Efforts towards the Total Synthesis of Azaspiracid-3

DISSERTATION

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By

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Abstract

Azaspiracid, a structurally complex marine toxin isolated from the mussel *Mytilus edulis* in Killary Harbor, Ireland, represents a new class of marine metabolites unrelated to any previous known agent of diarrhetic shellfish poisoning. As such, the natural product has spurred considerable interest among organic community. The thesis details the study towards the total synthesis of azaspiracid-3.

The C1-C21 domain and C22-C40 domain have been synthesized, which aims to assemble the molecule through Yamaguchi esterification. The ABCD domain involved an efficient NHK coupling reaction between C1-C12 segment and C13-C22 segment. The trioxadispiroketal skeleton was constructed under the influence of acid catalysis. The EFGHI domain highlighted a chelate controlled Mukaiyama aldol reaction to produce C22-C40 linear precursor, and a DIHMA process to assemble the bridged ketal.

With the recognition of bridged ketal and spiroaminal functionality in the FGHI domain, the gold-catalysis to achieve these moieties has been proposed. A novel gold-catalyzed spiroaminal formation has been systemically developed. The gold-catalyzed ketallization was then successfully implemented to construct the bridged ketal, while an inevitable elimination could not deliver the desired spiroaminal under gold conditions.

A NHK reaction to couple the C1-C21 and C22-C40 domains has also been proposed. The revised C22-C40 domain was achieved with a similar synthetic route.
Dedication

This document is dedicated to my family.
Acknowledgments

First of all, I would like to thank my advisor, Prof. Dr. Craig J. Forsyth, for allowing me to join his research group and explore the challenges of organic synthesis. I am very grateful to Dr. Forsyth for his extensive support, advice and help throughout my graduate research in the azaspiracid project.

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Vita

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Publications


Fields of Study

Major Field: Chemistry
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<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>ADmix-α</td>
<td>commercial reagent for asymmetric dihydroxylation</td>
</tr>
<tr>
<td>ADmix-β</td>
<td>commercial reagent for asymmetric dihydroxylation</td>
</tr>
<tr>
<td>BAIB</td>
<td>bis(acetoxy)iodobenzene</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butoxy carbonyl</td>
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<td>2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile</td>
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<td>benzyl</td>
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<td>Bu</td>
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<td>brsm</td>
<td>based on recovery of starting material</td>
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</tr>
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<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>DHP</td>
<td>3,4-dihydro-2-$H$ pyran</td>
</tr>
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<td>DIBAL</td>
<td>diisobutyl aluminum hydride</td>
</tr>
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<td>DIPT</td>
<td>diisopropyl tartrate</td>
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<td>DMAP</td>
<td>4-$N,N$-dimethyl amino pyridine</td>
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<td>$N,N$-dimethyl formide</td>
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<td>Dess Martin periodinane</td>
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<td>dimethyl sulfoxide</td>
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<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>ESI</td>
<td>electrospray ionization</td>
</tr>
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<td>hours</td>
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<td>hexa methyl disilyl amide</td>
</tr>
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<td>hertz</td>
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</tr>
<tr>
<td>Ipc</td>
<td>isopinocampheyl</td>
</tr>
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<td>IR</td>
<td>infrered specscopy</td>
</tr>
<tr>
<td>LC</td>
<td>liquid chromatography</td>
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<tr>
<td>LDA</td>
<td>lithium diisopropyl amide</td>
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<td>$m$CPBA</td>
<td>meta-chloro peroxy benzoic acid</td>
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<td>minute</td>
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<tr>
<td>modp</td>
<td>1-morpholino-carbamoyl-4,4-dimethyl-1,3-pentanedionato</td>
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</tr>
<tr>
<td>MS</td>
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</tr>
<tr>
<td>MTM</td>
<td>methyl thio methyl</td>
</tr>
<tr>
<td>NHK</td>
<td>Nozaki-Hiyama-Kishi</td>
</tr>
<tr>
<td>NIS</td>
<td>N-iodo succinimide</td>
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<tr>
<td>NMO</td>
<td>N-methyl morpholine N-oxide</td>
</tr>
<tr>
<td>NMP</td>
<td>N-methyl morphline</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>NOE</td>
<td>nuclear Overhauser effect</td>
</tr>
<tr>
<td>OSu</td>
<td>N-oxysuccinimide</td>
</tr>
<tr>
<td>PFP</td>
<td>pentafluoro phenyl</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>Piv</td>
<td>pivaloyl</td>
</tr>
<tr>
<td>PMB</td>
<td>p-methoxy benzyl</td>
</tr>
<tr>
<td>PMP</td>
<td>p-methoxy phenyl</td>
</tr>
<tr>
<td>PPTS</td>
<td>pyridinium para-toluene sulfonate</td>
</tr>
<tr>
<td>Pr</td>
<td>propyl</td>
</tr>
<tr>
<td>Py</td>
<td>pyridine</td>
</tr>
<tr>
<td>R&lt;sub&gt;f&lt;/sub&gt;</td>
<td>retention factor</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>SAD</td>
<td>Sharpless asymmetric dihydroxylation</td>
</tr>
<tr>
<td>SAE</td>
<td>Sharpless asymmetric epoxidation</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetra butyl ammonium fluoride</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>TBAI</td>
<td>tetra butyl ammonium iodide</td>
</tr>
<tr>
<td>TBDPS</td>
<td>tert-butyl diphenyl silyl</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-butyl dimethyl silyl</td>
</tr>
<tr>
<td>TCA</td>
<td>trichloro acetamide</td>
</tr>
<tr>
<td>Teoc</td>
<td>trimethyl silyl ethoxy carbonyl</td>
</tr>
<tr>
<td>TEMPO</td>
<td>2,2,6,6-tetramethyl-1-piperidinyloxy</td>
</tr>
<tr>
<td>TES</td>
<td>triethyl silyl</td>
</tr>
<tr>
<td>Tf</td>
<td>trifluoro methyl sulfonyl</td>
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<td>TFA</td>
<td>trifluoro acetate</td>
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<td>TFAA</td>
<td>trifluoro acetic anhydride</td>
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<td>TFP</td>
<td>trifuranyl phosphine</td>
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<td>tetrahydro pyran</td>
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<td>TIPS</td>
<td>triisopropyl silyl</td>
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<td>TMS</td>
<td>trimethyl silyl</td>
</tr>
<tr>
<td>TMSE</td>
<td>trimethyl silyl ethyl</td>
</tr>
<tr>
<td>TPAP</td>
<td>tetrapropyl ammonium perhuthenate</td>
</tr>
<tr>
<td>Tris</td>
<td>triisopropyl phenyl sulfonyl</td>
</tr>
<tr>
<td>Ts</td>
<td>toluene sulfonyl</td>
</tr>
<tr>
<td>Xc</td>
<td>Evans auxiliary</td>
</tr>
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</table>
Chapter 1: Introduction

1.1 Shellfish Poisoning

Algae are very important to marine ecosystems, and normally most of algae are not harmful. Algal blooms occur in natural waters when certain types of algae grow quickly due to the changes in the levels of chemicals stimuli. Algal blooms can deplete oxygen and block the sunlight that other organisms need to live and some can produce toxins, which have been called harmful algal blooms (HABs). More importantly, the toxins can be accumulated in bivalve molluscs (such as mussels, clams, oysters and scallops) without being degraded. Normally, these toxins are harmless to the shellfish themselves, while they are very toxic to human being. As early as 1927, the first shellfish poisoning was reported in San Francisco, California. To date, there are five different types of shellfish poisoning that has been recognized: Amnesic shellfish poisoning (ASP), diarrhetic shellfish poisoning (DSP), paralytic shellfish poisoning (PSP), neurotoxic shellfish poisoning (NSP), and the newly discovered azaspiracid shellfish poisoning (AZP).

