SYNTHESIS OF THE ABCD DOMAIN OF THE AZASPIRACIDS

DISSERTATION

Presented in Partial Fulfillment of the Requirements for
the Degree Doctor of Philosophy in the Graduate
School of The Ohio State University

By

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Abstract

This thesis describes synthetic efforts toward the total synthesis of the azaspiracid marine toxins. The investigation here focuses on the synthesis of the ABCD bis-spiroketal domain. Several different approaches have been developed. One features a gold catalyzed spiroketalization, which used a triple bond as an oxidation-state equivalent of a ketone to establish a spiroketal structure. In the D-ring synthesis, a Co(modp)₂ (modp: 1-morpholinocarbamoyl-4,4-dimethyl-1,3-pentadione) catalyzed oxyetherification was applied. In the recently revised synthetic route, the D-ring was constructed through a tandem asymmetric epoxidation and epoxide opening process.
Acknowledgement

The past five and one half years of my graduate study (two and one half at the University of Minnesota, three years at the Ohio State University) was one precious experience for me. First, I would like to thank my advisor, Professor Craig J. Forsyth. He gave me this great opportunity and a wonderful project to work on. I got lots of guidance, advice and support from Professor Forsyth all the way since the first day I joined the group.

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<tr>
<td>(\alpha)</td>
<td>alpha</td>
</tr>
<tr>
<td>([\alpha])</td>
<td>specific rotation</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>(\beta)</td>
<td>beta</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>(t)-Bu</td>
<td>tertiary-butyl</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>°C</td>
<td>degrees Celsius</td>
</tr>
<tr>
<td>COSY</td>
<td>correlation spectroscopy</td>
</tr>
<tr>
<td>CSA</td>
<td>(1S)-(+)\text{-}10-camphorsulfonic acid</td>
</tr>
<tr>
<td>(\delta)</td>
<td>chemical shift in parts per million downfield from tetramethylsilane</td>
</tr>
<tr>
<td>d</td>
<td>doublet (spectra); day(s)</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
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<tr>
<td>DDQ</td>
<td>2,3-dichloro-5,6-dicyano-1,4-benzoquinone</td>
</tr>
<tr>
<td>DHP</td>
<td>3,4-dihdroy-2(H)-pyran</td>
</tr>
<tr>
<td>DIBAL</td>
<td>diisobutylaluminum hydride</td>
</tr>
<tr>
<td>DIPEA</td>
<td>diisopropylethylamine</td>
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<th>Full Form</th>
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<tr>
<td>DIPT</td>
<td>diisopropyltartrate</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-((N,N\text{-dimethylamino})\text{pyridine})</td>
</tr>
<tr>
<td>DMF</td>
<td>(N,N\text{-dimethylformamide})</td>
</tr>
<tr>
<td>DMP</td>
<td>Dess-Martin periodinane</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>dr</td>
<td>diastereomeric ratio</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>ESI</td>
<td>electrospray ionization</td>
</tr>
<tr>
<td>h</td>
<td>hour(s)</td>
</tr>
<tr>
<td>HMBC</td>
<td>heteronuclear multiple bond correlation</td>
</tr>
<tr>
<td>HMQC</td>
<td>heteronuclear multiple quantum coherence</td>
</tr>
<tr>
<td>HPLC</td>
<td>high performance liquid chromatography</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution mass spectrometry</td>
</tr>
<tr>
<td>HSQC</td>
<td>heteronuclear single quantum correlation</td>
</tr>
<tr>
<td>Hz</td>
<td>hertz (cycles/second)</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>k</td>
<td>kilo ((10^3))</td>
</tr>
<tr>
<td>KHMDS</td>
<td>potassium hexamethyldisilazide</td>
</tr>
<tr>
<td>L</td>
<td>liter(s)</td>
</tr>
<tr>
<td>LAH</td>
<td>lithium aluminum hydride</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>LC-MS</td>
<td>liquid chromatography/mass spectrometry</td>
</tr>
<tr>
<td>Symbol</td>
<td>Definition</td>
</tr>
<tr>
<td>--------</td>
<td>------------</td>
</tr>
<tr>
<td>m</td>
<td>milli ($10^{-3}$); multiplet (NMR)</td>
</tr>
<tr>
<td>μ</td>
<td>micro ($10^{-6}$)</td>
</tr>
<tr>
<td>M</td>
<td>moles per liter</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>min</td>
<td>minute(s)</td>
</tr>
<tr>
<td>mol</td>
<td>mole(s)</td>
</tr>
<tr>
<td>NaHMDS</td>
<td>sodium hexamethyldisilazide</td>
</tr>
<tr>
<td>NBS</td>
<td>$N$-bromosuccinimide</td>
</tr>
<tr>
<td>NHK</td>
<td>Nozaki-Hiyama-Kishi</td>
</tr>
<tr>
<td>NIS</td>
<td>$N$-iodosuccinimide</td>
</tr>
<tr>
<td>NMO</td>
<td>4-methylmorpholine $N$-oxide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>NOE</td>
<td>nuclear Overhauser effect</td>
</tr>
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<td>NOESY</td>
<td>nuclear Overhauser enhancement spectroscopy</td>
</tr>
<tr>
<td>$p$</td>
<td>para</td>
</tr>
<tr>
<td>PCC</td>
<td>pyridinium chlorochromate</td>
</tr>
<tr>
<td>PFP</td>
<td>pentafluorophenol</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>Piv</td>
<td>pivaloyl</td>
</tr>
<tr>
<td>PMB</td>
<td>$p$-methoxybenzyl</td>
</tr>
<tr>
<td>PPTS</td>
<td>pyridium $p$-toluenesulfonate</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>py</td>
<td>pyridine</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
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<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>q</td>
<td>quartet (NMR)</td>
</tr>
<tr>
<td>Rf</td>
<td>retention factor (distance traveled by analyte / distance traveled by mobile phase)</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>s</td>
<td>singlet (NMR); second(s)</td>
</tr>
<tr>
<td>t</td>
<td>tertiary (tert)</td>
</tr>
<tr>
<td>t</td>
<td>triplet (NMR)</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetra-$n$-butylammonium fluoride</td>
</tr>
<tr>
<td>TBAI</td>
<td>tetra-$n$-butylammonium iodide</td>
</tr>
<tr>
<td>TBDPS</td>
<td>$t$-butyldiphenylsilyl</td>
</tr>
<tr>
<td>TBHP</td>
<td>$t$-butylhydroperoxide</td>
</tr>
<tr>
<td>TBS</td>
<td>$t$-butyldimethylsilyl</td>
</tr>
<tr>
<td>Teoc</td>
<td>2-(trimethylsilyl)ethyloxycarbonyl</td>
</tr>
<tr>
<td>TES</td>
<td>triethyloxysilyl</td>
</tr>
<tr>
<td>Tf</td>
<td>trifluoromethanesulfonyl</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>THP</td>
<td>tetrahydropyranyl</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>TOCSY</td>
<td>total correlated spectroscopy</td>
</tr>
<tr>
<td>TPAP</td>
<td>tetra-$n$-propylammonium perruthenate</td>
</tr>
<tr>
<td>$p$-TsOH</td>
<td>$p$-toluenesulfonic acid</td>
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Chapter 1

Background of Azaspiracids

1-1. Introduction

Algal toxins enter the marine environment during blooms of particular naturally occurring marine algal species. Such blooms have been named as harmful algal blooms (HABs), toxic algal blooms and red tides. The occurrence of blooms of these toxic algae is natural. However, there are concerns that the increased frequency and magnitude of these events may be caused as a result of human activities that increase the supply of essential nutrients (such as nitrogen and phosphorus) to the marine environment. Algal toxins can produce a number of different poisoning syndromes, such as neurotoxic shellfish poisoning (NSP), paralytic shellfish poisoning (PSP), amnesic shellfish poisoning (ASP) and diarrhetic shellfish poisoning (DSP).¹

Neurotoxic shellfish poisoning (NSP) is caused by the brevetoxins (Figure 1) and related algal toxins. Nine analogues of this family have been discovered, which belong to one of two types of the structures shown in Figure 1. The symptoms of this intoxication include tingling and numbness of lips, tongue, throat and perioral area, muscular aches, gastrointestinal upset and dizziness.²
Figure 1. Neurotoxic Shellfish Poisoning (NSP) Toxins

Figure 2. Paralytic Shellfish Poisoning Toxins

Paralytic shellfish poisoning (PSP) is caused by a family of toxins known as saxitoxins (Figure 2). The consumption of contaminated mollusks caused poisoning symptoms such as aphasia, salivation, headache, thirst, nausea and vomiting. All saxitoxins bind to the surface of voltage-activated sodium channels in nerve cells and thereby stop signal transmission by interrupting the flow of Na$^+$ ions.$^3$
Amnesic shellfish poisoning (ASP) toxins were disclosed as the cause of the Prince Edward Island disease.\textsuperscript{4} Symptoms include nausea, vomiting, abdominal cramps, diarrhea, headache, anorexia, loss of balance, dizziness and memory loss, among which memory loss is heavily related to age. Through biological and chemical studies, domoic acid (Figure 3) was identified as the cause, which affects the nervous system and explains the memory loss symptom.\textsuperscript{4}

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{fig3}
\caption{Amnesic Shellfish Poisoning (ASP) Toxin}
\end{figure}

Diarrhetic shellfish poisoning (DSP) are caused by a series of polyether compounds (Figure 4), which consists of okadaic acid and related dinophysistoxins, pectenotoxins and yessotoxins. Symptoms of this class of intoxication include diarrhea, nausea, vomiting, abdominal pain and chills. Okadaic acid and dinophysistoxins have been demonstrated to have potent tumor-promoting activities.\textsuperscript{5, 6, 7}
Figure 4. Diarrhetic Shellfish Poisoning (DSP) Toxins
1-2. Discovery and Isolation of Azaspiracids

The story of azaspiracid-1 began in the Netherlands. In 1995, a food poisoning event occurred that caused at least eight people to become ill after they ate mussels (*Mytilus edulis*) cultivated at Killary Harbor, Ireland. Although the symptoms were very similar to diarrhetic shellfish poisoning (DSP), which is associated with okadaic acid (OA) and dinophysistoxins (DTXs), toxins in this class were detected in only tiny amounts. Later, mouse bioassays showed clear neurotoxic symptoms (respiratory difficulties, spasms, limb paralysis and death), which were totally different from the typical symptoms of the DSP bioassay. A subsequent investigation disclosed the fact that a new toxin class, the azaspiracid family, was involved in this event.

In 1998, 2 mg of a new marine toxin, named as azaspiracid-1, was isolated as a colorless, amorphous solid from 20 kg of mussel meat by Yasumoto, Satake and co-workers.

1-3. Structural Elucidation of Azaspiracid-1

At the time of the isolation of azaspiracid-1, Yasumoto et al. also proposed its original structure through mass spectrometry (HR-FAB MS, FAB MS/MS, CID MS/MS) and NMR (\(^1\)H, \(^{13}\)C, HSQC, HMBC, NOE, COSY, TOCSY, ROESY) spectroscopic studies. They named it azaspiracid because it has an unusual azaspiro ring system (azaspir-) and a carboxylic acid group (-acid).
Within its 40 carbon backbone skeleton, azaspiracid-1 features a unique trioxabisspiroketal fused to a tetrahydrofuran ring (ABCD rings), a piperidine-tetrahydrofuran spiroaminal system fused to a 2,9-dioxabicyclo[3.3.1]nonane system (FGHI rings), a connecting six-membered cyclic hemiketal bridge (E ring) and a γ,δ-unsaturated terminal carboxylic acid side chain. In total, there are 9 rings and 20 stereogenic centers in the molecule. The functionalization and relative stereochemistries within the ABCDE-ring domain and the FGHI-ring system were assigned individually by the application of NOE correlations and coupling constant analyses. However, the relative stereochemistry between these two major fragments was undetermined. Furthermore, the absolute stereochemistry of both pieces was also unknown.

One of the four originally proposed structures for azaspiracid-1 (1998) [incorrect]

Newly proposed structure for azaspiracid-1 (2004) [correct]

\textbf{Figure 5.} The Originally Proposed Structure and the Correct Structure.
The Nicolaou group claimed to have finished the first total synthesis of the proposed structure of azaspiracid-1 in 2003 and concluded that the originally proposed structure was wrong. The Nicolaou group’s plan for determining the correct structure of azaspiracid-1 was based on the degradation of the natural material into smaller pieces, which helped to narrow down the location of the structural discrepancy between the synthetic and naturally derived structures. They compared $^1$H NMR spectroscopic data of synthetic materials with samples derived from the natural product to confirm the relative stereochemistry, and they compared the optical rotation between synthetic products and the fragments derived from natural azaspiracid-1 to determine the absolute configuration. An independent analysis of the ROSY NMR spectrum of the ABCD bis-spiroketal domain of azaspiracid-1 provided the basis for a revised, and correct structure that was corroborated by synthesis in 2004. In the same year, Nicolaou et al. reported a revision of the initial structure (Figure 5) and assigned the correct structure of azaspiracid-1 as confirmed by total synthesis.

As shown in Figure 5, the major revisions of the originally proposed structure of azaspiracid-1 are in the A-ring and E-ring. In the revised structure of azaspiracid-1, the originally assigned absolute stereochemistry of the E-ring relative to that of the ABCD-ring system is inverted. The double bond in the A ring was relocated between C7 and C8 from between C8 and C9 was as originally proposed. In addition, the stereochemistry at C6, C10 and C13 were inverted. As originally proposed, the structure of this bis-spiroketal was thermodynamically unstable with only one anomeric effect at C10. In the corrected structure, the ABC-ring system of azaspiracid-1 benefits from a double
anomeric effect\textsuperscript{12} (right structure in Figure 6), which is thermodynamically favored. This revision led to remarkable changes in subsequent synthetic efforts.

![Figure 6. Different Configurations of the ABCD Bis-spiroketal](image)

1-4. Azaspiracid-1 and Its Analogues

After the first reported food poisoning associated with azaspiracid-1, it recurred in the Arranmore Island region of Donegal, Ireland in 1997 and also in some other European locations. Later, along with the isolation of azaspiracid-1 (11 mg) from 40 kg of mussel meat, several other closely related analogues were also identified, which include azaspiracid-2 (3 mg), azaspiracid-3 (0.6 mg), azaspiracid-4 (0.5 mg) and azaspiracid-6 (0.3 mg).\textsuperscript{13}
Up to now, there are over 30 analogues in the azaspiracid family, which are widespread around the world from western Europe to the east coast of Canada. As shown in Figure 7, the 12 most abundant analogues of azaspiracids are listed. Interestingly, they share the same structure in the FGHI ring system. The differences among them are the substituents at the C3, C8, C22 and C23 positions, which could be hydrogen, methyl group or hydroxyl group.

Figure 7. Azaspiracid-1 and Some of Its Analogues
1-5. Biogenetic Origin of Azaspiracids

The real origin of the neurotoxin azaspiracids was not clear for more than a decade until a recent study was reported.\textsuperscript{14} It was once believed that \textit{Protoperidinium crassipes} (Figure 8) was the origin of these new marine toxins. The James group collected substantial quantities of dinoflagellates from the southwest coast of Ireland.\textsuperscript{14} They detected azaspiracid-1, -2 and -3 in a sample and concluded that the \textit{P. crassipes}, previously regarded as harmless, was the origin. Because no other analogues were identified from the dinoflagellates, the James group speculated that other azaspiracid analogues were produced by bioconversion in shellfish.

