Enantioselective Total Synthesis of (-)-Galiellalactone and Biological Evaluation of Novel Galiellalactone-Based Analogues as STAT3 inhibitors

(-)-Galiellalactone의 입체선택적인 전합성 및 Galiellalactone 기반 STAT3를 저해하는 신규 유도체의 활성 연구

2016년 2월

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Abstract

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(-)-Galiellalactone (1), a fungal metabolite originally isolated from the Galiella rufa in 1990, has been reported to be a potent and specific inhibitor of signal transducer and activator of transcription 3 (STAT3), which is involved in numerous signaling pathways. (-)-Galiellalactone covalently binds to one or more cysteine residues in STAT3 and subsequently blocks the DNA binding of phosphorylated STAT3 without inhibition of phosphorylation and dimerization. (-)-Galiellalactone also induces apoptosis and growth inhibition of human prostate cancer cells expressing constitutively active STAT3 both in vitro and in vivo. For these reasons, (-)-galiellalactone has recently been considered to be a potential therapeutic agent against hormone-refractory prostate cancer.

First, we have accomplished an enantioselective total synthesis of (-)-galiellalactone. The key features of our synthesis involve the highly stereoselective construction of the cis-trisubstituted cyclopentane intermediate by a Pd(0)-catalyzed cyclization, the stereospecific introduction of an angular hydroxyl group by Riley oxidation, and the efficient construction of the tricyclic system of (-)-galiellalactone via a combination of diastereoselective Hosomi-Sakurai crotylation and ring-closing metathesis (RCM). Next, we applied the synthetic strategy established in a process of total synthesis of (-)-galiellalactone into the syntheses of tricyclic or bicyclic galiellalactone analogues. In the present study, we investigated the inhibitory effects of (-)-galiellalactone and its structure variants on STAT3 activation and its applications in TNBC (triple-negative breast cancer) cells.

Keywords : (-)-Galiellalactone, STAT3, Pd(0)-catalyzed cyclization, cis-trisubstituted cyclopentane, Riley oxidation, Hosomi-Sakurai crotylation.
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Abbreviations

ABL: Abelson leukaemia protein
ACN: Acetonitrile
AcOH: Acetic acid
AIBN: Azobisisobutyronitrile
ALDH+: Aldehyde dehydrogenase
Alloc: Allyloxycarbonyl
Bcl: B-cell lymphoma
Boc: t-butyloxycarbonyl
CSA: Camphorsulfonic acid
DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene
DCE: Dichloroethane
DDQ: 2,3-Dichloro-5,6-dicyano-p-benzoquinone
DIBAL: Diisobutylaluminum hydride
DIPEA: N,N-Diisopropylethylamine
DMAP: N,N-Dimethylaminopyridine
DMF: N,N-Dimethylformamide
DMP: Dess-Martin periodinane
DMSO: Dimethyl sulfoxide
DNA: Deoxyribonucleic acid
DPPB: 1,4-Bis(diphenylphosphino)butane
DPPE: 1,2-Bis(diphenylphosphino)ethane
DPPF: 1,1′-Bis(diphenylphosphino)ferrocene
DPPP: 1,3-Bis(diphenylphosphino)propane
EGF: Epidermal growth factor
HER: Human EGF receptor
IFN: Interferon
IL: Interleukin
JAK: Janus kinase
LDA: Lithium diisopropylamide
LIF: Leukemia inhibitory factor
MMP: Matrix metalloproteinase
Ms: Methanesulfonyl
mTOR: Mammalian target of rapamycin
NF-κB: Nuclear factor-κB
OSM: Oncostatin M
PCC: Pyridinium chlorochromate
PMB: p-Methoxybenzyl
PPTS: Pyridinium p-toluenesulfonate
PTPs: Protein tyrosine phosphatases
PTSA: p-toluenesulfonic acid
RCM: Ring-closing metathesis
SAR: Structure-activity relationship
SEAP: Secreted alkaline phosphatase
Ser: Serine
SH2: Src homology 2
SOCS: Suppressors of cytokine signalling
STAT: Signal transducer and activator of transcription
TBAF: Tetrabutylammonium fluoride
TBDPS: t-Butyldiphenylsilyl
TBS: t-Butyldimethylsilyl
TEA: Triethylamine
TES: Triethylsilyl
TFA: Trifluoroacetic acid
T<sub>H1</sub>: T helper type 1
THF: Tetrahydrofuran
TMS: Trimethylsilyl
TNBC: Triple-negative breast cancer
TPAP: Tetrapropylammonium perruthenate
Ts: p-toluenesulfonyl
VEGF: Vascular endothelial growth factor
1. Introduction of STAT proteins

Signal transducers and activators of transcription (STATs) are proteins playing crucial roles as signal transducers and transcription factors that transmit signals from cytokines and growth factor receptors in the plasma membrane to the nucleus where they control gene transcription.\(^1\) STAT protein family is composed of seven members including STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, STAT6 (Figure 1).\(^2\) They are structurally related and share five domains including N-terminal domain, coiled-coil domain, DNA-binding domain, Src homology 2 (SH2) domain and transactivation domain with a crucial tyrosine residue, which is phosphorylated and then promotes STAT activation and dimerization between to STAT monomer through a reciprocal phosphor-Tyr-SH2 domain interaction. The serin residue in the transactivation domain of STAT proteins induces transcriptional activity after it becomes activated by phosphorylation.\(^3\)

Figure 1. A schematic representation of the structures of the STAT proteins\(^2\)

STAT proteins are normally activated in a regulated fashion when protein ligands interact
their cell-surface receptor and activate tyrosine kinases. However, persistent and aberrant activation of STATs has been detected in several tumors. Activation of STATs is initiated when a ligand binds its receptor. Upon cellular stimulation by growth factor receptor kinases, cytoplasmic kinases, such as cytokine receptor-associated Janus kinase (JAKs) and the Src family kinase, this ligand-receptor interaction induces STATs activation by phosphorylation on a single tyrosine residue in STAT proteins. Two phosphorylated STAT monomers dimerize through reciprocal SH2-phosphotyrosine interaction and the STAT-STAT dimers translocate to the nucleus where they bind to STAT-specific DNA response elements in the target gene promoters to induce gene expression (Figure 2). Thus, the activation of STATs promotes fundamental cellular and biological processes including cell growth, proliferation, differentiation, survival, development, apoptosis, immune response and inflammation.¹ᵇ, ⁵

Figure 2. Signaling pathway of STATs¹ᵇ
In the normal biological conditions, thand protein tyrosine phosphatases (PTPs). However, abnormal ST e activation of normal STATs singaling is regulated by physiological negative modulators, such as suppressors of cytokine signalling (SOCS) AT signaling pathway is constitutively activated by cellular stimulation and also implicated in many human diseases such as cancer, immune disorders, rheumatoid arthritis, asthma and diabetes (Figure 3).

Figure 3. STAT signaling pathway, functions and associated diseases
STAT1 is activated by interferon stimulation and supports immune function by regulating the growth and apoptosis of immune cells. STAT1 signaling modulates cytokine production that controls both immune function and the inflammatory responses. Moreover, the loss of responsiveness to IFNγ by STAT1-deficiency provides malignant cells and occurs tumor formation.

STAT2 protein mediated by IFNα and IFNβ signaling modulates antiviral responses and apoptosis. Moreover, it contributes to carcinogenesis by upregulating the cytokine production, such as interleukin-6, which promotes overexpression of STAT3 signaling pathway. In normal cells, and under physiological conditions, STAT3 activation is a tightly regulated transient process. However, STAT3 signaling is persistently and aberrantly activated by both receptor and non-receptor tyrosine kinases via the tyrosine phosphorylation cascade. Especially, interleukins and oncostatin M leads to activation of STAT3 signaling pathway. This overactive STAT3 is closely related to inflammation, immune responses and carcinogenesis.

STAT4 regulates the differentiation of T\textsubscript{H}1 cells and their inflammatory responses mediated by interleukin-12. For these reasons, STAT4 signaling could induce autoimmune diseases. STAT5 has two isoforms, STAT5a and STAT5b, which have notable differences occurring in the transactivation domain. STAT5 signaling is important for cell proliferation and survival. STAT5 promotes malignant transformation, including of pro-proliferative and anti-apoptotic genes with STAT3 in the similar way.

STAT6 is induced by interleukin-4 and interleukin-13 and controls immune functions by regulating the inflammatory and allergic immune responses. In the light of these roles in biological processes, STAT proteins have recently been received much attention since they were reported and considered to be therapeutic molecular target.
2. STAT3 and cancer

2-1. STAT3 as a molecular target for cancer treatment

Overexpression or constitutive activation of STAT3 has been detected in several human solid and hematological cancer cells, including breast, colon, ovarian, lung, brain, pancreatic, prostate cancer and so on (Figure 4), whereas it is tightly regulated in normal cells.\(^7\) In addition, tumor cells are more dependent on the function of STAT3 than normal cells. Phosphorylated STAT3 protein (Y705) levels are closely related to tumor development compared with total STAT3. Unlike the activation of Stat3 in normal cells, constitutively and persistently active STAT3 is easily detected in several human cancer cells (Figure 5). These different cancer cells implicate dysfunction of STAT3 as a key factor in tumor growth, proliferation, survival, angiogenesis, metastasis and invasion. For these reasons, STAT3 is validated as a promising therapeutic target for drug discovery related in human cancers.\(^{1a}\)

**Figure 4. STAT3 expression and activation in human normal and cancer tissues and cell lines**
2-2. STAT3 protein

In 1994, STAT3 protein, discovered by two research groups independently is a DNA-binding factor. STAT3 have many isoforms. First, STAT3α is considered as most common form in many cell types. STAT3β is replaced by seven distinct amino acids from STAT3α in the transactivation domain. STAT3γ is another truncated form of STAT3α and considered as a novel form. The domain structure of STAT3 includes an N-terminal, coiled-coil, DNA-binding, linker, SH2, transactivation and C-terminal domain (Figure 6).
2-3. Role of STAT3 in cancer

In human solid and hematological cancer cells, STAT1, STAT3 and STAT5 are constitutively and aberrantly activated (Table 1). Unlike STAT3 and STAT5, STAT1 induces inflammatory responses, which is antagonistic to biological function of STAT3. As mentioned above, overexpressed STAT3 suppresses several biological functions and induces tumor development, which is intact from apoptosis. Cell proliferation is stimulated by STAT3-mediated genes, such as Bcl-XL, Mcl-1, Bcl-2, Fas, cyclin D1, survivin and c-Myc. Furthermore, cell proliferation and apoptosis occur by downregulating the tumor suppressor TP5 via STAT3 overexpression. Moreover, STAT3 induces tumor migration and invasion. Therefore, STAT3 is promising target for cancer therapy.
Table 1. Activation of STATs in human cancers\textsuperscript{1b}

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Activated STAT</th>
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<tr>
<td><strong>Blood tumours</strong></td>
<td></td>
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<tr>
<td>Multiple myeloma</td>
<td>STAT1, STAT3</td>
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<td>Leukaemias:</td>
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<tr>
<td>Erythroleukaemia</td>
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<td>Acute myelogenous leukaemia (AML)</td>
<td>STAT1, STAT3, STAT5</td>
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<tr>
<td>Chronic myelogenous leukaemia (CML)</td>
<td>STAT5</td>
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<tr>
<td>Large granular lymphocyte leukaemia (LGL)</td>
<td>STAT3</td>
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<tr>
<td><strong>Lymphomas:</strong></td>
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3. (-)-Galiellalactone

(-)-Galiellalactone (1), a fungal metabolite originally isolated from the ascomycete Galiella rufa\textsuperscript{11} (Figure 7 and 8), has been reported to be a potent and specific inhibitor of signal transducer and activator of transcription 3 (STAT3), which is involved in numerous signaling pathways. (-)-Galiellalactone covalently binds to one or more cysteine residues in STAT3 and subsequently blocks the DNA binding of phosphorylated STAT3 without inhibition of phosphorylation and dimerization.\textsuperscript{12} The (-)-galiellalactone alkylated cysteine residues in STAT3 are located in the linker domain (Cys-542) and DNA binding domain (Cys-367 and Cys-468) where Cys-468 is in direct contact with bound DNA (Figure 9).\textsuperscript{12} Importantly, persistent and aberrant activation of STAT3 has been detected in several human solid and hematological cancer cells, whereas it is tightly regulated in normal cells, which supports STAT3 as a promising molecular target for cancer therapy. (-)-
Galiellalactone also induces apoptosis and growth inhibition of human prostate cancer cells expressing constitutively active STAT3 both \textit{in vitro} and \textit{in vivo} \cite{13} and suppresses stem cell-like ALDH+ prostate cancer cells.\cite{14} For these reasons, (-)-galiellalactone has recently been considered to be a potential therapeutic agent against hormone-refractory prostate cancer.

\textbf{Figure 7. Structure of (-)-galiellalactone (1)}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{structure.png}
\caption{X-ray structure with the absolute configuration of natural (-)-galiellalactone (1)\cite{15}}
\end{figure}

The structure of (-)-galiellalactone (1) features a unique and highly congested [5,5,6]-tricyclic ring system that consists of a reactive $\alpha,\beta$-unsaturated lactone functionality and
four stereocenters (Figure 7 and 8). The tertiary stereogenic center possesses an angular hydroxyl group, which is essential for the biological activity of 1.\textsuperscript{15}

\textbf{Figure 9. STAT3 monomer bound to DNA}\textsuperscript{12}

\textbf{3-1. Biosynthetic process for (-)-galiellalactone}

(-)-Galiellalactone (1), a tetrahydro-isobenzofuranone derivative, was formed through an intramolecular Diels-Alder reaction, which is the first example of an intramolecular Diels-Alder reaction with inverse electron demand in a polyketide biosynthetic pathway.\textsuperscript{16} The conversion of (-)-pregaliellalactone to 1 occurs in two discrete steps. When (-)-pregaliellalactone or (+)-deoxygaliellalactone are fed to the mycelium of the \textit{Galiella rufa} strain A75-86, these co-metabolites are converted to 1 \textit{in vivo} (Scheme 1).\textsuperscript{17}
3-2. Previous synthetic approaches for (-)-galiellalactone

Sterner and Johansson reported the first and efficient synthesis of (-)-galiellalactone and established the absolute configuration of the natural product.\textsuperscript{18} However, the stereoselective introduction of a tertiary hydroxyl group remains a formidable task because introduction of an epoxide, as a precursor of the tertiary hydroxyl group, into the hydrindane system of 1 has only been reported with a moderate diastereoselectivity. In addition, chemical hydroxylation at the central angular position could not directly elaborate the tertiary hydroxyl group.\textsuperscript{19}

As mention above, (-)-pregaliellalactone 2, the biosynthetic precursor of 1 can efficiently be converted into (+)-deoxygaliellalactone 3 through an intramolecular Diels-Alder cycloaddition. Although the chemical oxidation of 3 to (-)-galiellalactone (1) has proven difficult, the hydroxylation of the central carbon of 1 in the mycelium gives 1 in high yields. Thus, efficient and short procedure for the preparation of enantiomerically pure 2 has been developed from 4-pentenal 4 in 4 steps (Scheme 2).\textsuperscript{20} This scalable procedure can be utilized for large amounts of 1.
Reagents and conditions: a) ethyl propiolate, Trost’s (S,S)-bis-ProPhenol ligand, Me₂Zn, toluene, 2 °C, 54%; b) trans-1-propen-1-ylboronic acid, Pd(OAc)₂, (t-Bu)₃P, AcOH, THF, 60 °C; c) THF/H₂O (1:3), 110 °C, 38% (in 2 steps)

In 2001, the first total synthesis of (+)-galiellalactone was accomplished by Sterner and co-workers and established the absolute configuration of the natural product (Scheme 3). The starting material 6 possessing the six-membered ring moiety of galiellalactone, annulation of the five-membered ring was carried out by a conjugate addition followed by hydrolysis and condensation. Treatment of the bicyclic ketone 10 with triflating agent followed by palladium-catalyzed carbonylation of the enol triflate provided the methyl ester 12. Stereoselective epoxidation of the cyclopentene 12 provided a β-epoxide as a major product. Subsequent acid-catalyzed epoxide opening provided the (+)-galiellalactone and introduced the angular hydroxyl group. This concise synthesis has been efficiently accomplished in 11 linear steps. The synthetic galiellalactone was identical to the natural product in all aspects, except its optical rotation. Thus, absolute configuration of (-)-galiellalactone was revised.
Scheme 3. The first total synthesis of (+)-galiellalactone