Amnesic shellfish poisoning (ASP). The first incident of shellfish poisoning associated with ASP was reported in 1987 when a serious outbreak food poisoning occurred in eastern Canada. Quickly after the incident, a team of scientists discovered the cause, which was consumption of the marine biotoxin called domoic acid. The toxin is produced by marine diatoms, which belongs to the genus *Pseudo-nitzschia* and *Nitzschia*.
navis-varingica. Domoic acid can cause permanent short-term memory loss, brain damage, and death in severe cases.

![Domoic Acid](image.png)

**Figure 1. Domoic Acid**

**Diarrhetic shellfish poisoning (DSP).** The first DSP incident were in Netherlands in 1960s, followed by similar reports in late 1979 from Japan. DSP toxins can be divided into three different groups based on chemical structures. The first group, acidic toxin, includes okadaic acid (OA)\(^8\) and its derivatives dynophysistoxins (DTXs).\(^9\) The second group, neutral toxins, includes polyether lactones pectenotoxins (PTXs).\(^10\) The third group includes disulfated ployethers yessotoxins (YTXs).\(^11\) These toxins usually produced by dinoflagellates species of *Dinophysis spp.* and *Prorocentrum*. As the name implies, the syndrome manifests itself as diarrhea, although nausea, vomiting and abnormal cramps are all common.
Paralytic shellfish poisoning (PSP). The main toxins associated with PSP are saxitoxins (STX)\textsuperscript{12} which are neurotoxins. STX are naturally produced by
dinoflagellates (genera *Alexandrium*, *Gymnodinium* and *Pyrodinium*) and cyanobacteria (*Anabaena, cylindrosoermopis, Lyngbya*, etc).\textsuperscript{13} The major symptoms are neurological, including tingling, numbness in the mouth and fingertips, ataxia, giddiness, drowsiness, fever, rash. Similar to ASP, PSP can be fatal in some extreme cases, especially in immunocompromised individuals.

![Figure 3. Saxitoxin](image)

**Neurotoxic shellfish poisoning (NSP).** NSP is normally associated with the red tides in Florida, Texas, North Carolina, and Mexico. The cause of NSP is the consumption of shellfish, which are contaminated by brevetoxins (PbTx).\textsuperscript{14} These toxins are produced naturally by the dinoflagellate *Karenia brevis*. Moreover, PtTx can bind to voltage-gated sodium channels in nerve cells, which can lead to disruption of normal neurological process. Symptoms caused by NSP include vomiting, nausea, and a variety of neurological symptoms, such as slurred speech, abdominal pain, while NSP is not fatal to humans.
**Azaspiracid shellfish poisoning (AZP).** AZP is newly defined shellfish poisoning syndrome, which is associated with marine toxin azaspiracid.

### 1.2 Discovery of Azaspiracid

The discovery of Azaspiracid started with a seafood-poisoning incident in Netherland, in 1995. At least eight people became sick after consumption of blue mussel *Mytilus edulis*, which was collected in Killary Harbor, Ireland. The symptoms were very similar to that of diarrhetic shellfish poisoning (DSP), including nausea, vomiting, diarrhea and stomach cramps. But further analysis showed that the contaminations of the major DSP toxins okadaic acid (OA) and dinophysistoxins (DTXs) were very low, which means that the cause must be an unknown toxin.

In order to solve this puzzle, Yasumoto and co-workers collected 20 kg of whole mussel meat at Killary Harbor in February 1996 and succeeded in isolating 2 mg of the causative toxin named azaspiracid, which was a colorless amorphous solid. They also
proposed the structure (Figure 5) based on the extensive study of $^1$H-NMR, $^1$H- $^1$H Cosy, $^{13}$C- NMR, ROESY, HSQC, TOCSY, HMBC, FAB MS/MS, and (CID) MS/MS. As shown, azaspiracid-1 ($C_{47}H_{71}NO_{21}$) has 47 carbons (40 on the parent chain), 9 rings, and 20 stereogenic centers. The unique array of molecular frameworks includes a trioxadispiroketal fused with a trans tetrahydrofuran ring (ABCD domain), a six-membered hemiketal bridge (E domain), and a spiroaminal fused with a 2,9-dioxabicyclo[3.3.1] nonane ring (FGHI domain). At the point of isolation, the absolute configuration of azaspiracid was unknown.

![Proposed Structure of Azaspiracid-1](image)

**Figure 5. Proposed Structure of Azaspiracid-1**

### 1.3 Structure Revision of Azaspiracid-1

Due to the uncertainty of the intriguing chemical structure and the scarcity in nature, azaspiracid has spurred considerable interest among the organic chemistry community. After extensive synthetic studies, the Nicolaou group claimed to have completed the total synthesis of proposed azaspiracid-1,$^{16}$ but to their disappointment, all of the isomers $^1$, FGHI-epi-$^1$, C20-epi-$^1$ and C20-epi-FGHI-epi-$^1$ did not match the data, by TLC and
HPLC, from the naturally derived sample of azaspiracid-1, which indicated that the original proposed structure was in error.

Scheme 1. Key Degradation Intermediates of Natural Azaspiracid-1

In collaboration with the Satake group, the Nicoloau group then utilized degradation of natural samples into smaller fragments, whose chemical synthesis could narrow down
the location of structure error between synthetic and natural compounds. As shown in scheme 1, the natural sample was degraded into three key intermediates: 3, 4, 5, and 6. After comparing $^1$H-NMR spectrum from 4, the relative stereochemistry for EFGHI domain of azaspiracid-1 was predicated as the structure FGHI-epi-4. The absolute stereochemistry was further established as FGHI-epi-4, by comparison of optical rotation and $^1$H-NMR spectrum of the derived ester from 6. The biggest challenge for the structure elucidation was the ABCD part. With the huge difference in the $^1$H-NMR spectra and clue from another marine natural product lissoketal, the Nicolau group first suspected the endocyclic double bond between C8-C9 should be moved to C7-C8 in 3. Through further extensive synthetic study on 5, the relative stereochemistry of the ABCD domain was settled down, as AB-epi-5, to further accommodate the thermodynamic stability and NOE effect between 6-H and the methyl group on C13. Finally, the absolute stereochemistry (Figure 6) between the ABCD and EFGHI domains was established by total synthesis.

