4, and filtered. Removal of the solvent afforded crude phenol, which was used for the next reaction without further purification.

To a stirred solution of the phenol in DMF (7 mL) was added K_2CO_3 (719 mg, 5.20 mmol) and BnBr (0.31 mL, 2.59 mmol) at room temperature. After stirring for 12 h at 40 ℃, the mixture was diluted with H_2O (25 mL) and extracted with Et_2O (3 × 15 mL). The combined extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified by column chromatography on silica gel (12 g, hexane–EtOAc 4 : 1) to afford indanone **67** (285 mg, 83%) as a pale yellow solid.

R_f = 0.34 (hexane : EtOAc = 2 : 1)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 8.5 Hz, 1H), 7.44–7.39 (m, 2H), 7.39–7.30 (m, 3H), 6.99 (d, J = 8.5 Hz, 1H), 2.89 (t, J = 5.9 Hz, 2H), 2.58 (t, J = 5.9 Hz, 2H).

Ester **67**



(Preparation of ketene silyl acetal)

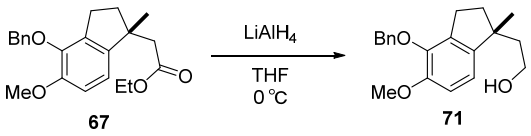
To a stirred solution of $^{i}Pr_2NH$ (8.7 mL, 62.4 mmol) in THF (120 mL), BuLi (2.60 M solution hexane, 21.6 mL, 56.2 mmol), was added dropwise at 0 °C, and the whole was stirred for 15 min. After cooling to –78 °C, a mixture of AcOEt (5.1 mL, 52.1 mmol), and TMSCl (9.4 mL, 74.1 mmol) in THF (30 mL) was dropped to the mixture. After the addition was completed, the mixture was stirred for 3 h at room temperature. Then, THF was evaporated and hexane was added. The resulting precipitate was filtered through a pad of Celite® with hexane. The filtrate was evaporated, and the resulting residue was purified by distillation (b.p. 55 ℃/ 4 kPa) to give ketene silyl acetal (3.25 g, 39%).

To a stirred solution of indanone **57** (100 mg, 0.352 mmol) in THF (1.8 mL) was added MeMgBr (3.0 M Et_2O, 0.29 mL, 0.87 mmol) at 0 °C. After stirring for 2 h at room temperature, the mixture was diluted with saturated aqueous NH_4Cl (1 mL) and extracted with EtOAc (3 × 2 mL). The combined extracts were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was partially purified by column chromatography on silica gel (3 g, hexane–EtOAc 3 : 1). The resultant tertiary alcohol was used for the next reaction without further purification.

To a stirred solution of the tertiary alcohol and distilled ketene silyl acetal (179 mg, 1.12 mmol) in CH_2Cl_2 (1.8 mL) was added $ZnCl_2$ (1.9 M 2-methyl THF, 0.24 mL, 0.456 mmol) at –78 °C. After stirring for 2 h at –78 °C, the mixture was diluted with saturated aqueous EDTA·2Na (1 mL) and extracted with CH_2Cl_2 (3 × 2 mL). The combined extracts were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (4 g, hexane–EtOAc 1 : 0 → 20 : 1) to afford ester **67** (107 mg, 78% in 2 steps) as a colorless oil.

R_f = 0.71 (hexane : EtOAc = 2 : 1)
IR ($CHCl_3$) 3019, 2960, 1721, 1486, 1266, 1077, 790 cm^{-1}
^1H NMR (400 MHz, $CDCl_3$) δ 7.45–7.38 (m, 2H), 7.37–7.26 (m, 3H), 6.83 (d, *J* = 8.2 Hz, 1H), 6.78 (d, *J* = 8.2 Hz, 1H), 5.03 (s, 2H), 4.10 (dq, *J* = 10.8, 7.2 Hz, 1H), 4.06 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.86 (s, 3H), 2.74 (dd, *J* = 7.2, 7.2 Hz, 2H), 2.53 (d, *J* = 13.7 Hz, 1H), 2.42 (d, *J* = 13.7 Hz, 1H), 2.21 (ddd, *J* = 13.6, 6.4, 6.4 Hz, 1H), 1.87 (ddd, *J* = 13.6, 6.4, 6.4 Hz, 1H), 1.32 (s, 3H), 1.21 (dd, *J* = 7.2, 7.2 Hz, 3H)
^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 151.5, 144.1, 143.8, 138.1, 136.7, 128.3, 128.2 (2C), 127.8 (2C), 117.6, 111.4, 74.4, 60.0, 56.2, 46.1, 45.4, 39.2, 27.0, 26.4, 14.2
HRMS (ESI) *m/z* 377.1729, calcd for $C_{22}H_{26}NaO_4$ $[M+Na]^+$ 377.1738.

Alcohol **71**

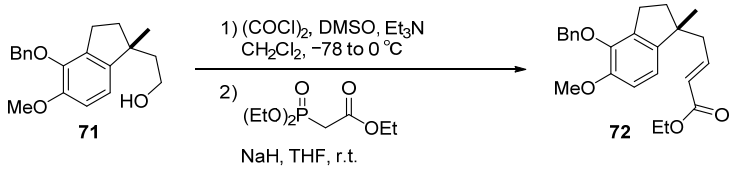


67 **71**

To a solution of ester **67** (660 mg, 1.86 mmol) in THF (9.0 mL) was added $LiAlH_4$ (78 mg, 2.06 mmol) at 0 °C. After stirring for 1 h at the same temperature, the mixture was diluted with saturated aqueous Na/K tartrate (10 mL) and stirred for 30 min at room temperature. The resultant mixture was extracted with EtOAc (3 × 5 mL). The combined extracts were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (20 g, hexane–EtOAc 5 : 1 → 3 : 1) to afford alcohol **71** (551 mg, 93%) as a colorless oil.

R_f = 0.31 (hexane : EtOAc = 2 : 1)
IR ($CHCl_3$) 3624, 3010, 2955, 1604, 1485, 1266, 1077, 1010, 761 cm^{-1}
^1H NMR (400 MHz, $CDCl_3$) δ 7.43–7.40 (m, 2H), 7.37–7.27 (m, 3H), 6.81 (d, *J* = 8.7 Hz, 1H), 6.79 (d, *J* = 8.7 Hz, 1H), 5.06 (d, *J* = 11.4 Hz, 1H), 5.02 (d, *J* = 11.4 Hz, 1H), 3.86 (s, 3H), 3.64 (ddd, *J* = 10.5, 8.7, 6.0 Hz, 1H), 3.57 (ddd, *J* = 10.5, 8.5, 6.3 Hz, 1H), 2.75 (ddd, *J* = 15.5, 8.6, 5.5 Hz, 1H), 2.68 (ddd, *J* = 15.5, 7.9, 7.1 Hz, 1H), 1.98 (ddd, *J* = 12.9, 7.9, 5.5 Hz, 1H), 1.91–1.75 (m, 3H), 1.23 (s, 3H). A signal due to a proton (OH) was not observed.
^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 144.6, 143.5, 138.1, 137.0, 128.32 (2C), 128.26 (2C), 127.8, 117.6, 111.5, 74.4, 60.4, 56.2, 46.0, 44.1, 39.3, 27.5, 27.3
HRMS (ESI) *m/z* 335.1632, calcd for $C_{20}H_{24}NaO_3$ $[M+Na]^+$ 335.1623.

Conjugated ester **72**

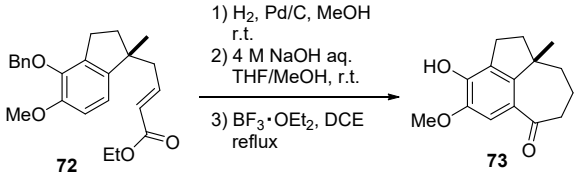


To a solution of $(COCl)_2$ (0.22 mL, 2.57 mmol) in CH_2Cl_2 (7.0 mL) was added DMSO (0.39 mL, 4.99 mmol) in CH_2Cl_2 (3.0 mL) at –78 °C. After stirring for 30 min at –78 °C, alcohol **71** (361 mg, 1.16 mmol) in CH_2Cl_2 (2 mL) was added to the reaction mixture. After stirring for further 30 min at 0 °C, Et_3N (0.72 mL, 5.17mmol) was added to the reaction mixture. The mixture was stirred for 2 h at 0 °C and diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was partially purified by column chromatography on silica gel (7 g, hexane–EtOAc 6 : 1). The resultant aldehyde was used for the next reaction without further purification.

To a stirred solution of ethyl diethylphosphonoacetate (0.43 mL, 1.68 mmol) in THF (10 mL) was added 60% NaH (63.1 mg, 1.58 mmol) at 0 °C. After stirring for 30 min at 0 °C, a solution of the aldehyde in THF (2.0 mL) was added to the reaction mixture. The mixture was stirred for 12 h at room temperature, diluted with saturated aqueous NH_4Cl (4 mL), and extracted with EtOAc (3 × 6 mL). The combined extracts were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (12 g, hexane–EtOAc 8 : 1) to afford conjugated ester **72** (420 mg, 96% in 2 steps) as a colorless oil.

R_f = 0.58 (hexane : EtOAc = 3 : 1)
IR ($CHCl_3$) 3019, 3011, 2957, 1709, 1485, 1266, 1186, 1077, 736 cm^{-1}
^1H NMR (400 MHz, $CDCl_3$) δ 7.45–7.39 (m, 2H), 7.38–7.27 (m, 3H), 6.88 (ddd, *J* = 15.5, 7.7, 7.7 Hz, 1H), 6.79 (s, 2H), 5.80 (ddd, *J* = 15.5, 1.1, 1.1 Hz, 1H), 5.03 (s, 2H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.86 (s, 3H), 2.75 (ddd, *J* = 15.5, 8.4, 5.3 Hz, 1H), 2.68 (ddd, *J* = 15.5, 7.8, 7.3 Hz, 1H), 2.40 (ddd, *J* = 14.8, 7.7, 1.1 Hz, 1H), 2.36 (ddd, *J* = 14.8, 7.7, 1.1 Hz, 1H), 1.96 (ddd, *J* = 13.1, 7.8, 5.3 Hz, 1H), 1.78 (ddd, *J* = 13.1, 8.4, 7.3 Hz, 1H), 1.28 (dd, *J* = 7.2, 7.2 Hz, 3H), 1.23 (s, 3H)
^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 151.5, 146.2, 144.0, 143.9, 138.1, 136.7, 128.27 (2C), 128.26 (2C), 127.8, 123.6, 117.6, 111.5, 74.4, 60.1, 56.2, 47.2, 44.1, 38.9, 27.0, 26.7, 14.3
HRMS (ESI) *m/z* 403.1895, calcd for $C_{24}H_{28}NaO_4$ $[M+Na]^+$ 403.1885.

Tricyclic compound **73**



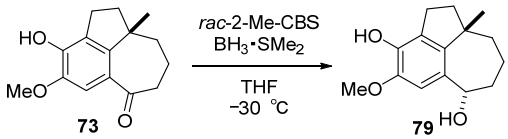
To a stirred solution of conjugated ester **72** (2.19 g, 5.76 mmol) in MeOH (28 mL) was added 10% Pd/C (184 mg, 0.173 mmol) at room temperature. After stirring under hydrogen atmosphere for 1 h at same temperature, the mixture was filtered through a pad of Celite® with MeOH (100 mL), and the filtrate was concentrated. The crude product was used for the next reaction without further purification.

To a stirred solution of the phenol in THF (14 mL) and MeOH (7 mL) was added 4.0 M NaOH aq. (7 mL, 28 mmol) at room temperature. After stirring for 12 h at room temperature, the mixture was acidified to pH 3 with 4.0 M HCl aq. and extracted with EtOAc (3 × 10 mL). The combined extracts were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated. The crude phenolic acid was used for next reaction without further purification.

To a stirred solution of the phenolic acid in $ClCH_2CH_2Cl$ (115 mL) was added $BF_3 \cdot OEt_2$ (2.45 mL, 17.3 mmol) at room temperature. After stirring for 18 h at reflux, the mixture was diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography on silica gel (40 g, hexane–EtOAc 4 : 1) to afford tricyclic compound **73** (1.39 g, 98% in 3 steps) as a pale yellow solid.