As the initially proposed absolute configuration of galiellalactone was wrong, synthesis of (-)-galiellalactone was carried out by the same synthetic strategy for (+)-galiellalactone. From same starting material, annulation reaction of five-membered ring was initiated by 1,2-addition of the acetal-containing Grignard reagent, not conjugate addition by adjusting the reaction temperature. Subsequent oxidative rearrangement with PCC gives the enone 8b, which is an enantiomer of 8a (Scheme 4).18b
Scheme 4. The synthesis of (-)-galiellalactone

Reagents and conditions: a) 2-(2-bromoethyl)-1,3-dioxolane, Mg, I₂, 1,2-dibromoethane, THF, rt, 42%; b) PCC, CH₂Cl₂, rt, 73%; c) 10% Pd/C, H₂, THF, 100%; d) 1 M HCl, THF, 87%; e) KHMDS, N-phenyltrifluoromethylsulfonimide, THF, 94%; f) CO, Pd(OAc)₂, PPh₃, DIPEA, MeOH, 74%; g) 70% m-CPBA, CH₂Cl₂, 0 °C, 93% (ent-13a/ent-13b 3.5:1); h) LiOH-H₂O, THF/water (1:1); i) 10% H₂SO₄, 40 °C, 55% (in 2 steps)

In 2010, Sterner and co-workers has reported the syntheses of novel 7-substituted galiellalactone analogues. As mentioned above, previous SAR studies have shown that the angular hydroxyl group and the α,β-unsaturated lactone functionality are absolutely essential for biological activity of 1. Thus, they tried to synthesize the analogues possessing the substituents at cyclopentane ring system. These analogues were prepared via a tandem palladium-catalyzed carbonylation of 16 and intramolecular Diels-Alder cycloaddition of dienyne carbonate 17a-e (Scheme 5).
Scheme 5. Synthesis of galiellalactone analogues

Reagents and conditions: a) 2 equiv. BuLi, THF; b) 2,2-Dimethylpent-4-enal; c) Methyl chloroformate, 65% from 15; d) Pd(dba)$_2$, DPPP, CO, MeOH, toluene, 10%; e) 70% m-CPBA, CH$_2$Cl$_2$, 0 $^\circ$C; f) LiOH, THF/H$_2$O;

In 2013, Ghosh and co-workers has reported the intramolecular Diels-Alder route to hydrindanes of (-)-galiellalactone.$^{19a}$ They utilized trienones intermediate embedded in a sugar derivative as an equivalent of the angular hydroxyl group, because chemical hydroxylation at the central angular position could not directly elaborate the tertiary hydroxyl group. They attempted to synthesize the (-)-galiellalactone, but ended up with a synthesis of (+)-dihydro-C-7a-epi-seco-galiellalactone because of migration of internal olefin of 21 and low diastereoselectivity of hydrogenation of 21 and 22b (Scheme 6).

Scheme 6. Synthetic approach to functionalized bicyclic skeleton of galiellalactone
3-3. Previous SAR studies on (-)-galiellalactone

Preliminary SAR studies have shown that natural galiellalactone is equipotent to its enantiomer, unnatural galiellalactone, as well as its 4-methyl epimer (Figure 10).\textsuperscript{21}

Figure 10. Structures of unnatural, natural and epi-galiellalactone

(-)-Galiellalactone has been known to selectively inhibits interleukin-6 induced SEAP expression in HepG2 cells mediated by STAT3.\textsuperscript{22} Thus, Nussbaum and co-workers have reported the syntheses of IL-6 antagonistic analogues of (-)-galiellalactone, which also inhibit STAT3 signaling pathway.\textsuperscript{15} For the structure diversification, they prepared the synthetic analogues from natural galiellalactone, focused on the angular hydroxyl group and α,β-unsaturated lactone functionality, which are absolutely essential for biological activity of 1. Catalytic hydrogenation, Michael additions, epoxidation and acetylation of the angular hydroxyl group of (-)-galiellalactone afforded the synthetic analogues 24-31 by its inherent convex selectivity. However, these compounds are inactive within IL-6 responsive assay systems (Scheme 7).
4. Pd(0)-catalyzed cyclization

Asymmetric metal-catalyzed chemical reactions play crucial roles in allowing synthetic approach to biologically active natural or unnatural molecules. Since metal-catalyzed alkylation using Pd(0) has been developed by Jiro Tsuji and co-workers, asymmetric metal-catalyzed reactions has been developed by many synthetic chemists (Scheme 8). Compared to dihydroxylation, epoxidation, and hydrogenation, asymmetric allylic alkylation reaction forms diverse type of bonds including C-C, C-S and C-O bond. For these reasons, Pd(0)-catalyzed cyclization reaction has been considered and utilized as one of the most useful synthetic tool for establishment of complex carbo- and hetero-cycled skeleton of natural product.
Scheme 8. Palladium catalyzed allylic alkylation

\[
\begin{align*}
\text{Pd(0) complex} & \quad \text{oxidative addition} \\
\pi\text{-allylpalladium complex} & \quad \text{alkylation} \\
\text{optically active substrates} & \quad \text{retention of configuration}
\end{align*}
\]

-allylpalladium complex is formed by the oxidative addition of palladium to allylic species including leaving group, such as carbonates, ester and halide. The alkyl substituted π-allylpalladium complex could be alkylated with soft carbon nucleophiles. The formation of π-allylpalladium complex involves inversion of stereochemistry, and the attack of the soft nucleophile on the π-allylpalladium complex inverts the stereochemistry. Thus, optically active substrates are substituted with an overall retention of configuration (double inversion).

4-1. Previous studies on Pd(0)-catalyzed cyclization

In our laboratory, intramolecular Pd(0)-catalyzed allylic alkylation has been developed. At first, Pd(0)-catalyzed cyclization reaction was investigated with the acyclic allylic precursors 32, 34 and 36 (Scheme 9). Having successfully prepared the cyclization precursor possessing two anion stabilizing groups, such as benzenesulfonate and ester or nitrile, Pd(0)-catalyzed cyclization of allylic carbonates afforded the 1,1,2-trisubstituted cyclobutane 33a, cyclopentane 35a and cyclohexane 37a with high diastereoselectivities and chemical yields.23
However, asymmetric control of the stereochemistry of the nucleophilic carbon center with two anion stabilizing groups is very difficult because of the loss of the stereochemistry upon removal of the anion stabilizing auxiliary. To employ these strategies for construction of carbocycle of natural product, γ-butyrolactone and δ-valerolactone was provided which include the chiral hydroxyl group (Scheme 10). With these γ-butyrolactone 38 and δ-valerolactone 40 in hand, the [2.1.2] bicyclic lactone 39 and [2.2.1] bicyclic lactone 41 were produced by Pd(0)-catalyzed cyclization with high diastereoselectivities (Scheme 10). More specifically, desulfonylation of 39 and 41 produced trisubstituted cyclopentane system with retention of stereochemistry. Especially, trisubstituted cyclopentane system have all cis relationships, which are very difficult to access by conventional cyclization methods. For these reasons, optically active cis-trisubstituted cyclopentane obtained by this strategy is considered as a useful synthetic intermediate for the stereoselective synthesis of bioactive natural products.
4-2. Synthetic applications of bridged bicyclic lactones

With these bicyclic lactones, we have reported the synthetic applications for natural products.

In our laboratory, the total synthesis of (+)-brefeldin A, having a wide range of biological activities and unique structure, has been reported employing Pd(0)-catalyzed cyclization (Scheme 11).\(^\text{24}\) To introduce the three carbons to lactone group of [2.1.2] bicyclic lactone \(\text{46}\), the 1-[(\text{E})-2-Iodoethenyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]-octane (\(\text{42}\), OBO ortho ester)\(^\text{35}\) was prepared as an equivalent of the carboxyl group, which is resistant by strong nucleophiles and easily hydrolyzed under mild reaction conditions. In additions, to afford structurally diversified brefeldin A derivatives, further studies were performed for more practical and versatile synthetic strategy. As a result, we also afforded the brefeldin A via the intramolecular HWE olefination of \(\text{48}\).
Iridoid lactone 60 was isolated from the Nardostachys chinensis Batalin (Valerianaceae).

We have worked on the development of an efficient synthetic route to the new iridoid lactone 60. In our laboratory, we developed the efficient synthetic route to the 60. The key features of this synthesis includes facile construction of the [2.1.2] bicyclic lactone intermediate 54 and tetrasubstituted cyclopentanol intermediate 59 via intramolecular Pd(0)-catalyzed allylic alkylation and the efficient transformation of this intermediate into the iridoid skeleton employing silicon tethered radical cyclization followed by Tamao-Fleming oxidation for the asymmetric elaboration of the hydroxymethyl group.
The enantioselective synthesis of 7-epi-incarvilline is described (Scheme 13). The key features of the synthesis involve stereoselective construction of the optically active [2.1.2] bicyclic lactone 64 via Pd(0)-catalyzed allylic alkylation, efficient transformation of the bicyclic lactone into the key bicyclic lactam compound 66, and stereoselective introduction of two stereogenic centers via a substrate-controlled hydrogenation followed by a 1,4-addition. This synthesis was accomplished from the known intermediate 61 via substrate controlled stereocontrol.
Scheme 13. Stereoselective synthesis of 7-epi-incarvilline

Bacillariolide III, a new carbocyclic oxylipin, was isolated from the marine diatom *Pseudonitzschia multiseries*. In our group, we have reported diastereoselective total synthesis of bacillariolide III.\(^{28}\) The key feature of this synthesis involves the highly stereoselective construction of the vinyl-substituted [2.2.1] bicyclic lactone 41 by an intramolecular Pd(0)-catalyzed allylic alkylation and its facile conversion to the hydroxy bicyclic lactone skeleton 79 of bacillariolide III, induced by stereoselective vinylcerium addition to the aldehyde. In addition, the (Z)-pentenoic acid was efficiently introduced by
the internal hydroxy group tethered ring-closing metathesis (Scheme 14). The asymmetric total synthesis of bacillariolide III has been achieved via 15 linear steps in 14.6% overall yield.

Scheme 14. Total synthesis of bacillariolide III

Reagents and conditions: a) Pd(PPh₃)₄, CH₂Cl₂, reflux, 88%, dr 30:1; b) 6% Na/Hg, B(OH)₃, MeOH, rt, 88%; c) O₃, CH₂Cl₂, -78 °C, then Me₂S; d) vinylmagnesium bromide, CeCl₃, THF, -78 °C, 65% (in 2 steps); e) 4-pentenoyl chloride, TEA, DMAP, CH₂Cl₂; f) Grubbs catalyst, 2nd generation, CH₂Cl₂, reflux, 83% (in 2 steps); g) LiOH-H₂O, THF/H₂O (5:1), then TFA, 71%
II. Results and Discussion

1. Enantioselective total synthesis of (-)-Galiellalactone

Recently, we have reported the highly diastereoselective construction of bridged bicyclic lactone skeletons as equivalents of the contra thermodynamic tri-\(cis\)-substituted cyclopentane,\(^{29}\) which were utilized for the total syntheses of bioactive natural products. Encouraged by these versatile strategies, we undertook the total synthesis of (-)-galiellalactone.

1.1 Retrosynthetic analysis

Our synthetic approach for 1 is outlined in scheme 15, which includes a stereoselective construction to the tricyclic intermediate containing three contiguous stereocenters as well as a methyl substituent. (-)-Galiellalactone (1) was anticipated to be obtained from homoallylic alcohol 82, which comprises all four stereocenters of the natural product, by ring-closing metathesis (RCM) and subsequent Barton-McCombie deoxygenation of the secondary hydroxyl group at the final stage. The C5a-side chain of 82 can be installed into the key bicyclic intermediate 83 by deprotection of dioxolane group followed by a substrate-controlled asymmetric crotylation. The stereochemistry of the C7b-stereocenter was predicted based on the stereospecific introduction of an angular hydroxyl group by a substrate-controlled oxidation of the \(cis\)-fused 5,5-bicyclic lactone system, which can be efficiently produced from the \(cis\)-trisubstituted cyclopentane 84. Cyclopentane 84 is accessible by reduction of the [2.2.1] bridged bicyclic lactone 41, which can be efficiently prepared by a diastereoselective Pd(0)-catalyzed cyclization of \(\delta\)-valerolactone 40 that was developed by our group although the substituents are quite different. \(\delta\)-Valerolactone 40 was expected to be conveniently prepared from the known starting material 77.
1-2. Preliminary studies from known [2.2.1] bridged bicyclic lactone

As mentions above, the stereoselective introduction of a tertiary hydroxyl group remains a formidable task because introduction of an epoxide, as a precursor of the tertiary hydroxyl group, into the hydrindane system of 1 has only been reported with a moderate diastereoselectivity. So, we undertook the efficient introduction of angular hydroxyl group into the cis-fused 5,5-bicyclic lactone system (Scheme 16). From the intermediate of bacillariolide Ⅲ 85, the synthesis commenced with the preparation of bicyclic lactone 88, as shown in Scheme 16. Partial reduction and acetalization of [2.2.1] bicyclic lactone 85 afforded cyclopentane intermediate 86, which was converted to diol 87 via hydroboration reaction. TEMPO oxidation of 87 followed by olefination of 88 provided a synthetic precursor of stereoselective Riley oxidation. Riley oxidation of 89 with SeO₂ in 1,4-dioxane successfully provided the oxygenated bicyclic lactone 83 as a single diastereomer. With this intermediate, we attempted to deprotect a dioxolane protecting group in various acidic conditions, but can’t afford to desired aldehyde 90 because of an inherent instability.
Scheme 16. Preliminary Study for introduction of angular hydroxyl group

Reagents and conditions: a) DIBAL-H, toluene, -78 °C; b) Ethylene glycol, PTSA, benzene, reflux, Dean-stark trap, 73% (in 2 steps); c) BH₃·THF, THF, 0 °C, 63%; d) TEMPO, BAIB, CH₂Cl₂, rt, 76%; e) paraformaldehyde, NaH, THF, 0 °C to reflux, 90%; f) SeO₂, reflux, 86%; g) various acidic conditions;

1-3. Synthetic approach for cis-fused 5,5-bicyclic lactone intermediate 94

From these results, it turned out that deprotection of dioxolane group of bicyclic lactone 83 was not successful for our system. Thus, to solve this instability problem, we envisaged an advanced [2.2.1] bridged bicyclic lactone 91 to establish the aldehyde group of bicyclic lactone for stereoselective crotylation reaction (Scheme 17). We carried out the selective functionalization of primary alcohol of 92 for construction of bicyclic lactone, which contains primary alcohol as a equivalent of β-aldehyde group for stereoselective crotylation. We attempted to introduce various functional group into the primary alcohol, such as THP (tetrahydropyran), TBDPS (tert-butyldiphenylsilyl), Ts (p-toluenesulfonyl), Ms(methanesulfonyl), Alloc (allyloxycarbonyl), and Boc(tert-butoxycarbonyl) group. However, we can’t afforded the bicyclic lactone intermediate 94, because of the highly congested steric environments of cyclopentanes 93a-f.

First, we carried out deprotection of primary alcohol as THP or TBDPS group. However, selective protections of primary alcohol were not successful, because of the steric repulsion between primary alcohol and allyloxy silyl ether side chain. Tosylation or mesylation of 92
afforded eliminated cyclopentene as a major product. Alloc protection of 92 is successfully proceeded, but deprotection of alloc group was failed after construction of bicyclic lactone.