Figure 6. Corrected Structure of Azaspiracid-1
1.4 Analog of Azaspiracid

Shortly after the isolation of azaspiracid-1 (AZA1), four additional analogs of this toxin were isolated,\textsuperscript{19, 20} and the structures of these four analogs were also determined by MS and NMR spectroscopy techniques. Compared to AZA1, AZA2 possesses an additional methyl group on C8, and AZA3 has a C22-demethyl structure. The other two analogs (AZA4 and AZA5) proved to have oxidized structures of AZA3, showing the presence of an additional OH at either C3 (AZA4) or at C23 (AZA5).

Up to now, only AZAs 1 to 5 have had their structures verified with NMR techniques, while there are over 30 analogues\textsuperscript{21} in this toxin family, which spread from west Europe to the east coast of United States. The structures of other analogs have been solely predicted based on the analysis of fragmentation patterns of MS/MS spectra. As shown in Figure 7, the most abundant 11 analogs have been listed. The structures of AZA 6 to 11 were proposed based on those of AZA 1 to 5. Interestingly, all of them share the same FGHI domain, while the differences are mainly at the C3, C8, C22, and C23 positions.

![Figure 7. Analogs of Azaspiracids](image-url)

<table>
<thead>
<tr>
<th>Azaspiracid</th>
<th>R\textsubscript{1}</th>
<th>R\textsubscript{2}</th>
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1.5 Origin of Azaspiracid

The polyether structures of azaspiracids suggest that this neurotoxin may be produced by some kind of dinoflagellate. There have been several attempts to discover the progenitor of azaspiracids. The James Group collected the dinoflagellate sample in the southeast coast of Ireland.22 Each species of dinoflagellate was tested for the existence of azaspiracid. Only *protoperidium crassipes* (Figure 8), were found to be positive. More interestingly, only AZA1, AZA2, and AZA3 were found in the dinoflagellate, so it is believed that AZA1, AZA2 and AZA3 are likely to be the genuine products of a causative marine organism and the other analogs may be the degradation products in shellfish.

![Figure 8. *Protoperidinium crassipes* under a Microscopic view](image)

Nevertheless, detailed investigation have been conducted by the Irish Marine Institute, which failed to show any correlation between occurrence of azaspiracids in shellfish and blooms of *Protoperidinium crassipes* in a four year period (2002-2006).23 The role of *Protoperidium crassipes* was proposed by Krock and Tillmann to be an AZA
vector following grazing upon a proximal source. At the same time, they discovered a new species named *Azadinium spinosum* (Figure 9). They also proved that this newly discovered dinoflagellate did produce azaspiracids in cell culture. More interestingly, they only found AZA1 and AZA2 in the species. The question of origin of AZA3 is still unanswered.

![Figure 9. The Origin of Azaspiracids: Azadinium spinosum](image)

### 1.6 Biological Activity

*In vivo toxicology*

Before people realized the causative toxin for the food poisoning incident, toxicological studies had been carried out in mice. The intraperitoneally (IP) injected acetone extracts of contaminated blue mussels caused sluggishness, respiratory difficulties, spasms, progressive paralysis, and even death within 20-90 mins. When the partially purified azaspiracids were used in the study, it shows that IP injection of a lethal dose (> 150 µg/kg) caused swelling of the stomach and liver concurrent with reduction in size/weight of the thymus and spleen. With the assumption of the same purity degree,
the order of azaspiacid analog potency seems to be AZA2 > AZA3 > AZA1 > AZA4 > AZA4.

In an accurate oral administration, the study showed that an approximate oral minimum lethal dose was 500 µg/kg. Lower doses (300 µg/kg) induced fatty acid droplet accumulation in the liver, followed by sporadic degeneration and erosion of the small intestinal microvilli, vacuole degeneration in epithelial cells, and atrophy of the lamina propria. With mide-level doses (500 to 700 µg/kg), AZA1 could cause the injuries of both T and B lymphocytes in the spleen.\textsuperscript{27}

In another series of \textit{in vivo} studies, mice were monitored for recovery, while orally administered with repeated doses of AZA1. The recovery times for each tissue: liver = 7 days; lymphoid = 10 days; lung = 56 days, and the stomach => 12 weeks, which were much slower, compared to that associated with DSP. As far as the chronic effects, low doses repeated exposures to AZA1 could cause the lung tumor formation, which potentially poses a threat to human health.\textsuperscript{28}

\textit{In vitro toxicology}

Compared to okadaic acid (OA), AZA1 did not show any inhibition effect on PP1\textsuperscript{29} or PP2A.\textsuperscript{30} However, OA and genistein could modulate the cytosolic calcium response induced by AZA1 in human lymphocytes cells.\textsuperscript{31} With the neuroblastoma cells tested, it has been shown that AZA1 disrupts cytoskeletal structure and induces a time and dose dependent decrease of F-actin pools.\textsuperscript{30}

The effects of azaspiracids on the cytosolic [Ca\textsuperscript{2+}], intracellular pH in human T lymphocytes cells were also investigated. AZA1 induces a significant increase of [Ca\textsuperscript{2+}],
both in calcium-free and a calcium-containing medium. AZA2 could also increase the 
\([\text{Ca}^{2+}]\) level, while only in a calcium-free medium. AZA3 could also increase the calcium 
levels, while AZA4 has an opposite effect, by reducing the calcium influx. However, 
AZA5 has no effect on intracellular calcium homeostasis. The intracellular pH also has 
response with AZAs. AZA1 and AZA2 did not modify intracellular pH both in calcium-
free and a calcium-containing medium. AZA3 slightly increased pH by 0.16 units with 
the presence of extracellular calcium. AZA4 inhibited the basal pH increase, while AZA5 
did not have any effect on intracellular pH.

Unlike DSP toxins, the fact that different AZA analogs show distinct different 
biological activities is interesting and unusual for a marine toxin series of toxins, since 
each series generally show the same mechanism of action but with different potencies. 
Their different mechanistic behavior opens attractive possibilities to further SAR studies.
Chapter 2: Synthetic Efforts

2.1 Synthetic Study on the Originally Proposed Structure

Before 2004, the relative stereochemistry between the ABCDE and the FGHI domains was unknown. Moreover, the biological study of azaspiracids indicated that the basis of the toxicity also remained a mystery which made the structure-activity relationship study urgent for both of chemists and biologists. Several research groups had contributed to solve the structure puzzle through extensive synthetic studies.