\textbf{Figure 8.} Marine Dinoflagellate: \textit{Protoperidinium crassipes}\textsuperscript{14}

However, in a recent study by Dr. Urban Tillmann and Dr. Bernd Krock, they were able to show that \textit{P. crassipes} is only the vector, not the origin of the toxins.\textsuperscript{14} At the same time, they isolated another small alga from the North Sea off the Scottish east coast and named it as a new dinoflagellate species \textit{Azadinium spinosum} (Figure 9). They also
provided evidence that this alga is the true producer of azaspiracids in the laboratory.\textsuperscript{14} This dinoflagellate was proven to produce AZA-1, AZA-2 and an isomer of AZA-2 in unialgal and axenic culture.

\textbf{Figure 9.} The Origin of Azaspiracids: \textit{Azadinium spinosum}\textsuperscript{14}

\textbf{1-6. Biological Activities of Azaspiracids}

Shellfish intoxications belonging to the azaspiracid family were first identified in The Netherlands in 1995 after consumption of mussels cultivated in Killary Harbor, Ireland.\textsuperscript{8} The new toxic syndrome was called azaspiracid shellfish poisoning (AZP).\textsuperscript{6} In vivo studies of azaspiracids (AZAs) were carried out in mice to elucidate the pathological injuries. The toxin caused necrosis in the lamina propria of the small intestine and in lymphoid tissues such as thymus, spleen and the Peyer's patches.\textsuperscript{15} Additionally, a fatty change was observed in the liver. These injuries distinctly differed from those caused by the representative diarrhetic shellfish toxin okadaic acid.\textsuperscript{16}
The lowest-observable-adverse-effect-level (LOAEL) of AZAs has been estimated by Ofuji et al.\textsuperscript{12} In poisoning incidents, a level for total AZAs in raw mussel meat is 1.4 µg/g of meat, which corresponds to an intake of 140 to 420 µg AZAs per person at a consumption of 100 to 300 g per meal. A no-observable-adverse-effect-level (NOAEL) is usually estimated at one-tenth the LOAEL and is used as the maximum allowance levels in food. Thus, the NOAEL would be 14 to 42 µg per person at a consumption of 100 to 300 g shellfish meat/meal. As a consequence the maximum permitted concentration in shellfish meat would be 14 µg/100 g. A comparison of toxin limits in foods of the European Parliament 2004 shows the limits for marine toxins in foods are 800 µg/kg for Paralytic Shellfish Poison (PSP), 20 µg of domoic acid/kg for Amnesic Shellfish Poison (ASP), 160 µg of okadaic acid equivalents/kg for okadaic acid, dinophysitoxins and pectenotoxins together (DSP), 1 mg/kg for yessotoxins (DSP) and 160 µg/kg for AZAs (AZP).\textsuperscript{17}

Up to now, neither the cellular target nor the mechanism of its action of the AZAs is known. Previous studies of AZA-1 on neuroblastoma cells and human lymphocytes suggested that the toxin reduces cellular F-actin in a nonapoptotic manner.\textsuperscript{18} A high cytotoxicity of AZA-1 has been recently shown in several cell lines,\textsuperscript{19} and even more recently it has been described that this toxin inhibits the electrical activity of neuronal networks.\textsuperscript{20} However, the mechanisms of action of these toxins are still unclear.

The effect of azaspiracid-1 (AZA-1) on the cytosolic calcium concentration ([Ca\textsuperscript{2+}]\textsubscript{c}), intracellular pH (pH\textsubscript{i}) and neuron viability in neuronal cultures were also investigated.\textsuperscript{20} AZA-1 increased [Ca\textsuperscript{2+}]\textsubscript{c}, and lowered neuronal viability. The ent-ABCD-azaspiracid-1 caused a [Ca\textsuperscript{2+}]\textsubscript{c} increase similar to AZA-1 but with a higher cytotoxicity than AZA-1. The
compounds containing only the ABCD or the ABCDE ring domains increased [Ca$^{2+}$]$_c$ but
did not alter cell viability. The chemical structures containing only the FGHI ring domain
of AZA-1 did not modify the [Ca$^{2+}$]$_c$ or the cell viability. Therefore, the effect of AZA-1
on [Ca$^{2+}$]$_c$ depends on the presence of the ABCD or the ABCDE-ring structure, but the
complete chemical structure is needed to produce neurotoxic effects.$^{21}$
Chapter 2

Synthetic Efforts Towards Azaspiracid-1

2-1. Synthetic Efforts Towards the Originally Proposed Structure

2-1-1. Forsyth’s Approaches

In 2001, Amy Dounay finished the first attempted synthesis of the originally proposed structure of the ABCD domain of azaspiracid-1 (Scheme 1), which was described in one of the earliest publications on this topic.\textsuperscript{22} In the presence of NaHMDS, the primary hydroxy moiety of the tetraol 1 was converted into a triisopropylbenzenesulfonyl group, which was subsequently displaced by the adjacent secondary alkoxide to form epoxide 2 (Scheme 1). The in situ generated epoxide was then opened intramolecularly by the C16 alkoxide group to form the tetrahydrofuran 3. After a series of manipulations, enone 4 was synthesized and finally cyclized under acidic conditions giving the bis-spiroketal structure 5.
Scheme 1. Initial Synthetic Attempt at the Originally Proposed ABCD Domain

The bis-spiroketal 5 synthesized under acidic conditions was thermodynamically favored, benefitting from a double anomic stabilization effect. In contrast, the initially proposed natural product stereochemistry was thermodynamically unaccessible from 4 or 5 under a wide variety of Lewis and Brönsted acid conditions. These initial results lent skepticism to the validity of the originally proposed structure. This was also observed by the Nicolaou group in a subsequent publication.22

2-1-2 Nicolaou’s Synthesis

Nicolaou’s approach to access the contra-thermodynamic bis-spiroketal was to install a hydroxyl group on carbon 9, which directed hydrogen bonds with the oxygens on the B and C rings (Scheme 2). In this way, they overcame the double anomic effect and equilibrated 6 to the desired structure 7 with only one anomic effect. A 56% yield of the desired product 7 was isolated along with 44% of the starting material 6. Recycling
the starting material 6 raised the total yield of 7 to 80%. However, this necessitated subsequent removal of the hydroxyl group.

**Scheme 2.** Nicolaou’s Synthesis of the ABCD Domain with a Single Anomeric Effect

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**2-1-3 Nishiyawa’s Synthesis**

Later, the Nishiyama group utilized a cyclic sulfide to lock the configuration of their synthesized spiroketal structure of the BCD ring system without the stabilization of the anomeric effect (Scheme 3).\(^{22}\)

They utilized the sulfide so that the ketalization at C13 could only be formed from one side, which gave the non-anomeric effect stabilized product. After the reduction of the sulfide by Raney Ni, the desired ketal was produced.
Scheme 3. Nishiyawa’s Synthesis of the BCD System without Anomeric Effect

Stabilization

2-2. Synthetic Efforts Towards the Revised Structure of Azaspiracids

2-2-1 Nicolaou’s Total Synthesis of Azaspiracid-1

In 2003, after the Nicolaou group attempted to finish the synthesis of the proposed structure of azaspiracid-1, they declared that the originally proposed structure was wrong. In the following year, they determined the correct structure in collaboration with Satake by completing the first total synthesis of azaspiracid-1.
In Scheme 4 is their retrosynthesis. They disconnected the bond between C20 and C21 and the bond between C27 and C28. In the forward direction, they planned to use a dithiane coupling and a Stille coupling to combine the fragments sequentially.

They started the total synthesis with enantiomerically pure acetonide methyl ester 15, which was derived from L-malic acid as previously reported (Scheme 5). Ketophosphonate 16 was derived from the reaction of methyl ester 15 with the lithium anion resulting from combining dimethylmethylphosphonate and n-BuLi. In the presence of LiCl and i-Pr₂NEt, an excess of this ketophosphonate 16 reacted with enantiomerically pure aldehyde 17, to give α, β-unsaturated ketone 18. The desired secondary alcohol 31 was obtained from a chelation-controlled reduction of ketone 18 with LiAlH₄, facilitated by LiCl in ether at -100 °C with high selectivity. The acetonide group was then removed in the presence of acetic acid, providing triol 19. This compound was submitted to an
iodoetherification in the presence of NIS and NaHCO₃ in THF at 0 °C to construct the tetrahydrofuran 20 as a single isomer. Next, the primary hydroxyl group of diol 20 was selectively protected as a TBDPS ether and the remaining secondary alcohol was then protected as a TBS ether (21). The iodide in the tetrahydrofuran system 21 was reduced to an alkane with Raney nickel, followed by the removal of the benzyl protecting group by hydrogenation and oxidation of the resulting primary alcohol to aldehyde 22 with Dess-Martin periodinane. A Grignard reaction of aldehyde 22 with 3-butenyl magnesium bromide gave a secondary alcohol, which was then oxidized to ketone 23. The carbonyl group of 23 was protected as a ketal (24). The next three steps were protecting group transformations, in which the secondary TBS ether was switched for the sterically smaller TES ether 26. The double bond was oxidatively cleaved to aldehyde 27, which was then coupled with the anion of dithiane 28. A Dess-Martin oxidation of the product 29 provided ketone 30. In the presence of TMSOTf, cyclization of 30 occurred with removal of the acetonide to provide the ABCD-ring system 31 of azaspiracid-1. This primary alcohol was oxidized to aldehyde 32, followed by methylenation to alkene 33.
Scheme 5. Nicolaou’s Construction of the ABCD-Ring System of Azaspiracid-1
Scheme 6. Nicolaou’s Installation of the Side Chain upon the ABCD-Ring System

The side chain was then installed on the terminal olefin 33 by a cross metathesis with excess alkene 35 in the presence of Grubbs’ second generation catalyst 34\textsuperscript{24} (Scheme 6). The dithiane group was removed from 36 to produce ketone 37. However,
the conversion of ketone 37 into the corresponding enone 38 proved to be challenging. After a series of studies, a three-step protocol was found to be reliable during which 37 was first transformed into a TMS enol ether then reacted with PhSeCl and the resulting phenylseleno derivative finally oxidatively removed with NaIO₄, leading to the desired enone 38. The reduction of enone 38 furnished allylic alcohol 39, which was further converted into a methyl carbonate 40 and then deoxygenated to the desired product 41 in the presence of Pd₂dba₃·CHCl₃, n-Bu₃P and LiBH₄ in DME. The TBDPS protecting group was removed by TBAF to give primary alcohol 42. Sequential Swern and NaClO₂ oxidations of 42 generated carboxylic acid 43. Esterification with pentafluorophenol in the presence of DCC furnished activated ester 44, which was ready to couple with the E-ring dithiane fragment.

The dithiane anion, derived from 45 upon reaction with n-BuLi and n-Bu₂Mg, was added to activated ester 44 to give ketone 46 (Scheme 7). Following reduction of this ketone, the removal of the silyl groups with TBAF afforded tetraol 47. Two of the hydroxyl groups in tetraol 47 were first selectively protected as a diacetate 48, then the C25 alcohol was protected as a TBS ether (49). The dithiane on 49 was removed in the presence of PhI(OCOCF₃)₂. A Stille coupling was then carried out on this allylic acetate 50 with the FHI stannane 51 in the presence of Pd₂dba₃, LiCl and i-Pr₂NEt under heating (40 °C). Thus, the whole carbon backbone of azaspiracid-1 was established. At 0 °C, the TES group was selectively removed and the TBS group was left untouched by the action of TBAF. Ring I was then closed by an iodoetherification to give iodoether 64.
Scheme 7. Nicolaou’s Completion of the Total Synthesis of Azaspiracid-1

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The remaining iodide was reduced by \( n \)-Bu\(_3\)SnH in toluene in the presence of a catalytic amount of the radical initiator Et\(_3\)B. Before cleavage of the acetate by K\(_2\)CO\(_3\) in MeOH, the C20 hydroxyl group was protected as a TES ether (56). The obtained primary alcohol 57 was then oxidized to carboxylic acid 59 in a two-step sequence of Swern and NaClO\(_2\) oxidations. Finally, a global deprotection of carboxylic acid 59 completed the total synthesis of azaspiracid-1 (11). The number of the longest linear steps is 49 with a 0.028% overall yield.

2-2-2. Evans’ Total Synthesis of (+)-Azaspiracid-1

Recently, the Evans group published their work of the total synthesis of (+)-azaspiracid-1 60, which is the unnatural enantiomer of the natural product.\(^{25}\) In their retrosynthesis, they also cut the molecule at the C20 and C21 bond, as the Nicolaou group did, through a sulfone anion coupling in the forward direction (Scheme 8).

\[ \text{Scheme 8. Evans’ Retrosynthesis of (+)-Azaspiracid-1} \]
The synthesis of the A ring precursor started with a cross metathesis of alkene 63
and acrylate 64 with Grubbs-Hoveyda catalyst 65 (Scheme 9). The acetylene 67 derived
dianion was added to Weinreb amide 66 by a selective 1, 2-addition, affording enone 68.
The enantioselective reduction of ene-ynone 68 was carried out by a CBS reduction with
2 equiv of oxazaborolidone 69 to introduce the C6 stereocenter. Semihydrogenation of
alkyne 70 gave the corresponding alkene under Lindlar conditions. The hydroxyl group
was then protected as a TBS ether. Following the cleavage of the acetate moiety, the
resulting alcohol was oxidized to ketone 71 by a Parikh-Doering oxidation. The TBS
protecting group was removed by pyridine buffered HF-py. The resulting cyclic
intramolecular hemiketal was transformed into a mixed methyl ketal and the terminal
sulfide was then oxidized to the desired sulfone 72. The t-butyl ester was reduced and the
resulting alcohol was protected as its TIPS ether derivative, thus concluding the synthesis
of the AB-ring fragment 74.
Scheme 9. Evans’ Synthesis of the A Ring of (+)-Azaspiracid-1
The synthesis of the CD-ring fragment started with a bis(aquo)Cu$^{2+}$ complex (77) catalyzed glyoxylate-ene reaction to give $\alpha$-hydroxyl ester 78, which was converted into the corresponding Weinreb amide (Scheme 10). The hydroxyl group was then protected as PMB ether 79. Lithium-halogen exchange of iodide 80 was followed by the addition to Weinreb amide 79. The resulting ketone was reduced with lithium tri-sec-butyl{(hydrido)borate to afford as a single diastereomer alcohol 81. Ozonolysis cleaved the olefin in the presence of Sudan III dye as an indicator to avoid the oxidation of the PMB ether protecting group. Under acidic reaction conditions in methanol, a cyclic
mixed methyl ketal was formed. Subsequent reduction was carried out with high stereoselectivity, affording the desired trisubstituted tetrahydrofuran 82. The PMB group was switched to a TES protecting group in 2 steps, followed by the removal of the benzyl group in the presence of LIDBB. The resulting alcohol was then oxidized to aldehyde 83 by a Perikh-Doering oxidation.