Scheme 17. Functionalization of primary alcohol of cyclopentane 92

Finally, Boc protection\textsuperscript{30} of 92 by utilizing a carbonyl imidazole intermediate afforded 93\textsubscript{f}, which was converted to 95 by TBS deprotection. Next, TEMPO oxidation of primary alcohol of 95 and subsequent lactonization of lactol provided \textit{cis}-fused 5,5-bicyclic lactone intermediate 96. As illustrated in Scheme 17, we carried out the introduction of angular hydroxyl group into the bicyclic lactone 96 to afford 99. Finally, we attempt to deprotect the Boc protecting group. After intensive screening of deprotection conditions (Entries 1-5), we afforded \textit{cis}-fused 5,6-bicyclic lactone 98 or 100, not \textit{cis}-fused 5,6-bicyclic lactone 97 or 94. In acidic conditions, after deprotection of Boc group, construction of the 5,6-fused bicyclic lactone was more favorable than the 5,5-fused bicyclic lactone. Thus, we undertook the protecting group-free strategy for construction of thermodynamically less favorable \textit{cis}-trisubstituted cyclopentriol 101.
Scheme 18. Synthetic approach to the bicyclic lactones 94 and 97

Table 2. Deprotection conditions of bicyclic lactone 96 or 99

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Temperature</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TFA, CH₂Cl₂</td>
<td>rt</td>
<td>trans lactonization product 98 or 100</td>
</tr>
<tr>
<td>2</td>
<td>K₂CO₃, MeOH</td>
<td>rt</td>
<td>decomposed or methanolysis</td>
</tr>
<tr>
<td>3</td>
<td>CAN, ACN</td>
<td>reflux</td>
<td>trans lactonization product 98 or 100</td>
</tr>
<tr>
<td>4</td>
<td>4N HCl, 1,4-dioxane</td>
<td>rt to 40°C</td>
<td>NR</td>
</tr>
<tr>
<td>5</td>
<td>PTSA, EtOH</td>
<td>reflux</td>
<td>NR</td>
</tr>
</tbody>
</table>

1-4. Revised retrosynthetic analysis for (-)-galiellalactone (1)

Our revised synthetic approach for 1 is shown in scheme 19, which includes a stereoselective construction to the tricyclic intermediate containing three contiguous stereocenters as well as a methyl substituent. (-)-Galiellalactone (1) was anticipated to be obtained from homoallylic alcohol 82a, which comprises all four stereocenters of the natural product, by ring-closing metathesis (RCM) and subsequent Barton-McCombie
deoxygenation of the secondary hydroxyl group at the final stage. The C5a-side chain of 82a can be installed into the key bicyclic intermediate 94 by oxidation of the alcohol followed by a substrate-controlled stereoselective crotylation. The stereochemistry of the C7b-stereocenter was predicted based on the stereospecific introduction of an angular hydroxyl group by a substrate-controlled oxidation of the cis-fused 5,5-bicyclic lactone system, which can be efficiently produced from the cis-trisubstituted cyclopentanetriol 101. Cyclopentanetriol 101 is accessible by reduction of the [2.2.1] bridged bicyclic lactone 102, which can be efficiently prepared by a diastereoselective Pd(0)-catalyzed cyclization of δ-valerolactone 103a. δ-Valerolactone 103a was expected to be conveniently prepared from the known alcohol 104.

Scheme 19. Revised retrosynthetic analysis of (-)-galiellalactone.

1-5. Preparation of allylic alcohol 107

We first prepared the known starting material 107 in 5 steps as shown in scheme 20. TBS protection of α-hydroxy-γ-butyrolactone afforded 77, which was converted to alcohol 104
via DIBAL-H reduction and Wittig olefination. Tosylation of 104 and TBS deprotection afforded allylic alcohol 107 in a high yield. However, commercially available (R)-(+)−α-hydroxy-γ-butyrolactone is very expensive. Thus, we designed another synthetic route, which was anticipated to obtain large amounts of known starting material 00.

Scheme 20. Preparation of allylic alcohol 107

\[
\begin{array}{c}
\text{Reagents and conditions: a) TBSCl, imidazole, DMF, 0 °C to rt, 95%; b) DIBAL-H, CH}_2\text{Cl}_2, -78 °C; c) Ph}_3\text{PCH}_3\text{Br, }t\text{-BuOK, THF, -78 °C to rt, 74% (in 2 steps); d) TsCl, TEA, DMAP, CH}_2\text{Cl}_2, 0 °C to rt; e) CSA, MeOH, rt, 95% (in 2 steps).}
\end{array}
\]

From D-(+)-malic acid, reduction of diacid group followed by acetalization afforded 109. Swern oxidation of 109 and subsequent Wittig olefination of resulting aldehyde provided 110. Finally, PMP deprotection of 110 with DIBAL-H afforded large amounts of 104 (Scheme 21).

Scheme 21. Scalable synthetic pathway for allylic alcohol 107

\[
\begin{array}{c}
\text{Reagents and conditions: a) BH}_3\text{-Me}_2\text{S, (MeO)}_3\text{B, THF, 0 °C to rt, 98%; b) p-Anisaldehyde dimethyl acetal, CSA, DMF, rt, 77%; c) (COCl)}_2, \text{DMSO, TEA, CH}_2\text{Cl}_2, -78 °C; d) Ph}_3\text{PCH}_3\text{Br, }n\text{-BuLi, THF, 0 °C to rt, 67% (in 2 steps); e) DIBAL-H, CH}_2\text{Cl}_2, 0 °C, 85%}
\end{array}
\]
1.6 Preparation of Pd(0)-catalyzed cyclization precursor 103a

The synthesis commenced with the preparation bicyclic lactone 103a, as shown in Scheme 22. Tosylation of the known alcohol 104 and PMB deprotection with DDQ afforded the allylic alcohol 107, which was converted to bis-alkoxysilane 109 via a sequence of double silylation with another allylic alcohol fragment and tosylate substitution with the anion of benzenesulfonyl acetate in a 91% yield. Ring closing metathesis (RCM) of diene 110 in the presence of 2nd generation Grubbs catalyst afforded a cyclic bis-alkoxysilane 111 in a quantitative yield. Cleavage of the silicon tether of 111 resulted in a spontaneous lactonization of the resulting dihydroxy ester, followed by TBS-protection of the allylic alcohol to produce δ-valerolactone 103a.

Scheme 22. Synthesis of δ-valerolactone 103a

Reagents and conditions: a) TsCl, TEA, DMAP, CH2Cl2, 0 °C to rt, 93%; b) DDQ, CH2Cl2/pH 7 phosphate buffer solution (9:1), rt, 98%; c) iPr2SiCl, imidazole, CH2Cl2, 0 °C to rt, 96%; d) methyl phenylsulfonylacetate, NaH, DMF, rt to 80 °C, 78%; e) Grubbs catalyst, 2nd generation, toluene, reflux; f) TBAF, THF, rt, 79%; g) TBSCl, imidazole, DMF, 0 °C to rt, 89%

1.7 Pd(0)-catalyzed cyclization of δ-valerolactone 103a

With the cyclization precursor 103a in hand, we performed the diastereoselective Pd(0)-catalyzed cyclization of 103a. After intensive optimization of the cyclization conditions including various ligands and solvents as summarized in Table 3, it was determined that the
intramolecular allylic alkylation of 103a in the presence of Pd(dppf)2 in CH2Cl2 afforded the bicyclic lactone 102a in an 87% yield with the best diastereoselectivity (7.2:1, Entry 16), which was determined by the isolation of each isomer. Cyclization of 103a in the presence of Pd(PPh3)4 resulted in low stereoselectivity regardless of the solvents (Entries 1-6). Cyclization in the presence of Pd(OAc)2 with dppe, dppp or dppb also showed a disappointingly low stereoselectivity (Entries 7-15). Interestingly, the cyclization in the presence of Pd(dppp)2 in THF showed the opposite diastereoselectivity (Entry 11).

Table 3. Pd(0)-catalyzed cyclization of δ-valerolactone 103a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (5 mol%)</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Ratio (102a:102b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(PPh3)4</td>
<td>CH2Cl2</td>
<td>reflux</td>
<td>5:1</td>
</tr>
<tr>
<td>2</td>
<td>Pd(PPh3)4</td>
<td>THF</td>
<td>reflux</td>
<td>1.3:1</td>
</tr>
<tr>
<td>3</td>
<td>Pd(PPh3)4</td>
<td>CH3CN</td>
<td>reflux</td>
<td>2.5:1</td>
</tr>
<tr>
<td>4</td>
<td>Pd(PPh3)4</td>
<td>DCE</td>
<td>reflux</td>
<td>3:1</td>
</tr>
<tr>
<td>5</td>
<td>Pd(PPh3)4</td>
<td>toluene</td>
<td>reflux</td>
<td>1.1:1</td>
</tr>
<tr>
<td>6</td>
<td>Pd(PPh3)4</td>
<td>DMSO</td>
<td>80 °C</td>
<td>3:1</td>
</tr>
<tr>
<td>7</td>
<td>Pd(dppb)2</td>
<td>CH2Cl2</td>
<td>reflux</td>
<td>trace</td>
</tr>
<tr>
<td>8</td>
<td>Pd(dppb)2</td>
<td>toluene</td>
<td>reflux</td>
<td>trace</td>
</tr>
<tr>
<td>9</td>
<td>Pd(dppb)2</td>
<td>THF</td>
<td>reflux</td>
<td>2:1</td>
</tr>
<tr>
<td>10</td>
<td>Pd(dppp)2</td>
<td>CH2Cl2</td>
<td>reflux</td>
<td>NR</td>
</tr>
<tr>
<td>11</td>
<td>Pd(dppp)2</td>
<td>THF</td>
<td>reflux</td>
<td>1:1.5</td>
</tr>
<tr>
<td>12</td>
<td>Pd(dppe)2</td>
<td>CH2Cl2</td>
<td>reflux</td>
<td>1.3:1</td>
</tr>
<tr>
<td>13</td>
<td>Pd(dppe)2</td>
<td>THF</td>
<td>reflux</td>
<td>1.3:1</td>
</tr>
<tr>
<td>14</td>
<td>Pd(dppe)2</td>
<td>CH3CN</td>
<td>reflux</td>
<td>1.5:1</td>
</tr>
<tr>
<td>15</td>
<td>Pd(dppe)2</td>
<td>DCE</td>
<td>reflux</td>
<td>1.3:1</td>
</tr>
<tr>
<td><strong>16</strong></td>
<td>Pd(dppf)2</td>
<td>CH2Cl2</td>
<td>reflux</td>
<td>7.2:1</td>
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<tr>
<td>17</td>
<td>Pd(dppf)2</td>
<td>THF</td>
<td>reflux</td>
<td>1:1</td>
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</table>
To improve the diastereoselectivity of Pd(0)-catalyzed cyclization, we carried out the cyclization of 103b, 103c or 103d, which contain different π-allylpalladium complexes in the transition state (Table 4). We originally envisioned that Pd(0)-catalyzed cyclization of 103d including a bulky side chain, such as CH$_2$OPMB group could provide more increased diastereoselectivity than CH$_2$OTBS, CH$_2$OMOM, or methyl side chain. However, we didn’t provide an optimum condition to afford [2.2.1] bridged bicyclic lactone 102c, 102e with high diastereoselectivity except entry 18. Most conditions showed the low diastereoselectivity regardless of the catalysts and solvents.

Table 4. Pd(0)-catalyzed cyclization of δ-valerolactone 103b, 103c or 103d

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Catalyst (5 mol%)</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Ratio (102c/e:102d/f)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>103b</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>CH$_2$Cl$_2$</td>
<td>reflux</td>
<td>2:1</td>
</tr>
<tr>
<td>2</td>
<td>103b</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>THF</td>
<td>reflux</td>
<td>1.1:1</td>
</tr>
<tr>
<td>3</td>
<td>103b</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>ACN</td>
<td>reflux</td>
<td>3:1</td>
</tr>
<tr>
<td>4</td>
<td>103b</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>DMSO</td>
<td>80 °C</td>
<td>3:1</td>
</tr>
<tr>
<td>5</td>
<td>103b</td>
<td>Pd(dppe)$_2$</td>
<td>CH$_2$Cl$_2$</td>
<td>reflux</td>
<td>1.2:1</td>
</tr>
<tr>
<td>Entry</td>
<td>Catalyst</td>
<td>Ligands</td>
<td>Solvent</td>
<td>Temperature</td>
<td>Ratio</td>
</tr>
<tr>
<td>-------</td>
<td>------------</td>
<td>---------</td>
<td>---------</td>
<td>-------------</td>
<td>-------</td>
</tr>
<tr>
<td>6</td>
<td>103b</td>
<td>Pd(dppp)$_2$</td>
<td>CH$_2$Cl$_2$</td>
<td>reflux</td>
<td>NR</td>
</tr>
<tr>
<td>7</td>
<td>103b</td>
<td>Pd(dppp)$_2$</td>
<td>THF</td>
<td>reflux</td>
<td>NR</td>
</tr>
<tr>
<td>8</td>
<td>103b</td>
<td>Pd(dppf)$_2$</td>
<td>CH$_2$Cl$_2$</td>
<td>reflux</td>
<td>5:1</td>
</tr>
<tr>
<td>9</td>
<td>103c</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>CH$_2$Cl$_2$</td>
<td>reflux</td>
<td>4:1</td>
</tr>
<tr>
<td>10</td>
<td>103c</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>CH$_2$Cl$_2$</td>
<td>rt</td>
<td>4:1</td>
</tr>
<tr>
<td>11</td>
<td>103c</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>THF</td>
<td>reflux</td>
<td>2:1</td>
</tr>
<tr>
<td>12</td>
<td>103c</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>ACN</td>
<td>reflux</td>
<td>3:1</td>
</tr>
<tr>
<td>13</td>
<td>103c</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>DMSO</td>
<td>reflux</td>
<td>2.4:1</td>
</tr>
<tr>
<td>14</td>
<td>103c</td>
<td>Pd(dppf)$_2$</td>
<td>CH$_2$Cl$_2$</td>
<td>reflux</td>
<td>5:1</td>
</tr>
<tr>
<td>15</td>
<td>103c</td>
<td>Pd(dppf)$_2$</td>
<td>CH$_2$Cl$_2$</td>
<td>rt</td>
<td>NR</td>
</tr>
<tr>
<td>16</td>
<td>103d</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>CH$_2$Cl$_2$</td>
<td>reflux</td>
<td>3.5:1</td>
</tr>
<tr>
<td>17</td>
<td>103d</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>CH$_2$Cl$_2$</td>
<td>rt</td>
<td>4.3:1</td>
</tr>
<tr>
<td>18</td>
<td>103d</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>CH$_2$Cl$_2$</td>
<td>0 °C</td>
<td>7:1</td>
</tr>
<tr>
<td>19</td>
<td>103d</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>CH$_2$Cl$_2$</td>
<td>-15 °C</td>
<td>NR</td>
</tr>
<tr>
<td>20</td>
<td>103d</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>ACN</td>
<td>reflux</td>
<td>2.6:1</td>
</tr>
<tr>
<td>21</td>
<td>103d</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>DMSO</td>
<td>reflux</td>
<td>2.2:1</td>
</tr>
<tr>
<td>22</td>
<td>103d</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>THF</td>
<td>reflux</td>
<td>1.3:1</td>
</tr>
<tr>
<td>23</td>
<td>103d</td>
<td>Pd(dppf)$_2$</td>
<td>CH$_2$Cl$_2$</td>
<td>reflux</td>
<td>3.2:1</td>
</tr>
<tr>
<td>24</td>
<td>103d</td>
<td>Pd(dppp)$_2$</td>
<td>CH$_2$Cl$_2$</td>
<td>reflux</td>
<td>NR</td>
</tr>
</tbody>
</table>

The observed high diastereoselectivity is presumably arise due to the differences of steric interaction between bulky benzenesulfonyl group and π-allylpalladium complex. Consequently, Pd(0)-catalyzed cyclization proceeds through more favorable transition state via rapid π-σ-π isomerization of π-allylpalladium complex with a least steric interaction (Figure 11).
1.8 Synthesis of dihydroxy bicyclic lactone 00 and introduction of angular hydroxyl group.