2.1.1 Forsyth’s Approach

In 2001, the Forsyth group reported first synthetic study on construction of the C5-C20 trioxadispiroketal domain, which was considered the earliest publication on this topic (Scheme 2). The synthetic study highlighted a novel method for construction of highly substituted trans-tetrahydrofuran in a one-pot conversion (scheme 2). In the presence of KHMDS, the C20 primary hydroxyl group in 8 was selectively sulfonylated, which was followed by base-induced epoxide formation and intramolecular trans ring closure to furnish 10. After a series of manipulations, enone 11 was synthesized in high yields, which was planned to form the ABCD skeleton under acidic conditions.
Treatment of 11 with numerous Brønsted or Lewis acids in a variety of solvents resulted in trioxadispiroketal 12. The configurations at C10 and C13 were assigned as 10-\(R\) and 13-\(S\), based on the NOE studies and X-ray crystallography of a C5-OH derivative. Compared to the proposed ABCD structure (10\(R\),13\(R\)), molecular mechanics calculations indicated that spiroketal 12 actually was thermodynamically favored because of a double anomeric stabilization from the bis-spiroketal.

The Forsyth group also reported their synthetic effort on the C26-C40 domain of AZA1 (Scheme 3).\(^{35}\) The F-I linear precursor was synthesized through a Felkin aldol reaction between a C27-C34 aldehyde 14 and C35-C40 methyl ketone 13. A four-step transformation provided 16. After screening a variety of Lewis acid and solvent combinations, treatment of 16 with Yb(OTf)\(_3\) in CH\(_3\)CN efficiently yielded spiroaminal 17 as a single diastereoisomer. The relative configuration of the newly formed C36 stereogenic center was further confirmed by NOE studies. After a series of protecting group manipulations and E ring model coupling, a novel double intramolecular hetero-
Michael addition (DIHMA) was applied to construct the F and G rings of AZAs, which involved fluoride-induced *in situ* desilylation-bis conjugate addition.

![Scheme 3. Forsyth’s C26-C40 Domain Synthesis](image)

### 2.1.2 Nicolaou’s Approach

In 2001, the Nicolaou group also reported a synthetic study on the fragment synthesis. With the result from Forsyth’s group about the ABCD domain synthesis in mind, two different synthetic routes were tested to get the desired 13R-dispiroketal. As shown in Scheme 4, the first hypothesis was tested to use a tolyl sulfoxide (ArSO) as an...
auxiliary group to construct spiroketals. Treatment of 20 with TMSOTf removed the acetonide and TBS groups, and led to a tetracyclic system 22. NOE studies of the derived 23 showed that 22 was an undesired stereoisomeric product, which meant that the bulky tolyl sulfoxide group did not overcome the double anomeric effects.

Scheme 4. Nicolaou’s 1st Attempt towards the ABCD Domain

The second hypothesis was to utilize a hydrogen bonding effect to invert the 13S configuration of the double spiroketal system of the ABCD domain to the 13R form (Scheme 5). By a similar synthetic route, a hydroxyl group was installed at the C9 position in 24. Epimerization at C13 was achieved with acid catalysis. Upon exposure of 24 to TFA in CH₂Cl₂ at ambient temperature, an equilibrium was soon reached, providing the desired 13R product 25 in 56% yield. Recycling the starting material twice raised the yield up 80%, which made the synthetic route scalable. The structural assignment of 25
was also confirmed by observing the expected NOEs. The conformations of the two epimers 24 and 25 showed the hydrogen bonding effect between the C9 hydroxyl and the oxygen inside the BC rings with only a single anomic effect to stabilize the desired isomer, compared with the undesired, but thermodynamically favored product 24.

Scheme 5. Nicolaou’s 2nd Attempt towards the ABCD Domain

Nicolaou’s approach towards the FGHI domain is shown in Scheme 6.\textsuperscript{36} The C26-C40 precursor was synthesized through a boron-mediated aldol reaction between aldehyde 26 and ketone 13, while a chelation-controlled Mukaiyama aldol only resulted in extensive decomposition of the aldehyde 26. After a series of transformations, the spiroaminal functionality was assembled under BF\textsubscript{3}•OEt\textsubscript{2} conditions. After several steps of protecting group manipulations and C34 stereogenic center inversion, the final intramolecular ketalization was planned to furnish the FGHI skeleton of AZA1. The
condition of Hg(OAc)$_2$ in THF/H$_2$O (3:1) followed by quenching with NaBH$_4$ was found to be optimal for G ring formation, providing the desired product in 65%.

Scheme 6. Nicolaou’s Synthesis of the FGHI Domain

2.2 Synthetic Study on Revised Structure

In 2004, the Nicolaou group finally settled the debate about the structure of azaspiracid-1 through collaborative degradation and total synthesis, but the synthetic efforts towards the total synthesis never stopped, due to the challenging chemistry involved and interesting biological activity that requires SAR studies.
2.2.1 Nicolaou’s Total Synthesis of Azaspiroacids

The correct structure of azaspiracid-1 was finally assigned through Nicolaou’s first total synthesis, although the synthetic route was quite similar to previously published synthetic work towards the natural product with the originally proposed structure.\textsuperscript{18} As shown in Scheme 7, the strategic disconnections were at C20-C21 and C27-C28, providing the key synthetic precursors 32 (C1-C20 ABCD domain), 33 (C21-C27 E domain), and 34 (C28-C40 FGHI domain). The lithiated dithiane coupling strategy was planned to couple the ABCD and E domains, and a C(sp\textsuperscript{2})-C(sp\textsuperscript{3}) Stille coupling was applied to link ABCDE and FGHI domains. The main benefit of this synthetic plan was to allow the necessary flexibility to address the relative stereochemistry issue of the natural product.