Scheme 11. Evans’ Synthesis of the ABCD-Ring of (+)-Azaspiracid-1
With two pieces in hand, sulfone 74 was deprotonated by LDA and added to aldehyde 83 (Scheme 11). The resulting alcohol was then oxidized to provide ketone 84. The sulfone group was subsequently reductively removed, affording the corresponding ketone 85. The TES group was selectively removed at -20 °C in the presence of TBAF to produce cyclic hemi-ketal 86. The bis-spiroketal 87 was then constructed under acidic conditions at 0 °C. The TBDPS group was removed with TBAF in DMF and the resulting primary alcohol 88 was oxidized to afford aldehyde 61, which was ready to couple with the EFGHI fragment.
Scheme 12. Evans’ Synthesis of the EFGHI Domain of (+)-Azaspiracid-1

The FGHI linear precursor 89 (Scheme 12) was coupled with the E-ring fragment 90 through an aldol addition in the presence of Cy₂BCl (Scheme 13). The desired aldol product was then exposed to aqueous HF in acetonitrile to remove the lone TBS group. The desired FG bicyclic ketal was spontaneously formed. Next, the C26 hydroxyl group was oxidized to the corresponding ketone 92 with Dess-Martin periodinane. Subsequent oxidative removal of the PMB group and reduction of the terminal azide led to the spontaneous formation of the HI-spiroaminal 93, as a single diastereomer which was
thermodynamically favored. The free amine was then protected as its Teoc derivative. Application of the Tebbe reagent then converted the C26 ketone into an alkene, and subsequent oxidation of the sulfide with H₂O₂ and (NH₄)₆Mo₇O₂₄ afforded the final EFGHI coupling partner 62.

**Scheme 13.** Evans’ Completion of the Total Synthesis of (+)-Azaspiracid-1

In the final coupling stage, the EFGHI sulfone 62 was deprotonated by n-BuLi and the lithium anion was added to ABCD aldehyde 61 (Scheme 13). The reaction was quenched at -78 °C with pH 5 buffer. This coupling only gave a 50% overall yield for the combined two diastereomers in about equal amounts. The direct yield of the desired diastereomer 96 was 23%. The major product, undesired diastereomer 95 was obtained in 27% yield. Next, an oxidation-reduction protocol converted the undesired C20
stereocenter of 95 into the desired one of 96 in 35% yield. Thus, the desired product 96 was obtained in 33% combined yield from coupling partners 61 and 62, including the two-step inversion of configuration of C20 in the major undesired coupled product 95. Finally, global deprotection with TBAF removed the Teoc and TIPS protecting groups. The C1 primary alcohol was selectively oxidized to an aldehyde with Dess-Martin periodinane, which left the C21 secondary alcohol untouched. The last step was to oxidize the aldehyde to the corresponding carboxylic acid to finish the total synthesis of (+)-azaspiracid-1 (60). The total synthesis was finished in 26 longest linear steps with 2.7% overall yield.

2-2-3 Carter’s Synthetic Efforts towards the ABCDE Domain

The Carter group also put many efforts towards the synthesis of azaspiracid-1. They synthesized the ABCDE domain and the FGHI domain.26 Here, only the synthesis of the ABCDE fragment will be introduced.

They started their synthesis with the commercially available malic acid 97 (Scheme 14). After a known four-step sequence, the cis-\(\alpha,\beta\)-unsaturated ester 98 was produced. Subsequent reduction of the ester and conversion of the corresponding allylic alcohol led to allylic bromide 99. Following the coupling of allylic bromide 99 with deprotonated sulfone 100, the acetonide group was removed in the presence of HCl in acetonitrile.
Scheme 14. Carter’s Synthesis of the ABCDE Domain of Azaspiracid-1
The resulting diol was then sequentially protected as its TBDPS ether and TES ether derivative 101. In the next step, the sulfone group was converted in to the $\beta,\gamma$-unsaturated ketone 102. After selective removal of the TES group, methyl ketal 103 was constructed in the presence of PPTS in methanol. Following the oxidation of sulfide into sulfone 104, coupling of it and CD-aldehyde 105 was carried out and the resulting alcohol was oxidized into ketone 106. The carbon bearing the sulfone group was then reduced with Na/Hg amalgam. Cyclization of the bis-spiroketal took place in the presence of PPTS in THF/H$_2$O (4:1). The primary TBDPS was removed with TBAF and the resulting alcohol was reprotected as TBS ether 107. LIDBB removed the both benzyl groups and TPAP/NMO oxidized the corresponding diol to a five-member lactone, which was subsequently reduced to hemi-ketal 108. Wadsworth-Emmons coupling connected E-ring fragment 109 onto the ABCD bis-spiroketal domain 108. Under the reaction condition, intramolecular hetero-Michael addition afforded tetrahydrofuran 110 as a single diastereomer. Davis oxidation at C20 afforded secondary alcohol 111, yet with the undesired configuration. Next, a two-step protocol, conversion of alcohol into triflate and Mitsunobu reaction, converted the wrong stereocenter back to the desired one. Following cleavage of the primary TBS ether, selenation, oxidation/elimination, and a cross metathesis with 113 using Grubbs’ II catalyst afforded the ABCDE domain 114 with the C1-C5 side chain in place.
Chapter 3
Research Progress and Discussion

3-1. The Original Retrosynthesis of Azaspiracid-3

Azaspiracids have a unique structure and can cause acute human intoxication. As such, these compounds have been the foci of comprehensive studies, including numerous synthetic reports. The goals of our group include two major aspects: 1. to develop an efficient and flexible synthetic entry to the azaspiracids; 2. to make use of the synthesis for biological studies, such as making haptens of azaspiracids to develop antibodies that can be used for the detection of the natural products.

Like the Nicolaou group and the Evans group did, our original retrosynthetic plan (Scheme 15) was to form the C20 and C21 bond through a Stille coupling. We planned to form the C26-C27 bond with a Takai-Nozaki coupling to connect the E-ring with the FGHI-ring. The whole molecule was now broken into three major fragments: the ABCD domain acid chloride 116, E-ring stannane 117 and FGHI domain alkynyliodide 118. The author’s work has focused on the synthesis of the ABCD bis-spiroketal system. So the discussion of this will be emphasized. The ABCD-ring system was further disconnected between C12-C13, giving iodoalkyne 119 and aldehyde 120,
which could be connected again by a NHK coupling in the forward direction.

\[ \text{Scheme 15. Forsyth’s Original Retrosynthesis of Azaspiracid-3} \]

The synthesis of the A-ring iodide commenced with the bis-acetonide protection of D-mannitol (Scheme 16),\(^{30}\) which was followed by an oxidative cleavage with NaIO\(_4\). The resulting aldehyde 122 reacted with allyl Grignard in THF at 0 °C to provide the secondary alcohol 123. The free hydroxyl group was protected as a PMB ether (124). A hydroboration/oxidation was then carried out to produce the primary alcohol 125, which was oxidized to aldehyde 126. TMS acetylene was deprotonated with \(n\)-BuLi and added to aldehyde 126. The resulting propargyl alcohol 127 was then oxidized to ynone 128. In the presence of TsOH in methanol, the acetonide group was removed and the A-ring was cyclized to form a mixed methyl ketal 129. The primary alcohol was then protected as its benzoate ester derivative 130.

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Synthesis of CD-ring fragment started with Evans’ oxazolidinone 131 (Scheme 17). After being deprotonated by $n$-BuLi, it was coupled with propionyl chloride. The resulting intermediate 132 was reacted with trans-1,4-dibromo-2-butene by using NaHMDS as base. Enyne 134 was made from 133 by an attack of a cuprate acetylene nucleophile. The TMS group was then removed with PPTS neutralized TBAF. Lactone 136 was produced from enyne 135 by a Sharpless asymmetric dihydroxylation. One of
the generated hydroxyl groups spontaneously displaced the oxazolidinone to form the five-membered lactone. The remaining hydroxyl group was then protected as its THP acetal derivative 137. Lactone 137 was reduced with LiBH₄ in Et₂O into diol 138. The primary alcohol was protected as TBS ether 139 and the secondary hydroxyl group was left untouched. The alkyne of 139 was partially reduced to alkene 140 by using Lindlar catalyst, which was further poisoned with quinoline. The cobalt-catalyzed etherification in the next step gave tri-substituted tetrahydrofuran system 141,³⁴ the free primary hydroxyl group of which was protected as TBDPS ether 142. The TBS group was selectively removed by a catalytic amount of PPTS in a 5 : 1 ratio of CH₂Cl₂ and EtOH solvent mixture, affording alcohol 143.
Scheme 17. Synthesis of the CD-Ring Precursor
In the cobalt catalyzed cyclization reaction (Scheme 18), which was initially developed by Mukaiyama,\textsuperscript{34} the alkyl substituent blocked the $\alpha$-face, so the bulky cobalt catalyst could only chelate to the oxygen from the $\beta$-face. A migratory insertion formed the \textit{trans}-tetrahydrofuran D ring with an $\alpha$ C-Co bond, which was further oxidized into an alcohol to complete this oxyetherification process. The reaction required 30 mol\% of Co(modp)\textsubscript{2} (1-morpholinocarbamoyl-4,4-dimethyl-1,3-pentadione) catalyst.

\textbf{Scheme 18.} Mechanism of Cobalt Catalyzed Etherification

With the A-ring acetylene \textbf{130} and CD-ring fragment alcohol \textbf{143} in hand, coupling of the two pieces was next (Scheme 19). Alcohol \textbf{143} was oxidized into aldehyde \textbf{144}. TMS acetylene was converted into alkynyliodide \textbf{145}, which was then coupled with \textbf{144} through a Takai-Nozaki coupling\textsuperscript{29} to afford the whole carbon backbone \textbf{146} of the ABCD bis-spiroketal. After oxidation of propargyl alcohol \textbf{146} and complete reduction of the triple bond by hydrogenation, cyclization was carried out in the presence of TMSOTf at -78 °C, giving ABCD-ring system \textbf{149} of the azaspiracids devoid of the A-ring alkene.
Scheme 19. Synthesis of the ABCD Domain

Installation of the A-ring alkene was attempted earlier in the synthetic sequence to streamline the latter stages of the total synthesis effort (Scheme 20). A TBS ether was used to protect the primary alcohol of TMS alkyne 129. The PMB protecting group of the secondary alcohol was then removed with DDQ,\textsuperscript{35} and the resulting alcohol 151 was oxidized into ketone 152 with Dess-Martin periodinane. Ketone 152 was then deprotonated with KHMDS and converted into vinyl triflate 153, which was reduced with \textit{n}-Bu\textsubscript{3}SnH under Stille conditions.\textsuperscript{22} Finally, the TMS group was removed with K\textsubscript{2}CO\textsubscript{3} in MeOH.
Scheme 20. Installation of the A-Ring Double Bond

For the CD-ring fragment, the TBS and THP protecting groups of tetrahydrofuran 142 were removed simultaneously in the presence of PPTS in methanol (Scheme 21) to produce diol 156, which was then oxidized to lactone 157 with TPAP and NMO in CH₂Cl₂.²⁷

Scheme 21. Synthesis of the CD-Ring Lactone

For the coupling this time, we used a simple anion addition of alkyne 155 onto lactone 157 (Scheme 22). In this way, we could avoid the use of sensitive, expensive and
toxic CrCl$_2$, which was used in large excess in the previous NHK coupling. Terminal alkyne 155 was deprotonated with $n$-BuLi and coupled with lactone 157 to produce ynone 158. The secondary alcohol was protected as its TES ether derivative 159. The triple bond was then fully reduced into alkane with Stryker’s reagent.$^{36}$ Finally, bis-spiroketal 161 was formed in the presence of PPTS in methanol.

\[ \text{Scheme 22. Synthesis of the ABCD Bis-spiroketal With C7-C8 Double Bond} \]
3-2. Gold Catalyzed Strategy for the ABCD Domain

During our efforts towards the total synthesis of azaspiracids, we are more interested in using novel methods in our synthesis. Traditionally, to construct a spiroketal, a ketone is attacked by two hydroxyl groups as Nicolaou’s and Evans’ groups did in their syntheses. Yet in our new proposal, a triple bond was used as the oxidation state equivalent to a ketone (Scheme 23). We put a triple bond between C10 and C11, which would be activated by a metal catalyst, followed by the attacks of the oxygens on the chain to form the bis-spiroketal. This linear enyne was made from a Sonogashira coupling between allyl iodide 3 and alkyne 4.\textsuperscript{32} After the screen of different conditions, AuCl was chosen as the catalyst and performed very well in the synthesis.\textsuperscript{33}

\begin{center}
\textbf{Scheme 23.} Retrosynthesis of Gold Catalyzed ABCD Bis-spiroketal Formation
\end{center}
3-2-1 Background of Gold Catalysis of Alkyne Ketalization

Mercury(II)-catalyzed addition of alcohol to alkynes has been known for more than 80 years. Since mercury is toxic and not efficient enough, an alternative non-mercury catalyst has been long sought. Gold, which was previously thought to be catalytically inactive, was proven to be highly efficient in catalyzing the addition of alcohols to alkynes by Teles Group.\textsuperscript{37} In their examples (Scheme 24), cationic methyl(triphenylphosphane)gold(I) complex and methanesulfonic acid worked as precursors and generated the excellent catalyst for the addition reaction in situ. These catalysts are highly efficient (total turnover numbers of up to $10^5$ with turnover frequencies of up to 5400 h$^{-1}$). At the same, they are neither air nor moisture sensitive.

\textit{Scheme 24.} Gold Catalyzed the Addition of Alcohols to Alkynes
3-2-2 Gold Catalyzed Bis-spiroketalization

Inspired by the precedent work, we started our synthesis of A-ring allylic iodide from allylic alcohol 164, which was protected as PMB ether 165 (Scheme 25). Subsequent ozonolysis cleaved the double bond and provided α-hydroxyaldehyde 166. Then, a coupling of aldehyde 166 and TBS protected alkyne 167 afforded propargyl alcohol 168. Resulting alkyne 168 was partially reduced to the cis-alkene followed by a kinetic resolution giving the desired stereocenter on C6. The free secondary alcohol of allylic alcohol 169 was protected as its acetate derivative 170. The TBS protecting group was then removed with PPTS in methanol. Next, the primary free hydroxyl group was converted to allylic iodide 172.

Scheme 25. Synthesis of the A-ring Iodide
Scheme 26. Gold Catalyzed Synthesis of the ABCD Domain

For the other part, from lactone 157, an allenyl Grignard addition provided the alkyne, which was followed by a conversion to methyl mixed ketal 173 (Scheme 26). Next, alkyne 173 was coupled with allyl iodide 172 under Sonogashira coupling conditions, giving enyne 174. The acetate was removed with DIBAL and afforded allylic alcohol 175, which was ready to test our golden idea. In the next step, the bis-spiroketal was cyclized very successfully under the catalysis of AuCl in the presence of PPTS in methanol, producing the ABCD system (176) of azaspiracids.
The mechanism we proposed (Scheme 27) started with the coordination of the Au(I) with the hydroxyl group on C6 and activation of the triple bond. Then, the hydroxyl group and the gold ion added across the alkyne. Protio-deauration then led to an enol ether that upon acidification would form an oxocarbenium ion. The exo-oxygen of the mixed methyl ketal then added to the oxocarbenium carbon. Loss of the methyl group would result in the ABCD system. 39
3-3. Current Synthesis of Azaspiracid-3

3-3-1 Current Retrosynthesis of Azaspiracid-3

As mentioned before, we planned to use a Stille coupling to connect the whole backbone of azaspiracid-3. Yet after several different approaches, Stille coupling was not successful. It was difficult to convert the E-ring lactone into vinyl triflate or phosphate. Recently, a new retrosynthetic plan (Scheme 28) was proposed. This time we disconnected the molecule at the C21 and C22 bond, which will be connected through a Barbier reaction to close the E-ring in the forward direction. Then ester 177 would be broken into C1 to C21 ABCD acid 178 and C22 to C40 EFGHI alcohol 179.