Having successfully prepared the optically pure bicyclic intermediate 102a, we executed the construction of the cis-fused 5,5-bicyclic lactone 97 and the stereoselective introduction of the angular hydroxyl group as shown in Scheme 23. To the best of our knowledge, direct introduction of the angular hydroxyl group to the bicyclic or tricyclic backbone of 1 has not been reported. Thus, we undertook the stereoselective construction of the functionalized cis-fused 5,5-bicyclic lactone system. We first transformed the bridged bicyclic lactone 102a into the cis-1,2,3-trisubstituted cyclopentanetriol 113, which is difficult to access by conventional cyclization procedures.\(^3\)

Desulfonylation of 102a with 5% Na/Hg in the presence of B(OH)\(_3\) afforded the desulfonylated bridged bicyclic lactone 91 in a 93% yield.\(^3\) Reduction of 91 with LiBH\(_4\) in the presence of MeOH and subsequent TBS deprotection afforded the thermodynamically less favorable cis-1,2,3-trisubstituted cyclopentanetriol 113. Allylic oxidation of 113 with excess MnO\(_2\) followed by spontaneous lactonization of the resulting lactol effectively produced the bicyclic lactone 97.\(^4\) For the pivotal introduction of the angular hydroxyl
group, we envisioned the stereoselective oxidation of the \textit{exo}-methylene moiety of the \textit{cis}-fused bicyclic lactone system because of its inherent convex-face selectivity. To our delight, Riley oxidation\textsuperscript{35} of 97 with SeO\textsubscript{2} in 1,4-dioxane provided the dihydroxy bicyclic lactone 94 as a single diastereomer in a 90\% yield (Scheme 23).

\begin{figure}
\centering
\includegraphics[width=\textwidth]{scheme23.png}
\caption{Construction of \textit{cis}-fused 5,5-bicyclic lactone system}
\end{figure}

Reagents and conditions: a) 5\% Na/Hg, B(OH)\textsubscript{3}, MeOH, rt, 93\%; b) LiBH\textsubscript{4}, MeOH, Et\textsubscript{2}O, 0 °C to rt, 96\%; c) TBAF, THF, rt, 100\%; d) MnO\textsubscript{2}, THF, rt, 91\%; e) SeO\textsubscript{2}, 1,4-dioxane, reflux, 90\%

1.9 Stereoselective crotylation of dihydroxy bicyclic lactone 94.

Next, we turned our attention to the stereoselective elaboration of the C5a-side chain as summarized in Table 5. We first carried out oxidation of primary alcohol in Swern and Ley oxidation conditions. However, we can’t afford the desired aldehyde, because of its inherent instability of aldehyde. Next, we envisioned that Dess-Martin oxidation of 94 could directly provide the desired aldehyde without further purification steps. To our delight, Dess-Martin oxidation\textsuperscript{36} of 94 afforded aldehyde 13 without epimerization of the labile C5a stereocenter.
Table 5. Oxidation of primary alcohol of dihydroxy bicyclic lactone 94

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Temperature</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(COCl)$_2$, DMSO, TEA, CH$_2$Cl$_2$</td>
<td>-78 °C</td>
<td>degradation</td>
</tr>
<tr>
<td>2</td>
<td>TPAP, NMO, 4 Å MS, CH$_2$Cl$_2$</td>
<td>rt</td>
<td>degradation</td>
</tr>
<tr>
<td>3</td>
<td>DMP, NaHCO$_3$, CH$_2$Cl$_2$</td>
<td>rt</td>
<td>degradation+epimerization</td>
</tr>
<tr>
<td>4</td>
<td>DMP, CH$_2$Cl$_2$</td>
<td>rt</td>
<td>90 (without purification)</td>
</tr>
</tbody>
</table>

We originally anticipated an efficient elaboration of the C5a-side chain unit that utilized the Brown$^{37}$ or Roush$^{38}$ crotylation procedure. However, our attempts to directly install the C5a-side chain unit were not successful. The aldehyde was unexpectedly intact under those conditions. Thus, we employed the diastereoselective Hosomi-Sakurai crotylation$^{39}$ to directly introduce the C5a-side chain unit, which contains both the C4 unit and a requisite terminal alkene for RCM at a later stage (Table 6). We expected a diastereoselective coupling in a chelation-controlled fashion to elaborate the C4-stereocenter of 1.

Interestingly, the treatment of 90 with (E)-crotyltrimethylsilane and BF$_3$·Et$_2$O in CH$_2$Cl$_2$ afforded the isomer 82b as a major product, along with the desired isomer 82a, in an 88% yield (Entry 1). The undesired diastereoselectivity can be explained by Felkin-Anh control as shown in Figure 12. However, diastereoselective Hosomi-Sakurai crotylation in the presence of TiCl$_4$ provided a reversed diastereoselectivity with a ratio of 5:1 presumably via chelation-controlled asymmetric induction as we anticipated (Entry 2). Crotylation in the presence of SnCl$_4$ resulted in a low diastereoselectivity (Entry 3), although the yield was quantitative. The variation in diastereoselectivity is likely due to complexation of the lactone moiety with Lewis acids, although it is not clear at this stage. The structure of the
C4-stereocenter was confirmed by comparison of its spectral data with that of the natural (-)-galiellalactone after completion of the synthesis.

**Table 6. Stereoselective Hosomi-Sakurai crotylation of dihydroxy bicyclic lactone 94**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid</th>
<th>Yield (%)</th>
<th>Ratio  (82a : 82b)$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BF$_3$·Et$_2$O</td>
<td>88</td>
<td>1:5</td>
</tr>
<tr>
<td>2</td>
<td>TiCl$_4$</td>
<td>78</td>
<td>5:1</td>
</tr>
<tr>
<td>3</td>
<td>SnCl$_4$</td>
<td>97</td>
<td>1:1</td>
</tr>
<tr>
<td>4</td>
<td>MgBr$_2$·Et$_2$O</td>
<td>NR$^d$</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Et$_2$AlCl</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>AlCl$_3$ complex mixture</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$ All reactions were conducted with (E)-crotyltrimethylsilane (10 eq) and Lewis acid (2 eq) in 0.1 M solution at -78 °C for 12 h. $^b$ Isolated yield of the diastereomeric mixture. $^c$ Determined by isolation of each isomer after TES protection (See Scheme 4). $^d$ No reaction.

The observed diastereoselectivity in the Lewis acid mediated Hosomi-Sakurai crotylation can be explained by chelation or Felkin-Ahn model (Figure 12). Syn selectivity for crotylation of aldehyde 90 is rationalized by an antiperiplanar or a synclinal approach of crotyltrimethylsilane, which take places through the conformation where steric interactions between the bulky backbone of (-)-galiellalactone and the Me group of nucleophile are minimized. As mentioned above, diastereoselective Hosomi-Sakurai crotylation by the complexation with the TiCl$_4$ between the aldehyde and tertiary hydroxyl group afforded homoallylic alcohol 82a through transition state, which involves nucleophilic attack on the less hindered convex face.
1.10 Deoxygenation of secondary hydroxyl group

We first anticipated facile deoxygenation of the secondary hydroxyl group right after stereoselective crotylation reaction employing Barton-McCombie deoxygenation reaction. However, preparation of the deoxygenation precursor 114a-d under various reaction conditions was not successful because of the steric congestion on the concave face (Scheme 24).

![Scheme 24. Deoxygenation of secondary hydroxyl group of bicyclic lactone 114a-d](image)

Reagents and conditions: a) NaH, CS$_2$, MeI, THF, 0 °C to reflux for 114a; CIC(S)OPh, DMAP, CH$_2$Cl$_2$, reflux for 114b; Pentafluorophenyl chlorothioformate, pyridine, CH$_2$Cl$_2$ for 114c; 1,1'-thiocarbonyldiimidazole, DMAP, DCE, reflux for 114d; b) n-Bu$_3$SnH, AIBN, toluene, reflux;

1.11 Ring-closing metathesis of bicyclic lactone 82a.

We originally anticipated facile construction of tricyclic system of (-)-galiellalactone by ring-closing metathesis of bicyclic lactone 82a as well as deoxygenation of secondary hydroxyl group right after stereoselective crotylation reaction. However, construction of tricyclic lactone skeleton under various reaction conditions was not successful because of
the degradation of starting material and migration of terminal olefin.

Table 7. Contraction of tricyclic lactone system by RCM

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Additive</th>
<th>Solvent</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Grubbs 1st cat.</td>
<td></td>
<td>CH₂Cl₂</td>
<td>trace</td>
</tr>
<tr>
<td>2</td>
<td>Grubbs 1st cat.</td>
<td>2,6-dichlorobenzoquinone</td>
<td>CH₂Cl₂</td>
<td>trace</td>
</tr>
<tr>
<td>3</td>
<td>Grubbs 1st cat.</td>
<td></td>
<td>toluene</td>
<td>trace</td>
</tr>
<tr>
<td>4</td>
<td>Grubbs 2nd cat.</td>
<td></td>
<td>CH₂Cl₂</td>
<td>trace</td>
</tr>
<tr>
<td>5</td>
<td>Grubbs 2nd cat.</td>
<td>2,6-dichlorobenzoquinone</td>
<td>CH₂Cl₂</td>
<td>10%</td>
</tr>
<tr>
<td>6</td>
<td>Grubbs 2nd cat.</td>
<td></td>
<td>toluene</td>
<td>trace</td>
</tr>
<tr>
<td>7</td>
<td>Grubbs 2nd cat.</td>
<td>2,6-dichlorobenzoquinone</td>
<td>toluene</td>
<td>10%</td>
</tr>
<tr>
<td>8</td>
<td>Hoveyda-Grubbs 2nd cat.</td>
<td></td>
<td>CH₂Cl₂</td>
<td>trace</td>
</tr>
<tr>
<td>9</td>
<td>Hoveyda-Grubbs 2nd cat.</td>
<td>2,6-dichlorobenzoquinone</td>
<td>CH₂Cl₂</td>
<td>trace</td>
</tr>
</tbody>
</table>

1.12 Completion of total synthesis of (−)-galiellalactone

The diastereomeric mixture of homoallylic alcohols 82a and 82b, which were prepared in the presence of TiCl₄ and inseparable by column chromatography, was purified after TES protection of the alcohol to afford optically pure RCM precursor 117a in a 59% yield in 3 steps (Scheme 26). The tricyclic lactone 116 was obtained in a high yield from 117a by RCM in the presence of 2nd generation Grubbs catalyst, followed by TES deprotection of the resulting tricyclic lactone 118 with CSA in MeOH. Then, we carried out the deoxygenation reaction after constructing the tricyclic lactone system of 1.
Although we carried out intensive screening of the deoxygenation conditions including various xanthates and radical initiators, we afforded the Chugaev-type eliminated product, not (-)-galiellalactone (Table 8). However, deoxygenation of 116 with the Barton-McCombie reaction via careful acylation with pentafluorophenyl chlorothionoformate and \( n\)-Bu\(_3\)SnH treatment of the resulting xanthate\(^{41}\) finally furnished (-)-galiellalactone (1) in a 76% yield in 2 steps. Synthetic 1 was identical to the natural product in all aspects, including optical rotation.\(^{42}\)

Scheme 25. Completion of galiellalactone synthesis

Reagents and conditions: a) TESOTf, pyridine, -40 °C, 90% (75% for major and 15% for minor); b) 117a, 2nd generation of Grubbs catalyst, CH\(_2\)Cl\(_2\), reflux, 99%; c) CSA, MeOH, rt, 83%; d) Pentafluorophenyl chlorothionoformate, pyridine, CH\(_2\)Cl\(_2\); e) \( n\)-Bu\(_3\)SnH, AIBN, toluene, 80 °C to 100 °C, 76% (in 2 steps);
Table 8. Deoxygenation of secondary hydroxyl group

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Temperature</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C\textsubscript{4}Br\textsubscript{4}, (\text{P}(\text{n-Oct})_3), toluene</td>
<td>80 °C</td>
<td>119</td>
</tr>
<tr>
<td>2</td>
<td>TsCl, TEA, DMAP, CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>rt</td>
<td>119</td>
</tr>
<tr>
<td>3</td>
<td>1,1’-thiocarbonyldiimidazole, DMAP, DCE</td>
<td>reflux</td>
<td>119</td>
</tr>
<tr>
<td>4</td>
<td>Phenyl chlorothioformate, pyridine, CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>rt</td>
<td>119</td>
</tr>
<tr>
<td>5</td>
<td>Phenyl chlorothioformate, DMAP, pyridine, CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>rt</td>
<td>119</td>
</tr>
<tr>
<td>6</td>
<td>Pentafluorophenyl chlorothioformate, pyridine, CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>rt</td>
<td>1</td>
</tr>
</tbody>
</table>

2. Syntheses and biological evaluation of (-)-galiellalactone and its analogues as STAT3 inhibitors in breast cancer cell lines.

Recently, we have been interested in studies on (-)-galiellalactone, particularly on the cyclohexene system for which the role in its biological activity has not been explored much; however, the [3.3] bicyclic lactone system has been extensively studied. Thus, we envisioned a unique and versatile synthetic strategy, in which the [3.3] bicyclic lactone system and the cyclohexene moiety are sequentially constructed starting from cyclopentane system because most of the previous synthetic studies pursued the strategy. From the
viewpoint of medicinal chemistry, we realized that the structural variation of the cyclohexene system is restricted because early construction of the hydrindane system would limit late steps of the synthesis. Thus, we undertook an enantioselective syntheses of (-)-galiellalactone analogues.

Our synthetic approach for galiellalactone analogues is outlined in Scheme 27, which were modified on the C4, C5, C5a, or C6 stereocenter in bicyclic or tricyclic lactone skeleton. First, tricyclic lactone analogues can be prepared from bicyclic lactone analogues by the same synthetic strategy established in a process of enantioselective total synthesis of (-)-galiellalactone. These bicyclic lactone analogues are also prepared from highly congested tetrasubstituted cyclopentane systems by Riley oxidation and subsequent various common reactions. Stereochemistry of C6-stereocenter can be installed by conjugate addition of nucleophiles into the Michael acceptor of allylic carbonate and subsequent Pd(0)-catalyzed cyclization of C6-substituted intermediates.

**Scheme 26. Synthetic strategy for galiellalactone analogues**

2-1. Syntheses of (-)-galiellalactone analogues

Methyl substituent in 1 has previously been reported to be less crucial for the biological activity. Therefore, we planned the synthetic strategy for desmethyldeliellalactone
analogues. First, we made an attempt to construct tricyclic lactone system lacking methyl group at C4-stereocenter. From the dihydroxy bicyclic lactone intermediate 94, Hosomi-Sakurai allylation afforded homoallylic alcohols 120a and 120b in 99%. TES protection of 120a and 120b followed by ring-closing metathesis in the presence of 2nd generation Grubbs catalyst provided tricyclic lactone intermediate, which were converted to desmethyl hydroxygaliellalactone 121a and 121b by TES deprotection. In addition, from the bicyclic lactone 82b, which is the minor product of Hosomi-Sakurai crotylation in the presence of BF₃·Et₂O, we afforded a diastereomer of hydroxygaliellalactone 122. Dess-Martin oxidation of 122 also provided ketone 123.

Next, we undertook the syntheses of cyclohexene-truncated bicyclic lactone analogues to establish a structure-activity relationship (Scheme 29). From the cis-fused 5,5-bicyclic lactone intermediate, we commenced with the preparation of functionalized bicyclic lactones. 

**Scheme 27. Syntheses of tricyclic lactone analogues**

![Scheme 27](image)

Reagents and conditions: a) i) DMP, CH₂Cl₂, rt; ii) allyltrimethylsilane, BF₃·Et₂O, CH₂Cl₂, 99% (in 2 steps), dr 5:1; b) TESCl, TEA, DMAP, DMF, rt, 100%; c) Grubbs’ 2nd cat., CH₂Cl₂, reflux, 99% for 120a and 120b; d) CSA, CH₂Cl₂, rt, % for 121a and % for 121b; e) TESOTf, pyridine, -40 °C, 90%; f) Grubbs’ 2nd cat., CH₂Cl₂, reflux, 99%; g) CSA, MeOH, rt, 90%; h) DMP, CH₂Cl₂, rt, 90%;
Appel reaction. From the dihydroxy bicyclic lactone 94, we afforded the homoallylic alcohols 120a and 120b and subsequent oxidation provided ketone 124. Finally, methylation of 94 provided mixture of methylated bicyclic lactone compounds 127a-c. From these synthetic analogues, we evaluated an antitumor activity mediated by active STAT3 in breast cancer cell lines.

![Scheme 28. Syntheses of bicyclic lactone analogues](image)

Reagents and conditions: a) SeO₂, 1,4-dioxane, reflux, 90%; b) CBr₄, P(n-Oct)₃, toluene, 80 °C, 84% for 94 and quant. for 97; c) MeI, Ag₂O, CH₂Cl₂, reflux, 60% for 127a, 25% for 127b and 11% for 127c; d) i) DMP, CH₂Cl₂, rt; ii) allyltrimethylsilane, BF₃·Et₂O, CH₂Cl₂, -78 °C, 99% (in 2 steps), dr 5:1; e) DMP, CH₂Cl₂, rt, 90%.

### 2-2. Biological evaluation of (-)-galiellalactone

As mentioned above, constitutively activated STAT3 has been found in numerous human solid cancer cells, including breast, prostate, pancreas, and ovarian cancers. Especially, in 70% of breast cancer cells, active STAT3 has been detected and is closely related with triple-negative breast cancer (TNBC), which lacks estrogen receptors, progesterone
receptors, and HER2 expression. MDA-MB-468 and MDA-MB-231 cells are TNBC cells, which express activated STAT3. In addition, TNBC cells provide a high amount of interleukin-6, which activates STAT3 in an autocrine manner. Therefore, STAT3 in TNBC could be a promising molecular target for cancer therapy. To clarify the molecular mechanism by which (-)-galiellalactone inhibits STAT3 activation in TNBC cells, cell viabilities were determined by MTT assay in MDA-MB-468, MDA-MB-231 and BT-549 cells. As shown in Figure 13, (-)-galiellalactone exhibited moderate cytotoxicity against the tested breast cancer cell lines with IC\textsubscript{50} values from 14.36 μM in MDA-MB-468, 9.21 μM in MDA-MB-231 and 15.23 μM in BT-549.