R_f = 0.45 (hexane : EtOAc = 2 : 1)
m.p. 161.5–162.7 °C
IR ($CHCl_3$) 3531, 3018, 2946, 1659, 1493, 1378, 1291, 1078, 819 cm^{-1}
^1H NMR (400 MHz, $CDCl_3$) δ 7.04 (s, 1H), 5.92 (s, 1H), 3.88 (s, 3H), 2.99–2.78 (m, 3H), 2.74 (ddd, *J* = 13.4, 11.2, 4.0 Hz, 1H), 2.20–1.83 (m, 6H), 1.13 (s, 3H)
^{13}C NMR (100 MHz, $CDCl_3$) δ 204.5, 145.3, 145.1, 145.0, 128.4, 128.1, 109.3, 56.3, 49.4, 46.1, 42.9, 40.8, 26.1, 25.9, 21.6
HRMS (ESI) *m/z* 269.1162, calcd for $C_{15}H_{18}NaO_3$ $[M+Na]^+$ 269.1154.

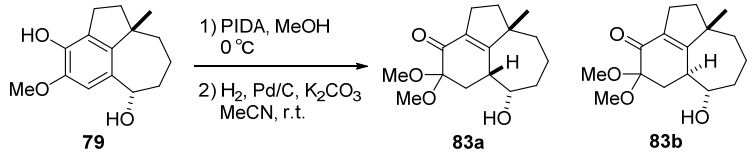
Alcohol **79**



To a stirred solution of tricyclic compound **73** (73.1 mg, 0.296 mmol) and *rac*-2-Me-CBS-oxazaborooridine (1.0 M toluene, 0.06 mL, 0.06 mmol) in THF (1.5 mL) was added $BH_3 \cdot SMe_2$ (2.0 M THF, 0.37 mL, 0.740 mmol) at –30 °C. After stirring for 6 h at the same temperature, the mixture was diluted with MeOH (0.5 mL) and H_2O (3 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3 g, hexane–EtOAc 8 : 1 → 5 : 1) to afford alcohol **79** (69.5 mg, 94%, *d.r.* = 16/1) as a colorless oil.

R_f = 0.38 (hexane : EtOAc = 1 : 1)
IR ($CHCl_3$) 3545, 3007, 2932, 1497, 1291, 1094, 793 cm^{-1}
^1H NMR (600 MHz, $CDCl_3$) δ 7.05 (s, 1H), 5.50 (s, 1H), 4.82 (br d, *J* = 7.3 Hz, 1H), 3.88 (s, 3H), 2.92 (ddd, *J* = 10.7, 5.3, 1.6 Hz, 1H), 2.87 (m, 1H), 2.16 (m, 1H), 1.98–1.76 (m, 5H), 1.66–1.43 (m, 3H), 1.14 (s, 3H)
^{13}C NMR (151 MHz, $CDCl_3$) δ 144.8, 139.9, 139.8, 132.4, 129.2, 105.5, 72.2, 56.3, 48.9, 43.6, 41.5, 39.8, 26.0, 23.5, 22.6
HRMS (ESI) *m/z* 269.1162, calcd for $C_{15}H_{20}NaO_3$ $[M+Na]^+$ 269.1154.

α,α-Dimethoxy enone **83a** and **83b**



To a stirred solution of alcohol **79** (40.2 mg, 0.162 mmol) in MeOH (1.6 mL) was added PIDA (62.6 mg, 0.194 mmol) at 0 °C. After stirring for 1 h at the same temperature, the mixture was diluted with saturated aqueous $NaHCO_3$ (3 mL) and extracted with CH_2Cl_2 (3 mL × 3). The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was partially purified by column chromatography on silica gel (1 g, hexane–EtOAc 5 : 1 → 1 : 1). The resultant *o*-quinone monoacetal was used for the next reaction without further purification.

To a stirred solution of the *o*-quinone monoacetal in MeCN (1.6 mL) were added K_2CO_3 (55.9 mg, 0.405 mmol) and 10% Pd/C (3.4 mg, 3.24 μmol) at room temperature. After stirring under hydrogen atmosphere for 1 h at the same temperature, the mixture was filtered through a pad of Celite® with EtOAc (50 mL), and the filtrate was concentrated. The crude product was purified by column chromatography on silica gel (2 g, hexane–EtOAc 6 : 1 → 4 : 1 → 3 : 1) to afford alcohol **83a** (22.6 mg, 50%) as a colorless oil and alcohol **83b** (8.4 mg, 19%) as a white solid.

Alcohol **83a**
R_f = 0.17 (hexane : EtOAc = 1 : 1)
IR ($CHCl_3$) 3409, 3008, 2949, 1665, 1624, 1451, 1217, 1094, 793, 716 cm^{-1}
^1H NMR (600 MHz, $CDCl_3$) δ 4.62 (br s, 1H), 4.10 (m, 1H), 3.33 (s, 6H), 2.73 (m, 1H), 2.55 (br dd, *J* = 8.6, 16.2 Hz, 1H), 2.45 (dddd, *J* = 2.3, 7.1, 9.5, 16.2 Hz, 1H), 2.41 (dd, *J* = 2.1, 14.2 Hz, 1H), 2.35 (dd, *J* = 6.8, 14.2 Hz, 1H), 2.02 (m, 1H), 1.84 (ddd, *J* = 9.5, 9.5, 12.1 Hz, 1H), 1.80 (dd, *J* = 7.9, 14.6 Hz, 1H), 1.71–1.54 (m, 3H), 1.53–1.30 (m, 2H), 1.01 (s, 3H)
^{13}C NMR (151 MHz, $CDCl_3$) δ 188.5, 170.9, 137.9, 96.0, 72.7, 51.7, 50.8, 48.9, 39.6, 39.5, 39.4, 37.8, 37.2, 26.4, 25.6, 18.0
HRMS (ESI) *m/z* 303.1585, calcd for $C_{16}H_{24}NaO_4$ $[M+Na]^+$ 303.1572; alcohol

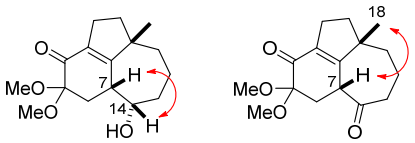
Alcohol **83b**
R_f = 0.14 (hexane : EtOAc = 1 : 1)
m.p. 126.4–129.2 °C; IR ($CHCl_3$) 3452, 3009, 2940, 1670, 1605, 1453, 1208, 1077, 1045, 731 cm^{-1}
^1H NMR (600 MHz, $CDCl_3$) δ 3.72 (m, 1H), 3.37 (s, 3H), 3.20 (s, 3H), 2.94 (dd, *J* = 3.6, 13.0 Hz, 1H), 2.81 (m, 1H), 2.58–2.47 (m, 2H), 2.19 (m, 1H), 1.85–1.48 (m, 7H), 1.42 (br s, 1H), 1.24 (dd, *J* = 7.0, 7.0 Hz, 1H), 1.03 (s, 3H)
^{13}C NMR (151 MHz, $CDCl_3$) δ 191.1, 170.7, 135.7, 97.1, 70.9, 52.1, 50.4, 49.0, 44.9, 42.7, 41.5, 38.3, 38.0, 26.0, 23.0, 21.4
HRMS(ESI) *m/z* 303.1557, calcd for $C_{16}H_{24}NaO_4$ $[M+Na]^+$ 303.1572.

Determination of the relative configurations at C7, C14 and C18 in **83a** and **86a**

diketone **86**

To a stirred solution of alcohol **83** (*d.r.* = 3/1, 5.9 mg, 0.0210 mmol) in CH_2Cl_2 (1.0 mL) was added Dess–Martin periodinane (17.9 mg, 0.0422 mmol) at room temperature. The mixture was stirred at room temperature for 1 h, poured into a mixture of saturated aqueous $Na_2S_2O_3$ (1.0 mL), saturated aqueous $NaHCO_3$ (1.0 mL), and H_2O (1.0 mL), and extracted with CH_2Cl_2 (3 × 3 mL). The combined extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatography on silica gel (2 g, hexane–EtOAc 6 : 1→3 : 1) to afford diketone **86** (4.7 mg, 81% , *d.r.* = 3.5/1) as a colorless oil: R_f = 0.52 (hexane : EtOAc = 1 : 1)

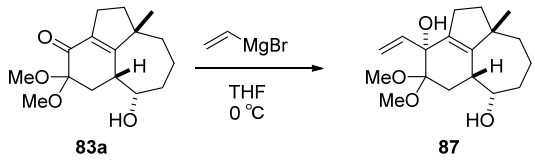
The stereochemistry of 6/5/7-ring systems **83a** and **83b** were determined by NOE correlations of **83a** and the corresponding diketone **86a** oxidized by Dess–Martin periodinane.



83a **86a**

Determination of the relative configuration in **83a** and **86a**

Double allylic alcohol **87**



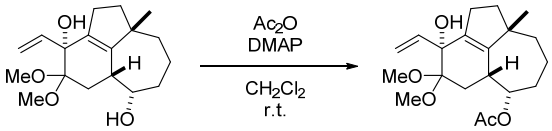
83a **87**

To a stirred solution of α,α-dimethoxy enone **83a** (81.7 mg, 0.291 mmol) in THF (2.9 mL) was added vinyl Grignard reagent (1.0 M Et_2O, 0.87 mL, 0.87 mmol) at 0 °C. After stirring for 3 h at room temperature, the mixture was diluted with saturated aqueous NH_4Cl (4 mL) and extracted with EtOAc (5 mL × 3). The combined extracts were with brine (8 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3 g, hexane–EtOAc 5 : 1 → 4 : 1 → 3 : 1) to afford double allylic alcohol **87** (64.8 mg, 72%) as a colorless oil.

R_f = 0.39 (hexane : EtOAc = 4 : 1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.92 (dd, *J* = 17.0, 10.7 Hz, 1H), 5.36 (dd, *J* = 17.0, 1.7 Hz, 1H), 5.23 (dd, *J* = 10.7, 1.7 Hz, 1H), 4.15 (br dd, *J* = 8.0 ,8.0 Hz, 1H), 3.39 (s, 3H), 3.33 (s, 3H), 3.05 (m, 1H), 2.64 (m, 1H), 2.43–2.08 (m, 4H), 1.77–1.40 (m, 7H), 1.10 (s, 3H). Two signals due to a proton (OH) were not observed.

Acetate **90**



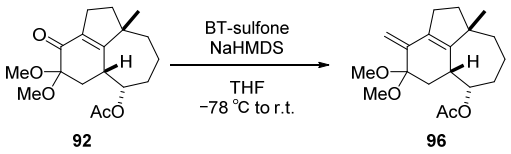
87 **90**

To a stirred solution of double allylic alcohol **87** (4.3 mg, 0.0123 mmol) in THF (1.0 mL) was added DMAP (15.0 mg, 0.123 mmol) and Ac_2O (6.5 µL, 0.0694 mmol) at 0 °C. After stirring for 3 h at room temperature, the mixture was diluted with H_2O (2 mL) and extracted with EtOAc (3 × 2 mL). The combined extracts were with brine (3 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (2 g, hexane–EtOAc 7 : 1 → 5 : 1) to afford acetate **90** (4.6 mg, 94%) as a colorless oil.

R_f = 0.73 (hexane : EtOAc= 1 : 1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (dd, *J* = 17.2, 10.8 Hz, 1H), 5.34 (dd, *J* = 17.2, 1.8 Hz, 1H), 5.23 (dd, *J* = 10.8, 1.8 Hz, 1H), 5.15 (m, 1H), 3.40 (s, 3H), 3.28 (s, 3H), 3.05 (m, 1H), 2.83 (m, 1H), 2.38–2.01 (m, 4H), 2.03 (s, 3H), 1.73–1.41 (m, 7H), 1.16 (s, 3H). A signal due to a proton (OH) was not observed.