Scheme 28. Current Retrosynthesis of Azaspiracid-3
3-3-2 Synthesis of the C13 to C21 Domain

We would like to apply gold chemistry in this new approach of the total synthesis as well. A similar approach was used here to synthesize C13 to C21 CD-ring fragment (Scheme 29).

PMB protected propargyl alcohol 180 was deprotonated, converted into a cuprate nucleophile and added onto the same previous precursor allylic bromide 133 (Scheme 28). Then a Sharpless asymmetric dihydroxylation was carried out on this enyne 181 and one of the resulting two hydroxyl groups displaced the oxazolidinone, affording the five-member lactone 182. During this synthetic route, previously used cobalt catalyzed etherification didn’t work for this internal alkene. So a Sharpless asymmetric epoxidation would be used instead. For the secondary alcohol of 182, A TES group was chosen as the protecting group to replace the THP group in the previous synthesis. Because the THP group showed a strong chelation with titanium catalyst in Sharpless epoxidation, the reaction was slow and the resulting epoxide won’t be opened in situ. After the TES protection, lactone 183 was reduced with LiBH₄. The primary hydroxyl group of the resulting diol 184 was selectively protected as its TBS ether 185. The triple bond of alkyne 185 was then partially reduced to the alkene under hydrogenation by further poisoned Lindlar catalyst. The PMB protecting group was removed with DDQ, affording allylic alcohol 187. Then Sharpless asymmetric epoxidation was carried out and the epoxide formed under the activation by titanium in solution was opened by the secondary hydroxyl group on the chain to close the D ring in situ, providing tri-substituted tetrahydrofuran 188.⁴⁰
Scheme 29. Synthesis of the C13 to C21 CD-Ring Precursor
The primary alcohol was then protected as its pivolate ester 189. The other hydroxyl group was then converted into its TIPS ether derivative 190. In the presence of PPTS in methanol, TBS and TES protecting groups was removed at the same time. Resulting diol 191 was oxidized with TPAP and NMO in CH₂Cl₂, affording a six-membered lactone 192. Following the addition of an allenyl Grignard reagent, mixed-methyl ketal 193 was produced in the presence of PPTS in methanol.

### 3-3-3 Future Work

The new CD-ring alkyne 193 would be coupled with allylic iodide 172 (Scheme 30). Acetate and pivolate would be reduced with DIBAL to produce diol 195. Then gold catalyzed bis-spiroketalization would be carried out. The resulting alcohol 196 would be reprotected as its pivolate derivative. The PMB protecting group would be removed and resulting alcohol would be oxidized and converted into alkene 198. Next, the tail would be installed by a cross metathesis to afford the ABCD domain 200.
Scheme 30. Future Synthesis of the ABCD (C-5 to C-21) Domain

3-3-4 Alternative Retrosynthesis

Another retrosynthesis was proposed as an alternative plan (Scheme 31). Hemiketal E-ring would be opened, giving a protected alcohol and ketone 201. This ketone would be the reduced product from ynone 202. A cuprate hydride would be used, as in our previous synthesis of the ABCD domain. Ynone 202 would be further broken into C1 to C21
aldehyde \textbf{203} and C22 to C40 iodo-alkyne \textbf{204}. NHK coupling would be used in the forward direction to couple these two pieces together.

\textbf{Scheme 31.} Alternative Retrosynthesis of Azaspiracid-3
Chapter 4

Research Summary

Documented here are several approaches to the synthesis of the ABCD bis-spiroketal domain of the azaspiracids, which include a cobalt catalyzed etherification and a novel gold catalyzed spiroketalization. By using an alkyne as a ketone equivalent, the gold catalyzed etherification provided an efficient way to construct spiroketals. This work will contribute to continuing efforts to develop total syntheses of the azaspiracids and their analogs. These efficient methods for the construction of oxygen-containing heterocycles should find broader applications in organic chemistry as well.
References


(17) Anderson, W. A.; Whelan, P.; Ryan, M.; McMahon, T.; James, K. J. *Food Safety Authority of Ireland*, **2001**.


Appendix A: Experimental Sections

**General:** All air and moisture sensitive reactions were carried out under argon atmosphere in pre-dried glasswares using standard syringes, cannula and septa techniques. Tetrahydrofuran, dichloromethane and diethyl ether were purified by the purification column system. Flash chromatography was performed using Silicycle Flash silica gel 60 (40 μm). NMR spectra were obtained in CDCl₃ and referenced to residual CHCl₃ at 7.27 ppm (¹H) and 77.0 ppm (¹³C). Optical rotations were obtained using a Perkin Elmer 241 polarimeter at sodium D line (589 nm) and were reported in concentrations (c=g/100mL) at 23 °C. Infrared (IR) spectra were obtained using a Perkin Elmer FT-IR Spectrum RXI spectrometer. High resolution mass spectral analysis (ESI) was performed on a Bruker Microtof mass spectrometer. Part of the experimental sections was collaborated with Dr. Yongfeng Li and is published on Li, Y.; Zhou, F.; Forsyth, C. J. Angew. Chem., Int. Ed. 2007, 46, 279 - 282. and Dr. Yongfeng Li’s dissertation.
(S)-4-benzyl-3-((R,E)-6-bromo-2-methyl-hex-4-enoyl)-oxazolidin-2-one (133)

To a stirred solution of (S)-4-benzyl-3-propionyl-oxazolidin-2-one (132) (7.0 g, 30 mmol) in THF (300 mL) at -78 ºC under Ar atmosphere was added NaHMDS (18 mL of 2 M solution in THF, 36 mmol). After stirring for 45 min at this temperature, 1,4-dibromobutene (9.6 g, 45 mmol) was added in one portion as a solid. The reaction mixture was stirred for 2 h before it was allowed to warm up to -40 ºC. After overnight, the reaction mixture was quenched by saturated NH₄Cl aqueous solution (100 mL). The solution mixture was separated and the aqueous layer was abstracted by ethyl ether (3 x 50 mL). The combined organic layer was dried over Na₂SO₄, filtrated and concentrated by rotary evaporation. The crude mixture was purified by flash chromatography (hexanes : ethyl acetate, 3 : 1, v/v) to yield (S)-4-benzyl-3-((R,E)-6-bromo-2-methyl-hex-4-enoyl)-oxazolidin-2-one (133) (7.1 g, 65%) as a colorless oil.

HRMS-ESI (m/z) [M+Na⁺]: calc’d: 388.0540, found: 390.0524; ¹H NMR(500 MHz, CDCl₃, δ) 7.20-7.36 (m, 5 H), 5.77-5.81 (m, 2 H), 4.66-4.72 (m, 1 H), 4.19 (d, 1 H), 4.18 (d, 1 H), 3.94 (d, 2 H), 3.27-3.33 (dd, 1 H), 2.98 (m, 1 H), 2.69-2.74 (dd, 1 H), 2.49-2.55 (m, 1 H), 2.22-2.27 (m, 1 H), 1.20 (d, 3 H); ¹³C NMR(125 MHz, CDCl₃, δ) 176.6, 153.1, 135.4, 132.7, 129.4, 129.0, 127.3, 66.1, 55.4, 38.1, 34.2, 33.1, 32.8, 16.6; IR (neat) ν = 2977.1, 2936.7, 2356.7, 1778.0, 1699.0, 1455.6, 1386.1, 1351.4, 1240.4, 1208.1, 1106.4, 970.2, 762.8, 749.0, 703.1 cm⁻¹; [α]D²⁵ = 33.2 (c 1.05, CHCl₃); Rₜ = 0.59 (hexane : ethyl acetate, 3 : 1, v/v).
(S)-4-benzyl-3-((R,E)-2-methylnon-4-en-7-ynoyloxazolidin-2-one (135)

To a stirred solution of TMS acetylene (0.63 mL, 4.30 mmol) in THF (15 mL) at -78 ºC under Ar atmosphere, was added \( n \)-BuLi (1.70 mL of 2.5M solution in hexanes, 4.25 mmol). After the reaction mixture was stirred for 30 min, CuI (0.82 g, 4.30 mmol) was added and the suspension was then allowed to warm up to rt. Next, allylic bromide (133) (1.50 g, 4.10 mmol) in THF was added via cannula. The reaction was stirred for 3 h and quenched by saturated NH\(_4\)Cl aqueous solution (10 mL). The resulting solution was filtrated through a plug of celite. The solution mixture was separated and the aqueous layer was abstracted by ethyl ether (3 x 10 mL). The combined organic layer was dried over MgSO\(_4\), filtrated and concentrated by rotary evaporation to yield (S)-4-benzyl-3-((R,E)-2-methyl-8-trimethylsilanyl-oct-4-en-7-ynoyloxazolidin-2-one (134) as a yellowish oil.

The crude (S)-4-benzyl-3-((R,E)-2-methyl-8-trimethylsilanyl-oct-4-en-7-ynoyloxazolidin-2-one (134) was dissolved in THF (20 mL). A p-TSOH (404 mg, 2.35 mmol) neutralized TBAF (4.7 mL of 1 M solution in THF, 4.7 mmol) was added. After stirring for 1 h, the solution was diluted with Et2O (20 mL), washed with water (10 mL) and saturated aqueous NaCl (10 mL). The organic phase was dried over Na2SO4, filtrated and concentrated by rotary evaporation. The crude product was purified by flash chromatography (hexanes : ethyl acetate, 5 : 1, v/v) to yield (S)-4-benzyl-3-((R,E)-2-methylnon-4-en-7-ynoyloxazolidin-2-one (135)
HRMS-ESI (m/z) [M+Na⁺]: calc’d: 334.1419, found: 334.1444; ¹H NMR(500 MHz, CDCl₃, δ) 7.20-7.36 (m, 5 H), 5.72-5.78 (ddd, 1 H), 5.50-5.56 (ddd, 1 H), 4.66-4.73 (m, 1 H), 3.89 (m, 1 H), 3.31 (ddd, 1 H), 2.94 (m, 1 H), 2.75 (ddd, 1 H), 2.53 (ddd, 1 H), 2.26 (ddd, 1 H), 2.04 (s, 1 H), 1.19 (d, 3 H); ¹³C NMR(125 MHz, CDCl₃, δ) 176.5, 153.1, 135.4, 129.5, 129.4, 129.0, 128.9, 127.3, 126.3, 81.6, 70.3, 66.0, 57.3, 55.4, 55.3, 38.1, 37.5, 36.5, 21.6, 16.6; IR (neat) ν = 3293.3, 2977.4, 2878.2, 1782.1, 1699.4, 1455.2, 1350.4, 1289.1, 972.4 cm⁻¹; [α]D²⁵ = -5.9 (c 2.32, CHCl₃); Rf = 0.61 (hexane : ethyl acetate, 3 : 1, v/v).
(3R, 5R)-5-((R)-1-hydroxybut-3-ynyl)-3-methylidencyclopentanone-2(3H)-one (136)

The (S)-4-benzyl-3-((R,E)-2-methylnon-4-en-7-ynoyloxazolidin-2-one (135) (5.4 g, 17.5 mmol) was dissolved in a mixed solvent of 100 mL t-BuOH and 100 mL water, followed by the addition of AD-mix-β (15.01 g) and MeNH$_2$SO$_2$ (0.884 g, 9.29 mmol). The reaction mixture was then stirred for overnight. The reaction was quenched by 1M Na$_2$SO$_3$ aqueous solution (20 mL). The mixture was separated and the aqueous layer was abstracted by ethyl ether (3 x 30 mL). The combined organic layer was dried over Na$_2$SO$_4$, filtrated and concentrated. The crude product was purified by flash chromatography (hexanes : ethyl acetate, 3 : 1, v/v) to give (3R,5R)-5-((R)-1-hydroxy-3-ynyl)-3-methylidencyclopentanone-2(3H)-one (136) (2.34 g, 7.35 mmol, 79%) as a colorless oil.

$^1$H NMR (500 MHz, CDCl$_3$, δ) 4.50 (ddd, 1 H), 3.70 (ddd, 1 H), 3.15-3.16 (d, 1 H), 2.65-2.72 (m, 1 H), 2.50 (dd, 2 H), 2.37 (ddd, 1 H), 2.03 (t, 1 H), 1.83 (dd, 1 H), 1.23 (d, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$, δ) 179.3, 79.2, 78.5, 71.1, 70.8, 35.6, 32.3, 23.6, 15.0; IR (neat) ν = 3436.1, 3288.0, 2919.1, 2350.0, 2112.3, 1763.3, 1172.4, 1031.2, 945.0 cm$^{-1}$; $[\alpha]_D^{25} = -29.9$ (c 1.41, CHCl$_3$); $R_f = 0.30$ (hexane : ethyl acetate, 3 : 1, v/v).
To a solution of (3R, 5R)-5-((R)-1-hydroxybut-3-ynyl)-3-methylidihydrofuran-2(3H)-one (136) (2.3 g, 13.5 mmol) in CH₂Cl₂ (70 mL), was added pyridinium toluenesulfonate (340 mg, 1.35 mmol) and 3,4-dihydro-2H-pyran (45.4, 54 mmol) sequentially. The reaction mixture was stirred for 30 min at rt. The reaction was by saturated Na₂CO₃ aqueous solution (10 mL). The mixture was separated and the aqueous layer was abstracted by ethyl ether (3 x 30 mL). The combined organic layer was dried over Na₂SO₄, filtrated and concentrated. The crude product was purified by flash chromatography (hexanes : ethyl acetate, 3 : 1, v/v) to give (3R,5R)-3-methyl-5-((R)-1-(tetrahydro-2H-pyran-2-yloxy)but-3-ynyl)-dihydrofuran-2(3H)-one (137) (2.7 g, 1.04 mmol, 78%).

HRMS-ESI (m/z) [M+Na⁺]: calc’d: 275.1259, found: 275.1253; ¹H NMR(500 MHz, CDCl₃, δ) 4.76 (m, 1 H), 4.64 (m, 1 H), 3.88 (m, 1 H), 3.49 (m, 1 H), 2.00 (m, 1 H), 1.27 (m 3 H), partial; ¹³C NMR(125 MHz, CDCl₃, δ) 179.2, 179.0, 101.3, 100.9, 79.0, 78.1, 73.1, 66.3, 66.2, 62.8, 62.7, 35.4, 32.8, 32.7, 31.0, 30.7, 25.4, 22.1, 20.5, 20.4, 16.5; IR (neat) ν = 3272.0, 2942.1, 2878.3, 1767.3, 1447.2, 1182.0, 1045.3 cm⁻¹; [α]D²⁵ = -13.8 (c 1.56, CHCl₃); Rf = 0.31 (hexane : ethyl acetate, 3 : 1, v/v).
(2R,4R,5R)-2-methyl-5-(tetrahydro-2H-pyran-2-yloxy)oct-7-yn-1,4-diol (138)

2 M LiBH₄ THF solution (15 mL, 30 mmol) was added to the solution of (3R,5R)-3-methyl-5-((R)-1-(tetrahydro-2H-pyran-2-yloxy)but-3-ynyl)-dihydrofuran-2(3H)-one (137) (3.7 g, 15 mmol) in Et₂O (75 mL), which was followed by the addition of water (0.54 mL, 30 mmol). The reaction was stirred for 30 min and then quenched by saturated NH₄Cl aqueous solution (10 mL). The mixture was separated and the aqueous layer was abstracted by ethyl acetate (3 x 30 mL). The combined organic layer was dried over Na₂SO₄, filtrated and concentrated. The crude product was used directly for the next step.
(2R,4R,5R)-1-(t-butyldimethylsilyloxy)-2-methyl-5-(tetrahydro-2H-pyran-2-yloxy)oct-7-yne-4-ol (139)

Imidazole (1.33 g, 20 mmol) was added to the solution of (2R,4R,5R)-2-methyl-5-(tetrahydro-2H-pyran-2-yloxy)oct-7-yne-1,4-diol (138) in CH₂Cl₂ (75 mL). TBSCl (2.48 g, 16.5 mmol) was added sequentially. The reaction was stirred for 30 min and quenched by saturated NH₄Cl aqueous solution (10 mL). The mixture was separated and the aqueous layer was abstracted by ethyl ether (3 x 30 mL). The combined organic layer was dried over Na₂SO₄, filtrated and concentrated. The crude product was purified by flash chromatography (hexanes : ethyl acetate, 5 : 1, v/v) to give (2R,4R,5R)-1-(t-butyldimethylsilyloxy)-2-methyl-5-(tetrahydro-2H-pyran-2-yloxy)oct-7-yne-4-ol (139) (4.05 g, 11 mmol, 73% 2 steps) as a colorless oil.