Scheme 7. Nicolaou’s Retrosynthetic Analysis of Azaspiracid-1
Construction of the ABCD domain started with phosphonate 35, which was synthesized from L-malic acid (Scheme 8). Following the previously reported synthetic route, intermediate 36 was prepared in 12 steps in good yields. To facilitate the cyclization to the ABCD domain, the C17-O-TBS group of 36 was converted into an O-TES by a deprotection and selective reprotection process, followed by cleavage of the terminal olefin to give aldehyde 37. Lithiated dithiane coupling between C10-C20 domain 37 and C5-C9 domain 38 produced 39 as 1:1 mixture of diastereomers, which was then oxidized to a ketone with DMP. Exposure of the resultant ketone moiety to TMSOTf at low temperature (-90 °C) successfully triggered the deprotection-double spirocyclization process, which delivered the tetracyclic product 40 as a single stereoisomer. A following Swern oxidation converted the C5 primary alcohol to aldehyde 41, followed by a Wittig olefination to furnish the desired terminal olefin 42. Cross-metathesis of 42 with the side chain 43 was executed with the 2nd generation Grubbs catalyst, yielding the corresponding E-olefin 32 as the major product. Treatment of 32 with Ph(OCOCF₃)₂ removed the dithiane functionality, leading to the ketone 44. The endocyclic C7-C8 double bond was then set up through a Mukaiyama method with 81% yield. The C9 ketone moiety was then reduced in three steps, involving conversion of the ketone into allylic ester 45 and the application of a palladium-catalyzed reductive protocol to furnish 46. The C20 TBDPS protecting group was removed under TBAF conditions. The resulting primary alcohol was then oxidized into a carboxylic acid in two steps. After screening different leaving groups for the later dithiane coupling, the pentafluorophenyl ester 47 was chosen to be the C21-C40 coupling partner, which was
synthesized through DCC-catalyzed esterification between the resulting carboxylic acid and pentafluorophenol.
Scheme 8. Nicolaou’s Synthesis of the ABCD Domain
The preparation of the FGHI domain started with the same boron mediated aldol reaction between aldehyde 48 and ketone 49. The FGHI framework was constructed through a previously reported synthetic route. The ketone moiety was then functionalized into an enol triflate with the Comin’s reagent. The enol triflate was then converted into vinyl stannane 34 under palladium conditions.

Scheme 9. Nicolaou’s FGHI Domain Synthesis

Scheme 10 shows the final part of the Nicolaou’s total synthesis. The dithiane-based coupling was applied to link the ABCD domain 32 and 33. Initially, traditional bases (t-BuLi, n-BuLi) were applied to generate a carbon anion, which led to no product containing both domains in various solvents and different temperatures. Control
experiments revealed the reason that the derived anion could not be trapped with the ABCD aldehyde is due to a short lifetime of the anion itself. Then $n$-BuLi-$n$-Bu$_2$Mg was employed to provide a longer lived organometallic intermediate which delivered the desired product in 50% yield. The reduction of the C20 ketone functionality was then stereoselectively achieved under DIABL conditions, affording a diol intermediate formed by concomitant cleavage of the pivaloate ester at C1. A three-step protecting group manipulation produced 54. The Stille reaction was then planned to couple ABCDE domain 54 and FGHI domain 34. After screening conditions of catalysts and ligands, AsPh$_3$ was chosen to be an additional ligand which would result in the desired compromise between the reaction rate increment and stereochemical integrity preservation at C25. Under buffered condition of HF•Py, the TES group was then selectively removed, which was then followed by closure of the G ring promoted by NIS to produce the azaspiracid skeleton. The resulting iodide was then removed effectively. The C20 hydroxyl was then protected as TES ether. The C1 alcohol was revealed under basic conditions, and converted into a carboxylic acid in a two-step sequence. Finally, a global deprotection delivered the natural product. The Nicolaou group also completed the total synthesis of AZA2 and AZA3 with similar synthetic strategies.$^{38}$
Scheme 10. Nicolaou’s Total Synthesis of Azaspiracid-1
2.2.2 Evans’ Total Synthesis of (+)-Azaspiracid-1

In 2007, the Evans group finished the total synthesis of unnatural (+)-azaspiracid-1 in 26 linear steps and 2.7% overall yield from the aldol reaction between the siloxyfuran and ethyl glyoxalate in the FG fragment synthesis. As shown in Scheme 11, the disconnection was between C20 and C21 to provide precursors 58 and 59. The addition of an anomeric sulfone derived from 59 to the ABCD domain 58 was planned to give the azaspiracid skeleton. In the synthetic plan, all of the nine rings are fully constructed prior to the coupling, which reduced the number of manipulations after the coupling step.

Scheme 11. Evans’ Retrosynthetic Analysis
Scheme 12 shows the synthetic work on the ABCD domain. The A ring (pyran) and D ring (trans-furan) were set up before the sulfone coupling between 60 and 61. The sulfone deprotonation with LDA and addition to aldehyde 61 provided a C1-C20 precursor as a mixture of four hydroxyl sulfone, which was oxidized to produce a ketosulfone intermediate. Exposure of resulting ketone to sodium amalgam removed the sulfone moiety, providing the ketone 62 as a single diastereomer. For the later spiroketal cyclization, the TES ether was then selectively removed with one equivalent of TBAF at low temperature (-20 °C). The ABCD domain skeleton was then constructed under acidic conditions (PPTS, CH₂Cl₂). The chemoselective cleavage of the TBDPS ether and subsequent Parikh-Doering oxidation afforded the aldehyde 58.

![Scheme 12. Evans’ ABCD Domain Synthesis](image-url)
Scheme 13 shows the EFGHI synthetic work. A chelation-controlled Mukaiyama aldol reaction between aldehyde 64 and silyl enol ether 65 was planned to produce a C27-C40 linear precursor 66. After screening reaction conditions, the freshly prepared MgBr$_2$•OEt$_2$ was found to be superior to other Lewis acids such as TiCl$_4$, SnCl$_4$, MgI$_2$, MgBr$_2$ and commercial MgBr$_2$•OEt$_2$. The E ring domain 67 was then incorporated into 66 through a boron mediated aldol coupling to deliver 68 in quantitative yield. Upon exposure of 68 to aqueous HF, the TBS group was removed and the resulting triol cyclized to form the FG bridged ketal spontaneously. The C26 secondary alcohol was then converted to ketone 69 under DMP conditions. The PMB moiety in 69 was oxidatively removed and the azide functionality was then reduced using palladium, which also induced the thermodynamically favored spiroaminal formation to afford 70. The spiroaminal nitrogen was protected as Teoc carbamate. To avoid C36 epimerization, a buffered Tebbe reagent was applied to convert C26 ketone to an olefin. The sulfide was then oxidized to sulfone 59 as the coupling partner of 58. The synthesis of the EFGHI domain was achieved in 22 linear steps and 10% overall yield.
After extensive study, the sulfone anion derived from 59 generated from $n$-BuLi, was added to aldehyde 58. The reaction was quenched by pH = 5 aqueous buffer at $-78^\circ$C (Scheme 14). The products were separable C20 epimers (1:1) a 50% combined yield. The
undersired C20 isomer could be converted into the desired isomer 71 in an oxidation/reduction sequence. The two silyl protecting groups were then removed with buffered TBAF. A two-step oxidation of resultant C1-C40 alcohol delivered the unnatural azaspiracid-1.