Figure 13. Cell viabilities by MTT assay in breast cancer cell lines

![Cell viabilities by MTT assay in breast cancer cell lines](image)

To investigate the anticancer mechanism of (-)-galiellalactone in breast cancer cell, we assessed expression of STAT3 protein by western blot analysis using MDA-MB-468 and BT-49 cell lines. We first evaluated its effect on STAT3 phosphorylation at tyrosine 705 and serine 727 and STAT3 protein levels in MDA-MB-468 cell with sttatic and S3I-201 as positive controls. The cells were treated with the indicated concentrations of (-)-galiellalactone for 24 h. As shown in Figure 14, (-)-galiellalactone inhibited STAT3
phosphorylation at tyrosine 705 in a dose-dependent manner. However, this treatment did not affect STAT3 phosphorylation at serine 727. The total STAT3 protein levels were not affected by (-)-galiellalactone. And also, in BT-549 cell, (-)-galiellalactone inhibited STAT3 phosphorylation at tyrosine 705 in the same manner. These results suggest that (-)-galiellalactone suppress the STAT3 phosphorylation in MDA-MB-468 and BT-549 cell lines unlike studies on prostate cancer cells expressing constitutively active STAT3 from Sterner and coworkers.

Figure 14. Western blot assay using MDA-MD-468 and BT-549 cell lines
2-3. Biological evaluation of (-)-galiellalactone analogues

With the tricyclic and cyclohexene-truncated bicyclic analogues in hand (Scheme 28 and 29), cytotoxicity of 16 compounds against TNBC cell lines MDA-MB-468, MDA-MB-231 and BT-549 was evaluated by MTT method with (-)-galiellalactone as positive control. As mentioned above, (-)-galiellalactone exhibited moderate cytotoxicity against MDA-MB-468, MDA-MB-231 and BT-549 cell lines. Compared to the natural galiellalactone 1, SG-09 (126) was regarded as more potent analogue in three TNBC cell lines (Figure 16). SG-11 (120b), SG-12 (124) and SG-18 (125) showed low anti-proliferative activity. However other compounds showed no cytotoxicity. It seemed that the cyclohexene ring in the (-)-galiellalactone was not a prerequisite for its biological activity from an inhibitory property of SG-09. Syntheses and biological evaluation of antitumor activity of (-)-galiellalactone analogues are under good progress to establish a structure-activity relationship (SAR).

Figure 15. Evaluation of cytotoxicity of the (-)-galiellalactone analogues
Figure 16. Evaluation of cytotoxicity of SG-09
III. Conclusion

We have achieved the enantioselective total synthesis of (-)-galiellalactone (1). Our unique strategy based on substrate-controlled stereocontrol involves the diastereoselective construction of the contra-thermodynamic tri-\textit{cis}-substituted cyclopentanetriol, the stereospecific introduction of an angular hydroxyl group, and its efficient transformation into the tricyclic system of (-)-galiellalactone via a sequence of stereoselective Hosomi-Sakurai crotylation and RCM of the resulting diene. Our versatile and straightforward procedure is widely applicable to the syntheses of (-)-galiellalactone and its structural variants including the cyclohexene-modified analogs, which are quite useful in terms of synthetic and medicinal chemistry. In addition, we investigated the possibilities of galiellalactone and cyclohexene-modified analogues for application into breast cancer mediate by STAT3. The (-)-galiellalactone and representive inhibitor SG-09 exhibited moderate cytotoxicity and inhibitory activity of phosphorylated STAT3 against MDA-MB-468, MDA-MB-231 and BT-549 cell lines. Investigations on the precise mechanism of action are also in progress. Finally, a novel class of STAT3 inhibitors is suggested. Especially, simple structure modification of tricyclic lactone system to modulate electronic environment would enable the analogues to have improved anti-proliferative property as well as anti-STAT3 activity. Additionally, we truncated the cyclohexene, a privileged structure of (-)-galiellalactone to afford excellent STAT3 inhibitors. Structure modification studies based on SG-09 can provide various synthetic analogues for STAT3-related solid cancers.
IV. Experimental

General experimental procedure

Unless noted otherwise, all starting materials and reagents were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl. Dichloromethane, triethylamine and pyridine were freshly distilled from calcium hydride. All solvents used for the routine isolation of products and chromatography were reagent grade and glass distilled. Reaction flasks were dried at 100 °C. Air and moisture sensitive reactions were performed under an argon atmosphere. Flash column chromatography was performed using silica gel 60 (230-400 mesh, Merck) with the indicated solvents. Thin-layer chromatography was performed using 0.25 mm silica gel plates (Merck). Optical rotations were measured with a JASCO DIP-1000 or JASCO P-1020 digital polarimeter at ambient temperature using 100 nm cell of 2 mL capacity. Infrared spectra were recorded on a Perkin-Elmer 1710 FT-IR spectrometer. Mass spectra were obtained with a VG Trio-2 GC-MS instrument, a double focusing mass spectrometer (electrostatic analyser and magnetic analyser). High-resolution mass spectra were obtained with a JEOL JMS-AX 505WA instrument. \(^{1}\)H and \(^{13}\)C NMR spectra were recorded on a JEOL JNM-LA 300, Bruker AV 400, Bruker AMX 500 or JEOL ECA 600 spectrometer as solutions in deuteriochloroform (CDCl\(_3\)) or tetradeuteromethanol (methanol-d\(_4\)). Chemical shifts are expressed in parts per million (ppm, δ) downfield from tetramethylsilane and are referenced to the deuterated solvent (CDCl\(_3\)). \(^{1}\)H-NMR data were reported in the order of chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; dd, doublet of doublets; dt, doublet of triplet; td, triplets of doublets;
ddd, doublet of doublet of doublets; ddddd, doublet of doublet of doublet of doublets; qtd, quartet of triplet of doublets; br, broad; m, multiplet and/or multiple resonance), number of protons, and coupling constant in hertz (Hz).

**(R)-3-((4-methoxybenzyl)oxy)pent-4-en-1-yl 4-methylbenzenesulfonate (108).** To a mixture of alcohol 104 (4.09 g, 18 mmol) and triethylamine (5.1 mL, 36.8 mmol) in CH$_2$Cl$_2$ (46 mL) were added p-toluenesulfonyl chloride (5.27 g, 27.6 mmol) and 4-dimethylaminopyridine (674 mg, 5.5 mmol) at 0 ºC. After stirring for 3 h at ambient temperature, the reaction mixture was quenched with saturated NH$_4$Cl solution (30 mL) and diluted with CH$_2$Cl$_2$ (50 mL). The organic layer was separated, and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 × 50 mL). The combined organic layer was washed with brine, dried over MgSO$_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc:n-hexane = 1:6) to afford *p*-methoxybenzyl ether 108 (6.44 g, 93%) as a colorless oil: [α]$^\text{20}$D +11.46 (c 1.0, CHCl$_3$); $^1$H-NMR (CDCl$_3$, 400 MHz) δ 7.76 (d, 2H, $J =$ 8.3 Hz), 7.30 (d, 2H, $J =$ 8.1 Hz), 7.14 (d, 2H, $J =$ 8.5 Hz), 6.83 (d, 2H, $J =$ 8.6 Hz), 5.65 (m, 1H), 5.21 (d, 1H, $J =$ 1.7 Hz), 5.18 (d, 2H, $J =$ 9.5 Hz), 4.43 (d, 1H, $J =$ 11.0 Hz), 4.18 (m, 1H), 4.14 (d, 1H, $J =$ 11.1 Hz), 4.06 (dt, 1H, $J =$ 9.7 Hz, $J =$ 5.6 Hz), 3.84 (td, 1H, $J =$ 7.7 Hz, $J =$ 5.3 Hz), 3.78 (s, 3H), 2.41 (s, 3H), 1.89-1.82 (m, 2H); $^{13}$C-NMR (CDCl$_3$, 100 MHz) δ 159.1, 144.7, 137.7, 133.0, 130.2, 129.8, 129.3, 127.8, 117.9, 113.7, 70.0, 67.1, 55.2, 34.8, 21.5; IR (neat) ν$_{\text{max}}$ 2957, 1613, 1514, 1465, 1361, 1303, 1249, 1189, 1177, 1097, 1035, 916, 817, 770, 664 cm$^{-1}$; LR-MS (FAB+) $m/z$ 376 (M$^+$); HR-MS (FAB+) calcd for C$_{20}$H$_{24}$O$_5$S (M$^+$) 376.1344, found 376.1351.

**(R)-3-hydroxypent-4-en-1-yl 4-methylbenzenesulfonate (107).** To a solution of *p*-methoxybenzyl ether 108 (5.30 g, 14.1 mmol) in CH$_2$Cl$_2$/pH 7.2 buffer solution (9:1, 140 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (6.39 g, 28.2 mmol) in one portion at ambient temperature. After stirring for 3 h, the reaction mixture was filtered and quenched with a saturated NaHCO$_3$ solution (100 mL).
and the aqueous layer was extracted with CH₂Cl₂ (2 × 50 mL). The combined organic layer was washed with brine, dried over MgSO₄, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc:n-hexane = 2:3) to afford allylic alcohol 107 (3.57 g, 99%) as a colorless oil: [α]D⁺ +3.50 (c 2.0, CHCl₃); ¹H-NMR (CDCl₃, 400 MHz) δ 7.73 (d, 2H, J = 8.2 Hz), 7.30 (d, 2H, J = 8.0 Hz), 5.74 (m, 1H), 5.14 (d, 1H, J = 17.2 Hz), 5.04 (d, 1H, J = 10.5 Hz), 4.20-4.14 (m, 2H), 4.08-4.03 (m, 1H), 2.39 (s, 3H), 2.21 (br, 1H), 1.87-1.70 (m, 2H); ¹³C-NMR (CDCl₃, 100 MHz) δ 144.8, 139.7, 132.7, 129.8, 127.8, 115.3, 68.8, 67.3, 35.7, 21.5; IR (neat) νmax 3412, 2961, 1599, 1496, 1424, 1358, 1308, 1293, 1190, 1176, 1142, 1098, 1068, 996, 969, 916, 832, 816, 766, 664 cm⁻¹; LR-MS (FAB⁺) m/z 257 (M + H⁺); HR-MS (FAB+) calcd for C₁₂H₁₇O₄S (M + H⁺) 257.0848, found 257.0860.

(R)-10,10-diisopropyl-7-methylene-4-oxo-12-vinyl-3,5,9,11-tetraoxa-10-silatetradecan-14-yl 4-methylbenzenesulfonate (109). To a solution of imidazole (5.88 g, 86.4 mmol) in CH₂Cl₂ (140 mL) was added dichlorodiisopropylsilane (5.8 mL, 31.7 mmol) at 0 ºC. After stirring for 10 min, a solution of allylic alcohol 107 (7.38 g, 28.8 mmol) in CH₂Cl₂ (20 mL) was added dropwise. After stirring for 10 min at the same temperature, a solution of another allylic alcohol (5.53 g, 34.6 mmol) in CH₂Cl₂ (20 mL) was added at 0 ºC. The reaction mixture was warmed to ambient temperature and stirred for 12 h. The resulting mixture was quenched with a saturated NH₄Cl solution (30 mL). The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂ (2 × 30 mL). The combined organic layer was washed with brine, dried over MgSO₄, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc:n-hexane = 1:8) to afford bis-alkoxysilane 109 (14.62 g, 96%) as a colorless oil: [α]D⁻ -7.68 (c 2.0, CHCl₃); ¹H-NMR (CDCl₃, 400 MHz) δ 7.74 (d, 2H, J = 8.3 Hz), 7.29 (d, 2H, J = 8.2 Hz), 5.68 (m, 1H), 5.21 (s, 1H), 5.13 (s, 1H), 5.03 (dd, 2H, J = 18.3 Hz, J = 10.4 Hz), 4.58 (s, 2H), 4.36 (q, 1H, J = 6.2 Hz), 4.20 (s, 2H), 4.16 (q, 2H, J = 7.2 Hz), 4.11-4.02 (m, 2H), 3.86-3.78 (s, 4H), 3.67-3.58 (s, 4H), 3.47-3.32 (m, 2H), 2.74-2.58 (m, 1H), 2.22 (s, 3H), 1.89-1.70 (m, 2H), 1.24-1.18 (m, 24H), 0.98-0.92 (m, 12H), 0.90-0.84 (m, 6H).
2.40 (s, 3H), 1.89-1.78 (m, 2H), 1.26 (t, 3H, \( J = 7.1 \) Hz), 0.94-0.93 (m, 14H); \(^{13}\)C-NMR (CDCl\(_3\), 100 MHz) \( \delta \) 154.9, 144.6, 142.2, 139.6, 133.0, 129.7, 127.8, 115.2, 113.2, 70.1, 67.6, 67.0, 63.9, 63.3, 36.8, 21.5, 17.2, 14.2, 12.1; IR (neat) \( \nu_{\text{max}} \) 2946, 2868, 1748, 1599, 1466, 1367, 1189, 1097, 1000, 920, 885, 816, 664 cm\(^{-1}\); LR-MS (FAB\(^+\)) \( m/z \) 529 (M + H\(^+\)); HR-MS (FAB\(^+\)) calcd for C\(_{25}\)H\(_{41}\)O\(_8\)Si (M + H\(^+\)) 529.2291, found 529.2297.

**Methyl (12R)-10,10-diisopropyl-7-methylene-4-oxo-15-(phenylsulfonyl)-12-vinyl-3,5,9,11-tetraoxa-10-silahexadecan-16-oate (110).** To a suspension of 60% sodium hydride (727 mg, 18.2 mmol) in DMF (38 mL) was added methyl phenylsulfonylacetate (3.89 g, 18.2 mmol) in DMF (10 mL) at 0 ºC. After stirring for 1 h at 0 ºC, a solution of bis-alkoxysilane 109 (3.95 g, 7.48 mmol) in DMF (10 mL) was added. The reaction mixture was heated to 80 ºC, stirred for 9 h, and cooled to ambient temperature. The resulting mixture was quenched with a saturated NH\(_4\)Cl solution (30 mL) and diluted with ethyl acetate (100 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 \( \times \) 50 mL). The combined organic layer was washed with brine, dried over MgSO\(_4\), and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc:n-hexane = 1:4) to afford benzenesulfonyl bis-alkoxysilane 110 (3.32 g, 78%) as a colorless oil: \(^1\)H-NMR (CDCl\(_3\), 400 MHz, a mixture of diastereomers) \( \delta \) 7.82 (d, 2H, \( J = 7.3 \) Hz), 7.64 (t, 1H, \( J = 7.4 \) Hz), 7.52 (t, 2H, \( J = 11.9 \) Hz), 5.73-5.64 (m, 1H), 5.21 (d, 1H, \( J = 0.9 \) Hz), 5.13-5.08 (m, 2H), 5.04-5.00 (m, 1H), 4.58 (s, 2H), 4.29-4.20 (m, 3H), 4.15 (q, 2H, \( J = 7.1 \) Hz), 3.96 (ddd, 1H, \( J = 25.6 \) Hz, \( J = 11.2 \) Hz, \( J = 4.0 \) Hz), 3.63 (d, 3H, \( J = 0.9 \) Hz), 2.08-1.87 (m, 2H), 1.53-1.45 (m, 2H), 1.26 (t, 3H, \( J = 7.1 \) Hz), 0.98-0.90 (m, 14H); \(^{13}\)C-NMR (CDCl\(_3\), 100 MHz, a mixture of diastereomers) \( \delta \) 166.2, 154.9, 142.2, 139.8, 139.6, 137.1, 136.9, 134.1, 129.2, 128.9, 115.1, 115.0, 113.2, 72.5, 72.4, 70.6, 67.6, 64.0, 63.2, 52.8, 34.5, 34.4, 22.4, 22.1, 17.3, 17.2, 14.2, 12.2, 12.1; IR (neat) \( \nu_{\text{max}} \) 2947, 2868, 1746, 1448, 1375, 1328, 1260, 1150, 1085, 1011, 924, 884, 772, 724, 689 cm\(^{-1}\); LR-MS (FAB\(^+\)) \( m/z \) 571 (M + H\(^+\)); HR-MS (FAB\(^+\)) calcd for C\(_{27}\)H\(_{43}\)O\(_9\)Si
Methyl 4-((R)-6-(((ethoxycarbonyl)oxy)methyl)-2,2-diisopropyl-4,7-dihydro-1,3,2-dioxasilene-4-yl)-2-(phenylsulfonyl)butanoate (111). To a refluxing solution of benzenesulfonyl bis-alkoxysilane 110 (765 mg, 1.6 mmol) in toluene (160 mL, 0.01 M) was added 2nd generation Grubbs catalyst (135 mg, 0.2 mmol). After stirring for 30 min, the reaction mixture was cooled to ambient temperature and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc:n-hexane = 1:4) to afford the cyclic bis-alkoxysilane 111 (720 mg, 100%) as a colorless oil: ¹H-NMR (CDCl₃, 400 MHz, a mixture of diastereomers) δ 7.85 (d, 2H, J = 7.8 Hz), 7.66 (t, 1H, J = 7.4 Hz), 7.54 (t, 2H, J = 7.7 Hz), 5.55 (s, 1H), 4.66 (d, 1H, J = 18.4 Hz), 4.56 (d, 1H, J = 15.6 Hz), 4.44 (t, 2H, J = 15.3 Hz), 4.26 (dd, 1H, J = 15.5 Hz, J = 4.8 Hz), 4.17 (m, 2H), 4.09-4.02 (m, 1H), 3.67 (d, 3H, J = 6.8 Hz), 2.28-1.85 (m, 2H), 1.62-1.53 (m, 2H), 1.28 (td, 3H, J = 7.1 Hz, J = 1.5 Hz), 0.99 (s, 14H); ¹³C-NMR (CDCl₃, 100 MHz, a mixture of diastereomers) δ 170.9, 166.3, 166.2, 154.7, 137.1, 137.0, 136.6, 136.5, 134.1, 133.6, 133.4, 129.2, 128.9, 70.5, 70.4, 70.3, 69.9, 69.3, 64.1, 62.8, 62.7, 60.2, 52.8, 34.7, 34.5, 23.8, 22.9, 20.9, 17.3, 17.2, 17.1, 16.9, 14.1, 12.1, 12.0; IR (neat) νₘₐₓ 2949, 1746, 1259, 1220, 1149, 772, 688 cm⁻¹; LR-MS (FAB+) m/z 543 (M + H⁺); HR-MS (FAB+) calcd for C₂₅H₃₉O₉Si(M + H⁺) 543.2084, found 543.2077.