Exomethylene **96**



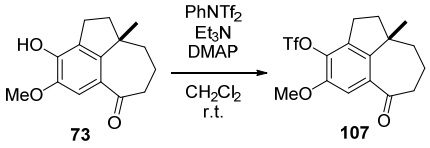
92 **96**

To a stirred solution of BT-sulfone (28.2 mg, 0.132 mmol) in THF (1.5 mL) was added NaHMDS (1.0 M THF, 0.145 mL, 0.145 mmol) at –78 °C. After stirring for 30 min at the same temperature, acetate **92** (21.3 mg, 0.0661 mmol) was added to the mixture at –78 °C. After stirring for 12 h at room temperature, the mixture was diluted with saturated aqueous NH_4Cl (3 mL) and extracted with EtOAc (3 × 3 mL). The combined extracts were with brine (4 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (2 g, hexane–EtOAc 12 : 1) to afford exomethylene **96** (64.8 mg, 72%) as a colorless oil.

R_f = 0.67 (hexane : EtOAc = 2 : 1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.36 (s, 1H), 5.30 (ddd, J = 9.0, 6.3, 2.4 Hz,1H), 5.05 (s, 1H), 3.32 (s, 3H), 3.04 (s, 3H), 3.03 (m, 1H), 2.49 (m, 1H), 2.31 (dd, *J* = 12.1, 4.7 Hz, 1H), 2.24 (ddd, *J* = 15.5, 7.6, 3.9 Hz, 1H), 2.38–2.20 (m, 1H), 2.04 (s, 3H), 1.79–1.23 (m, 8H), 1.20 (s, 3H).

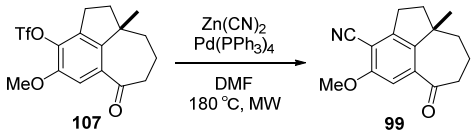
Triflate **107**



To a stirred solution of tricyclic compound **73** (15.1 mg, 0.0613 mmol) in CH_2Cl_2 (1.0 mL) was added Et_3N (25.3 µL, 0.184 mmol), $PhNTf_2$ (43.8 mg, 0.123 mmol), and DMAP (1.5 mg, 0.0123 mmol) at room temperature. After stirring for 1 h at same temperature, the mixture was diluted with saturated aqueous NH_4Cl (1.5 mL), and extracted with CH_2Cl_2 (3 × 3 mL). The combined extracts were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (2 g, hexane–EtOAc 16 : 1) to afford triflate **107** (23.2 mg, quant.) as a colorless oil.

R_f = 0.74 (hexane : EtOAc = 2 : 1)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (s, 1H), 3.89 (s, 3H), 3.06–2.98 (m, 2H), 2.90 (m, 1H), 2.72 (ddd, *J* = 12.8, 11.6, 4.1 Hz, 1H), 2.21–1.96 (m, 5H), 1.89 (ddd, *J* = 16.4, 16.4, 5.6 Hz, 1H), 1.14 (s, 3H).

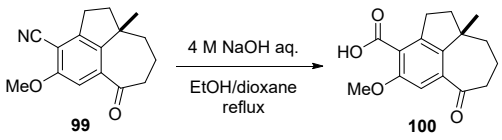
Nitrile **99**



To a stirred solution of triflate **107** (23.2 mg, 0.0613 mmol) in DMF (1.5 mL) was added $Zn(CN)_2$ (25.9 mg, 0.221 mmol) and $Pd(PPh_3)_4$ (10.6 mg, 9.17 μmol) at room temperature. After stirring for 20 min at 180 °C in microwave, the mixture was filtered through a pad of Celite® with EtOAc (30 mL), and the filtrate was concentrated. The crude product was purified by column chromatography on silica gel (3 g, hexane–EtOAc 12 : 1) to afford nitrile **99** (14.4 mg, 92%) as a colorless oil.

R_f = 0.74 (hexane : EtOAc = 2 : 1)
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (s, 1H), 3.91 (s, 3H), 3.19–3.03 (m, 2H), 2.89 (m, 1H), 2.72 (ddd, *J* = 12.2, 12.2, 3.8 Hz, 1H), 2.23–1.97 (m, 5H), 1.87 (m, 1H), 1.12 (s, 3H).

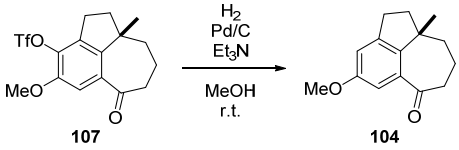
Carboxylic acid **100**



To a stirred solution of the nitrile **99** (14.1 mg, 0.0552 mmol) in dioxane (0.8 mL) and EtOH (0.4 mL) was added 4.0 M NaOH aq. (0.4 mL, 1.60 mmol). After stirring for 1.5 d at reflux, the mixture was acidified to pH 3 with 4.0 M HCl aq. and extracted with CH_2Cl_2 (3 × 3 mL). The combined extracts were combined, washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (2 g, hexane–Acetone 4 : 1 → 3 : 1) to afford carboxylic acid **100** (9.0 mg, 60%) as a white solid.

R_f = 0.58 (hexane : Acetone = 1 : 1)
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (s, 1H), 3.90 (s, 3H), 3.31 (ddd, *J* = 17.8, 6.9, 3.1 Hz, 1H), 3.17 (ddd, *J* = 17.8, 9.5, 8.6 Hz, 1H), 2.92 (ddd, *J* = 12.6, 6.6, 2.2 Hz, 1H), 2.77 (ddd, *J* = 12.6, 11.8, 3.7 Hz, 1H), 2.22–1.91 (m, 5H), 1.87 (ddd, *J* = 13.0, 13.0, 2.3 Hz, 1H), 1.12 (s, 3H). A signal due to a proton (COOH) was not observed.

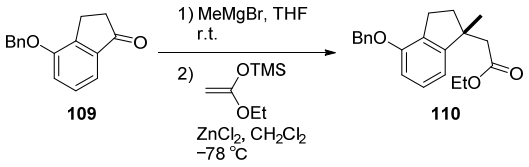
Tricyclic compound **104**



To a stirred solution of triflate **107** (152 mg, 0.402 mmol) in MeOH (2.0 mL) was added Et_3N (0.57 mL, 4.09 mmol) and 10% Pd/C (12.8 mg, 0.012 mmol) at room temperature. After stirring under hydrogen atmosphere for 3 h at the same temperature, the mixture was filtered through a pad of Celite® with MeOH (100 mL), and the filtrate was concentrated. The crude product was purified by column chromatography on silica gel (5 g, hexane–EtOAc 8 : 1) to afford tricyclic compound **104** (92.7 mg, 99%) as a white solid.

R_f = 0.64 (hexane : EtOAc = 3 : 1)
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (d, *J* = 2.3 Hz, 1H), 6.88 (d, *J* = 2.3 Hz, 1H), 3.81 (s, 3H), 2.97 (m, 1H), 2.92–2.82 (m, 2H), 2.78 (ddd, *J* = 12.2, 12.2, 3.9 Hz, 1H), 2.17 (m, 1H), 2.10–1.83 (m, 5H), 1.13 (s, 3H).

Ester **110**

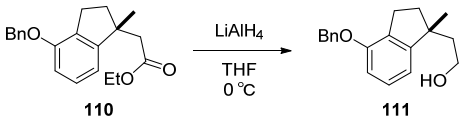


To a stirred solution of indanone **109** (601 mg, 2.52 mmol) in THF (8.0 mL) was added MeMgBr (3.0 M Et_2O, 1.7 mL, 5.40 mmol) at 0 °C. After stirring for 2 h at room temperature, the mixture was diluted with saturated aqueous NH_4Cl (6 mL) and extracted with EtOAc (3 × 6 mL). The combined extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was partially purified by column chromatography on silica gel (18 g, hexane–EtOAc 3 : 1). The resultant tertiary alcohol was used for the next reaction without further purification.

To a stirred solution of the tertiary alcohol and distilled ketene silyl acetal (1.44 g, 8.98 mmol) in CH_2Cl_2 (1.8 mL) was added $ZnCl_2$ (1.9 M 2-methyl THF, 1.42 mL, 2.70 mmol) at –78 °C. After stirring for 2 h at –78 °C, the mixture was diluted with saturated aqueous EDTA·2Na (2 mL) and extracted with CH_2Cl_2 (3 × 4 mL). The combined extracts were washed with brine (6 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (18 g, hexane–EtOAc 1 : 0 → 20 : 1) to afford ester **110** (424 mg, 52% in 2 steps) as a colorless oil.

R_f = 0.68 (hexane : EtOAc = 3 : 1)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.41 (m, 2H), 7.41–7.35 (m, 2H), 7.31 (m, 1H), 7.14 (dd, *J* = 7.8, 7.8 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 6.74 (d, *J* = 7.8 Hz, 1H), 5.09 (s, 2H), 4.11 (dq, *J* = 11.1, 7.2 Hz, 1H), 4.06 (dq, *J* = 11.1, 7.2 Hz, 1H), 2.92 (dd, *J* = 7.2, 7.2 Hz, 2H), 2.59 (d, *J* = 13.8 Hz, 1H), 2.49 (d, *J* = 13.8 Hz, 1H), 2.32 (ddd, *J* = 12.9, 7.2, 7.2 Hz, 1H), 1.97 (ddd, *J* = 12.9, 7.2, 7.2 Hz, 1H), 1.32 (s, 3H), 1.24 (dd, *J* = 7.2, 7.2 Hz, 3H).

Alcohol **111**



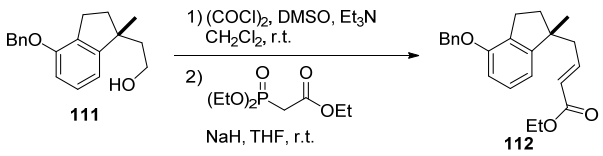
110 **111**

To a solution of ester **110** (424 mg, 1.31 mmol) in THF (3.0 mL) was added $LiAlH_4$ (53 mg, 1.40 mmol) at 0 °C. After stirring for 1 h at the same temperature, the mixture was diluted with saturated aqueous Na/K tartrate (10 mL) and stirred for 30 min at room temperature. The resultant mixture was extracted with EtOAc (3 × 5 mL). The combined extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (14 g, hexane–EtOAc 5 : 1 → 3 : 1) to afford alcohol **111** (313.6 mg, 85%) as a colorless oil.

R_f = 0.15 (hexane : EtOAc = 3 : 1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.41 (m, 2H), 7.41–7.35 (m, 2H), 7.32 (m, 1H), 7.15 (dd, *J* = 7.8, 7.8 Hz, 1H), 6.77 (d, *J* = 7.8 Hz, 1H), 6.74 (d, *J* = 7.8 Hz, 1H), 5.09 (s, 2H), 3.71–3.58 (m, 2H), 2.94–2.82 (m, 2H), 2.09 (ddd, *J* = 13.2, 7.1, 5.7 Hz, 1H), 1.98–1.82 (m, 3H), 1.28 (s, 3H). A signal due to a proton (OH) was not observed.

Conjugated ester **112**

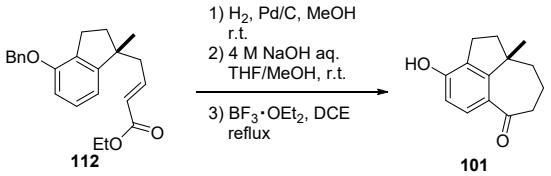


To a solution of $(COCl)_2$ (0.19 mL, 2.22 mmol) in CH_2Cl_2 (3.0 mL) was added DMSO (0.35 mL, 4.48 mmol) in CH_2Cl_2 (2.0 mL) at –78 °C. After stirring for 30 min at –78 °C, alcohol **111** (211 mg, 0.745 mmol) in CH_2Cl_2 (2.0 mL) was added to the reaction mixture. After stirring for further 30 min at 0 °C, Et_3N (0.66 mL, 4.74 mmol) was added to the reaction mixture. The mixture was stirred for 2 h at 0 °C and diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was partially purified by column chromatography on silica gel (7 g, hexane–EtOAc 6 : 1). The resultant aldehyde was used for the next reaction without further purification.

To a stirred solution of ethyl diethylphosphonoacetate (0.34 mL, 1.17 mmol) in THF (3.5 mL) was added 60% NaH (39.7 mg, 0.993 mmol) at 0 °C. After stirring for 30 min at 0 °C, a solution of the aldehyde in THF (1.5 mL) was added to the reaction mixture. The mixture was stirred for 12 h at room temperature, diluted with saturated aqueous NH_4Cl (3 mL), and extracted with EtOAc (3 × 5 mL). The combined extracts were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (8 g, hexane–EtOAc 15 : 1) to afford conjugated ester **112** (226 mg, 86% in 2 steps) as a colorless oil.