Scheme 14. Evans’ Total Synthesis of (+)-Azaspiracid-1

2.2.3 Forsyth’s Approach

In 2004, the Forsyth group reported the independent analysis of the relative stereochemistry of the A-D ring system through extensive NMR study and developed a revised structure model. As shown in Scheme 15, the model was then confirmed through synthesis. For convenience, the C19 epimer 73 was used for the later synthesis.
Addition of Gilman reagent 72 to aldehyde 73 provided secondary alcohol 74, which was then oxidized to a ketone intermediate. Removal of the TMS group with AgNO₃/KI resulted in partial cleavage of the TES ether, which was then re-protected to give 75. Iodination of the free alkyne was achieved with AgTFA/NIS at low temperature (0 °C). An organochromium-mediated coupling between alkynyl iodide 76 and aldehyde 77 efficiently delivered propargylic alcohols 78, which were then oxidized to ynone 79 as the precursor of the DIHMA process. Exposure of 79 to TsOH·H₂O promoted selective cleavage of the C6 and C17 silyl ethers and subsequent trioxadispiroketal formation. The structure of the thermodynamic product 80 was then established on the basis of MS and extensive NMR studies. More importantly, the NMR analysis showed the correlation of the synthetic compound 80 with the corresponding fragment of natural product, which validated the model proposed by the authors.
In 2007, the Forsyth group reported another novel synthesis of the C5-C20 domain of azaspiracid-1, which featured a gold(I)-catalyzed bis-spiroketalization.\(^{41}\) As shown in Scheme 16, the construction of the trisubstituted 2,5-trans tetrahydrofuran ring (D ring) was achieved through a cobalt-catalyzed oxyetherification methodology. A two-step protecting group manipulation converted \(\text{82 to 83,}\) which was then oxidized to lactone \(\text{84}\) using TEMPO/BAIB. Lactone \(\text{84}\) was then treated with a Grignard reagent followed by PPTS/MeOH to deliver alkynyl ketal \(\text{86}\) as a CD ring precursor. A copper-mediated coupling between A ring precursor \(\text{87}\) and \(\text{86}\) was applied to give enyne \(\text{88}\) with
moderate yield. The acetate was reductively removed to afford the allylic alcohol 89. After screening various metal salts, it was found that enyne 89 was cleanly converted into desired trioxadispiroketal 90 in excellent yield under gold (I) conditions. The authors also proposed the plausible mechanism for this efficient transformation. A syn addition of the C6 free hydroxyl to gold(I) activated C10-C11 alkyne initiated the whole process to form the pyran ring. The following protiodeauation liberated the catalyst and protonated the resulting enol ether. The C13 methoxy oxygen then nucleophilically attacked C10 to furnish the B ring. Transfer of the methyl group would quench the resulting oxocarbenium species and delivered the final product. The highlighted gold chemistry was one of the earliest applications in complex molecule synthesis.
Scheme 16. Forsyth’s Gold-Catalyzed ABCD Domain Synthesis
The Forsyth group also reported synthetic work on the FGHI domain of azaspiracids, which were used as synthetic haptens for biological studies. A chelate-controlled Mukaiyama aldol reaction coupled the FG aldehyde 91 and HI ketone 92, delivering FGHI linear precursor 93 (Scheme 17). A two-step protecting group manipulation converted 93 to 95, involving C34 silyl protection and C33 oxidative PMB cleavage. The resultant azido-keto-alcohol 95 was transformed to spiroaminal 96 through a one-pot Staudinger reduction/intramolecular aza-Wittig reaction. The spiroaminal amine was then protected as a carbamate and the TMS-alkyne was then converted into iodo alkyne 97. An NHK reaction was applied to couple 97 and ethyl 6-oxo-hexaoate. The resultant propargylic alcohols were then oxidized into ynone 98 under MnO2 conditions. The bridged ketal 99 was constructed by exposure of 98 to TBAF.
2.3 Carter’s approach

In 2006, the Carter group reported their initial synthetic study on the ABCDE domain. A sulfone derived anion from 100 under the influence of n-BuLi and 2,2,6,6-tetramethylpiperidine nucleophilically attacked aldehyde 101, yielding the C4-C19 domain of AZA1 (Scheme 18). The resultant secondary hydroxyl was then oxidized to a ketone. Exposure of ketone 103 to PPTS in THF/H2O cleaved the O-TES ether and initiated the spiroketalization process. Unfortunately, both of the thermodynamic and
kinetic dispiroketalts were obtained. It was found that a free C4 hydroxyl would facilitate a clean conversion of the undesired kinetic product cis-dispiroketal 105 into the desired trans-dispiroketal 106 under CSA conditions. The C4 hydroxyl was then reprotected as TBS ether, and debenzylation with LiDBB provided diol 107. An oxidation/reduction sequence was then applied to produce lactol 108 as the ABCD domain of AZA1. A Wadsworth-Emmons coupling between 108 and E ring precursor 109 with in situ, intramolecular hetero-Michael addition yielded 110 with the correct stereochemistry at C19 of the D ring. The C20 secondary hydroxyl was set up through treatment with NaHMDS and a large excess of Davis oxaziridine, which gave the undesired isomer based on Mosher ester analysis. A two-step sequence successfully inverted the C19 stereocenter, while a direct one-step Mitsunobu reaction proved to be problematic. The C4 O-TBS ether was cleaved with CSA to provide 111, which was prepared to set up the C1-C4 side chain of the ABCD domain. Selenation and oxidation/elimination with unusual TPAP/NMO conditions yielded the reactive bisallylic pyran 112. Finally, selective olefin metathesis using the 2nd generation of Grubbs catalyst with 113 delivered C1-C26 domain of AZA1.
Scheme 18. Carter’s C1-C26 Domain Synthesis
In the same year, the Carter group also reported a synthetic route to the FGHI domain.\textsuperscript{44} Similar to Forsyth’s 1\textsuperscript{st} generation FGHI synthesis,\textsuperscript{35} Felkin aldol reaction was applied to couple FG precursor 115 and HI precursor 116. The H ring methoxy ketal was formed in a two-step sequence, involving C32-O desilylation and acid-catalyzed ketalization. The undesired C34 stereocenter was inverted under Mitsunobu conditions. The C28 alkene was cleaved upon treatment with K$_2$OsO$_4$·2H$_2$O, followed by NaIO$_4$. Exposure of 120 to TBAF resulted in removal of the C32 TIPS ether as well as the C34 $p$-nitrobenzoate. After screening a variety of solvents, the CSA/MeOH was found to be optimal for the construction of FG bridged ketal. Azide reduction and Teoc protection provided 121. The I ring was finally closed under the influence of Yb(OTf)$_3$, which gave both the thermodynamic product 122 and kinetic product 123 in a 4:3 ratio. The minor product 123 was recycled by resubmission to the identical conditions to generate 122 and 123 with the same 4:3 ratio.
Scheme 19. Carter’s FGHI Domain Synthesis
Chapter 3: Research Progress and Discussion

In our group, we had previously synthesized both the ABCD and EFGHI domains. The current research mainly focuses on how to complete the total synthesis of natural products, exploring a reliable and efficient coupling strategy between corresponding ABCD and EFGHI domains. With this purpose, the author’s contributions to this research project are mainly in three parts: (1) A-I fragment synthesis in the Yamaguchi esterification route; (2) efforts on the optimization of the FGHI synthetic route highlighting gold-catalyzed spiroaminal and bridged ketal formation; (3) a new generation of the EFGHI domain for a Nozaki–Hiyama–Kishi (NHK) coupling route.