HRMS-ESI (m/z) [M+Na⁺]: calc’d: 393.2437, found: 393.2435; ¹H NMR(500 MHz, CDCl₃, δ) 4.79 (m, 0.5 H), 4.64 (m, 0.5 H), 0.91 (s, 9 H), 0.01 (s, 6 H), partial; ¹³C NMR(125 MHz, CDCl₃, δ) 100.7, 99.57, 98.4, 81.3, 81.1, 80.5, 80.1, 70.6, 69.9, 69.7, 69.1, 68.9, 37.6, 36.7, 32.7, 32.5, 31.6, 31.0, 30.9, 25.9, 25.3, 25.2, 22.6, 21.9, 20.7, 20.6, 19.8, 18.3, 16.7, 16.5, 14.1, -5.4; IR (neat) ν = 3500.2, 3313.1, 2951.3, 2389.9, 2120.2, 1471.3, 1256.0, 1087.3, 1034.2, 838.0, 776.1 cm⁻¹; [α]₀²⁵ = -25.4 (c 0.72, CHCl₃); Rᵣ = 0.62 (hexane : ethyl acetate, 3 : 1, v/v).
Lindlar catalyst (150 mg) and quinoline (22.5 μL) was added to the solution of (2R,4R,5R)-1-(t-butyldimethylsilyloxy)-2-methyl-5-(tetrahydro-2H-pyran-2-yloxy)oct-7-yn-4-ol (139) (500 mg, 1.4 mmol) in benzene (15 mL). The reaction flask was flushed with hydrogen gas three times and reaction mixture was stirred vigorously under hydrogen atmosphere for 20 min. The reaction mixture was filtered through celite. The crude product was purified by flash chromatography (hexanes : ethyl acetate, 5 : 1, v/v) to give (2R, 4R, 6R)-1-(t-butyldimethylsilyloxy)-2-methyl-5-(tetrahydro-2H-pyran-2-yloxy)oct-7-en-4-ol (140) (495 mg 99%) as a colorless oil.

HRMS-ESI (m/z) [M+Na⁺]: calc’d: 395.2594, found: 295.2576; ¹H NMR(500 MHz, CDCl₃, δ) 5.91 (m, 1 H), 5.10 (m, 2 H), 4.68 (m, 0.5 H), 4.53 (m, 0.5 H), 3.99 (m, 1 H), 3.62 (m, 1H), 0.91 (s, 9 H), 0.11 (s, 6 H), partial; ¹³C NMR(125 MHz, CDCl₃, δ) 134.6, 117.3, 111.8, 110.4, 83.5, 73.2, 69.2, 65.0, 36.7, 35.6, 33.4, 31.5, 25.9, 25.2, 21.3, 16.3, -5.4; IR (neat) ν = 3490.0, 2930.1, 2856.0, 1641.2, 1256.4, 1078.0, 1031.2, 837.3, 776.1 cm⁻¹; [α]D²⁵ = -20.7 (c 0.54, CHCl₃); R₇ = 0.64 (hexane : ethyl acetate, 3 : 1, v/v).
A solution of (2R, 4R, 6R)-1-(tert-butyldimethylsilyloxy)-2-methyl-5-(tetrahydro-2H-pyran-2-yl)oct-7-en-4-ol (140) (840 mg, 2.3 mmol), Co(modp)$_2$ (244 mg, 0.7 mmol), 4 Å molecular sieves (1 g) and TBHP (5.0 – 6.0 M in decane, 0.84 mL, 4.6 mmol) in isopropanol (23 mL) under O$_2$ atmosphere was heated to 60 ºC and stirred for 6 h. The reaction mixture was then cooled down to rt, filtrated through Celite and concentrated. The crude product was purified by flash chromatography (hexanes : ethyl acetate, 3 : 1, v/v) to give (2S, 4R, 5R)-5-((R)-3-((tert-butyldimethylsilyloxy)-2-methylpropyl)-4-(tetrahydro-2H-pyran-2-yl)tetrahydrofuran-2-yl)methanol (141) (201 mg, 1.7 mmol, 72%) as a colorless oil.

HRMS-ESI (m/z) [M+Na$^+$]: calc’d: 411.2543, found: 411.2550; $^1$H NMR(500 MHz, CDCl$_3$, $\delta$) 4.74 (m, 0.5), 4.65 (m, 0.5 H), 0.91 (s, 9 H), 0.11 (s, 6H), partial; $^{13}$C NMR(125 MHz, CDCl$_3$, $\delta$) 100.2, 95.0, 79.8, 75.5, 68.7, 64.7, 62.6, 61.7, 35.2, 32.7, 32.6, 31.4, 30.6, 26.9, 25.7, 25.3, 22.5, 19.4, 18.9, 16.7, 16.5, 13.9, -5.6; IR (neat) $\nu$ = 3490.3, 2928.0, 2855.1, 1471.3, 1257.2, 1025.0, 837.0, 775.0 cm$^{-1}$; $\alpha_D^{25}$ = -84.4 (c 0.48, CHCl$_3$); $R_f$ = 0.20 (hexane : ethyl acetate, 3 : 1, v/v).
To the solution of ((2S, 4R, 5R)-5-((R)-3-((tert-butyl(dimethyl)silyloxy)-2-methylpropyl)-4-(tetrahydro-2H-pyran-2-yloxy)-tetrahydrofuran-2-yl)methanol (141) (300 mg, 0.77 mmol) in CH2Cl2 (4 mL) was added TBDPSCl (0.22, 0.85 mmol) and imidazole (74 mg, 1.1 mmol). The reaction was stirred for 30 min and then quenched by saturated NH4Cl aqueous solution (3 mL). The mixture was separated and the aqueous layer was abstracted by ethyl ether (3 x 5 mL). The combined organic layer was dried over Na2SO4, filtrated and concentrated. The crude product was purified by flash chromatography (hexanes : ethyl acetate, 10 : 1, v/v) to give t-butyl-(((2S,4R,5R)-5-((R)-3-((tert-butyl(dimethyl)silyloxy)-2-methylpropyl)-4-(tetrahydro-2H-pyran-2-yloxy)-tetrahydrofuran-2-yl)methoxydiphenylsilane (142) (371 mg, 0.59 mmol, 77%) as a colorless oil.

HRMS-ESI (m/z) [M+Na+]: calcd: 649.3720, found: 649.3715. 1H NMR(500 MHz, CDCl3, δ) 7.75 (m, 4 H), 7.42 (m, 6 H), 4.80 (m, 0.5 H), 4.67 (m, 0.5 H), 1.16 (s, 9 H), 0.91 (s, 9 H), 0.12 (s, 6 H), partial; 13C NMR(125 MHz, CDCl3, δ) 135.6, 134.7, 129.5, 127.6, 100.2, 80.2, 799.9, 77.1, 75.8, 68.8, 66.2, 62.5, 61.5, 35.6, 34.5, 33.0, 32.8, 30.6, 26.6, 26.4, 25.8, 25.4, 25.3, 19.4, 19.1 18.8, 16.6, 16.4, -5.5; IR (neat) ν =2955, 2857, 2367, 2340, 1471, 1428, 113, 1024.3, 821, 739, 701, 628 cm⁻¹; [α]D 25 = 16.1 (c 0.46, CHCl3); Rf = 0.75 (hexane : ethyl acetate, 5 : 1, v/v).
(2R, 3R, 5S)-5-((t-butyldiphenylsilyloxy)methyl)-2-((R)-3-hydroxy-2-methylpropyl)-tetrahydrofuran-3-ol (156)

To a solution of t-buty1-(((2S,4R,5R)-5-((R)-3-((t-butyldimethylsilyloxy)-2-methylpropyl)-4-(tetrahydro-2H-pyran-2-yloxy)-tetrahydrofuran-2-yl)methoxydiphenylsilane (142) (400 mg, 0.64 mmol) in methanol (6 mL) was added PPTS (16 mg, 0.064 mmol). The reaction mixture was stirred at rt overnight. Solvent was removed by rotary evaporation. The crude product was purified by chromatography to yield (2R, 3R, 5S)-5-((t-butyldiphenylsilyloxy)methyl)-2-((R)-3-hydroxy-2-methylpropyl)-tetrahydrofuran-3-ol (156) (243 mg, 0.57 mmol, 89%) as a white crystal.

HRMS-ESI (m/z) [M+Na⁺]: calc’d: 451.2282, found: 451.2282; ¹H NMR(500 MHz, CDCl₃, δ) 7.71 (m, 4 H), 7.44 (m, 6 H), 4.40 (m, 1 H), 4.30 (t, 1 H), 4.05 (dt, 1 H), 3.78 (dd, 1 H), 3.65 (dd, 1 H), 3.48 (dd, 1 H), 2.19 (m, 1 H), 2.05 (dd, 1 H), 1.90 (m, 1 H), 1.67 (t, 1 H), 1.07 (s, 9 H), 0.9 (d, 3 H); ¹³C NMR(125 MHz, CDCl₃, δ) 135.5, 133.5, 129.6, 127.6, 81.5, 77.5, 74.4, 68.2, 65.8, 36.9, 34.5, 34.2, 26.6, 19.0, 17.9; IR (neat) ν = 3385, 3072, 3050, 2957, 2931, 2858, 1713, 1472, 1428, 1113, 823, 702 cm⁻¹; [α]D²⁵ = -2.0 (c 0.50, CHCl₃); Rf = 0.23 (diethyl ether).
To a solution of (2R, 3R, 5S)-5-((t-butyldiphenylsilyloxy)methyl)-2-((R)-3-hydroxy-2-methylpropyl)-tetrahydrofuran-3-ol (156) (250 mg, 0.58 mmol) in CH₂Cl₂ (6 mL) was added TPAP (20 mg, 0.058 mmol) and NMO (204 mg, 1.74 mmol). The reaction mixture was stirred for 2 h and then filtrated through a plug of celite. The solvent was removed by rotary evaporation. The crude product was purified by flash chromatography (hexanes : ethyl acetate, 5 : 1, v/v) to yield (2S, 3aR, 6R, 7aR)-2-((t-butyldiphenylsilyloxy)methyl)-6-methyl-tetrahydro-2H-furo[3,2-b]pyran-5(6H)-one (157) (187 mg, 0.44 mmol, 75%) as a colorless oil.

HRMS-ESI (m/z) [M+Na⁺]: calc’d: 447.1968, found: 447.1954; ¹H NMR(500 MHz, CDCl₃, δ) 7.68 (m, 4 H), 7.41 (m, 6 H), 5.04 (m, 1 H), 4.35 (m, 2 H), 3.83 (dd, 1 H), 3.65 (dd, H), 2.79 (m, 1 H), 2.36 (m, 1 H), 2.29 (m, 1 H, 1.81 (m, 1 H), 1.29 (d, 3 H), 1.07 (s, 9 H); ¹³C NMR(125 MHz, CDCl₃, δ) 174.0, 133.3, 129.9, 127.8, 83.5, 79.0, 74.6, 66.0, 36.6, 32.2, 31.0, 29.5, 26.9, 16.0; IR (neat) ν = 3385, 3072, 3050, 2957, 2931, 2858, 1713, 1472, 1428, 1113, 823, 702 cm⁻¹; [α]₀²⁵ = -14.2 (c 0.74, CHCl₃); Rₚ = 0.45 (hexanes : ethyl acetate, 5 : 1, v/v).
To a solution of TBS propargyl ether (167) (3 g, 17.6 mmol) in THF (60 mL) at -78 °C was added n-BuLi (7 mL, 2.5 M solution in hexanes, 17.6 mmol). The resulting mixture was stirred for 30 min under Ar atmosphere. Then (4-methoxy-benzyloxy)-acetaldehyde (166) (2.1 g, 11.7 mmol) in THF (30 mL) was added via cannula. The reaction was stirred for another 30 min and quenched by saturated aqueous NH₄Cl (30 mL). The mixture was separated and the aqueous layer was abstracted by ethyl ether (3 x 30 mL). The combined organic layer was dried over Na₂SO₄, filtrated and concentrated. The crude product was dissolved in methanol (5 mL) and PPTS (111 mg, 0.47 mmol) was added. After stirring for 1 h, solvent was removed by rotary evaporation. The crude product was purified by flash chromatography (hexanes : ethyl acetate, 15 : 1, v/v) to yield 5-(t-butyldimethylsilyloxy)-1-(4-methoxybenzyloxy)pent-3-yn-2-ol (168) (3.5 g, 9.9 mmol, 85%) as a colorless oil.

HRMS-ESI (m/z) [M+Na⁺]: calc’d: 373.1811, found: 373.1829; ¹H NMR(500 MHz, CDCl₃, δ) 7.27 (d, 2 H), 6.90 (d, 2 H), 4.57 (m, 1 H), 4.54 (d, 2 H), 3.81 (s, 3 H), 3.62 (d, 1 H), 3.53 (dd, 1 H), 0.90 (s, 9 H), 0.11 (s, 6 H); ¹³C NMR(125 MHz, CDCl₃, δ) 159.4, 129.7, 113.9, 84.2, 82.6, 77.1, 61.7, 55.3, 51.7, 25.8, 18.3, -5.1; IR (neat) ν = 3490, 2954, 2929, 2858, 2363, 2343, 1613, 1514, 1251, 1086, 836, 603 cm⁻¹; Rf = 0.44 (hexanes : ethyl acetate, 3 : 1, v/v).
(S, Z)-5-(t-butyldimethylsilyloxy)-1-(4-methoxybenzyloxy)pent-3-en-2-ol (170)

Lindlar catalyst (300 mg) and quinoline (45 μL) was added to the solution of 5-(t-butyldimethylsilyloxy)-1-(4-methoxybenzyloxy)pent-3-yn-2-ol (168) in benzene. The reaction flask was flushed with hydrogen gas three times and reaction mixture was stirred vigorously under hydrogen atmosphere for 20 min. The reaction mixture was filtered through celite. The crude product was directly used for the next step.