R_f = 0.64 (hexane : EtOAc = 3 : 1)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.41 (m, 2H), 7.41–7.34 (m, 2H), 7.33 (m, 1H), 7.15 (dd, *J* = 7.8, 7.8 Hz, 1H), 6.90 (ddd, *J* = 15.5, 7.7, 7.7 Hz, 1H), 6.76 (d, *J* = 7.8 Hz, 1H), 6.75 (d, *J* = 7.8 Hz, 1H), 5.83 (ddd, *J* = 15.5, 1.3, 1.3 Hz, 1H), 5.09 (s, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.96–2.80 (m, 2H), 2.45 (ddd, *J* = 13.9, 7.7, 1.3 Hz, 1H), 2.41 (ddd, *J* = 13.9, 7.7, 1.3 Hz, 1H), 2.06 (ddd, *J* = 13.0, 7.5, 5.3 Hz, 1H), 1.86 (ddd, *J* = 13.0, 8.4, 6.8 Hz, 1H), 1.279 (dd, *J* = 7.1, 7.1 Hz, 3H), 1.277 (s, 3H).

Tricyclic compound **101**



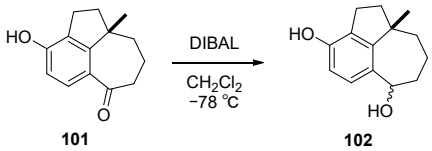
To a stirred solution of conjugated ester **112** (241 mg, 0.687 mmol) in MeOH (3.5 mL) was added 10% Pd/C (14.6 mg, 0.014 mmol) at room temperature. After stirring under hydrogen atmosphere for 1 h at same temperature, the mixture was filtered through a pad of Celite® with MeOH (50 mL), and the filtrate was concentrated. The crude product was used for the next reaction without further purification.

To a stirred solution of the phenol in THF (3.0 mL) and MeOH (3.0 mL) was added 4.0 M NaOH aq. (1.5 mL, 6.0 mmol) at room temperature. After stirring for 12 h at room temperature, the mixture was acidified to pH 3 with 4.0 M HCl aq. and extracted with EtOAc (3 × 10 mL). The combined extracts were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated. The crude phenolic acid was used for next reaction without further purification.

To a stirred solution of the phenolic acid in $ClCH_2CH_2Cl$ (13 mL) was added $BF_3 \cdot OEt_2$ (0.26 mL, 2.07 mmol) at room temperature. After stirring for 18 h at reflux, the mixture was diluted with H_2O (15 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography on silica gel (7 g, hexane–EtOAc 4 : 1) to afford tricyclic compound **101** (138 mg, 93% in 3 steps) as a white solid.

R_f = 0.50 (hexane : EtOAc = 1 : 1)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.3 Hz, 1H), 6.65 (d, *J* = 8.3 Hz, 1H), 5.46 (br s, 1H), 2.94–2.78 (m, 3H), 2.74 (ddd, *J* = 13.2, 11.6, 4.0 Hz, 1H), 2.20–1.87 (m, 6H), 1.13 (s, 3H).

Benzylic alcohol **102**



101 **102**

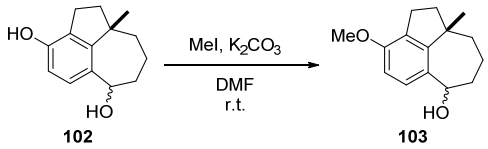
To a stirred solution of phenol **101** (53.4 mg, 0.247 mmol) in CH_2Cl_2 (2.5 mL) was added DIBAL (1.06 M hexane, 0.62 mL, 0.657 mmol) at 0 °C. After stirring for 1 h at the same temperature, the mixture was diluted with saturated aqueous Na/K tertrate (3 mL) and stirred for 2 h at room temperature. The resultant mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography on silica gel (5 g, hexane–EtOAc 5 : 1) to afford benzylic alcohol **102** (48.9 mg, 90%, *d.r.* = 3/1) as a colorless oil.

major diastereoisomer

R_f = 0.36 (hexane : EtOAc = 2 : 1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.3 Hz, 1H), 6.65 (d, *J* = 8.3 Hz, 1H), 4.83 (br d, *J* = 10.3 Hz, 1H), 4.65 (br s, 1H), 2.87–2.77 (m, 2H), 2.17 (m, 1H), 2.02–1.73 (m, 5H), 1.66–1.55 (m, 2H), 1.17 (s, 3H).

Methyl ether **103**

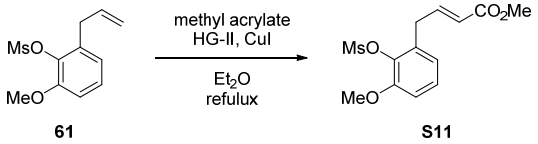


102 **103**

To a stirred solution of benzylic alcohol **102** (7.0 mg, 0.0321 mmol) in DMF (2.0 mL) was added K_2CO_3 (22.2 mg, 0.161 mmol) and MeI (20 μL, 0.321 mmol) at room temperature. After stirring for 12 h at the same temperature, the mixture was diluted with saturated aqueous NH_4Cl (3 mL) and extracted with Et_2O (3 × 4 mL). The combined extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by column chromatography on silica gel (2 g, hexane–EtOAc 7 : 1) to afford methyl ether **103** (5.9 mg, 80%, *d.r.* = 3/1) as a colorless oil.

major diastereoisomer
R_f = 0.57 (hexane : EtOAc = 2 : 1)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.5 Hz, 1H), 6.70 (d, *J* = 8.5 Hz, 1H), 4.84 (br d, *J* = 11.2 Hz, 1H), 3.83 (s, 3H), 2.90 (ddd, *J* = 16.5, 3.3, 2.3 Hz, 1H), 2.78 (ddd, *J* = 16.5, 8.5, 7.9 Hz), 2.18 (m, 1H), 2.01–1.75 (m, 5H), 1.67–1.49 (m, 2H), 1.17 (s, 3H).

Conjugated ester **S11**

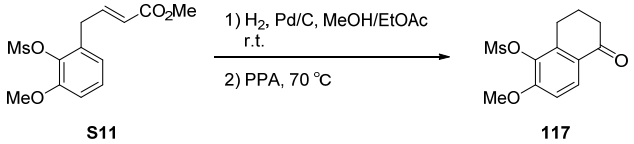


To a stirred solution of *o*-eugenol mesylate **61** (2.29 g, 9.45 mmol) in Et_2O (100 mL) was added methyl acrylate (2.54 mL, 28.3 mmol), HG-II (101 mg, 0.161 mmol) and CuI (54.0 mg, 0.284 mmol) at room temperature. After stirring for 12 h at reflux, the mixture was concentrated. The crude product was purified by column chromatography on silica gel (65 g, hexane–EtOAc 6 : 1 → 4 : 1 → 3 : 1) to afford conjugated ester **S11** (2.27 g, 80%) as a colorless oil.

R_f = 0.46 (hexane : EtOAc = 3 : 1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.06 (dt, *J* = 15.6, 6.8, 6.8 Hz, 1H), 6.89 (dd, *J* = 8.0, 1.1 Hz, 1H), 6.82 (dd, *J* = 8.0, 1.1 Hz, 1H), 5.85 (dt, *J* = 15.6, 1.5, 1.5 Hz, 1H), 3.89 (s, 3H), 3.71 (s, 3H), 3.66 (dd, *J* = 6.8, 1.5 Hz, 2H), 3.34 (s, 3H).

Tetralone mesylate **117**



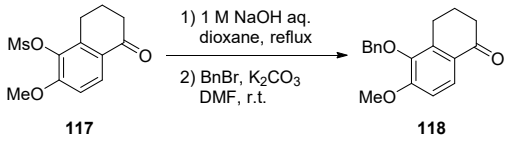
S11 **117**

To a stirred solution of conjugated ester **S11** (2.27 g, 7.56 mmol) in MeOH (14 mL) and AcOEt (28 mL) was added 10% Pd/C (402 mg, 0.378 mmol) at room temperature. After stirring under hydrogen atmosphere for 3 h at the same temperature, the mixture was filtered through a pad of Celite® with AcOEt (100 mL), and the filtrate was concentrated. The crude ester was used for the next reaction without further purification.

A round-bottomed flask was charged with PPA (40 g) and the ester at room temperature. After stirring for 5 h at 70 °C, the resulting hot mixture was poured into ice water (30 mL). The solution was alkalinized to pH 10 with 1.0 M NaOH aq. and extracted with AcOEt (3 × 40 mL). The combined extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography on silica gel (40 g, hexane–EtOAc 4 : 1) to afford tetralone mesylate **117** (1.83 g, 90% in 2 steps) as a white solid.

R_f = 0.33 (hexane : EtOAc = 3 : 1)
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.8 Hz, 1H), 6.96 (d, *J* = 8.8 Hz, 1H), 3.96 (s, 3H), 3.17 (s, 3H), 3.07 (t, *J* = 6.1 Hz, 2H), 2.62 (t, *J* = 6.6 Hz, 2H), 2.15–2.05 (m, 2H).

Tetralone Bn ether **118**



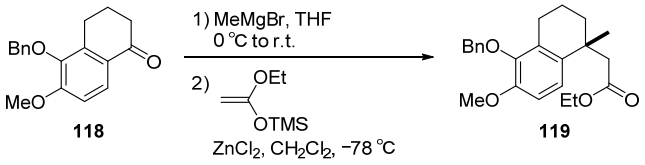
117 **118**

To a stirred solution of the tetralone mesylate **117** (1.83 g, 6.77 mmol) in dioxane (35 mL) was added 1.0 M NaOH aq. (16.9 mL, 16.9 mmol) at room temperature. After stirring for 14 h at reflux, the mixture was acidified to pH 3 with 3.0 M HCl aq. and extracted with EtOAc (3 × 20 mL). The combined extracts were washed with brine (30 mL), dried over Na_2SO_4, and filtered. Removal of the solvent afforded crude phenol, which was used for the next reaction without further purification.

To a stirred solution of the phenol in DMF (35 mL) was added K_2CO_3 (1.68 g, 12.2 mmol) and BnBr (1.05 mL, 8.84 mmol) at room temperature. After stirring for 12 h at room temperature, the mixture was diluted with H_2O (40 mL) and extracted with Et_2O (3 × 40 mL). The combined extracts were washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified by column chromatography on silica gel (60 g, hexane–EtOAc 4 : 1 → 3 : 1 → 1 : 1) to afford tetralone Bn ether **118** (1.69 g, 88% in 2 steps) as a white solid.

R_f = 0.60 (hexane : EtOAc = 2 : 1)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.6 Hz, 1H), 7.44–7.32 (m, 5H), 6.91 (d, *J* = 8.6 Hz, 1H), 5.00 (s, 2H), 3.95 (s, 3H), 2.83 (t, *J* = 6.1 Hz, 2H), 2.55 (t, *J* = 6.1 Hz, 2H), 2.04–1.95 (m, 2H).

Ester **119**

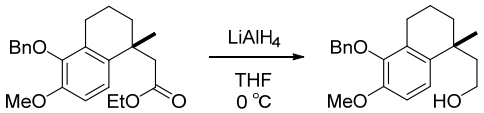


To a stirred solution of tetralone Bn ether **118** (1.48 g, 5.25 mmol) in THF (26 mL) was added MeMgBr (3.0 M THF, 4.38 mL, 13.1 mmol) at 0 °C. After stirring for 2 h at room temperature, the mixture was diluted with saturated aqueous NH_4Cl (5 mL) and extracted with EtOAc (3 × 10 mL). The combined extracts were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was partially purified by column chromatography on silica gel (20 g, hexane–EtOAc 3 : 1 → 1 : 1). The resultant tertiary alcohol was used for the next reaction without further purification.

To a stirred solution of the tertiary alcohol and distilled ketene silyl acetal (2.53 g, 15.8 mmol) in CH_2Cl_2 (13 mL) was added $ZnCl_2$ (1.9 M 2-methyl THF, 4.15 mL, 7.89 mmol) at –78 °C. After stirring for 2 h at –78 °C, the mixture was diluted with saturated aqueous EDTA·2Na (1 mL) and extracted with CH_2Cl_2 (3 × 8 mL). The combined extracts were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (40 g, hexane–EtOAc 1 : 0 → 20 : 1) to afford ester **119** (1.48 g, 77% in 2 steps) as a colorless oil.