ethyl ((E)-2-(hydroxymethyl)-3-((2R)-6-oxo-5-(phenylsulfonyl)tetrahydro-2H-pyran-2-yl)allyl) carbonate (112). To a solution of the cyclic bis-alkoxysilane 111 (10.04 g, 18.5 mmol) in THF (185 mL) was added tetra-n-butyllammonium fluoride (1.0 M solution in THF, 37.0 mL, 37.0 mmol) at ambient temperature. After stirring for 12 h, the reaction mixture was quenched with a saturated NH₄Cl solution (50 mL) and diluted with ethyl acetate (100 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 50 mL). The combined organic layer was washed with brine, dried over MgSO₄, and concentrated in vacuo. The residue was purified by flash column
chromatography on silica gel (EtOAc:n-hexane = 3:1) to afford hydroxyl valerolactone 112 (5.83 g, 79%) as a colorless oil: $^1$H-NMR (CDCl$_3$, 400 MHz, a mixture of diastereomers) δ 7.93-7.90 (m, 2H), 7.69-7.65 (m, 1H), 7.56 (td, 2H, $J = 7.9$ Hz, $J = 2.9$ Hz), 5.83 (d, 0.5H, $J = 8.8$ Hz), 5.72 (d, 0.5H, $J = 8.7$ Hz), 5.46-5.41 (m, 0.5H), 5.34-5.27 (m, 0.5H), 4.79 (dd, 1H, $J = 12.7$ Hz, $J = 3.7$ Hz), 4.65 (dd, 1H, $J = 12.7$ Hz, $J = 7.4$ Hz), 4.22-4.00 (m, 5H), 2.90-2.86 (m, 0.5H), 2.72-2.64 (m, 0.5H), 2.47-2.38 (m, 0.5H), 2.36-2.13 (m, 1H), 1.99-1.93 (m, 0.5H), 1.86-1.70 (m, 1H), 1.33-1.27 (m, 3H); $^{13}$C-NMR (CDCl$_3$, 100 MHz, a mixture of diastereomers) δ 162.9, 162.7, 154.9, 139.0, 138.6, 138.0, 137.5, 134.5, 134.3, 129.3, 129.2, 129.1, 129.0, 128.4, 127.7, 77.2, 76.3, 68.6, 68.4, 64.4, 63.4, 58.6, 27.4, 25.9, 20.0, 19.5, 14.2; IR (neat) $\nu_{\text{max}}$ 2994, 1758, 1374, 1246, 1059 cm$^{-1}$; LR-MS (FAB+) m/z 399 (M + H$^+$); HR-MS (FAB+) calcd for C$_{18}$H$_{23}$O$_8$S (M + H$^+$) 399.1114, found 399.1105.

(Z)-2-(((tert-Butyldimethylsilyl)oxy)methyl)-3-((2R)-6-oxo-5-(phenylsulfonyl)tetrahydro-2H-pyran-2-yl)allyl ethyl carbonate (103a). To a mixture of hydroxyl valerolactone 112 (260 mg, 0.7 mmol) and imidazole (67 mg, 1.0 mmol) in DMF (7 mL) was added tert-butyldimethylsilyl chloride (148 mg, 1.0 mmol) at 0 ºC. After stirring for 10 min at ambient temperature, the reaction mixture was quenched with H$_2$O (10 mL) and diluted with ethyl acetate (10 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layer was washed with brine, dried over MgSO$_4$, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc:n-hexane = 1:2) to afford δ-valerolactone 130a (334 mg, 89%) as a colorless oil: $^1$H-NMR (CDCl$_3$, 400 MHz, a mixture of diastereomers) δ 7.90 (m, 2H), 7.67-7.63 (m, 1H), 7.56-7.52 (m, 1H), 5.74 (dd, 0.5H, $J = 34.3$ Hz, $J = 8.8$ Hz), 5.60 (dd, 0.5H, $J = 38.5$ Hz, $J = 8.5$ Hz), 5.46-5.38 (m, 0.5 H), 5.29 (td, 0.5H, $J = 9.5$ Hz, $J = 3.7$ Hz), 4.73 (dd, 0.5H, $J = 12.5$ Hz, $J = 3.7$ Hz), 4.68-4.53 (m, 1.5H), 4.30-4.00 (m, 5H), 2.83-2.78 (m, 0.5H), 2.67-2.59 (m, 0.5H), 2.44-2.08 (m, 2H), 1.95-1.90 (m, 0.5H), 1.77-1.66 (m, 0.5H), 1.30-1.24 (m, 3H), 0.88-0.85 (m, 9H), 0.08-0.02
(1R,4R,7R)-7-(3-((tert-Butyldimethylsilyl)oxy)prop-1-en-2-yl)-4-(phenylsulfonyl)-2-oxabicyclo[2.2.1]heptan-3-one (102a). To a refluxing solution of δ-valerolactone 103a (5.38 g, 10.5 mmol) in CH$_2$Cl$_2$ (210 mL) was added a mixture of palladium acetate (118 mg, 0.5 mmol) and 1,1′-bis(diphenylphosphino)ferrocene (582 mg, 1.1 mmol) in CH$_2$Cl$_2$ (2 mL). After stirring for 6 h, the reaction mixture was cooled to ambient temperature and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc:n-hexane = 1:3) to afford [2.2.1] bridged bicyclic lactone 102a (3.84 g, 87%) as a colorless oil and the minor product 102b (533 mg, 12%) as a white solid: [α]$^\text{D}_{20}$ +44.13 (c 1.0, CHCl$_3$); $^1$H-NMR (CDCl$_3$, 400 MHz) δ 8.11 (d, 2H, $J = 7.9$ Hz), 7.65 (t, 1H, $J = 7.4$ Hz), 7.53 (t, 1H, $J = 8.0$ Hz), 5.34 (d, 2H, $J = 19.1$ Hz), 4.82 (s, 1H), 4.17 (q, 2H, $J = 13.6$ Hz), 3.20 (s, 1H), 2.54 (td, 1H, $J = 12.0$ Hz, $J = 4.6$ Hz), 2.08 (m, 1H), 1.89 (m, 1H), 1.69 (m, 1H), 0.89 (s, 9H), 0.06 (s, 6H); $^{13}$C-NMR (CDCl$_3$, 100 MHz) δ 169.1, 139.8, 137.2, 134.4, 130.2, 128.8, 116.1, 83.2, 73.0, 65.7, 57.1, 29.1, 28.0, 25.9, 18.3, -5.4; IR (neat) $\nu_{\text{max}}$ 2954, 2929, 2856, 1791, 1463, 1448, 1326, 1256, 1158, 1119, 1076, 1037, 924, 839, 782, 759, 717, 688, 604 cm$^{-1}$; LR-MS (FAB+) $m/z$ 423 (M + H$^+$); HR-MS (FAB+) calcd for C$_{21}$H$_{31}$O$_5$SSi (M + H$^+$) 423.1661, found 423.1663.

(1R,4R,7S)-7-(3-((tert-Butyldimethylsilyl)oxy)prop-1-en-2-yl)-4-(phenylsulfonyl)-2-oxabicyclo[2.2.1]heptan-3-one (102b). $[\alpha]^\text{D}_{20}$ +40.16 (c 2.0, CHCl$_3$); $^1$H-NMR (CDCl$_3$, 400 MHz) δ 8.02 (d, 2H, 7.6 Hz), 7.67 (t, 1H, $J = 7.5$ Hz), 7.53 (t, 1H, $J = 7.9$ Hz), 5.65 (s, 1H), 5.50 (s, 1H), 4.84 (s, 1H), 4.12 (q, 2H, $J = 13.6$ Hz), 3.20 (s, 1H), 2.54 (td, 1H, $J = 12.0$ Hz, $J = 4.6$ Hz), 2.08 (m, 1H), 1.89 (m, 1H), 1.69 (m, 1H), 0.89 (s, 9H), 0.06 (s, 6H); $^{13}$C-NMR (CDCl$_3$, 100 MHz) δ 169.1, 139.8, 137.2, 134.4, 130.2, 128.8, 116.1, 83.2, 73.0, 65.7, 57.1, 29.1, 28.0, 25.9, 18.3, -5.4; IR (neat) $\nu_{\text{max}}$ 2954, 2929, 2856, 1791, 1463, 1448, 1326, 1256, 1158, 1119, 1076, 1037, 924, 839, 782, 759, 717, 688, 604 cm$^{-1}$; LR-MS (FAB+) $m/z$ 423 (M + H$^+$); HR-MS (FAB+) calcd for C$_{21}$H$_{31}$O$_5$SSi (M + H$^+$) 423.1661, found 423.1663.
2H, J = 13.0 Hz), 3.10 (s, 1H), 2.90-2.84 (m, 1H), 2.39-2.33 (m, 1H), 2.08-1.96 (m, 2H),
0.87 (s, 9H), 0.05 (s, 6H); $^{13}$C-NMR (CDCl$_3$, 100 MHz) δ 169.4, 139.0, 137.3, 134.4, 130.2,
128.8, 116.6, 81.1, 74.2, 67.2, 55.6, 28.8, 25.9, 23.2, 18.3; IR (neat) ν$_{max}$ 2954, 2857, 1794,
1471, 1448, 1326, 1254, 1155, 1119, 1055, 1008, 943, 838, 779, 720, 688, 603 cm$^{-1}$; LR-
MS (FAB+) m/z 423 (M + H$^+$); HR-MS (FAB+) calcd for C$_{21}$H$_{31}$O$_5$SSi (M + H$^+$) 423.1661,
found 423.1666.

$(1R,4S,7R)$-7-(3-((tert-butyldimethylsilyl)oxy)prop-1-en-2-yl)-2-
oxabicyclo[2.2.1]heptan-3-one (91). To a mixture of [2.2.1] bridged bicyclic lactone 102a
(324 mg, 0.8 mmol) and boric acid (475 mg, 7.7 mmol) in MeOH (8 mL) was added 5%
sodium mercury amalgam (2.35 g, 6.1 mmol) at ambient temperature. After stirring for 3 h,
the reaction mixture was decanted with diethyl ether and quenched with a saturated NH$_4$Cl
solution (30 mL). The organic layer was separated, and aqueous layer was extracted with
diethyl ether (2 × 20 mL). The combined organic layer was washed with brine, dried over
MgSO$_4$, and concentrated in vacuo. The residue was purified by flash column
chromatography on silica gel (EtOAc:n-hexane = 1:6) to afford desulfonylated bicyclic
lactone 91 (200 mg, 93%) as a white solid: [α]$_D$ -8.35 (c 1.0, CHCl$_3$); 1H-NMR (CDCl$_3$,
400 MHz) δ 5.18 (s, 1H), 5.04 (s, 1H), 4.86 (s, 1H), 4.13 (t, 2H, J = 14.7 Hz), 2.94 (d, 1H, J
= 3.4 Hz), 2.66 (s, 1H), 2.05-1.92 (m, 3H), 1.81-1.75 (m, 1H), 0.88 (s, 9H), 0.05 (s, 6H);
$^{13}$C-NMR (CDCl$_3$, 100 MHz) δ 177.7, 142.4, 113.1, 82.0, 66.1, 53.7, 45.5, 29.0, 25.8, 23.1,
18.3, -5.4; IR (neat) ν$_{max}$ 2954, 2857, 1789, 1471, 1333, 1255, 1149, 1097, 1047, 955, 907,
839, 778 cm$^{-1}$; LR-MS (FAB+) m/z 283 (M + H$^+$); HR-MS (FAB+) calcd for C$_{15}$H$_{27}$O$_3$Si
(M + H$^+$) 283.1729, found 283.1736.

$(1R,2R,3S)$-2-(3-((tert-butyldimethylsilyl)oxy)prop-1-en-2-yl)-3-
(hydroxymethyl)cyclopentan-1-ol (92). To a solution of desulfonylated bicyclic lactone 91
(212 mg, 0.8 mmol) in diethyl ether (8 mL) were added lithium borohydride (3.0 M in THF,
1.0 mL, 3.0 mmol) and methanol (0.18 mL, 4.5 mmol) at 0 ºC. After stirring for 4 h, the
reaction mixture was quenched with \( \text{H}_2\text{O} \) (10 mL) and diluted with diethyl ether (10 mL). The organic layer was separated, and the aqueous layer was extracted with diethyl ether (2 \( \times \) 10 mL). The combined organic layer was washed with brine, dried over \( \text{MgSO}_4 \), and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc: \( n \)-hexane = 1:2) to afford cyclopentane silyl ether \( \mathbf{92} \) (206 mg, 96\%) as a colorless oil: \( [\alpha]^\text{D}_2 \) -5.00 (c 1.0, CHCl\(_3\)); \(^1\)H-NMR (CDCl\(_3\), 400 MHz) \( \delta \) 5.28 (s, 1H), 5.13 (s, 1H), 4.30-4.26 (m, 1H), 4.18 (d, 1H, \( J = 12.2 \) Hz), 4.10 (d, 1H, \( J = 12.2 \) Hz), 3.62 (dd, 1H, \( J = 12.5 \) Hz, \( J = 3.4 \) Hz), 3.35 (dd, 1H, \( J = 11.1 \) Hz, \( J = 5.5 \) Hz), 2.69 (dd, 1H, \( J = 8.6 \) Hz, \( J = 4.3 \) Hz), 2.40 (m, 1H), 1.89-1.73 (m, 4H), 0.90 (s, 9H), 0.09 (s, 6H); \(^{13}\)C-NMR (CDCl\(_3\), 100 MHz) \( \delta \) 145.0, 116.4, 74.0, 68.2, 62.4, 51.0, 43.2, 33.6, 25.8, 24.5, 18.3, -5.3; IR (neat) \( \nu_{\text{max}} \) 3278, 2954, 2858, 1472, 1255, 1022, 837, 775 cm\(^{-1}\); LR-MS (FAB+) \( m/z \) 287 (M + H\(^+\)); HR-MS (FAB+) calcd for C\(_{15}\)H\(_{31}\)O\(_3\)Si (M + H\(^+\)) 287.2042, found 287.2038.