(+)-Diisopropyl-L-tartrate (765 mg, 3.43 mmol) was added to the solution of titanium(IV) isopropoxide (0.83 mL, 2.86 mmol) in CH₂Cl₂ (2 mL) at -20 ºC and stirred for 20 min. A solution of (Z)-5-(t-butyldimethylsilyloxy)-1-(4-methoxybenzyloxy)pent-3-en-2-ol (170) (1.00g, 2.86 mmol) in CH₂Cl₂ (15 mL) was added into the reaction mixture by cannula. After another 20 min, TBHP (5.0 – 6.0 M in decane, 0.52 mL) was then added at -20 ºC. The reaction was stirred at -20 ºC for 36 h. Following the addition of celite to the reaction mixture, 30% NaOH in saturated NaCl aqueous solution (15 mL) was added at 0 ºC. The mixture was stirred for 2 h and filtered through celite. The mixture was separated and the aqueous layer was abstracted by ethyl acetate (3 x 10 mL). The combined organic layer was dried over Na₂SO₄, filtrated and concentrated. The crude product was purified by flash chromatography (hexanes : ethyl acetate, 3 : 1, v/v) to (S, Z)-5-(t-butyldimethylsilyloxy)-1-(4-methoxybenzyloxy)pent-3-en-2-ol (170) (0.39 g, 0.39 mmol, 39% 2 steps, 98.5% ee by chiral HPLC) as a colorless oil.

HRMS-ESI (m/z) [M+Na⁺]: calc’d: 375.1968, found: 375.1979; ¹H NMR(500 MHz, CDCl₃, δ): 7.26 (d, 2 H), 6.89 (d, 2 H), 5.69 (m, 1 H), 3.36 (dd, 1 H), 0.90 (s, 9 H), 0.07 (s, 6 H); ¹³C NMR(125 MHz, CDCl₃, δ): 159.4, 133.02, 129.9, 129.5, 129.1, 113.9, 73.6,
73.1, 67.2, 59.7, 55.3, 26.0, 18.3, -5.1; IR (neat) ν = 3490, 3020, 2954, 2929, 2858, 2360, 2343, 1613, 1514, 1471, 1442, 1250, 1089, 836, 776, 601 cm⁻¹; [α]D²⁵ = -28.6 (c 0.45, CHCl₃); Rf = 0.37 (hexanes : ethyl acetate, 3 : 1, v/v).
To a solution of (S, Z)-5-(t-butyldimethylsilyloxy)-1-(4-methoxybenzyloxy)pent-3-en-2-ol (170) (500 mg, 1.43 mmol) in CH$_2$Cl$_2$ (7 mL) was added pyridine (0.58 mL, 7.15 mmol) and AcCl (0.51 mL, 7.15 mmol) sequentially. The resulting mixture was stirred for 30 min under Ar atmosphere and then quenched by saturated aqueous Na$_2$CO$_3$ solution (10 mL). The mixture was separated and the aqueous layer was abstracted by ethyl ether (3 x 10 mL). The combined organic layer was dried over Na$_2$SO$_4$, filtrated and concentrated. The crude product was purified by flash chromatography (hexanes : ethyl acetate, 10 : 1, v/v) to yield (S, Z)-5-(t-butyldimethylsilyloxy)-1-(4-methoxybenzyloxy)pent-3-en-2-yl acetate (171) (0.532 g, 1.36 mmol, 95%) as a colorless oil.

HRMS-ESI (m/z) [M+Na$^+$]: calc’d: 375.1968, found: 375.1979; $^1$H NMR(500 MHz, CDCl$_3$, $\delta$) 7.26 (d, 2 H), 6.88 (d, 2 H), 5.71 (m, 2 H), 5.39 (m, 1 H), 4.49 (dd, 2 H), 4.34 (ddd, 1 H), 4.28 (ddd, 1 H), 3.80 (s, 3 H), 3.54 (dd, 1 H), 3.48 (dd, 1 H), 2.07 (s, 3 H), 0.90 (s, 9 H), 0.06 (s, 6 H); $^{13}$C NMR(125 MHz, CDCl$_3$, $\delta$) 170.2, 159.3, 133.0, 129.3, 125.0, 113.9, 73.0, 71.1, 69.33, 59.9, 55.3, 26.0, 18.4, -5.2; IR (neat) $\nu$ = 2954, 2929, 2858, 1613, 1514, 1248, 1095, 1037, 837, 777 cm$^{-1}$; $[^\alpha]_D^{25}$ = -3.33 (c 0.43, CHCl$_3$); $R_f$ = 0.65 (hexanes : ethyl acetate, 3 : 1, v/v).
To a solution of (S, Z)-5-((t-butyldimethylsilyloxy)-1-(4-methoxybenzyloxy)pent-3-en-2-yl acetate (171) (500 mg, 1.3 mmol) in methanol (13 mL) was added PPTS (33 mg, 0.13 mmol). The resulting mixture was stirred for 1 h and then the solvent was removed by rotary evaporation. The reaction residue was purified by flash chromatography (hexanes : ethyl acetate, 10 : 1, v/v) to yield (S, Z)-5-hydroxy-1-(4-methoxybenzyloxy)pent-3-en-2-yl acetate (172) (309 g, 87%) as a colorless oil.

HRMS-ESI (m/z) [M+Na^+]: calc’d: 375.1968, found: 375.1979; ^1H NMR(500 MHz, CDCl₃, δ) 7.28 (d, 2 H), 6.92 (d, 2 H), 5.941 (m, 1 H), 5.77 (m, 1 H), 5.47 (m, 1 H), 4.53 (s, 2 H), 4.34 (m, 1 H), 4.13 (m, 1 H), 3.84 (s, 3 H), 3.62 (dd, 1 H), 3.48 (dd, 1 H), 2.09 (s, 3 H); ^13C NMR(125 MHz, CDCl₃, δ) 170.1, 159.3, 133.5, 129.3, 127.2, 126.9, 113.7, 73.0, 70.3, 69.1, 60.3, 55.1, 20.8; IR (neat) ν = 3456, 3010, 2937, 2860, 1738, 1612, 1514, 1371, 1247, 1033, 820 cm⁻¹; [α]D^25 = -14.71 (c 0.68, CHCl₃); Rf = 0.35 (hexanes : ethyl acetate, 1 : 1, v/v).
(S, Z)-acetic acid-4-iodo-1-(4-methoxybenzyloxy)-but-2-enyl ether (173)

To a solution of (S, Z)-5-hydroxy-1-(4-methoxybenzyloxy)pent-3-en-2-yl acetate (172) (150 mg, 0.54 mmol) in CH₂Cl₂ (5 mL) was added PPh₃ (210 mg, 0.13 mmol), imidazole (73 mg, 1.07 mmol) and I₂ (204 mg, 0.804 mmol). The resulting mixture was stirred for 15 min in dark and then was quenched by saturated aqueous Na₂S₂O₃ (5 mL). The mixture was separated and the aqueous layer was abstracted by ethyl ether (3 x 10 mL). The combined organic layer was dried over Na₂SO₄, filtrated and concentrated. The reaction residue was purified by flash chromatography (hexanes : ethyl acetate, 5 : 1, v/v) to yield (S, Z)-acetic acid-4-iodo-1-(4-methoxybenzyloxy)-but-2-enyl ether (173) (130 mg, 63%) as a colorless oil.
To suspension of Mg (226 mg, 9.4 mmol) and HgCl$_2$ (32 mg, 0.12 mmol) in Et$_2$O (3 mL) was added propargyl bromide (262 mL, 2.4 mmol). The resulting mixture was sonicated for 30 min under Ar atmosphere until the solution turned green and was then cooled down to -78 °C. A solution of (2S, 3aR, 6R, 7aR)-2-((t-butyldiphenylsilyloxy)methyl)-6-methyl-tetrahydro-2H-furo[3,2-b]pyran-5(6H)-one (157) (200 mg, 0.47 mmol) in Et$_2$O (5 mL) was added via cannula. The reaction mixture was stirred for 30 min and quenched by saturated aqueous NH$_4$Cl (10 mL). The mixture was separated and the aqueous layer was abstracted by ethyl ether (3 x 5 mL). The combined organic layer was dried over Na$_2$SO$_4$, filtrated and concentrated. The crude product was dissolved in methanol (5 mL) and PPTS (111 mg, 0.47 mmol) was added. After stirring for 1 h, solvent was removed by rotary evaporation. The crude product was purified by flash chromatography (hexanes : ethyl acetate, 15 : 1, v/v) to yield $t$-butyl(((2S, 3aR, 6R, 7aR)-5-methoxy-6-methyl-5-(prop-2-ynyl)-hexahydro-2H-furo[3,2-b]pyran-2-yl)methoxy)diphenylsilane (173) (156 mg, 1.7 mmol, 73%) as a colorless oil.

HRMS-ESI $(m/z)$ [M+Na$^+$]: calc’d: 501.2437, found: 501.2436; $^1$H NMR(500 MHz, CDCl$_3$, $\delta$) 7.72 (m, 4 H), 7.42 (m, 6 H), 4.41 (m, 1 H), 4.07 (m, 1 H), 3.93 (m, 1 H), 3.84 (dd, 1 H), 3.67 (dd, 1 H), 3.28 (s, 3 H), 2.69 (dd, 1 H), 2.47 (dd, 1 H), 2.39 (m, 1 H), 2.10 (m, 2 H), 2.01 (t, 1 H), 1.81 (dd, 2 H), 1.07 (s, 9 H), 0.96 (d, 3 H); $^{13}$C NMR(125 MHz, CDCl$_3$, $\delta$) 135.5, 133.6, 129.3, 127.6, 100.1, 79.7, 78.6, 75.5, 72.7, 70.4, 69.8, 66.1, 48.2, 35.6, 31.4, 30.8, 26.7, 25.7, 19.1, 15.4; IR (neat) $\nu$ = 3071, 2930, 2858, 1428, 1113, 1071,
1031, 832, 702 cm$^{-1}$; $[\alpha]_D^{25} = -24.721$ (c 0.54, CHCl3); $R_f = 0.59$ (hexanes : ethyl acetate, 3 : 1, v/v).
(S, Z)-8-((2S, 3aR, 6R, 7aR)-2-((t-butyldiphenylsilyloxy)methyl)-5-methoxy-6-methyl-hexahydro-2H-furo[3,2-b]pyran-5-yl)-1-(4-methoxybenzylxyloxy)oct-3-en-6-yn-2-yl acetate (174)

To a stirred solution of t-butyldiphenylsilyl((2S, 3aR, 6R, 7aR)-5-methoxy-6-methyl-5-(prop-2-ynyl)-hexahydro-2H-furo[3,2-b]pyran-2-yl)methoxydiphenylsilane (173) (50 mg, 0.105 mmol) in DMF under Ar atmosphere, was added CuI (20 mg, 0.105 mmol) and Cs₂CO₃ (30 mg, 0.105 mmol). After the reaction mixture was stirred for 20 min, (S, Z)-acetic acid-4-iodo-1-(4-methoxy-benzyloxymethyl)-but-2-enyl ether (172) (82 mg, 0.21 mmol) in DMF (1 mL) was added. The reaction was stirred for 8 h and quenched by saturated NH₄Cl aqueous solution (5 mL). The solution mixture was diluted with ethyl ether (5 mL) and separated. The aqueous layer was abstracted by ethyl ether (3 x 30 mL). The combined organic layer was dried over MgSO₄, filtrated and concentrated by rotary evaporation. The crude product was purified by flash chromatography (hexanes : ethyl acetate, 5 : 1, v/v) to yield (S, Z)-8-((2S, 3aR, 6R, 7aR)-2-((t-butyldiphenylsilyloxy)methyl)-5-methoxy-6-methyl-hexahydro-2H-furo[3,2-b]pyran-5-yl)-1-(4-methoxybenzylxyloxy)oct-3-en-6-yn-2-yl acetate (174) (35 mg, 46%).

HRMS-ESI (m/z) [M+Na⁺]: calc’d: 484.2094, found: 484.2091; ¹H NMR(500 MHz, CDCl₃, δ) 7.69 (m 4 H), 7.36 (m, 6 H), 7.21 (d, 2 H), 6.97 (d, 2 H), 5.65 (m, 2 H), 5.40 (dd, 1 H), 4.49 (dd, 2 H), 4.37 (m 1 H), 4.06 (m, 1 H), 3.90 (m, 1 H), 3.80 (s, 3 H), 3.67 (dd, 2 H), 3.54 (dd, 1 H), 3.48 (dd, 1 H), 3.26 (s, 3 H), 3.20 (m, 1 H), 2.60 (d, 1 H), 2.43 (d, 1 H), 2.33 (m, 1 H), 2.13 (m, 1 H), 2.06 (m, 1 H), 2.04 (s, 3 H), 1.76 (m, 2 H), 1.05 (s 9 H), 0.93 (d, 3 H); ¹³C NMR(125 MHz, CDCl₃, δ) 180.2, 159.2, 135.6, 133.6, 130.6, 81
129.6, 129.2, 127.6, 125.8, 113.8, 111.7, 100.3, 79.6, 78.8, 76.6, 75.9, 72.8, 70.9, 68.9,
66.4, 66.1, 55.3, 48.3, 35.7, 30.3, 30.1, 26.9, 26.2, 21.2, 19.3, 15.3; IR (neat) \( \nu = 2960, 
2933, 2857, 2355, 1743, 1237, 1108, 1032 \text{ cm}^{-1}; [\alpha]_D^{25} = -84.2 \text{ (c 0.33, CHCl}_3); R_f = 0.54 
(\text{hexane : ethyl acetate, 3 : 1, v/v}).
To a stirred solution of (S, Z)-8-((2S, 3aR, 6R, 7aR)-2-((t-butyldiphenylsilyloxy)methyl)-5-methoxy-6-methyl-hexahydro-2H-furo[3,2-b]pyran-5-yl)-1-(4-methoxybenzyloxy)oct-3-en-6-yn-2-ol acetate (174) (40 mg, 0.054 mmol) in CH₂Cl₂ (2 mL) under Ar atmosphere at -78 ºC, was added DIBAL (0.22 mL, 1 M solution in toluene, 0.22 mmol). After the reaction mixture was stirred for 20 min, methanol (0.1 mL) was added. The reaction was allowed to warm up and saturated aqueous sodium potassium tartrate solution (5 mL) and CH₂Cl₂ (2 mL) were added. The separated aqueous layer was abstracted by CH₂Cl₂ (3 x 5 mL). The combined organic layer was dried over Na₂SO₄, filtrated and concentrated by rotary evaporation. The crude product was purified by flash chromatography (hexanes : ethyl acetate, 5 : 1, v/v) to yield (S, Z)-8-((2S, 3aR, 6R, 7aR)-2-((t-butyldiphenylsilyloxy)methyl)-5-methoxy-6-methyl-hexahydro-2H-furo[3,2-b]pyran-5-yl)-1-(4-methoxybenzyloxy)oct-3-en-6-yn-2-ol (175) (26 mg, 71%).