R_f = 0.64 (hexane : EtOAc = 3 : 1)
IR ($CHCl_3$) 3017, 2938, 1719, 1489, 1276, 1087, 1031, 743 cm^{-1}
^1H NMR (400 MHz, $CDCl_3$) δ 7.50–7.44 (m, 2H), 7.40–7.26 (m, 3H), 7.03 (d, *J* = 8.7 Hz, 1H), 6.79 (d, *J* = 8.7 Hz, 1H), 4.98 (d, *J* = 11.1 Hz, 1H), 4.95 (d, *J* = 11.1 Hz, 1H), 4.08 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.04 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.85 (s, 3H), 2.76 (ddd, *J* = 17.3, 6.4, 6.4 Hz, 1H), 2.69 (ddd, *J* = 17.3, 7.4, 7.4 Hz, 1H), 2.62 (d, *J* = 13.6 Hz, 1H), 2.55 (d, *J* = 13.6 Hz, 1H), 2.00 (ddd, *J* = 12.9, 9.1, 3.5 Hz, 1H), 1.84–1.64 (m, 2H), 1.58 (m, 1H), 1.38 (s, 3H), 1.18 (dd, *J* = 7.1, 7.1 Hz, 3H)
^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 150.3, 144.9, 138.2, 137.1, 131.5, 128.3, 128.0 (2C), 127.7 (2C), 122.1, 110.1, 73.9, 59.9, 55.8, 47.6, 36.2, 35.4, 29.8, 24.4, 18.8, 14.2
HRMS (ESI) *m/z* 391.1863, calcd for $C_{23}H_{28}NaO_4$ $[M+Na]^+$ 391.1885.

Alcohol **120**

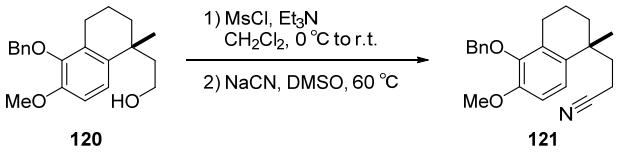


119 **120**

To a stirred solution of ester **119** (1.72 g, 4.67 mmol) in THF (23 mL) was added $LiAlH_4$ (195 mg, 5.13 mmol) at 0 °C. After stirring for 1 h at the same temperature, the mixture was diluted with saturated aqueous Na/K tartrate (10 mL), and stirred at room temperature for 30 min. The resultant mixture was extracted with EtOAc (3 × 10 mL). The combined extracts were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (35 g, hexane–EtOAc 5 : 1 → 3 : 1) to afford alcohol **120** (1.48 g, 97%) as a colorless oil.

R_f = 0.17 (hexane : EtOAc = 3 : 1)
IR ($CHCl_3$) 3616, 3010, 2938, 1601, 1488, 1276, 1087, 1011, 795 cm^{-1}
^1H NMR (400 MHz, $CDCl_3$) δ 7.48–7.43 (m, 2H), 7.40–7.28 (m, 3H), 7.04 (d, *J* = 8.6 Hz, 1H), 6.80 (d, *J* = 8.6 Hz, 1H), 5.00 (d, *J* = 11.1 Hz, 1H), 4.95 (d, *J* = 11.1 Hz, 1H), 3.86 (s, 3H), 3.63 (ddd, *J* = 10.3, 9.3, 5.6 Hz, 1H), 3.53 (ddd, *J* = 10.3, 8.8, 6.0 Hz, 1H), 2.79 (ddd, *J* = 17.1, 5.5, 5.6 Hz, 1H), 2.55 (m, 1H), 2.02 (ddd, *J* = 13.8, 9.3, 6.0 Hz, 1H), 1.84 (ddd, *J* = 13.8, 8.8, 5.6 Hz, 1H), 1.79–1.56 (m, 3H), 1.53 (m, 1H), 1.28 (s, 3H). A signal due to a proton (OH) was not observed.
^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 144.9, 138.1, 137.4, 131.8, 128.2 (2C), 128.0 (2C), 127.7, 122.0, 110.2, 73.9, 60.0, 55.8, 46.0, 35.7, 35.5, 31.0, 24.5, 19.0
HRMS (ESI) *m/z* 349.1794, calcd for $C_{21}H_{26}NaO_3$ $[M+Na]^+$ 349.1780.

Nitrile **121**



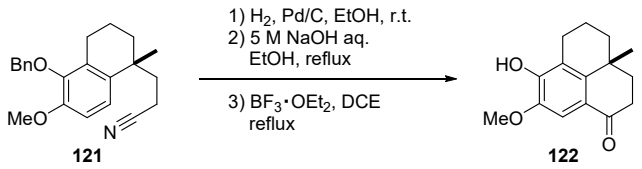
120 **121**

To a stirred solution of alcohol **120** (1.46 g, 4.47 mmol) in CH_2Cl_2 (22 mL) were added Et_3N (1.5 mL, 10.7 mmol) and MsCl (0.42 mL, 5.37 mmol) at 0 °C. After stirring for 3 h at room temperature, the mixture was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated. The crude mesylate was used for the next reaction without further purification.

To a stirred solution of the mesylate in DMSO (22 mL) was added NaCN (1.09 g, 22.4 mmol) at room temperature. After stirring for 1.5 h at 60 °C, the mixture was diluted with H_2O (30 mL), and extracted with Et_2O (3 × 10 mL). The combined extracts were washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (35 g, hexane–EtOAc 8 : 1 → 6 : 1) to afford nitrile **121** (1.41 g, 94% in 2 steps) as a colorless oil.

R_f = 0.65 (hexane : EtOAc = 2 : 1)
IR ($CHCl_3$) 3019, 2938, 2247, 1489, 1455, 1276, 1087, 1020, 700 cm^{-1}
^1H NMR (400 MHz, $CDCl_3$) δ 7.51–7.42 (m, 2H), 7.39–7.28 (m, 3H), 6.92 (d, *J* = 8.7 Hz, 1H), 6.82 (d, *J* = 8.7 Hz, 1H), 5.01 (d, *J* = 11.1 Hz, 1H), 4.95 (d, *J* = 11.1 Hz, 1H), 3.87 (s, 3H), 2.82 (ddd, *J* = 17.5, 5.1, 5.1 Hz, 1H), 2.46 (ddd, *J* = 17.5, 9.0, 5.9 Hz, 1H), 2.20–1.85 (m, 4H), 1.80–1.46 (m, 4H), 1.28 (s, 3H)
^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4, 145.0, 138.1, 135.1, 132.2, 128.2 (2C), 128.1 (2C), 127.8, 121.7, 120.4, 110.5, 73.9, 55.8, 38.7, 36.4, 34.6, 30.5, 24.4, 18.8, 12.7
HRMS (ESI) *m/z* 358.1800, calcd for $C_{22}H_{25}NaNO_2$ $[M+Na]^+$ 358.1783.

Tricyclic compound **122**



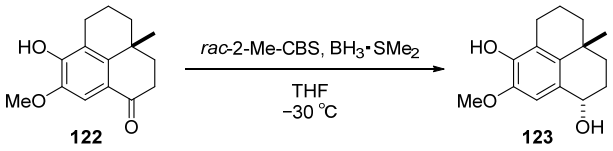
To a stirred solution of nitrile **121** (457 mg, 1.36 mmol) in EtOH (7 mL) was added 10% Pd/C (43.5 mg, 0.0409 mmol). After stirring under a hydrogen atmosphere for 2 h at room temperature, the mixture was filtered through a pad of Celite® with EtOH (40 mL). The filtrate was concentrated, and the crude phenol was used for the next reaction without further purification.

To a stirred solution of the phenol in EtOH (7 mL) was added 5.0 M NaOH aq. (1.4 mL, 7 mmol). After stirring for 12 h at reflux, the mixture was acidified to pH 3 with 4.0 M HCl aq. and extracted with EtOAc (3 × 10 mL). The extracts were combined, washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The crude phenolic acid was used for next reaction without further purification.

To a stirred solution of the phenolic acid in $ClCH_2CH_2Cl$ (20 mL) was added $BF_3 \cdot OEt_2$ (0.51 mL, 4.67 mmol) at room temperature. After stirring for 18 h at reflux, the mixture was diluted with H_2O (15 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (7 g, hexane–EtOAc 4 : 1) to afford tricyclic compound **122** (284 mg, 86% in 3 steps) as a pale yellow solid.

R_f = 0.39 (hexane : EtOAc = 3 : 1)
m.p. 166.9–168.6 °C
IR ($CHCl_3$) 3522, 3012, 2940, 1657, 1581, 1479, 1307, 1207, 1092, 772 cm^{-1}
^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 1H), 6.24 (s, 1H), 3.90 (s, 3H), 2.95–2.81 (m, 2H), 2.66–2.52 (m, 2H), 2.09–1.85 (m, 4H), 1.71 (ddd, *J* = 12.1, 3.2, 3.2 Hz, 1H), 1.55 (ddd, *J* = 13.1, 13.1, 4.1 Hz, 1H), 1.24 (s, 3H)
^{13}C NMR (100 MHz, $CDCl_3$) δ 197.7, 148.2, 144.4, 143.4, 123.7, 121.3, 106.8, 56.0, 37.3, 37.0, 34.4, 32.4, 26.1, 21.9, 17.3
HRMS (ESI) *m/z* 269.1174, calcd for $C_{15}H_{18}NaNO_3$ $[M+Na]^+$ 269.1154.

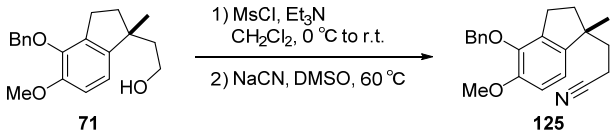
Benzylic alcohol **123**



To a stirred solution of tricyclic compound **122** (80.5 mg, 0.327 mmol) and *rac*-2-Me-CBS-oxazaborooridine (1.0 M toluene, 0.066 mL, 0.066 mmol) in THF (1.6 mL) was added $BH_3 \cdot SMe_2$ (2.0 M THF, 0.41 mL, 0.82 mmol) at –30 °C. After stirring for 6 h at the same temperature, the mixture was diluted with MeOH (0.5 mL) and H_2O (3 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3 g, hexane–EtOAc 8 : 1 → 5 : 1) to afford benzylic alcohol **123** (69.5 mg, 94%, *d.r.* = 23/1) as a white solid

R_f = 0.22 (hexane : EtOAc = 3 : 1)
m.p. 150.9–152.8 °C
IR ($CHCl_3$) 3527, 3017, 2940, 1656, 1479, 1307, 1091, 806 cm^{-1}
^1H NMR (600 MHz, $CDCl_3$) δ 6.94 (s, 1H), 5.67 (s, 1H), 4.82 (ddd, *J* = 8.3, 8.3, 8.3 Hz, 1H), 3.87 (s, 3H), 2.85–2.73 (m, 2H), 2.23 (dddd, *J* = 13.2, 7.2, 3.6, 3.6 Hz, 1H), 2.13–1.95 (m, 2H), 1.86 (m, 1H), 1.73–1.55 (m, 4H), 1.42 (ddd, *J* = 13.1, 13.1, 5.3, 1H), 1.21 (s, 3H)
^{13}C NMR (151 MHz, $CDCl_3$) δ 144.3, 142.2, 135.1, 128.5, 121.6, 106.9, 70.0, 55.9, 37.35, 37.28, 32.6, 29.9, 26.8, 20.8, 17.0
HRMS (ESI) *m/z* 271.1302, calcd for $C_{15}H_{20}NaO_3$ $[M+Na]^+$ 271.1310.

Nitrile **125**

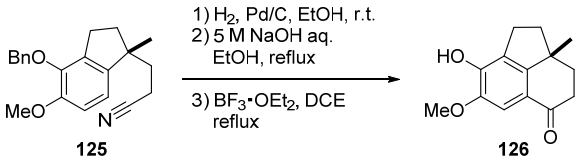


To a stirred solution of alcohol **71** (426 mg, 1.36 mmol) in CH_2Cl_2 (7 mL) were added Et_3N (0.42 mL, 3.01 mmol) and MsCl (0.12 mL, 1.55 mmol) at 0 °C. After stirring for 13 h at room temperature, the mixture was diluted with H_2O (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined extracts were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated. The crude mesylate was used for the next reaction without further purification.