3.1 Yamaguchi Esterification Route

As show in Scheme 20, our current synthetic target is azaspiracid-3 (AZA3). The strategic disconnection is at the C21-C22 linkage to yield intermediate 125 (Scheme 20). An intramolecular Babier-type reaction\textsuperscript{45} was planned to form the hemi-ketal moiety. To avoid potential C26 alkene migration, a lithium-halogen exchange was preferred using the samarium conditions. Disconnection at the ester bond divided the molecule into two parts: the C1-C21 domain 126 and C22-C40 domain 127.\textsuperscript{46}
Scheme 20. Retrosynthetic Analysis

3.1.1 ABCD Domain Synthesis

Compared with previous C1-C20 domain syntheses, the current ABCD target contains one more carbon, that represents C1-C21 part of azaspiracid-3. So our synthetic plan was also revised, especially on the CD ring fragment synthesis. With this in mind, the construction of the trioxadispiroketal, as shown in Scheme 21, relied on an acid-catalyzed spiroketalization of hydroxy ketone 128. Disconnection of C12-C13 linkage gave a chance to utilize a reliable and efficient NHK coupling reaction\(^47\) between C1-C12 iodide 129 and C13-C21 aldehyde 130. It is worth to mention that the C1-C5 side chain was set up prior to the NHK coupling reaction. The trisubstituted \textit{trans}-tetrahydronfuran ring was functionalized through a Kishi protocol.\(^48\)
Scheme 21. Retrosynthetic Analysis of the ABCD Domain

Starting from D-mannitol, glyceraldehyde 132 was synthesized in two steps (Scheme 22). A mild Reformatsky reaction was preferred over the Grignard reaction, providing exclusive S-homo allylic alcohol, which was then protected as PMB ether 134. The following hydroboration and oxidation process transformed the terminal olefin into primary alcohol 135. A Swern oxidation\(^4^9\) was applied to produce aldehyde 136. Addition of TMS acetylide to aldehyde 136 delivered a mixture of propargylic alcohols, which was then oxidized into ketone 138 under the Parikh-Doering conditions.\(^5^0\)
Once having ynone 138, a short sequence was allowed to construct the A ring skeleton (Scheme 23). Exposure of ynone 138 to TsOH•H2O/MeOH triggered the removal of the acetonide moiety and cyclization to form ketal 139 as a major product. The anomeric unfavored C10-S ketal was separable from 139 through flash chromatography and could be transformed to the thermodynamic product 139 on resubmission to the same acid conditions. The C5 primary alcohol was then oxidized to aldehyde 140. Because of the instability of the α-H, the resultant aldehyde was quickly converted into vinyl iodide 141 under Takai olefination conditions. A co-solvent of 1,4-dioxane and THF was used to increase the E/Z ratio up to above 15:1. A sp³-sp² Suzuki coupling was then applied to install the C1-C4 side chain, efficiently delivering C1-C12 domain of azaspiracid-3.
As shown in Scheme 24, the installation of the C7-C8 double bond was then addressed. Oxidative removal of the C7-O-PMB group resulted in the corresponding secondary alcohol, which was then oxidized into a ketone. Under the influence of kinetic conditions, the ketone moiety 144 was then functionalized into vinyl triflate 145 with Comins’ reagent.\(^{53}\) It is worth mentioning that no epimerization was found at the C6-bis allylic position during the oxidation and the vinyl triflate formation process. A Stille reduction\(^ {54}\) with LiCl additive was then applied to fully set up the endocyclic double bond with excellent yield. The TMS-alkyne was then converted into iodide 129 under AgTFA/NIS conditions.
Scheme 24. Synthesis of the Iodide 129

Scheme 25 summarized the synthesis of CD ring precursor aldehyde 149 and silyl enol ether 154. The synthesis of the C13-C17 segment started with the known compound 147. The alcohol functionality in 147 was first protected as a benzylidene acetal, which was then kinetically opened to afford primary alcohol 148. The resultant alcohol was oxidized to aldehyde 149. The C18-C21 segment synthesis started with the commercially available ester 150. The Sharpless asymmetric dihydroxylation (SAD) of ethyl crotonate 150 produced diol 151 with excellent yield. Due to being slightly more accessible than the β-hydroxyl, the α-hydroxyl in 151 was selectively protected as its triisopropylsilyl ether. The ethyl ester was reduced by DIBAL to afford a diol which was then selectively protected as a pivaloate ester. The C19 secondary alcohol was oxidized to ketone 153, which was then converted into silyl enol ether 154 under Et$_3$N/TMSOTf conditions.
Once we had aldehyde 149 and silyl enol ether 154 in hand, we started to address the combination of the two segments into our planned CD fragment 130 (Scheme 26). A chelate controlled Mukaiyama aldol reaction\(^{57}\) was applied to couple 149 and 154. After screening a variety of Lewis acids and chelation groups on the \(\alpha\)-position of the carbonyl,\(^{58}\) it was found that the combination of \(\text{SnCl}_4\) and \(O\)-Bn provided the best result with 76% yield and 10:1 diastereoselectivity. A two-step protecting group manipulation converted the resultant \(\alpha\)-hydroxy ketone 155 into \(\beta\)-hydroxy ketone 156. Upon purification, 156 was obtained as an equilibrium mixture of hydroxyl ketone and hemiketal. A Kishi reduction was then planned to deliver the trisubstituted tran-
tetrahydrofuran. The typical conditions (BF$_3$•OEt$_2$/Et$_3$SiH, at –78 °C) could afford the desired product and the C13 O-TBS was concomitantly cleaved. But a significant amount of side products were also detected. Different Lewis acids were screened, providing SnCl$_4$ as the best choice for the Kishi reduction. The trans-selectivity of Kishi reduction could be explained in terms of stereoelectronic effect (Figure 10). Mechanistically, the initially formed oxocarbenium ion would adopt a half envelop conformation, in which the large alkyl side chain is in a pseudo equatorial postion. Based on Woerpel’s research, the hydride would have the “inside attack” to yield the trans product with lowest energy conformation. The C13 primary alcohol was oxidized to aldehyde 130 as the NHK coupling partner.