HRMS-ESI (m/z) [M+Na⁺]: calc’d: 721.3536, found: 721.3544; ¹H NMR(500 MHz, CDCl₃, δ) 7.62 (m 4 H), 7.39 (m, 6 H), 7.26 (d, 2 H), 7.24 (d, 2 H), 5.65 (m, 1 H), 5.41 (dd, 1 H), 4.65 (dt, 1 H), 4.50 (s, 2 H), 4.39 (m 1 H), 3.43 (dd, 1 H), 3.36 (t, 1 H), 3.26 (s, 3 H), 2.95 (m, 2 H), 2.61 (dd, 1 H), 2.42 (d, 1 H), 2.37 (m, 1 H), 2.10 (m, 1 H), 1.77 (dd, 2 H), 1.05 (s 9 H), 0.93 (d, 3 H); ¹³C NMR(125 MHz, CDCl₃, δ) 159.3, 135.6, 133.7, 130.0, 129.9, 129.8, 128.5, 127.7, 113.9, 111.8, 79.7, 78.8, 76.0, 73.5, 73.4, 73.0, 66.8, 66.1, 55.3 48.3, 35.7, 30.5, 26.9, 26.0, 19.3, 17.8, 15.7; IR (neat) ν = 3440, 3070, 2937, 83
2857, 2355, 1511, 1249, 1108, 1066, 1025, 812, 706 cm$^{-1}$; $[\alpha]_D^{25} = 54.8$ (c 0.50, CHCl$_3$); 

$R_f = 0.24$ (hexane : ethyl acetate, 3 : 1, v/v).
the ABCD bis-spiroketal (176)

To a stirred solution of (S, Z)-8-((2S, 3aR, 6R, 7aR)-2-((t-
butyldiphenylsilyloxy)methyl)-5-methoxy-6-methyl-hexahydro-2H-furo[3,2-b]pyran-5-
yl)-1-(4-methoxybenzyl)oct-3-en-6-yn-2-ol (175) (8 mg, 0.011 mmol) in methanol (1
mL) under Ar atmosphere at -78 ºC, was added AuCl (0.2 mg, 0.86 mol) and PPTS (0.2
mg, 0.86 mol). After the reaction mixture was stirred for 30 min, the solvent was
removed by rotary evaporation. The crude product was purified by flash chromatography
(hexanes : ethyl acetate, 3 : 1, v/v) to yield the ABCD bis-spiroketal (176) (5.9 mg, 75%)
as a colorless oil.

HRMS-ESI (m/z) [M+Na^+]: calc’d: 707.3380, found: 707.3389; ¹H NMR(500 MHz,
CDCl₃, δ) 7.62 (m 4 H), 7.39 (m, 6 H), 7.26 (d, 2 H), 7.24 (d, 2 H), 4.57 (m, 1 H), 4.52 (d,
2 H), 4.33 (m, 1 H), 4.23 (m, 1 H), 3.91 (m, 1 H), 3.80 (s, 3 H), 3.76 (dd, 1 H), 3.66 (dd,
1 H), 3.56 (dd, 1 H), 3.47 (dd, 1 H), 2.54 (d, 1 H), 2.29 (m, 1 H), 1.90-2.20 (m, 5 H), 1.75
(m, 2 H), 1.67 (dd, 1 H), 1.20 (s, 9 H), 0.93 (d, 3 H); ¹³C NMR(125 MHz, CDCl₃, δ)
158.9, 135.6, 133.6, 129.6, 129.4, 129.2, 127.6, 126.6, 123.7, 113.7, 112.1, 104.8, 78.6,
72.9, 72.3, 72.1, 69.2, 66.3, 55.3, 36.6, 35.7, 35.1, 33.6, 32.2, 31.4, 29.6, 19.3, 16.2; IR
(neat) ν = 3070, 3040, 2956, 2933, 2363, 1652, 1515, 1249, 1111, 808, 705 cm⁻¹; [α]D²⁵ =
-41.3 (c 0.50, CHCl₃); Rf = 0.57 (hexane : ethyl acetate, 3 : 1, v/v).
(S)-4-benzyl-3-((R,E)-9-((4-methoxybenzyl)oxy)-2-methylnon-4-en-7-ynoyl)oxazolidin-2-one (181)

To a stirred solution of PMB protected propargyl alcohol (3.190 g, 18.08 mmol) in THF at -78 ºC under Ar atmosphere, was added \( n \)-BuLi (6.9 mL of 2.5M solution in hexanes, 17.26 mmol). After the reaction mixture was stirred for 30 min, Cul (3.130 g, 16.44 mmol) was added and the suspension was then allowed to warm up to rt. Next, allylic bromide (133) (6.020 g, 16.44 mmol) in THF was added via cannula. The reaction was stirred for 4 h and quenched by saturated NH\(_4\)Cl aqueous solution (30 mL). The resulting solution was filtrated through a plug of celite. The solution mixture was separated and the aqueous layer was abstracted by ethyl ether (3 x 30 mL). The combined organic layer was dried over MgSO\(_4\), filtrated and concentrated by rotary evaporation. The crude product was purified by flash chromatography (hexanes : ethyl acetate, 5 : 1, v/v) to yield (S)-4-benzyl-3-((R,E)-9-((4-methoxybenzyl)oxy)-2-methylnon-4-en-7-ynoyl)oxazolidin-2-one (181) as a yellowish oil (6.29 g, 13.63 mmol, 83%).

HRMS-ESI (\(m/z\)) [M+Na\(^+\)]: calc’d: 484.2094, found: 484.2091; \(^1\)H NMR(500 MHz, CDCl\(_3\), \(\delta\)) 7.31-7.35 (t, 2 H), 7.26-7.29 (m, 5 H), 7.19-7.22 (d, 2 H), 6.87-6.90 (d, 2 H), 5.72-5.78 (dt, 1 H), 5.52-5.58 (dt, 1 H), 4.67-4.72 (m, 1 H), 4.48-4.51 (s, 2 H), 4.13-4.22 (m, 2 H), 4.08-4.11 (t, 2 H), 3.80-3.84 (s, 3 H), 3.27-3.33 (dd, 1 H), 2.98-3.02 (d, 2 H), 2.69-2.74 (dd, 1 H), 2.49-2.55 (m, 1 H), 2.22-2.27 (m, 1 H), 1.19-1.22 (d, 3 H); \(^1\)H NMR(125 MHz, CDCl\(_3\), \(\delta\)) 178.5, 159.3, 153.1, 135.4, 129.7, 129.4, 129.0, 128.7, 127.3, 136.8, 113.8, 84.0, 77.9, 71.1, 66.0, 57.3, 55.4, 55.3, 38.1, 37.5, 36.6 22.1, 16.5; IR (neat)
ν = 3054.1, 2984.7, 1778.7, 1733.0, 1374.0, 1265.6, 1046.1, 738.4, 704.4 cm⁻¹; \([\alpha]_D^{25} = 5.3\) (c 0.975, CHCl₃); Rₓ = 0.29 (hexane : ethyl acetate, 3 : 1, v/v).
(3R, 5R)-5-((R)-1-hydroxy-5-((4-methoxybenzyl)oxy)pent-3-yn-1-yl)-3-methyldihydrofuran-2(3H)-one (182)

The (S)-4-benzyl-3-((R,E)-9-((4-methoxybenzyl)oxy)-2-methylnon-4-en-7-ynoyl)oxazolidin-2-one (181) (4.29 g, 9.29 mmol) was dissolved in a mixed solvent of 50 mL t-BuOH and 50 mL water, followed by the addition of AD-mix-β (15.01 g) and MeNH₂SO₂ (0.884 g, 9.29 mmol). The reaction mixture was then stirred for overnight. The reaction was quenched by 1M Na₂SO₃ aqueous solution (10 mL). The mixture was separated and the aqueous layer was abstracted by ethyl ether (3 x 30 mL). The combined organic layer was dried over Na₂SO₄, filtrated and concentrated. The crude product was purified by flash chromatography (hexanes : ethyl acetate, 3 : 1, v/v) to give (3R,5R)-5-((R)-1-hydroxy-5-((4-methoxybenzyl)oxy)pent-3-yn-1-yl)-3-methyldihydrofuran-2(3H)-one (182) (2.34 g, 7.35 mmol, 79%) as a colorless oil.
(3R,5R)-5-((R)-5-((4-methoxybenzyl)oxy)-1-((triethylsilyl)oxy)pent-3-yn-1-yl)-3-methylidihydrofuran-2(3H)-one (183)

To a solution of (3R,5R)-5-((R)-1-hydroxy-5-((4-methoxybenzyl)oxy)pent-3-yn-1-yl)-3-methylidihydrofuran-2(3H)-one (2.34 g, 7.35 mmol) (182) in CH₂Cl₂ (50 mL), was added imidazole (1.501 g, 22.05 mmol). Next, TESCl (1.25 mL, 7.35 mmol) was added sequentially. The reaction was by saturated NH₄Cl aqueous solution (10 mL). The mixture was separated and the aqueous layer was abstracted by ethyl ether (3 x 30 mL). The combined organic layer was dried over Na₂SO₄, filtrated and concentrated. The crude product was purified by flash chromatography (hexanes : ethyl acetate, 3 : 1, v/v) to give (3R,5R)-5-((R)-5-((4-methoxybenzyl)oxy)-1-((triethylsilyl)oxy)pent-3-yn-1-yl)-3-methylidihydrofuran-2(3H)-one (183) (2.67 g, 6.17 mmol, 84%).

HRMS-ESI (m/z) [M+Na⁺]: calc’d: 455.2224, found: 455.2253; ¹H NMR(500 MHz, CDCl₃, δ) 7.27-7.30 (d, 2 H), 6.88-6.91 (d, 2H), 4.54-4.58 (m, 1 H), 4.52-4.54 (s, 2 H), 4.13-4.16 (t, 2 H), 3.80-3.84 (s, 4 H), 2.65-2.72 (m, 1 H), 2.62-2.65 (dt, 1 H), 2.46-2.52 (m, 1 H), 2.33-2.39 (m, 1 H), 1.77-1.83 (q, 1 H), 1.28-1.31 (d, 3 H), 0.97-1.02 (t, 9 H), 0.63-0.70 (q, 6 H); ¹³C NMR(125 MHz, CDCl₃, δ) 179.0, 159.4, 129.7, 129.6, 113.8, 82.5, 79.1, 78.5 71.7, 71.2, 57.3, 55.3, 35.6, 32.1 24.3, 15.2, 6.8, 5.0; IR (neat) v = 2953.1,
2875.2, 1774.3, 1611.7, 1513.2, 1455.1, 1248.7, 1169.6, 1069.9, 1033.4 cm\(^{-1}\); \([\alpha]_D^{25} = -21.8\) (c 1.43, CHCl\(_3\)); R\(_f\) = 0.39 (hexane : ethyl acetate, 3 : 1, v/v).
(2R,4R,5R)-9-((4-methoxybenzyl)oxy)-2-methyl-5-((triethylsilyl)oxy)non-7-yne-1,4-diol (184)

2 M LiBH₄ THF solution (12.3 mL, 24.55 mmol) was added to the solution of (3R,5R)-5-((R)-5-((4-methoxybenzyl)oxy)-1-((triethylsilyl)oxy)pent-3-yn-1-yl)-3-methyldihydrofuran-2(3H)-one (183) (3.54 g, 8.18 mmol) in Et₂O (50 mL), which was followed by the addition of water (0.44 mL, 24.55 mmol). The reaction was quenched by saturated NH₄Cl aqueous solution (10 mL). The mixture was separated and the aqueous layer was abstracted by ethyl acetate (3 x 30 mL). The combined organic layer was dried over Na₂SO₄, filtrated and concentrated. The crude product was purified by flash chromatography (hexanes : ethyl acetate, 2 : 1, v/v) to give (2R,4R,5R)-9-((4-methoxybenzyl)oxy)-2-methyl-5-((triethylsilyl)oxy)non-7-yne-1,4-diol (184) as a colorless oil (2.90 g, 6.64 mmol, 81%).

HRMS-ESI (m/z) [M+Na⁺]: calc’d: 459.2537, found: 459.2540; ¹H NMR(500 MHz, CDCl₃, δ) 7.28-7.30 (d, 2 H), 6.89-6.91 (d, 2H), 4.53 (s, 2 H), 4.13-4.15 (t, 2 H), 3.82 (s, 3 H), 3.77-3.81 (dt, 1 H), 3.69-3.72 (m, 1 H), 3.56-3.59 (dd, 1 H), 3.43-3.46 (dd, 1 H), 2.79-2.90 (b, 1 H), 2.65-2.74 (b, 1 H), 2.58-2.63 (m, 1 H), 2.38-2.44 (m, 1 H), 1.86-1.93 (m, 1 H), 1.46-1.54 (m, 1 H), 1.38-1.45 (m, 1 H), 0.97-1.02 (t, 9 H), 0.94-0.97 (d, 3 H), 0.64-0.70 (q, 6 H); ¹³C NMR(125 MHz, CDCl₃, δ) 159.4, 129.7, 129.6, 113.8, 83.2, 78.3, 74.4, 71.8, 71.1, 68.8, 57.3, 55.3, 39.5, 34.4, 24.5, 17.8, 6.8, 5.0; IR (neat) ν = 3391.6, 91
2953.3, 2874.9, 1612.1, 1513.5, 1249.0, 1076.3, 743.5 \, \text{cm}^{-1}; [\alpha]_D^{25} = 1.2 \ (c \ 1.75, \ \text{CHCl}_3);

R_f = 0.28 \ (\text{hexane} : \text{ethyl acetate}, 1 : 1, \text{v/v}).
(5R,6R,8R)-3,3-diethyl-5-(4-((4-methoxybenzyl)oxy)but-2-yn-1-yl)-8,11,11,12,12-pentamethyl-4,10-dioxo-3,11-disilatridecan-6-ol (185)

Imidazole (1.45 g, 21.30 mmol) was added to the solution of (2R,4R,5R)-9-((4-methoxybenzyl)oxy)-2-methyl-5-((triethylsilyl)oxy)non-7-yn-1,4-diol (184) (3.10 g, 7.10 mmol) in CH₂Cl₂ (50 mL). TBSCl (1.07 g, 7.10 mmol) was added sequentially. The reaction was quenched by saturated NH₄Cl aqueous solution (10 mL). The mixture was separated and the aqueous layer was abstracted by ethyl ether (3 x 30 mL). The combined organic layer was dried over Na₂SO₄, filtrated and concentrated. The crude product was purified by flash chromatography (hexanes : ethyl acetate, 5 : 1, v/v) to give (5R,6R,8R)-3,3-diethyl-5-(4-((4-methoxybenzyl)oxy)but-2-yn-1-yl)-8,11,11,12,12-pentamethyl-4,10-dioxo-3,11-disilatridecan-6-ol (185) (2.89 g, 5.25 mmol, 74%) as a colorless oil.