To a stirred solution of the mesylate in DMSO (7 mL) was added NaCN (201 mg, 4.10 mmol) at room temperature. After stirring for 1.5 h at 60 °C, the mixture was diluted with H_2O (10 mL) and extracted with Et_2O (3 × 10 mL). The combined extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (12 g, hexane–EtOAc 8 : 1 → 6 : 1) to afford nitrile **125** (380 mg, 87% in 2 steps) as a colorless oil.

R_f = 0.60 (hexane : EtOAc = 3 : 1)
IR ($CHCl_3$) 3017, 2957, 2247, 1486, 1441, 1266, 1077, 994, 781 cm^{-1}
^1H NMR (400 MHz, $CDCl_3$) δ 7.42–7.28 (m, 5H), 6.81 (d, *J* = 8.2 Hz, 1H), 6.73 (d, *J* = 8.2 Hz, 1H), 5.07 (d, *J* = 11.4 Hz, 1H), 5.03 (d, *J* = 11.4 Hz, 1H), 3.88 (s, 3H), 2.74 (ddd, *J* = 16.5, 8.8, 5.2 Hz, 1H), 2.59 (ddd, *J* = 16.5, 8.0, 8.0 Hz, 1H), 2.19–1.90 (m, 2H), 1.96–1.75 (m, 4H), 1.28 (s, 3H)
^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 143.8, 142.2, 137.9, 137.2, 128.5 (2C), 128.2 (2C), 128.0, 120.3, 117.5, 111.6, 74.3, 56.2, 46.8, 38.3, 37.0, 27.2, 26.8, 13.1
HRMS (ESI) *m/z* 344.1648, calcd for $C_{21}H_{23}NaNO_2$ $[M+Na]^+$ 344.1627.

Tricyclic compound **126**



125 **126**

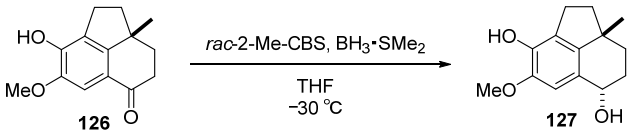
To a stirred solution of nitrile **125** (380 mg, 1.18 mmol) in EtOH (5.6 mL) was added 10% Pd/C (25.1 mg, 0.0236 mmol). After stirring under a hydrogen atmosphere for 20 h at room temperature, the mixture was filtered through a pad of Celite® with EtOH (30 mL). The filtrate was concentrated, and the crude phenol was used for the next reaction without further purification.

To a stirred solution of the phenol in EtOH (5.6 mL) was added 5.0 M NaOH aq. (1.2 mL, 6.0 mmol). After stirring for 6 h at reflux, the mixture was acidified to pH 3 with 4.0 M HCl aq. and extracted with EtOAc (3 × 5 mL). The extracts were combined, washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The crude phenolic acid was used for next reaction without further purification.

To a stirred solution of the phenolic acid in $ClCH_2CH_2Cl$ (12 mL) was added $BF_3 \cdot OEt_2$ (0.44 mL, 3.50 mmol) at room temperature. After stirring for 18 h at reflux, the mixture was diluted with H_2O (15 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with brine (8 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (7 g, hexane–EtOAc 4 : 1) to afford tricyclic compound **126** (123 mg, 50% in 3 steps) as a pale yellow solid.

R_f = 0.26 (hexane : EtOAc = 3 : 1)
m.p. 149.2–150.8 °C
IR ($CHCl_3$) 3520, 3011, 2960, 1659, 1597, 1467, 1322, 1201, 1077, 820 cm^{-1}
^1H NMR (400 MHz, $CDCl_3$) δ 7.19 (s, 1H), 6.22 (s, 1H), 3.89 (s, 3H), 3.02 (dddd, *J* = 16.2, 11.0, 6.1, 0.7 Hz, 1H), 2.92 (dd, *J* = 16.2, 8.5 Hz, 1H), 2.81 (ddd, *J* = 18.5, 13.4, 5.4 Hz, 1H), 2.57 (ddd, *J* = 18.5, 5.0, 1.8 Hz, 1H), 2.18–2.07 (m, 2H), 2.01 (ddd, *J* = 13.2, 13.2, 5.0 Hz, 1H), 1.90 (ddd, *J* = 11.3, 11.0, 8.5 Hz, 1H), 1.27 (s, 3H)
^{13}C NMR (100 MHz, $CDCl_3$) δ 197.0, 153.4, 147.3, 146.7, 125.8, 121.2, 105.1, 56.4, 42.6, 42.4, 36.9, 35.2, 27.2, 23.0
HRMS (ESI) *m/z* 255.0981, calcd for $C_{14}H_{16}NaNO_3$ $[M+Na]^+$ 255.0997.

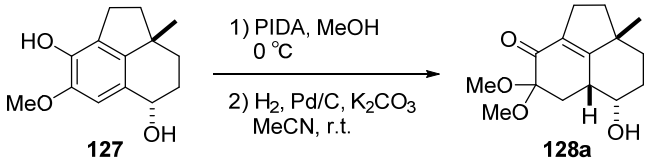
Benzylic alcohol **127**



To a stirred solution of tricyclic compound **126** (120 mg, 0.550 mmol) and *rac*-2-Me-CBS-oxazaborooridine (1.0 M toluene, 0.11 mL, 0.110 mmol) in THF (2.0 mL) was added $BH_3 \cdot SMe_2$ (2.0 M THF, 0.69 mL, 1.38 mmol) at –30 °C. After stirring for 6 h at the same temperature, the mixture was diluted with MeOH (0.5 mL) and H_2O (4 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3 g, hexane–EtOAc 8 : 1 → 5 : 1) to afford benzylic alcohol **127** (121 mg, quant., *d.r.* ＞25/1) as a colorless oil.

R_f = 0.22 (hexane : EtOAc = 3 : 1)
IR ($CHCl_3$) 3593, 3536, 3007, 2944, 2853, 1490, 1275, 908, 828 cm^{-1}
^1H NMR (400 MHz, $CDCl_3$) δ 6.79 (s, 1H), 5.69 (br s, 1H), 4.76 (br dd, *J* = 8.7, 7.2 Hz, 1H), 3.85 (s, 3H), 2.97 (ddd, *J* = 16.1, 11.0, 5.9 Hz, 1H), 2.80 (dd, *J* = 16.1, 8.1 Hz, 1H), 2.26 (dddd, *J* = 13.5, 7.2, 3.4, 3.4 Hz, 1H), 2.06–1.94 (m, 2H), 1.90 (ddd, *J* = 13.0, 3.4, 3.4 Hz, 1H), 1.79 (br s, 1H), 1.75 (ddd, *J* = 11.0, 11.0, 8.1 Hz, 1H), 1.62 (ddd, *J* = 13.0, 13.0, 3.4 Hz, 1H), 1.21 (s, 3H)
^{13}C NMR (100 MHz, $CDCl_3$) δ 146.3, 143.4, 141.1, 126.1, 125.9, 107.0, 69.0, 56.3, 43.4, 42.1, 36.1, 31.0, 26.7, 24.5
HRMS (ESI) *m/z* 257.1134, calcd for $C_{14}H_{18}NaO_3$ $[M+Na]^+$ 257.1154.

6/5/6-α,α-Dimethoxy enone **128a**



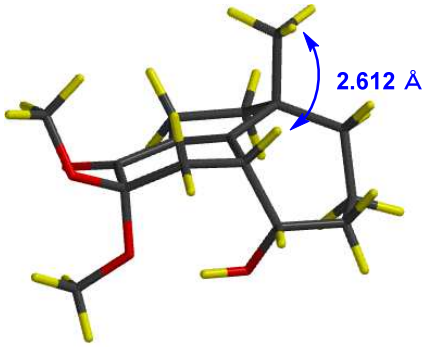
To a stirred solution of benzylic alcohol **127** (59.0 mg, 0.252 mmol) in MeOH (1.5 mL) was added PIDA (97.4 mg, 0.302 mmol) at 0 °C. After stirring for 1 h at the same temperature, the mixture was diluted with saturated aqueous $NaHCO_3$ (3 mL) and extracted with CH_2Cl_2 (3 × 3 mL). The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was partially purified by column chromatography on silica gel (1 g, hexane–EtOAc 5 : 1 → 1 : 1). The resultant *o*-quinone monoacetal was used for the next reaction without further purification.

To a stirred solution of the *o*-quinone monoacetal and K_2CO_3 (87.1 mg, 0.405 mmol) in MeCN (2.5 mL) was added 10% Pd/C (5.3 mg, 5.1 μmol) at room temperature. After stirring under hydrogen atmosphere for 1 h at the same temperature, the mixture was filtered through a pad of Celite® with EtOAc (40 mL) and the filtrate was concentrated. The crude product was purified by column chromatography on silica gel (2 g, hexane–EtOAc 6 : 1 → 4 : 1 → 3 : 1) to afford 6/5/6-α,α-dimethoxy enone **128a** (11.1 mg, 16% in 2 steps) as a white solid.

R_f = 0.20 (hexane : EtOAc = 1 : 1)
m.p. 144.9–145.5 °C
IR ($CHCl_3$) 3611, 3473, 3019, 2938, 1676, 1643, 1455, 1230, 1141, 1051, 794, 713 cm^{-1}
^1H NMR (400 MHz, $CDCl_3$) δ 3.35 (s, 3H), 3.33 (m, 1H), 3.14 (s, 3H), 2.86 (dd, *J* = 13.5, 5.1 Hz, 1H), 2.63 (ddd, *J* = 15.9, 9.7, 1.2 Hz, 1H), 2.60–2.45 (m, 2H), 1.95–1.53 (m, 7H), 1.42 (ddd, *J* = 13.3, 13.3, 3.4 Hz, 1H), 1.16 (s, 3H)
^{13}C NMR (100 MHz, $CDCl_3$) δ 191.0, 169.8, 132.8, 97.7, 76.3, 50.4, 49.1, 47.3, 39.8, 39.6, 37.0, 35.2, 31.6, 27.2, 23.2
HRMS (ESI) *m/z* 289.1416, calcd for $C_{15}H_{22}NaO_4$ $[M+Na]^+$ 289.1417.

[Cartesian Coordinates of **83a**, **86a**, and **128a-d**]

All calculations were performed with the program package Spartan *'08* v1.2.0 of Wavefunction Inc. All structures were optimized and subjected to frequency analysis with B3LYP/6-31G* method, followed by single point calculations to provide the thermodynamic properties.