\((1\text{R},2\text{R},3\text{S})\)-3-(Hydroxymethyl)-2-(3-hydroxyprop-1-en-2-yl)cyclopentan-1-ol (113). To a solution of cyclopentane silyl ether \( \mathbf{92} \) (206 mg, 0.7 mmol) in THF (15 mL) was added tetra-\( n \)-butylammonium fluoride (1.0 M solution in THF, 0.8 mL, 0.8 mmol) at ambient temperature. After stirring for 30 min, the reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (CH\(_2\)Cl\(_2\):MeOH = 9:1) to afford cyclopentanetriol \( \mathbf{113} \) (124 mg, 100\%) as a colorless oil: \( [\alpha]^\text{D}_2 \) +37.84 (c 0.5, MeOH); \(^1\)H-NMR (CD\(_3\)OD, 400 MHz) \( \delta \) 5.25 (d, 2H, \( J = 18.4 \) Hz), 4.26 (q, 1H, \( J = 4.4 \) Hz), 4.01 (s, 2H), 3.51 (m, 2H), 2.63 (dd, 1H, \( J = 8.2 \) Hz, \( J = 4.5 \) Hz), 2.40-2.38 (m, 1H), 1.89-1.82 (m, 2H), 1.79-1.69 (m, 2H); \(^{13}\)C-NMR (CD\(_3\)OD, 100 MHz) \( \delta \) 147.8, 114.7, 76.2, 68.4, 64.3, 51.3, 44.0, 35.4, 26.6; IR (neat) \( \nu_{\text{max}} \) 3313, 2942, 1648, 1472, 1338, 1129, 1019, 945, 908, 798 cm\(^{-1}\); LR-MS (FAB+) \( m/z \) 173 (M + H\(^+\)); HR-MS (FAB+) calcd for C\(_9\)H\(_{17}\)O\(_3\) (M + H\(^+\)) 173.1178, found 173.1177.

\((3\text{aR,4S,6aR})\)-4-(Hydroxymethyl)-3-methylenehexahydro-2H-cyclopenta[b]furan-2-one (97). To a solution of cyclopentanetriol \( \mathbf{113} \) (52.5 mg, 0.3 mmol) in THF (12 mL) was
added manganese dioxide (1.06 g, 12.2 mmol) at ambient temperature. After stirring for 12 h, the reaction mixture was filtered through a pad of Celite and concentrated \textit{in vacuo}. The residue was purified by flash column chromatography on silica gel (EtOAc:n-hexane = 2:1) to afford \textit{cis}-fused 5,5-bicyclic lactone \textit{97} (46.7 mg, 91\%) as a colorless oil: [\(\alpha\)]\textsubscript{D} \textsuperscript{+}39.36 (c 0.25, CHCl\textsubscript{3}); \textsuperscript{1}H-NMR (CDCl\textsubscript{3}, 400 MHz) \(\delta\) 6.39 (d, 1H, \(J = 1.8\) Hz), 5.85 (d, 1H, \(J = 1.0\) Hz), 5.00 (t, 1H, \(J = 5.9\) Hz), 3.69 (dd, 1H, \(J = 10.5\) Hz, \(J = 5.6\) Hz), 3.64-3.56 (m, 2H), 2.32-2.24 (m, 1H), 2.14 (dd, 1H, \(J = 13.4\) Hz, \(J = 6.4\) Hz), 1.79-1.69 (m, 2H), 1.29-1.18 (m, 1H); \textsuperscript{13}C-NMR (CDCl\textsubscript{3}, 125 MHz) \(\delta\) 171.1, 134.7, 125.6, 83.5, 62.2, 46.2, 44.3, 32.9, 25.9; IR (neat) \(\nu\)\textsubscript{max} 3460, 2962, 1757, 1313, 1268, 1220, 1158, 1026, 985, 772 cm\textsuperscript{-1}; LR-MS (FAB+) \textit{m/z} 169 (M + H\textsuperscript{+}); HR-MS (FAB+) calcd for C\textsubscript{9}H\textsubscript{13}O\textsubscript{3} (M + H\textsuperscript{+}) 169.0865, found 169.0874.

\textbf{(3aS,4R,6aR)-3a-hydroxy-4-(hydroxymethyl)-3-methylenehexahydro-2H-cyclopenta[b]furan-2-one (94).} To a refluxing solution of bicyclic lactone \textit{97} (27.0 mg, 0.1 mmol) in 1,4-dioxane (2 mL) was added selenium dioxide (178.0 mg, 1.6 mmol). After stirring for 24 h, the reaction mixture was filtered through a pad of Celite and concentrated \textit{in vacuo}. The residue was purified by flash column chromatography on silica gel (EtOAc only) to afford dihydroxy bicyclic lactone \textit{94} (26.5 mg, 90\%) as a colorless oil: [\(\alpha\)]\textsubscript{D} \textsuperscript{+}16.25 (c 1.0, CHCl\textsubscript{3}); \textsuperscript{1}H-NMR (CDCl\textsubscript{3}, 400 MHz) \(\delta\) 6.60 (s, 1H), 6.20 (s, 1H), 4.70 (d, 1H, \(J = 2.0\) Hz), 3.83 (dd, 1H, \(J = 10.1\) Hz, \(J = 5.0\) Hz), 3.58 (t, 1H, \(J = 10.0\) Hz), 2.81 (s, 1H), 2.44-2.36 (m, 1H), 2.06-2.01 (m, 2H), 1.78-1.72 (m, 1H), 1.60 (br, 1H), 1.17-1.13 (m, 1H); \textsuperscript{13}C-NMR (CDCl\textsubscript{3}, 125 MHz) \(\delta\) 169.5, 138.4, 128.4, 89.8, 85.1, 62.1, 53.3, 31.0, 25.7; IR (neat) \(\nu\)\textsubscript{max} 3420, 2967, 1748, 1408, 1300, 1220, 1193, 1146, 1089, 1024, 984, 819, 772 cm\textsuperscript{-1}; LR-MS (FAB+) \textit{m/z} 185 (M + H\textsuperscript{+}); HR-MS (FAB+) calcd for C\textsubscript{9}H\textsubscript{13}O\textsubscript{4} (M + H\textsuperscript{+}) 185.0814, found 185.0810.

Diastereomeric mixture of (3aS,4R,6aR)-3a-hydroxy-4-((1S,2R)-1-hydroxy-2-methylbut-3-en-1-yl)-3-methylenehexahydro-2H-cyclopenta[b]furan-2-one (82a) and

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To a solution of dihydroxy bicyclic lactone 94 (23.0 mg, 0.1 mmol) in CH$_2$Cl$_2$ (1 mL) was added Dess-Martin periodinane (106.0 mg, 0.3 mmol) at ambient temperature. After stirring for 30 min, the reaction mixture was filtered through a pad of anhydrous sodium sulfate and concentrated in vacuo. The residue was used in the next step without further purification.

To a solution of crude aldehyde 90 in CH$_2$Cl$_2$ (1.3 mL, 0.1 M) were added titanium tetrachloride (0.25 mL, 0.3 mmol) and (E)-crotyltrimethylsilane (160 mg, 1.3 mmol) at -78 °C. After stirring for 6 h, the reaction mixture was quenched with a saturated Na$_2$S$_2$O$_3$ solution (5 mL) and diluted with ethyl acetate (10 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with brine, dried over MgSO$_4$, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc:n-hexane = 1:2) to afford a diastereomeric mixture of homoallylic alcohol 82a/82b (23.2 mg, 78%, dr 5:1) as a colorless oil. The diastereomeric ratio was determined after the separation of each diastereomer as the silyl ethers 15 and 15' followed by desilylation.

**Major product 82a:** [α]$_D$$^{20}$ +50.16 (c 0.25, CHCl$_3$); $^1$H-NMR (CDCl$_3$, 400 MHz) δ 6.33 (s, 1H), 5.86 (s, 1H), 5.67 (dd, 1H, $J = 17.9$ Hz, $J = 9.6$ Hz, $J = 8.4$ Hz), 5.09-5.03 (m, 2H), 4.52 (d, 1H, $J = 4.3$ Hz), 3.51 (m, 1H), 2.35 (td, 1H, $J = 10.7$ Hz, $J = 2.8$ Hz), 2.26 (q, 1H, $J = 7.2$ Hz), 2.13-2.09 (m, 1H), 1.96-1.89 (m, 1H), 1.83-1.77 (m, 1H), 1.76 (s, 1H), 1.33 (d, 1H, $J = 5.2$ Hz), 1.23 (s, 1H), 1.05 (d, 3H, $J = 1.7$ Hz); $^{13}$C-NMR (CDCl$_3$, 150 MHz) δ 168.7, 142.7, 140.7, 122.4, 115.5, 90.4, 85.6, 72.2, 54.5, 43.2, 29.7, 22.5, 16.2; IR (neat) $\nu_{\text{max}}$ 3503, 2926, 1749, 1220, 773 cm$^{-1}$; LR-MS (FAB+) $m/z$ 239 (M + H$^+$); HR-MS (FAB+) calcd for C$_{13}$H$_{19}$O$_4$ (M + H$^+$) 239.1283, found 239.1290.

**Minor product 82b:** [α]$_D$$^{20}$ +23.28 (c 0.25, CHCl$_3$); $^1$H-NMR (CDCl$_3$, 500 MHz) δ 6.60 (s, 1H), 6.24 (s, 1H), 5.86 (m, 1H), 5.24 (d, 1H, $J = 10.7$ Hz), 5.15 (d, 1H, $J = 7.6$ Hz), 4.72 (s, 1H), 3.57 (d, 1H, $J = 10.4$ Hz), 3.39 (s, 1H), 2.32 (s, 1H), 2.20 (ddd, 1H, $J = 13.6$ Hz, $J =$
7.0 Hz, $J = 5.8$ Hz), 2.05-2.02 (m, 1H), 1.78 (s, 1H), 1.71-1.68 (m, 1H), 1.25-1.13 (m, 1H), 1.02 (d, 3H, $J = 7.0$ Hz); $^{13}$C-NMR (CDCl$_3$, 125 MHz) $\delta$ 169.7, 140.2, 138.6, 128.7, 116.8, 88.8, 85.2, 72.9, 54.5, 39.5, 31.3, 25.1, 9.7; IR (neat) $\nu_{\text{max}}$ 3472, 2970, 1702, 1284, 1197, 1144, 1099, 987 cm$^{-1}$; LR-MS (FAB+) $m/z$ 239 (M + H$^+$); HR-MS (FAB+) calcd for C$_{13}$H$_{19}$O$_4$ (M + H$^+$) 239.1283, found 239.1282.

(3aS,4R,6aR)-3a-hydroxy-4-((1S,2R)-2-methyl-1-((triethylsilyl)oxy)but-3-en-1-yl)-3-methylenehexahydro-2H-cyclopenta[b]furan-2-one (117a). To a solution of diastereomeric mixture of homoallylic alcohol 82a/82b (5:1) (23.2 mg, 0.1 mmol) in pyridine (1 mL) was added triethylsilyl trifluoromethanesulfonate (0.1 mL, 0.3 mmol) at -40 ºC. After stirring for 30 min, the reaction mixture was quenched with H$_2$O (1 mL) and diluted with ethyl acetate (5 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 5 mL). The combined organic layer was washed with brine, dried over MgSO$_4$, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc: n-hexane = 1:10 to 1:6) to afford the bicyclic lactone silyl ether 117a (25.7 mg, 75%) as a white solid and the minor (1R, 2S) isomer 117b (5.2 mg, 15%) as a white solid.

**Major product 117a:** $[\alpha]_{20}^{\circ} +37.60$ (c 0.5, CHCl$_3$); $^1$H-NMR (CDCl$_3$, 500 MHz) $\delta$ 6.48 (s, 1H), 5.90 (s, 1H), 5.87 (m, 1H), 5.04-4.97 (m, 2H), 4.57 (d, 1H, $J = 3.5$ Hz), 3.69 (dd, 1H, $J = 7.0$ Hz, $J = 2.0$ Hz), 2.55-2.51 (m, 1H), 2.26-2.20 (m, 1H), 2.03-1.99 (m, 1H), 1.92-1.83 (m, 2H), 1.83 (s, 1H), 1.49-1.43 (m, 1H), 1.01 (d, 3H, $J = 6.8$ Hz), 0.90 (t, 9H, $J = 8.0$ Hz), 0.53 (q, 6H, $J = 8.0$ Hz); $^{13}$C-NMR (CDCl$_3$, 150 MHz) $\delta$ 168.6, 141.6, 140.2, 126.3, 114.1, 91.1, 84.8, 74.6, 53.9, 41.6, 29.9, 26.8, 12.6, 7.0, 5.5; IR (neat) $\nu_{\text{max}}$ 3434, 2958, 1749, 1261, 1220, 1011, 772 cm$^{-1}$; LR-MS (FAB+) $m/z$ 353 (M + H$^+$); HR-MS (FAB+) calcd for C$_{19}$H$_{33}$O$_4$Si (M + H$^+$) 353.2148, found 353.2138.

**Minor product 117b:** $[\alpha]_{20}^{\circ} -29.78$ (c 0.5, CHCl$_3$); $^1$H-NMR (CDCl$_3$, 600 MHz) $\delta$, 6.54 (s, 1H), 6.03 (ddd, 1H, $J = 17.4$ Hz, $J = 10.8$ Hz, $J = 4.6$ Hz), 5.99 (s, 1H), 5.16 (dt, 1H, $J = 2.0$ Hz, $J = 7.0$ Hz), 2.55-2.51 (m, 1H), 2.26-2.20 (m, 1H), 2.03-1.99 (m, 1H), 1.92-1.83 (m, 2H), 1.83 (s, 1H), 1.49-1.43 (m, 1H), 1.01 (d, 3H, $J = 6.8$ Hz), 0.90 (t, 9H, $J = 8.0$ Hz), 0.53 (q, 6H, $J = 8.0$ Hz); $^{13}$C-NMR (CDCl$_3$, 150 MHz) $\delta$ 168.6, 141.6, 140.2, 126.3, 114.1, 91.1, 84.8, 74.6, 53.9, 41.6, 29.9, 26.8, 12.6, 7.0, 5.5; IR (neat) $\nu_{\text{max}}$ 3434, 2958, 1749, 1261, 1220, 1011, 772 cm$^{-1}$; LR-MS (FAB+) $m/z$ 353 (M + H$^+$); HR-MS (FAB+) calcd for C$_{19}$H$_{33}$O$_4$Si (M + H$^+$) 353.2148, found 353.2138.
11.0 Hz, J = 1.4 Hz), 5.09 (dt, 1H, J = 17.4 Hz, J = 1.8 Hz), 4.62 (d, 1H, J = 5.5 Hz), 3.81 (dd, 1H, J = 9.6 Hz, J = 2.8 Hz), 3.69 (s, 1H), 2.55-2.50 (m, 1H), 2.17 (m, 1H), 1.97-1.86 (m, 2H), 1.68 (quint, 1H, J = 6.0 Hz), 1.18-1.10 (m, 1H), 1.00-0.97 (m, 12H), 0.74-0.65 (m, 6H); ¹³C-NMR (CDCl₃, 150 MHz) δ 169.6, 139.8, 137.9, 127.1, 115.2, 88.2, 85.2, 77.9, 55.9, 42.3, 31.4, 25.1, 14.6, 7.0, 6.0; IR (neat) ν_max 3442, 2959, 2877, 1747, 1415, 1338, 1113, 1007, 977, 914, 819, 741 cm⁻¹; LR-MS (FAB+) m/z 353 (M + H⁺); HR-MS (FAB+) calcd for C₁₉H₃₃O₄Si (M + H⁺) 353.2148, found 353.2155.