HRMS-ESI (m/z) [M+Na⁺]: calc’d: 573.3402, found: 573.3418; ¹H NMR(500 MHz, CDCl₃, δ) 7.28-7.30 (d, 2 H), 6.89-6.91 (d, 2 H), 4.53 (s, 2 H), 4.13-4.15 (t, 2 H), 3.82 (s, 3 H), 3.72-3.79 (m, 1 H), 3.50-3.54 (dd, 1 H), 3.43-3.47 (dd, 1 H), 2.63-2.70 (m, 1 H), 2.60-2.63 (d, 1 H), 2.33-2.43 (m, 1 H), 1.84-1.93 (m, 1 H), 1.54-1.63 (m, 2 H), 1.24-1.33 (m, 1 H), 0.98-1.02 (t, 9 H), 0.93-0.95 (d, 3 H), 0.92 (s, 9 H), 0.65-0.70 (q, 6 H), 0.07 (s, 6 H); ¹³C NMR(125 MHz, CDCl₃, δ) 129.7, 129.6, 113.8, 83.2, 77.2, 74.3, 71.0, 69.1, 57.3, 55.3, 33.2, 25.9, 24.1, 16.9, 6.9, 5.0, -5.4; IR (neat) ν = 2953.1, 2358.9, 1613.8,
1513.8, 1463.8, 1249.3, 1085.5, 836.4, 775.5 cm\(^{-1}\); \([\alpha]_D^{25} = 7.2\) (c 1.17, CHCl\(_3\)); \(R_f = 0.67\)
(hexane : ethyl acetate, 3 : 1, v/v).
(5R, 6R, 8R)-3, 3-diethyl-5-((Z)-4-((4-methoxybenzyl)oxy)but-2-en-1-yl)-8, 11, 11, 12, 12-penta methyl-4, 10-dioxa-3,11-disilatridecan-6-ol (186)

Lindlar catalyst (62.2 mg) and quinoline (6.9 μL, 0.058 mmol) was added to the solution of (5R, 6R, 8R)-3, 3-diethyl-5-((4-((4-methoxybenzyl)oxy)but-2-yn-1-yl)-8, 11, 11, 12, 12-pentamethyl-4, 10-dioxa-3, 11-disilatridecan-6-ol (185) in benzene. The reaction flask was flushed with hydrogen gas three times and reaction mixture was stirred vigorously under hydrogen atmosphere for 30 min. The reaction mixture was filtered through celite. The crude product was purified by flash chromatography (hexanes : ethyl acetate, 5 : 1, v/v) to give (5R, 6R, 8R)-3, 3-diethyl-5-((Z)-4-((4-methoxybenzyl)oxy)but-2-en-1-yl)-8, 11, 11, 12, 12-penta methyl-4, 10-dioxa-3, 11-disilatridecan-6-ol (186) as a colorless oil.

HRMS-ESI (m/z) [M+Na⁺]: calc’d: 575.3558, found: 575.3563; ¹H NMR(500 MHz, CDCl₃, δ) 7.28-7.30 (d, 2 H), 6.89-6.91 (d, 2 H), 5.63-5.71 (m, 2 H), 4.46 (s, 2 H), 4.08-4.10 (t, 2 H), 3.83 (s, 3 H), 3.59-3.61 (m, 1 H), 3.49-3.52 (dd, 1 H), 3.42-3.46 (dd, 1 H), 2.81-2.82 (d, 1 H), 2.43-2.49 (m, 1 H), 2.15-2.22 (m, 1 H), 1.81-1.89 (m, 1 H), 1.48-1.54 (ddd, 1 H), 1.23-1.30 (ddd, 1 H), 0.95-1.01 (t, 9 H), 0.93-0.95 (d, 3 H), 0.93 (s, 9 H), 0.60-0.65 (q, 6 H), 0.07 (s, 6 H); ¹³C NMR(125 MHz, CDCl₃, δ) 159.2, 130.5, 129.4, 128.4, 113.8, 75.2, 71.9, 71.1, 69.2, 67.8, 65.7, 55.3, 38.0, 33.4, 31.8, 25.9, 18.3, 17.0, 6.9,
5.1, -3.8; IR (neat) $\nu = 2953.7, 2360.4, 1513.8, 1456.6, 1248.6, 1086.3, 836.0 \text{ cm}^{-1}$; $[\alpha]_{D}^{25}$ = 3.8 (c 1.57, CHCl$_3$); $R_f = 0.74$ (hexane : ethyl acetate, 3 : 1, v/v).
(5R, 6R, 8R, Z)-9-((tert-butyldimethylsilyl)oxy)-8-methyl-5-((triethylsilyl)oxy)non-2-ene-1, 6-diol (187)

0.5 mL of pH 7 buffer solution and DDQ (0.247 g, 1.09 mmol) was added to the solution of (5R, 6R, 8R)-3, 3-diethyl-5-((Z)-4-((4-methoxybenzyl)oxy)but-2-en-1-yl)-8, 11, 11, 12, 12-penta methyl-4, 10-dioxo-3, 11- disilatridecan-6-ol (186) (0.301 g, 0.54 mmol) in CH₂Cl₂ (5 mL). The reaction mixture was stirred for 1 h and quenched by saturated NaHCO₃ aqueous solution (2 mL). The mixture was separated and the aqueous layer was abstracted by diethyl ether (3 x 10 mL). The combined organic layer was dried over Na₂SO₄, filtrated and concentrated. The crude product was purified by flash chromatography (hexanes : ethyl acetate, 3 : 1, v/v) to give (5R, 6R, 8R, Z)-9-((tert-butyldimethylsilyl)oxy)-8-methyl-5-((triethylsilyl)oxy)non-2-ene-1, 6-diol (187) (0.141 g, 0.33 mmol, 60%) as a colorless oil.

HRMS-ESI (m/z) [M+Na⁺]: calc’d: 455.2983, found: 455.2982; ¹H NMR(500 MHz, CDCl₃, δ) 5.80-5.84 (m, 1 H), 5.57-5.62 (dd, 1 H), 4.23-4.27 (t, 1 H), 4.09-4.11 (t, 1 H), 3.65-3.69 (m, 1 H), 3.60-3.63 (m, 1 H), 3.46 (s, 2 H), 4.08-4.10 (t, 2 H), 3.83 (s, 3 H), 3.59-3.61 (m, 1 H), 3.53-3.56 (dd, 1 H), 3.40-3.44 (dd, 1 H), 3.04-3.05 (d, 1 H), 2.56-2.62 (m, 1 H), 2.45 (s, 1 H), 2.20-2.26 (m, 1 H), 1.80-1.86 (m, 1 H), 1.54-1.60 (ddd, 1 H), 1.31-1.35 (ddd, 1 H), 0.97-1.00 (t, 9 H), 0.92 (s, 9 H), 0.90-0.91 (d, 3 H), 0.62-0.68 (q, 6 H), 0.09 (s, 6 H); ¹³C NMR(125 MHz, CDCl₃, δ) 130.9, 129.3, 74.6, 71.2, 69.2, 67.8,
58.0, 38.0, 33.6, 32.0, 31.5, 25.9, 18.3, 17.3, 6.9, 5.1, -5.4; IR (neat) $\nu = 3369.6, 2954.2,$
2877.3, 1461.9, 1253.0, 1086.5, 1005.9, 836.4, 775.3, 741.8 cm$^{-1}$; $[\alpha]_{D}^{25} = 25.3$ (c 1.10,
CHCl$_3$); $R_f = 0.31$ (hexane : ethyl acetate, 3 : 1, v/v).
(+)-Diisopropyl-L-tartrate (0.164 mL, 0.784 mmol) was added to the solution of
titanium(IV) isopropoxide (0.194 mL, 0.663 mmol) in CH₂Cl₂ (2 mL) at -20 ºC and
stirred for 20 min. TBHP (5.0 – 6.0 M in decane, 0.548 mL) was then added at -20 ºC.
After another 20 min, a solution of (5R, 6R, 8R, Z)-9-((tert-butyldimethylsilyl)oxy)-8-
methyl-5-((triethylsilyl)oxy)non-2-ene-1, 6-diol (187) in CH₂Cl₂ (2 mL) was added into
the reaction mixture by cannula. The reaction was stirred at -20 ºC overnight. Following
the addition of celite to the reaction mixture, 30% NaOH in saturated NaCl aqueous
solution (5 mL) was added at 0 ºC. The mixture was stirred for 1 h and filtered through
celite. The mixture was separated and the aqueous layer was abstracted by ethyl acetate
(3 x 10 mL). The combined organic layer was dried over Na₂SO₄, filtrated and
concentrated. The crude product was purified by flash chromatography (hexanes : ethyl
acetate, 1 : 1, v/v) to give (S)-1-((2S, 4R, 5R)-5-((R)-3-((tert-butyldimethylsilyl)oxy)-2-methylpropyl)-4-
((triethylsilyl)oxy) tetrahydrofuran-2-yl)ethane-1,2-diol (188) (0.176 g,
0.39 mmol, 65%) as a colorless oil.

HRMS-ESI (m/z) [M+Na⁺]: calc’d: 471.2932, found: 471.2931; ¹H NMR(500 MHz,
CDCl₃, δ) 4.24-4.29 (m, 2 H), 3.96-3.99 (dt, 1 H), 3.73-3.76 (q, 2 H), 3.51-3.54 (m, 2 H),
3.41-3.44 (dd, 1 H), 2.57-2.58 (d, 1 H), 2.49-2.52 (dd, 1 H), 2.06-2.13 (m, 1 H), 1.88-1.92 (ddd, 1 H), 1.70-1.79 (d, 2 H), 1.28-1.34 (m, 2 H), 0.99-1.01 (t, 9 H), 0.93-0.94 (d, 3 H), 0.91 (s, 9 H), 0.61-0.66 (q, 6 H), 0.07 (s, 6 H); $^{13}$C NMR (125 MHz, CDCl$_3$, δ) 81.8, 78.8, 73.7, 72.5, 68.8, 65.2, 38.1, 33.1, 33.0, 25.9, 18.3, 16.7, 6.8, 4.9, -5.1; IR (neat) ν = 3413.6, 2953.9, 2358.6, 1461.7, 1250.3, 1089.2, 836.0 cm$^{-1}$; [$\alpha$]$_D^{25}$ = -1.6 (c 1.51, CHCl$_3$); R$_f$ = 0.47 (hexane : ethyl acetate, 1 : 1, v/v).
(S)-2-((2S,4R,5R)-5-((R)-3-((tert-butyldimethylsilyl)oxy)-2-methylpropyl)-4-((triethylsilyl)oxy)tetrahydrofuran-2-yl)-2-hydroxyethyl pivalate (189)

To the solution of (S)-1-((2S, 4R, 5R)-5-((R)-3-((tert-butyldimethylsilyl)oxy)-2-methylpropyl)-4-((triethylsilyl)oxy)tetrahydrofuran-2-yl)ethane-1,2-diol (188) (30.1 mg, 0.067 mmol) in pyridine (2.5 mL) and CH$_2$Cl$_2$ (1 mL) solvent mixture at 0 ºC, was pivaloyl chloride (9.1 μL, 0.074 mmol) added. The reaction mixture was allowed to warm up to rt slowly and stirred overnight. The reaction was then quenched by saturated NH$_4$Cl aqueous solution (1 mL). The mixture was separated and the aqueous layer was abstracted by ethyl ether (3 x 5 mL). The combined organic layer was dried over Na$_2$SO$_4$, filtrated and concentrated. The crude product was purified by flash chromatography (hexanes : ethyl acetate, 7 : 1, v/v) to give (S)-2-((2S,4R,5R)-5-((R)-3-((tert-butyldimethylsilyl)oxy)-2-methylpropyl)-4-((triethylsilyl)oxy)tetrahydrofuran-2-yl)-2-hydroxyethyl pivalate (189) (25.8 mg, 0.048 mmol, 72%) as a colorless oil.

HRMS-ESI (m/z) [M+Na$^+$]: calcd: 555.3508, found: 555.3500. $^1$H NMR(500 MHz, CDCl$_3$, δ) 4.28-4.31 (m, 1 H), 4.17-4.21 (m, 1 H), 4.13-4.16 (t, 2 H), 3.93-3.97 (dt, 1 H), 3.64-3.69 (m, 1 H), 3.52-3.55 (dd, 1 H), 3.41-3.44 (dd, 1 H), 2.40-2.42 (d, 1 H), 1.98-2.03 (ddd, 1 H), 1.89-1.94 (ddd, 1 H), 1.77-1.84 (m, 1 H), 1.69-1.75 (ddd, 1 H), 1.62 (s, 1 H), 1.29-1.36 (m, 1 H), 1.23 (s, 9 H), 0.97-1.00 (t, 9 H), 0.91 (s, 9 H), 0.60-0.65 (q, 6 H),

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0.05 (s, 6 H); $^{13}$C NMR (125 MHz, CDCl$_3$, δ) 178.6, 81.4, 73.9, 72.1, 68.8, 65.9, 38.8, 38.3, 33.1, 32.9, 27.2, 25.9, 18.3, 16.8, 6.8, 4.9, -5.5; IR (neat) ν = 3733.5, 2954.4, 2359.4, 1635.6, 1506.3, 1167.5, 1080.7, 1034.6, 835.8, 745.9 cm$^{-1}$; $[\alpha]_D^{25} = -2.5$ (c 1.17, CHCl$_3$); $R_f = 0.69$ (hexane : ethyl acetate, 3 : 1, v/v).
(S)-2-((2S,4R,5R)-5-((S)-3-((tert-butyldimethylsilyl)oxy)-2-methylpropyl)-4-((triethylsilyl)oxy)tetrahydrofuran-2-yl)-2-((triisopropylsilyl)oxy)ethyl pivalate (190)

To the solution of (S)-2-((2S,4R,5R)-5-((R)-3-((tert-butyldimethylsilyl)oxy)-2-methylpropyl)-4-((triethylsilyl)oxy)tetrahydrofuran-2-yl)-2-hydroxyethyl pivalate (189) (47.0 mg, 0.088 mmol) CH₂Cl₂ (1 mL) solvent mixture at 0 ºC, were 2, 6-lutidine (20.5 µL, 0.176 mmol) and TIPS triflate (29.4 µL, 0.106 mmol) added sequentially. The reaction mixture was allowed to warm up to rt slowly and stirred overnight. The reaction was then quenched by saturated NH₄Cl aqueous solution (1 mL). The mixture was separated and the aqueous layer was abstracted by ethyl ether (3 x 5 mL). The combined organic layer was dried over Na₂SO₄, filtrated and concentrated. The crude product was purified by flash chromatography (hexanes : ethyl acetate, 15 : 1, v/v) to give (S)-2-((2S,4R,5R)-5-((S)-3-((tert-butyldimethylsilyl)oxy)-2-methylpropyl)-4-((triethylsilyl)oxy)tetrahydrofuran-2-yl)-2-((triisopropylsilyl)oxy)ethyl pivalate (190) (45.5 mg, 0.066 mmol, 75%) as a colorless oil.

HRMS-ESI (m/z) [M+Na⁺]: calcd: 711.4842, found: 711.4839. ¹H NMR(500 MHz, CDCl₃, δ) 4.28-4.33 (dt, 1 H), 4.23-4.25 (t, 1 H), 4.17-4.21 (dd, 1 H), 4.08-4.12 (dd, 1 H), 3.99-4.03 (q, 1 H), 3.89-3.94 (dt, 1 H), 3.52-3.56 (dd, 1 H), 3.37-3.42 (dd, 1 H), 1.97-2.04 (ddd, 1 H), 1.85-1.91 (ddd, 1 H), 1.77-1.84 (m, 1 H), 1.22-1.24 (d, 3 H), 1.22 (s, 9 H), 103
1.07-1.12 (m, 3 H), 1.08-1.09 (d, 18 H), 0.97-1.00 (t, 9 H), 0.95-0.99 (m, 3 H), 0.91 (s, 9 H), 0.60-0.65 (q, 6 H), 0.05 (s, 6 H); $^{13}$C NMR(125 MHz, CDCl$_3$, δ) 177.8, 77.8, 74.0, 72.9, 68.9, 66.1, 38.8, 37.5, 33.1, 32.9, 27.2, 25.9, 18.3, 18.1, 17.7, 16.6, 12.7, 12.3, 6.9, 4.9, -5.5; IR (neat) ν = 3535.8, 2955.4, 2866.2, 1732.4, 1462.6, 1250.7, 1132.0, 1093.9, 836.3 cm$^{-1}$; [α]$_D^{25}$ = -3.8 (c 1.65, CHCl$_3$); R$_f$ = 0.81 (hexane : ethyl acetate, 5 : 1, v/v).
Appendix B: NMR Spectroscopy