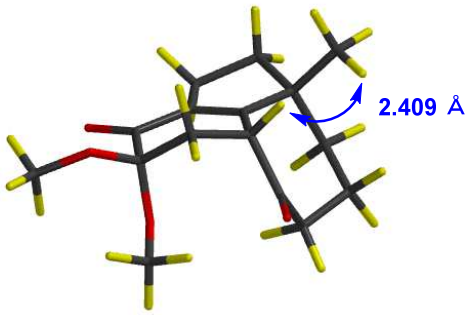
Compound **83a**
E(B3LYP/6-31G*//B3LYP/6-31G*) = -885.7119678 au

Cartesian Coordinates (Angstroms)

Atom	X	Y	Z
C	-1.009950	0.659515	-1.470117
H	-1.114529	-0.087831	-2.265229
H	-1.360922	1.612810	-1.881245
C	0.490312	0.728947	-1.092332
H	1.056360	0.712286	-2.035252
C	-1.991730	0.256365	-0.357308
C	-0.009427	-1.131833	0.523349
C	0.864075	-0.458114	-0.261363
C	-1.449816	-0.898713	0.538824
O	-2.218484	-1.547036	1.243402
C	0.668987	-2.210142	1.338150
H	0.436748	-3.208423	0.941325
H	0.335503	-2.208692	2.381098
C	2.163499	-1.849306	1.172084
H	2.824506	-2.722961	1.181832
H	2.473011	-1.192319	1.994124
C	2.259979	-1.066592	-0.171370
O	-3.262352	-0.018475	-0.905569
O	-2.172001	1.405548	0.465265
C	-3.179731	1.334314	1.487893
H	-4.148605	1.094876	1.046452
H	-3.203615	2.331045	1.933426

H	-2.929266	0.588595	2.247785
C	-3.490036	-1.294225	-1.490792
H	-4.484152	-1.237728	-1.940788
H	-3.472550	-2.091211	-0.741779
H	-2.764948	-1.523055	-2.285373
C	3.438859	-0.062198	-0.202876
H	3.724711	0.128698	-1.247679
H	4.301699	-0.573033	0.246658
C	2.436375	-2.058003	-1.350094
H	2.328234	-1.551227	-2.316751
H	1.704774	-2.872599	-1.311991
H	3.439448	-2.500840	-1.318131
C	3.224503	1.291360	0.493141
H	4.210589	1.729812	0.692171
H	2.743418	1.158818	1.469561
C	0.901188	2.073368	-0.388307
H	0.466098	2.872144	-1.016002
C	2.415219	2.308614	-0.330929
H	2.814191	2.358660	-1.354166
H	2.549917	3.304012	0.109303
O	0.429511	2.173347	0.937247
H	-0.537831	2.030936	0.920171

Requested basis set is 6-31G*
There are 120 shells and 329 basis functions



Compound **86a**

Cartesian Coordinates (Angstroms)

Atom	X	Y	Z

C	-1.910888	-0.128873	-0.286843
C	-1.094013	0.521255	-1.416432

H	-1.557585	1.464677	-1.713385
H	-1.139398	-0.149461	-2.280866
C	0.383624	0.758178	-1.035093
H	0.924682	0.984660	-1.965618
C	0.248525	-1.465319	0.120518
C	0.982757	-0.468409	-0.415584
C	-1.214469	-1.431095	0.219293
O	-1.853566	-2.357625	0.695410
O	-3.173300	-0.363491	-0.845420
O	-1.962846	0.680297	0.887300
C	-4.191541	-0.951741	-0.024535
H	-4.042047	-0.714007	1.031578
H	-4.207136	-2.037349	-0.143258
H	-5.139464	-0.525284	-0.368792
C	-2.706207	1.900897	0.787385
H	-2.184653	2.649115	0.181696
H	-2.797061	2.270800	1.811429
H	-3.703733	1.727043	0.373101
C	1.105144	-2.590787	0.648920
H	0.724826	-3.574798	0.355830
H	1.119128	-2.582376	1.747650
C	2.489091	-2.266652	0.036151
H	2.606047	-2.819155	-0.904122
H	3.325739	-2.548356	0.684829
C	2.479278	-0.736890	-0.275261
C	3.039074	0.050638	0.945330
H	4.119686	-0.141828	0.999721
H	2.604350	-0.373813	1.860981
C	2.809155	1.570195	0.968472
H	3.266059	2.049661	0.092394
H	3.347873	1.971468	1.835365
C	1.333653	2.020989	1.100263
H	0.803898	1.350822	1.791128
H	1.286398	3.033987	1.510251
C	0.552274	2.055771	-0.199854
O	0.066262	3.089711	-0.619529
C	3.283822	-0.409573	-1.544553
H	3.303410	0.663590	-1.764617
H	2.867779	-0.923026	-2.419240
H	4.323110	-0.739025	-1.427213

Requested basis set is 6-31G*

There are 120 shells and 329 basis functions

Compound **128a**

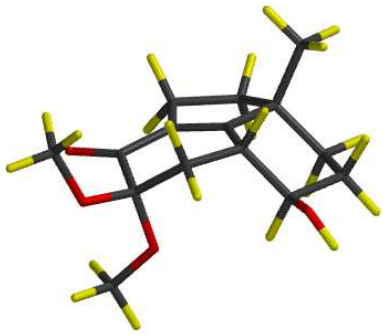
E(B3LYP/6-31G*//B3LYP/6-31G*) = -885.7207902 au

Cartesian Coordinates (Angstroms)

Atom	X	Y	Z
C	1.919072	0.363791	0.264268
C	0.875891	1.485245	0.239081
H	0.813781	1.886969	-0.775604
H	1.235404	2.285974	0.894682
C	0.018439	-1.133114	-0.553210
C	-0.532766	1.024422	0.655573
H	-0.558450	0.904372	1.748839
C	-0.864600	-0.303362	0.042509
C	1.454481	-0.873888	-0.568406
O	2.266329	-1.622048	-1.112077
O	2.021933	-0.045609	1.615143
O	3.199786	0.813448	-0.123466
C	3.045985	-0.988245	1.933569
H	4.041046	-0.580653	1.732250
H	2.931806	-1.930830	1.384244
H	2.941302	-1.182395	3.003747
C	3.370837	1.259943	-1.463699
H	2.868109	2.218288	-1.647558
H	3.026714	0.519984	-2.195013
H	4.446282	1.404860	-1.596637
C	-0.657944	-2.364692	-1.114586
H	-0.423542	-3.253196	-0.511293
H	-0.325598	-2.595901	-2.132592
C	-2.160969	-1.983730	-1.046497
H	-2.807408	-2.842207	-0.838025
H	-2.471746	-1.567174	-2.011735
C	-2.271427	-0.879062	0.048197
C	-2.558815	-1.519192	1.429986
H	-2.495519	-0.794044	2.248123
H	-1.850292	-2.324728	1.653027

H	-3.568599	-1.946240	1.441718
C	-3.304143	0.230183	-0.255065
H	-4.320023	-0.137548	-0.065863
H	-3.248398	0.487085	-1.319423
C	-1.626881	2.064010	0.309720
H	-1.462982	2.952874	0.937646
C	-3.036281	1.504096	0.563760
H	-3.776658	2.272658	0.305189
H	-3.159585	1.317729	1.638316
O	-1.458751	2.412606	-1.071359
H	-2.095294	3.118521	-1.271183

Requested basis set is 6-31G*
There are 120 shells and 329 basis functions



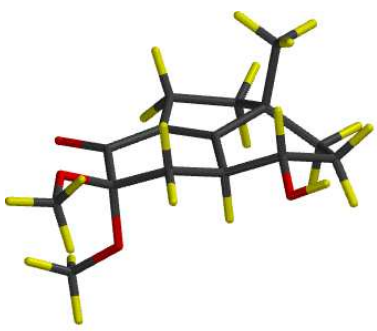
Compound **128b**
E(B3LYP/6-31G*//B3LYP/6-31G*) = -885.7178526 au

Cartesian Coordinates (Angstroms)

Atom	X	Y	Z
C	1.850123	0.311941	0.071609
C	0.942571	1.157044	0.973037
H	1.224233	2.206620	0.849850
H	1.161446	0.880488	2.009992
C	-0.572357	0.976718	0.740694
H	-1.081461	1.201384	1.690431
C	-0.036088	-1.405326	0.060163
C	-0.919200	-0.425795	0.345235
C	1.408620	-1.185805	0.039171
O	3.214681	0.454674	0.401939
O	1.695725	0.819315	-1.241777
C	3.643061	0.004026	1.681925
H	3.348301	0.696253	2.481179

H	4.734896	-0.027577	1.641227
H	3.276640	-1.002187	1.912988
C	2.562220	0.295808	-2.249918
H	2.258503	0.786194	-3.177740
H	2.459424	-0.790226	-2.367344
H	3.609275	0.531403	-2.038229
C	-0.724062	-2.705140	-0.291137
H	-0.622171	-3.434073	0.524278
H	-0.283443	-3.180247	-1.174801
C	-2.200938	-2.272034	-0.513173
H	-2.412530	-2.226625	-1.586816
H	-2.907919	-2.986611	-0.081224
C	-2.357824	-0.848215	0.120073
O	2.222482	-2.093785	-0.120725
C	-1.212156	1.947153	-0.279513
H	-0.697362	1.823658	-1.243273
C	-2.711147	1.643919	-0.440895
H	-3.210454	1.885310	0.506167
H	-3.134595	2.321861	-1.193921
C	-3.152762	-0.913237	1.442468
H	-3.208471	0.056167	1.947964
H	-2.697383	-1.624122	2.141707
H	-4.179578	-1.245489	1.250254
C	-2.985048	0.187759	-0.856041
H	-4.065190	0.014637	-0.942437
H	-2.560344	0.023176	-1.855175
O	-1.001872	3.268067	0.224674
H	-1.270022	3.890939	-0.470154

Requested basis set is 6-31G*
There are 120 shells and 329 basis functions

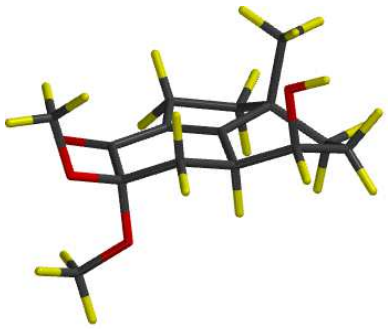


Compound **128c**
E(B3LYP/6-31G*//B3LYP/6-31G*) = -885.7119678 au

Cartesian Coordinates (Angstroms)

Atom	X	Y	Z
C	-6.709184	3.108660	-3.222375
C	-7.729271	4.196349	-2.834615
H	-7.872590	4.149744	-1.747782
H	-7.321933	5.179305	-3.081673
C	-9.075395	3.993413	-3.545979
H	-8.895712	4.116904	-4.626598
C	-8.725624	1.521249	-3.213908
C	-9.540928	2.588319	-3.336413
C	-9.515927	0.228280	-3.249731
H	-9.595270	-0.228282	-2.253664
H	-9.045945	-0.524240	-3.891950
C	-10.894415	0.706080	-3.790410
H	-11.729498	0.097673	-3.428476
H	-10.892095	0.647004	-4.885766
C	-11.004563	2.197845	-3.351272
C	-11.738549	3.157689	-4.307146
H	-12.812873	2.940537	-4.324936
H	-11.369897	2.976689	-5.324360
C	-11.507348	4.655739	-3.939357
H	-12.348615	5.031584	-3.345164
H	-11.491219	5.244874	-4.863104
C	-10.187391	4.981582	-3.182524
H	-10.359216	4.924190	-2.097130
O	-9.711124	6.289942	-3.508089
H	-10.385342	6.925789	-3.217099
C	-11.620567	2.261335	-1.929116
H	-11.103951	1.584538	-1.239890
H	-12.673031	1.955971	-1.971831
H	-11.587688	3.262598	-1.489497
C	-7.278654	1.657588	-3.080442
O	-6.528158	0.696986	-2.931563
O	-5.548274	3.140091	-2.429556
O	-6.424205	3.342314	-4.602233
C	-4.856676	4.389895	-2.381013
H	-3.855988	4.167205	-2.002384
H	-5.340078	5.096967	-1.695896
H	-4.771282	4.846644	-3.372874
C	-5.462519	2.485092	-5.217331
H	-4.569061	2.367619	-4.596124
H	-5.192898	2.968295	-6.159881
H	-5.872267	1.489467	-5.429443

Requested basis set is 6-31G*
There are 120 shells and 329 basis functions



Compound **128d**
E(B3LYP/6-31G*//B3LYP/6-31G*) = -885.7107134 au

Cartesian Coordinates (Angstroms)

Atom	X	Y	Z
C	1.926696	0.459740	-0.121524
C	0.815526	1.496934	0.112703
H	1.157496	2.444389	-0.318556
H	0.672630	1.648458	1.186391
C	-0.517286	1.043761	-0.503659
H	-0.359242	0.966047	-1.591121
C	0.085762	-1.297067	0.213805
C	-0.837151	-0.346059	-0.043349
C	1.509078	-0.992998	0.296848
O	2.360274	-1.826639	0.606666
O	3.148463	0.846651	0.469313
O	2.136329	0.445827	-1.522146
C	-0.567093	-2.655071	0.379111
H	-0.610385	-2.964223	1.432602
H	-0.017837	-3.443565	-0.146797
C	-1.983757	-2.404844	-0.217149
H	-2.755065	-3.039847	0.230870
H	-1.963059	-2.617519	-1.293570
C	-2.250607	-0.887002	0.014159
C	-3.066698	-0.150110	-1.064365
H	-2.658290	-0.423335	-2.046235
H	-4.110502	-0.486802	-1.061603
C	-3.019943	1.397082	-0.907243
H	-3.840809	1.732355	-0.262080
H	-3.207372	1.844982	-1.889517

C	-1.703757	1.999142	-0.324362
H	-1.475517	2.931999	-0.858836
O	-1.806136	2.290336	1.078195
H	-2.480690	2.981253	1.182558
C	-2.873807	-0.692059	1.420558
H	-3.908745	-1.056664	1.418889
H	-2.868015	0.354184	1.730741
H	-2.322020	-1.263298	2.176216
C	3.211377	0.888690	1.889899
H	4.261985	1.056683	2.139376
H	2.892289	-0.054508	2.348252
H	2.621093	1.715848	2.305250
C	3.228657	-0.329163	-2.017533
H	4.179946	0.007505	-1.595911
H	3.230790	-0.169780	-3.099119
H	3.107910	-1.399423	-1.811418

Requested basis set is 6-31G*
There are 120 shells and 329 basis functions

References

[1] (a) Seto, H. In *Tennenbutsukagaku* (*Natural product chemistry*), Corona Publishing, Tokyo, 2006.