(2aR,2a1S,4aR,5S,6R)-2a1-Hydroxy-6-methyl-5-((triethylsilyl)oxy)-2a1,3,4,4a,5,6-hexahydroindeno[1,7-bc]furan-1(2aH)-one (118). To a refluxing solution of bicyclic lactone silyl ether 117a (6.5 mg, 0.02 mmol) in CH₂Cl₂ (2 mL, 0.01 M) was added a 2nd generation Grubbs catalyst (0.9 mg, 0.9 μmol). After stirring for 6 h, the reaction mixture was cooled to ambient temperature and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc:n-hexane = 1:5) to afford the tricyclic lactone 118 (6.0 mg, 99%) as a white solid: [α]_D²⁰ -22.84 (c 0.5, CHCl₃); ¹H-NMR (CDCl₃, 500 MHz) δ 6.75 (d, 1H, J = 2.4 Hz), 4.81 (d, 1H, J = 8.4 Hz), 3.95 (d, 1H, J = 3.0 Hz), 2.14-2.06 (m, 1H), 1.76-1.67 (m, 2H), 1.30-1.21 (m, 1H), 0.96 (t, 9H, J = 7.9 Hz), 0.63 (q, 6H, J = 8.0 Hz); ¹³C-NMR (CDCl₃, 125 MHz) δ 169.9, 141.6, 129.6, 88.3, 80.0, 74.6, 48.4, 39.2, 30.8, 26.5, 19.1, 6.6, 4.6; IR (neat) ν_max 3414, 2958, 2877, 1761, 1673, 1459, 1283, 1221, 1193, 1096, 1051, 1029, 836, 745 cm⁻¹; LR-MS (FAB+) m/z 325 (M + H⁺); HR-MS (FAB+) calcd for C₁₇H₂₉O₄Si (M + H⁺) 325.1835, found 325.1840.

(2aR,2a1S,4aR,5S,6R)-2a1,5-Dihydroxy-6-methyl-2a1,3,4,4a,5,6-hexahydroindeno[1,7-bc]furan-1(2aH)-one (116). To a solution of tricyclic lactone 118 (17.7 mg, 0.1 mmol) in MeOH (1 mL) was added camphor-10-sulfonic acid (β) (1.3 mg, 5 μmol) at ambient temperature. After stirring for 1 min, the reaction mixture was quenched with a saturated NaHCO₃ solution (1.0 mL) and diluted with ethyl acetate (5.0 mL). The
organic layer was separated, and the aqueous layer was extracted with ethyl acetate (5 × 5.0 mL). The combined organic layer was washed with brine, dried over MgSO₄, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc:n-hexane = 4:1) to afford hydroxygaliellalactone 116 (9.5 mg, 83 %) as a white solid: [α]₂₀° -39.44 (c 0.5, MeOH); ¹H-NMR (CD₃OD, 500 MHz) δ 6.81 (d, 1H, J = 3.2 Hz), 4.62 (t, 1H, J = 4.7 Hz), 3.06 (dd, 1H, J = 7.0 Hz, J = 5.0 Hz), 2.59 (m, 1H), 2.23 (dd, 1H, J = 10.7 Hz, J = 4.5 Hz), 2.18-2.11 (m, 1H), 2.09-2.04 (m, 1H), 1.58-1.48 (m, 1H), 1.25 (d, 3H, J = 5.7 Hz); ¹³C-NMR (CD₃OD, 125 MHz) δ 177.6, 149.1, 134.5, 92.1, 84.5, 82.1, 54.5, 39.3, 33.0, 30.8, 18.0; IR (neat) νmax 3413, 2928, 1743, 1220, 1047, 772 cm⁻¹; LR-MS (FAB+) m/z 211 (M + H⁺); HR-MS (FAB+) calcd for C₁₁H₁₅O₄ (M + H⁺) 211.0970, found 211.0971.

(-)-Galiellalactone (1): To a mixture of hydroxygaliellalactone 116 (5.0 mg, 0.02 mmol) and pyridine (10 μL, 0.1 mmol) in CH₂Cl₂ (0.5 mL) was added pentafluorophenyl chlorothionoformate (13 μL, 0.1 mmol) at ambient temperature. After stirring for 3 h, the reaction mixture was quenched with H₂O (1 mL) and diluted with CH₂Cl₂ (1 mL). The organic layer was separated, and aqueous layer was extracted with CH₂Cl₂ (2 × 5 mL). The combined organic layer was washed with brine, dried over MgSO₄, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc:n-hexane = 1:2) to afford the crude xanthate.

To a mixture of tributyltin hydride (13 μL, 0.05 mmol) and azobisisobutyronitrile (0.4 mg, 2 μmol) in toluene (0.5 mL) was added the crude xanthate in toluene (0.5 mL) at 80 ºC. The reaction mixture was heated to 100 ºC. After stirring for 1 h, the resulting mixture was cooled to ambient temperature and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc:n-hexane = 1:3) to afford (-)-galiellalactone 1 (3.5 mg, 76% in 2 steps) as a white solid: [α]₂₀° -47.56 (c 0.25, CHCl₃) (lit.¹,² [α]₂₀° – 52.80 (c 0.20, CHCl₃); ¹H-NMR (CDCl₃, 500 MHz) δ 7.03 (d, 1H, J = 3.0 Hz), 4.76 (dd, 1H, J =
7.5 Hz, $J = 2.0$ Hz), 2.62 (qdt, 1H, $J = 14.6$ Hz, $J = 7.4$ Hz, $J = 3.1$ Hz), 2.43 (ddddd, 1H, $J = 10.5$ Hz, $J = 7.4$ Hz, $J = 7.2$ Hz, $J = 4.8$ Hz), 2.24 (dt, 1H, $J = 14.0$ Hz, $J = 7.4$ Hz), 2.07 (ddddd, 1H, $J = 14.6$ Hz, $J = 11.2$ Hz, $J = 7.6$ Hz, $J = 7.3$ Hz), 1.93 (s, 1H) 1.85 (ddddd, 1H, $J = 13.2$ Hz, $J = 7.2$ Hz, $J = 7.2$ Hz, $J = 2.9$ Hz), 1.74 (m, 1H), 1.18 (1H, m), 1.18 (d, 3H, $J = 7.4$ Hz), 1.07 (ddd, 1H, $J = 13.6$ $J = 8.0$ Hz, $J = 4.7$ Hz); $^{13}$C-NMR (CDCl$_3$, 125 MHz) $\delta$ 169.5, 150.2, 130.6, 89.7, 81.9, 43.1, 33.0, 31.3, 29.0, 20.9; IR (neat) $\nu_{ \text{max} }$ 2959, 2931, 1759, 1744, 1188, 1017, 971, 896 cm$^{-1}$; LR-MS (FAB+) $m/z$ 195 (M + H$^+$); HR-MS (FAB+) calcd for C$_{11}$H$_{15}$O$_3$ (M + H$^+$) 195.1021, found 195.1013.
### VI. Appendix

#### Table 1. $^1$H-NMR (CDCl$_3$, 500 MHz) data (δ) of (-)-galiellalactone (1)

<table>
<thead>
<tr>
<th>Carbon No.</th>
<th>Natural (Sterner) (-)-Galiellalactone</th>
<th>Synthetic (Suh) (-)-Galiellalactone</th>
</tr>
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<td>7.01 (d, 1H, $J = 3.1$ Hz)</td>
<td>7.03 (d, 1H, $J = 3.0$ Hz)</td>
</tr>
<tr>
<td>4</td>
<td>2.63 (dqddd, 1H, $J = 8.0$, 7.4, 7.3, 3.1 Hz)</td>
<td>2.62 (qtd, 1H, $J = 14.6$, 7.4, 3.1 Hz)</td>
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<tr>
<td>4a</td>
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<td>1.18 (d, 3H, $J = 7.4$ Hz)</td>
</tr>
<tr>
<td>5</td>
<td>1.06 (ddddd, 1H, $J = 13.9$, 8.0, 4.6 Hz)</td>
<td>1.07 (ddddd, 1H, $J = 13.6$, 8.0, 4.7 Hz)</td>
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<tr>
<td></td>
<td>2.24 (dt, 1H, $J = 13.9$, 7.4 Hz)</td>
<td>2.24 (dt, 1H, $J = 14.0$, 7.4 Hz)</td>
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<tr>
<td>5a</td>
<td>2.43 (ddddd, 1H, $J = 10.6$, 7.4, 7, 4.6 Hz)</td>
<td>2.43 (ddddd, 1H, $J = 10.5$, 7.4, 7.2, 4.8 Hz)</td>
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<td>6</td>
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<td>1.18 (1H, m)</td>
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<tr>
<td></td>
<td>1.85 (ddddd, 1H, $J = 13.4$, 7.2, 7.2, 3.0 Hz)</td>
<td>1.85 (ddddd, 1H, $J = 13.2$, 7.2, 7.2, 2.9 Hz)</td>
</tr>
<tr>
<td>7</td>
<td>1.73 (ddddd, 1H, $J = 14.7$, 7.0, 3.0, 2.0 Hz)</td>
<td>1.74 (m, 1H)</td>
</tr>
<tr>
<td></td>
<td>2.07 (ddddd, 1H, $J = 14.7$, 11.0, 7.5, 7.2 Hz)</td>
<td>2.07 (ddddd, 1H, $J = 14.6$, 11.2, 7.6, 7.3 Hz)</td>
</tr>
<tr>
<td>7a</td>
<td>4.77 (dd, 1H, $J = 7.5$, 2.0 Hz)</td>
<td>4.76 (dd, 1H, $J = 7.5$, 2.0 Hz)</td>
</tr>
<tr>
<td>7b</td>
<td>3.43 (s, 1H)</td>
<td>1.93 (s, 1H)</td>
</tr>
</tbody>
</table>
Table 2. $^{13}$C NMR (CDCl$_3$, 125 MHz) data ($\delta$) of (-)-galiellalactone (1)

<table>
<thead>
<tr>
<th>Carbon No.</th>
<th>Natural (Sterner)$^{1,2}$ (-)-Galiellalactone</th>
<th>$\Delta \delta$ (Natural-Synthetic)</th>
<th>Synthetic (Suh) (-)-Galiellalactone</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>169.7</td>
<td>0.2</td>
<td>169.5</td>
</tr>
<tr>
<td>2a</td>
<td>130.7</td>
<td>0.1</td>
<td>130.6</td>
</tr>
<tr>
<td>3</td>
<td>150.1</td>
<td>-0.1</td>
<td>150.2</td>
</tr>
<tr>
<td>4</td>
<td>33.0</td>
<td>0</td>
<td>33.0</td>
</tr>
<tr>
<td>4a</td>
<td>20.9</td>
<td>0</td>
<td>20.9</td>
</tr>
<tr>
<td>5</td>
<td>31.4</td>
<td>0.1</td>
<td>31.3</td>
</tr>
<tr>
<td>5a</td>
<td>43.1</td>
<td>0</td>
<td>43.1</td>
</tr>
<tr>
<td>6</td>
<td>29.0</td>
<td>0</td>
<td>29.0</td>
</tr>
<tr>
<td>7</td>
<td>31.4</td>
<td>0.1</td>
<td>31.3</td>
</tr>
<tr>
<td>7a</td>
<td>89.8</td>
<td>0.1</td>
<td>89.7</td>
</tr>
<tr>
<td>7b</td>
<td>81.8</td>
<td>-0.1</td>
<td>81.9</td>
</tr>
</tbody>
</table>
$^{1}H$-NMR (CDCl$_3$, 400 MHz)

$^{13}C$-NMR (CDCl$_3$, 100 MHz)
$^1$H-NMR (CDCl$_3$, 400 MHz)

$^{13}$C-NMR (CDCl$_3$, 100 MHz)
$^1$H-NMR (CDCl$_3$, 400 MHz)

$^{13}$C-NMR (CDCl$_3$, 100 MHz)
$^1$H-NMR (CDCl$_3$, 400 MHz)

$^{13}$C-NMR (CDCl$_3$, 100 MHz)
$^1$H-NMR (CDCl$_3$, 400 MHz)

$^{13}$C-NMR (CDCl$_3$, 100 MHz)
$^1$H-NMR (CDCl$_3$, 400 MHz)

$^{13}$C-NMR (CDCl$_3$, 100 MHz)
$^{1}$H-NMR (CDCl$_3$, 400 MHz)

![H-NMR spectrum](image1)

**103a**

$^{13}$C-NMR (CDCl$_3$, 100 MHz)

![C-NMR spectrum](image2)

**103a**
$^1$H-NMR (CDCl$_3$, 400 MHz)

$^{13}$C-NMR (CDCl$_3$, 100 MHz)
$^1$H-NMR (CDCl$_3$, 400 MHz)

$^{13}$C-NMR (CDCl$_3$, 100 MHz)
$^1$H-NMR (CDCl$_3$, 400 MHz)

$^{13}$C-NMR (CDCl$_3$, 100 MHz)
$^{1}H$-NMR (CDCl$_3$, 400 MHz)

$^{13}$C-NMR (CDCl$_3$, 100 MHz)
$^1$H-NMR (CD$_3$OD, 400 MHz)

$^{13}$C-NMR (CD$_3$OD, 100 MHz)
$^1$H-NMR (CDCl$_3$, 400 MHz)

$^{13}$C-NMR (CDCl$_3$, 125 MHz)
$^1$H-NMR (CDCl$_3$, 400 MHz)

$^{13}$C-NMR (CDCl$_3$, 125 MHz)
$^1$H-NMR (CDCl$_3$, 400 MHz)

$^{13}$C-NMR (CDCl$_3$, 150 MHz)
$^1$H-NMR (CDCl$_3$, 500 MHz)

$^{13}$C-NMR (CDCl$_3$, 125 MHz)
$^{1}$H-NMR (CDCl$_3$, 500 MHz)

$^{13}$C-NMR (CDCl$_3$, 150 MHz)
$^1$H-NMR (CDCl$_3$, 600 MHz)

$^{13}$C-NMR (CDCl$_3$, 150 MHz)
$^1$H-NMR (CDCl$_3$, 600 MHz)

$^{13}$C-NMR (CDCl$_3$, 125 MHz)
$^1$H-NMR (CD$_3$OD, 500 MHz)

$^{13}$C-NMR (CD$_3$OD, 125 MHz)
\( ^1H \text{-NMR (CDCl}_3, \ 500 \text{ MHz)} \)

\[
\begin{array}{c}
\text{NMR Spectrum} \\
\end{array}
\]

\( ^{13}C \text{-NMR (CDCl}_3, \ 125 \text{ MHz)} \)

\[
\begin{array}{c}
\text{NMR Spectrum} \\
\end{array}
\]
V. References


(16) Johansson, M. H., Biosynthetic and synthetic studies of the fungal metabolite


STAT3 (Signal Transducer and Activator of Transcription 3)는 cytokine과 growth factor의 신호를 획득하여 유전자 전사를 일으키는 단백질이다. STAT3 단백질은 일반적으로 평상시에는 그 활성이 억제되어 있으나, 고형 암과 혈액 암 등의 다양한 암에서 과 발현 및 지속적인 이상활성화를 일으켜 비정상적인 세포 성장과 악성세포로의 변화, 암세포 증식 등에 영향을 미친다. 따라서 STAT3 신호 전달 저해제의 개발은 향후 항암치료를 위해 중요한 연구과제로 생각된다. 1990년 분리 및 보고된 (-)-Galiellalactone은 선택적이고 효과적인 STAT3 저해제로 알려져 있다. 독특한 [5,5,6]-tricyclic lactone 구조는 합성적으로 가치가 높을 뿐만 아니라, 뛰어난 생리활성으로부터 많은 화학자 및 의약화학자들에게 관심을 받고 있다. 본 연구자는 본 연구실에서 이전에 개발한 intramolecular Tsuji-Trost allylic alkylation반응을 응용하여 (-)-galiellalactone의 전합성을 계획하였다. 알려진 출발 물질로부터 일련의 반응을 통해 얻은 전구체로부터, Pd(0)-catalyzed cyclization을 수행하여 [2.2.1] bridged bicyclic lactone화합물을 합성하였다. 이로부터 육영학적으로 선호되지 않으며, 합성적으로 접근이 용이하지 않은 cis-trisubstituted-cyclopentane 중간체를 임체선택적으로 함성할 수 있었다. 이로부터 효과적으로 cis-fused 5,5-bicyclic lactone화합물을 함성할 수 있었고, Riley oxidation을 통해 angular hydroxyl group을 임체선택적으로 도입할 수 있었다. 이후 Hosomi-Sakurai crotylation과 ring-closing metathesis (RCM)를 통해 (-)-galiellalactone의 tricyclic골격을 확립함과 동시에 천연물에 존재하는 4개의 chiral center를 성공적으로 도입하 여 전합성을 마무리 하였다. 이를 바탕으로 STAT3 신호전달을 효과적으로 저해할 수 있는 galiellalactone기반의 다양한 bicyclic/tricyclic 유도체를 합성하였고, 천연물보다 더욱 효과적인 hit화합물을 도출하기 위해 TNBC (Triple Negative Breast Cancer) cell based assay를 수행하였다. 현재 In vitro 활성 평가 결과를 기반으로 화합물간의 구조-활성 관계(SAR)를 확립하기 위해 추가적인 연구가 진행 중에 있다.