[2] Nes, W. N. *Chem. Rev.* **2011**, *111*, 6423.

[3] Ohyama, K.; Suzuki, M.; Kikuchi, J.; Saito, K.; Muranaka, T. *PNAS* **2009**, *106*, 725.

[4] David, K.; Dingemanse, E.; Freud, J.; Laqueur, E. *Z. physiol. Chem.* **1935**, *233*, 281.

[5] (a) Reichstein, von-T.; Euw, J. V. *Helv. Chim. Acta* **1938**, *21*, 1197. (b) Mason, H. L.; Hoehn, W. M.; Kendall, E. C. *J. Biol. Chem.* **1938**, *124*, 459.

[6] (a) "Russell Marker and the Mexican Steroid Hormone Industry". American Chemical Society. Retrieved 2012. (b) Marker, R. E. *J. Am. Chem. Soc.* **1940**, *62*, 2543. (c) Myers, R. L.; Myers, R. L. In *The 100 most important chemical compounds: a reference guide*, Greenwood Press, Westport, Conn, 2007.

[7] Stork, G.; West, F.; Lee, H. Y.; Richard, Isaacs, R. C. A.; Manabe, S. *J. Am. Chem. Soc.* **1996**, *118*, 10660.

[8] John, W. S.; Fletcher, V. R.; Chenera, B.; Bartlett, W. R.; Tham, F. S.; Kullnig, R. K. *J. Am. Chem. Soc.* **1993**, *115*, 497.

[9] Van Royen, L. A.; Mijngheer, R.; De Clercq, P. J. *Tetrahedron Lett.* **1983**, *24*, 3145.

[10] Cirigliano, A. M.; Veleiro, A. S.; Oberti, J. C.; Burton, G. *J. Nat. Prod.* **2002**, *65*, 1049.

[11] Aoki, S.; Watanabe, Y.; Sanagawa, M.; Setiawan, A.; Kotoku, N.; Kobayashi, M. *J. Am. Chem. Soc.* **2006**, *128*, 3148.

[12] Du, L.; Zhu, T.; Fang, Y.; Gu, Q.; Zhu, W. *J. Nat. Prod.* **2008**, *71*, 1343.

[13] Wang, Jia-P.; Cai, L.; Chen, Feng-Y.; Li, Yuan-Y.; Li, Yuan-Y.; Luo, P.; Ding, Zhong-T. *Tetrahedron Lett.* **2017**, *58*, 3590.

[14] Watanabe, Y.; Aoki, S.; Tanabe, D.; Setiawan, A.; Kobayashi, M. *Tetrahedron* **2007**, *63*, 4074.

[15] Gong, J.; Sun, P.; Jiang, N.; Riccio, R.; Lauro, G.; Bifulco, G.; Li, Tie-J.; Gerwick, W. H.; Zhang, W. *Org. Lett.* **2014**, *16*, 2224.

[16] Li, J.; Tang, H.; Kurtan, T.; Mandi, A.; Zhuang, Chun-L.; Su, L.; Zheng, Gui-L.; Zhang, W. *J. Nat. Prod.* **2018**, *81*, 1645.

[17] Zhou, S.; Guo, R.; Yang, P.; Li, A. *J. Am. Chem. Soc.* **2018**, *140*, 9025.

[18] Gon, J.; Chen, H.; Liu, X.; Wang, Z.; Nie, W.; Qin, Y. *Nat. Comm.* **2016**, *7*, 2183.

[19] Paladino, M.; Zaifman, J.; Ciufolin, A. M. *Org. Lett.* **2015**, *17*, 3422.

[20] (a) Horner, L.; Hoffmann, H. M. R.; Wippel, H. G. *Chem. Ber.* **1958**, *91*, 61. (b) Horner, L.; Hoffmann, H. M. R.; Wippel, H. G.; Klahre, G. *Chem. Ber.* **1959**, *92*, 2499. (c) Wadsworth, W. S., Jr.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733.

[21] Yamamoto, Y. *Angew. Chem. Int. Ed.* **1986**, *25*, 947.

[22] Xu, X.; Camp, J. V.; Scanio, M. J.; Bunnelle, W. H.; Shi, L.; Osuma, A. T.; DeGoey, D.; Perez-Medrano, A.; Peddi, S.; Patel, J. R. Preparation of pyrazolo[1,5-a]pyrimidine compounds as potassium channel modulators for treating pain. U. S. Patent 20120122888, 2012.

[23] (a) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495. (b) Oisaki, K.; Suto, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5644.

[24] Bauer, R. A.; Wenderski, T.; Tan, D. S. *Nat. Chem. Biol.* **2013**, *9*, 21-29.

[25] a) Brown, A. R.; Kuo, Wen-H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010**, *132*, 9286. b) Trifonidou, M.; Kokotos, C. G. *Eur. J. Org. Chem.* **2012**, 1563. c) Zhang, T.; Qiao, Z., Wang, Y.; Zhong, N.; Liu, L.; Wang, D.; Chen, Yong-J. *Chem. Commun.*, **2013**, *49*, 1636.

[26] Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357.

[27] Corey, E. J.; Baksi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551.

[28] (a) Crabtree, R. H. *Acc. Chem. Res.* **1979**, *12*, 331. (b) Crabtree, R. H. Davis, M. W. *J. Org. Chem.* **1986**, *51*,

2655.
[29] (a) Atkins, G. M.; Burgess, E. M. *J. Am. Chem. Soc.* **1968**, *90*, 4744. (b) Burgess, E. M.; Penton, H. R., Jr.; Taylor, A. E. *J. Am. Chem. Soc.* **1970**, *92*, 5224. (c) Burgess, E. M.; Penton, H. R.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26.
[30] Julia, M.; Paris, J. M. *Tetrahedron Lett.* **1973**, *14*, 4833.
[31] Baudin, J. B.; Hareau,G.; Julia, S. A.; Ruel, O. *Tetrahedron Lett.* **1991**, *32*, 1175.
[32] Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26.
[33] Ando, K.; Kobayashi, T.; Uchida, N. *Org. Lett.* **2015**, *17*, 2554.
[34] (a) Wittig, G.; Schöllkopf, U. *Chem. Ber.* **1954**, *87*, 1318. (b) Wittig, G.; Schöllkopf, U. *Chem. Ber.* **1955**, *88*, 1654.
[35] Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780.
[36] Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392.
[37] (a) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1958**, *80*, 5323. (b) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1959**, *81*, 4256. (c) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron Lett.* **1966**, *7*, 33539
[38] (a) King, A. O.; Okukado, N.; Negishi, E. *J. Chem. Soc., Chem. Commun.* **1977**, 683. (b) Negishi, E; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821. (c) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340.
[39] Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.
[40] König, G. M.; Wright, A. D.; Angerhofer, C. K. *J. Org. Chem.* **1996**, *61*, 3259.
[41] Ciavatta, M. L.; Fontana, A.; Puliti, R.; Scognamiglio, G.; Cimino, G. *Tetrahedron* **1999**, *55*, 12629.
[42] Yamamoto, T.; Izumi, N.; Ui, H.; Sueki, A.; Masuma, R.; Nonaka, K.; Hirose, T.; Sunazuka, T.; Nagai, T.; Yamada, H.; Ōmura, S.; Shiomi, K. *Tetrahedron* **2012**, *68*, 9267.
[43] Yamada, Y.; Arima, S.; Nagamitsu, T.; Johmoto, K.; Uekusa, H.; Eguchi, T.; Shin-ya, K.; Cane, D. E.; Ikeda, H. *J. Antibiot.* **2015**, *68*, 385.
[44] Suzuki, T.; Sasaki, A.; Egashira, N.; Kobayashi, S. *Angew. Chem. Int. Ed.* **2011**, *50*, 9177.
[45] Karplus, M. *J. Am. Chem. Soc.* **1963**, *85*, 2870.

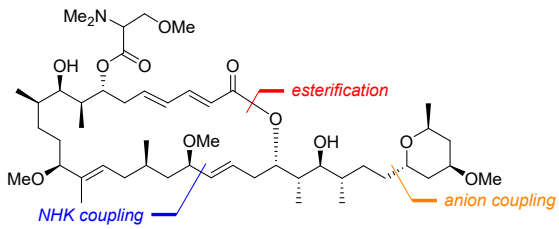
Chapter 4. Conclusion

Most drugs are developed by synthetic organic chemistry. Synthetic organic chemistry is a powerful tool to create even unknown compounds not existing in the nature. Nevertheless, natural products, which have unique structures and bioactivities, are useful as drug seeds. The author carried out researches about aplyronine A and swinhoeisterol A in order to make them foothold for creation of novel anticancer lead compounds.

In chapter 2, aplyronine A–swinholide A hybrid compound was designed as a simplified compound of aplyronine A. The hybrid compound was synthesized in 70 steps through esterification and NHK coupling as key steps (aplyronine A: 86 steps). Its cytotoxicity was strong, but which was some-what weaker than that of aplyronine A. From the evaluations of its actin-depolymerizing activity and tubulin polymerization inhibitory activity, the mode of action was confirmed to identify with that of aplyronine A.

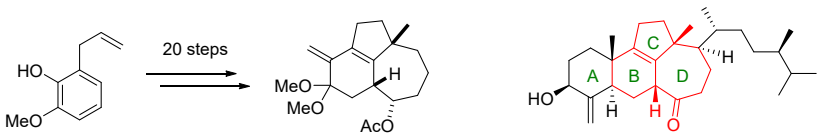
In chapter 3, swinhoeisterol A, a novel steroid with an unusual carbon skeleton was targeted. Before conducting the synthesis of the natural product, a model racemic compound was focused on to construct the carbon framework. A flexible synthetic route was planned to allow the preparation of various analogs. The synthetic strategy, based on the chemistry of benzene, allowed the preparation of model compound with BCD rings in 20 steps from *o*-eugenol through oxidative dearomatization as a key step.

Chapter 2)



aplyronine A–swinholide A hybrid compound
total 70 steps
cytotoxicity against HeLa S3 cells IC_{50} = 0.17 nM
actin-depolymerizing activity EC_{50} = 12.8 μM

Chapter 3)



swinhoeisterol A

Scheme 4-1. Conclusion

Through these researches, the author showed development of new useful compound to connect to a lead compound for anticancer drugs and synthesis of a 6/5/7-ring system. This work is expected to contribute to the elucidation of the binding site between aplyronine A and tubulin and development of new cytotoxic compound for drug discovery.

List of publications

1) Ohyoshi, T.; Takano, A.; Namiki, M.; Ogura, T.; Miyazaki, Y.; Ebihara, Y.; Takeno, K.; Hayakawa, I.; Kigoshi, H. Development of a novel inducer of protein-protein interactions based on aplyronine A. *Chem. Commun.* **2018**, *54*, 9537.

2) Takano, A.; Zhao, Y.; Ohyoshi, T.; Kigoshi, H. Synthetic studies toward swinhoeisterol A, a novel steroid with an unusual carbon skeleton. In press.

Supplementary list of publication

3) Suzuki, T.; Okuyama, H.; Takano, A.; Suzuki, S.; Shimizu, I.; Kobayashi, S. Synthesis of Dibarrelane, a Dibicyclo[2.2.2]octane Hydrocarbon. *J. Org. Chem.* **2014**, *79*, 2803.