Scheme 26. CD Fragment Synthesis
The advanced stage of the ABCD domain synthesis is illustrated in Scheme 27. The NHK reaction was applied to couple the iodide 129 and the aldehyde 130. The resultant mixture of propargyl alcohols 158 was oxidized into an ynone, which was then reduced to ketone 128 with the Stryker’s reagent in degassed solvent. The C17 O-acetate was removed under basic conditions. Exposure of the hydroxy ketone to acid conditions (PPTS, CH₂Cl₂, 0 °C) triggered the formation of the dispiroketal. The C10 and C13 contrathermodynamic dispiroketalts were not observed in the cyclization process. To this point, the protected C1-C21 domain of AZA3 was achieved convergently and efficiently. Then protecting group manipulations were investigated for the later Yamaguchi esterification. A C20 protected alcohol and C21 carboxylic acid was needed. Different α-O-protecting groups (PMB, TIPS, etc) were tested, while the electron withdrawing pivaloate (Piv) group at C20 gave the best result for the subsequent esterification coupling process. Selective desilylation was achieved with TBAF at low temperature. A migration process was needed for the installation of C20 pivaloate. After screening a variety of basic conditions, the combination of DBU/MeCN afforded the optimal result. The yield for pivaloate migration from C21-O to C20-O could be up to 80% after several recycle process. The resultant primary alcohol 160 was then converted into carboxylic
acid 126 through a two-step sequence: Parikh-Doering oxidation\textsuperscript{50} and Krause-Pinnick oxidation.\textsuperscript{61}

Scheme 27. Synthesis of the C1-C21 Carboxylic Acid 126

3.1.2 EFGHI Domain Synthesis

The synthetic plan is outlined in Scheme 28. The fully functionalized architecture 127 was planned to be assembled from the linear C22-C40 linear precursor 161. Disconnection at C26-C27 and C34-C35 linkage gave the E fragment 164, FG fragment
Compared with previous EFGHI domain syntheses,\textsuperscript{62} one less carbon (C21) was cut from the EFGHI domain and incorporated into ABCD carboxylic acid 126. A newly designed synthesis of 164 was needed, while FG fragment 163 and HI fragment 162 could be prepared from the previously developed synthetic route.\textsuperscript{62} A reliable and efficient NHK reaction was planned to couple aldehyde 164 and iodide 163. A chelate-controlled Mukaiyama aldol reaction was recognized to yield the β-hydroxy ketone 161 from an EFG ring precursor aldehyde and HI fragment 162.

\begin{verbatim}
Scheme 28. Rerosynthetic Analysis of the EFGHI Domain.
\end{verbatim}

The synthesis of the E fragment aldehyde 164 commenced with the protection of the secondary alcohol as an MTM acetal in 165 (Scheme 29). The MTM protecting group
deserves a comment. The C28 ketal in this domain was constructed under TBAF conditions, while silyl protecting groups in the same position consistently gave low yields of desired product. Through extensive analysis and experiments, Dr. Ding chose the MTM as the C25 protecting group. Hydroboration and oxidation of olefin 166 afforded alcohol 167 in moderate yield. Because the MTM group was sensitive to oxidation conditions, the alkyl boron intermediate was treated with care to avoid potential oxidation of the sulfide into a sulfoxide. A two-step protecting group manipulation converted the resultant 167 into C26 primary alcohol 168. A Parikh-Doering oxidation of 168 efficiently delivered aldehyde 164.

Scheme 29. Synthesis of the Aldehyde 164

With aldehyde 164 in hand, the process for the assembly of the EFG linear precursor began (Scheme 30). The secondary alcohol 169, with 6:1 diastereomeric ratio at C32 stereocenter, could be synthesized by a well-established route. Alcohol 169 was
converted into iodide 163 in two steps: silyl protection and conversion of the TMS-alkyne into an iodo-alkyne. During the silyl protection step, it was noticed that the undesired C32 isomer was silylated slower than the desired C32 isomer, due to the steric effect, resulting in increment of the C32 diastereomeric ratio, which could also be considered as a kinetic resolution step. A NHK coupling between resultant iodide 163 and aldehyde 164 efficiently delivered propargylic alcohols 170. A selective desilylation with HF·Py/Py liberated the C34 alcohol which was then oxidized into aldehyde 171 under Parikh-Doering conditions. The propargylic alcohol moiety was concomitantly converted into an ynone, which acted as a Michael acceptor in the later DIHMA process.

Scheme 30. Synthesis of the EFG aldehyde 171

The final construction of the complex EFGHI architecture is outlined in Scheme 31. As planned, a chelate-controlled Mukaiyama aldol reaction between silyl enol ether 92 and aldehyde 171 was applied to deliver the C22-C40 domain linear precursor 161 with
excellent yield and high diastereoselectivity. Silylation of the resultant β-hydroxy ketone and oxidative cleavage of the C33 PMB ether efficiently afforded a γ-hydroxy ketone intermediate. The H ring was first cyclized as cyclic mixed methyl ketal 172 under acid conditions (PPTS/MeOH). Exposure of resultant methoxy ketal 172 to TBAF conditions initiated the double intramolecular-hetero-Michael addition (DIHMA) process. More specifically, the silyl groups on C32 and C34 were removed to generate the nucleophilic oxygen anions, which attacked the C26-C28 Michael acceptor ynone functionality. Subsequently, the azide functional group was reduced into an amine, by Ph₃P/MeOH/MeCN, and the amine was protected as Teoc carbamate in-situ. A Wittig reaction converted the C26 carbonyl into olefin 174 in moderate yield. During the Wittig process, a side product was observed, which was identified as a C22 primary alcohol. Re-acylation easily transformed the alcohol into acetate 174. Treatment of 174 with Nd(OTf)₃ delivered the spiroaminal intermediate, in which a separable C36 epimers with a 3:1 ratio were obtained. The use of the unusual Nd(OTf)₃ was essential for the effective formation of spiroaminal functionality. As aforementioned in Chapter 2, the Forsyth group first discovered Yb(OTf)₃ catalyzed spiroaminal formation in the FGHI domain synthesis of AZA1. Following Forsyth’s result, Nicolaou and co-workers systematically screened lanthanide Lewis acids to further optimize the ring closure process, which revealed Nd(OTf)₃ to be optimal. The undesired epimer could be isomerized into desired one when submitted into the same reaction conditions. Finally, the C25 O-MTM was cleaved under customized conditions, delivering a fully functionalized C22-C40 domain of AZA3.
Scheme 31. Synthesis of the C21-C40 Domain of AZA3
3.2 Efforts towards FGHI Domain Synthesis with Gold(I) Catalysis

As shown in Scheme 31, several steps in the final stage of the EFGHI domain synthesis consistently gave unacceptably low yields and limited our scale-up process for the total synthesis of target molecule, which made this fragment synthesis route impractical. We then planned to explore an alternative route to construct the same architecture. It was recognized that the oxidation state of a ketone is equivalent to that of an alkyne. As shown in Figure 11, the FGHI domain of AZA3 bears the bridged ketal at C28 and spiroaminal at C36 carbons as ketone oxidation state. It was realized that there were unique opportunities to develop and apply emergent gold chemistry to build the complex architecture of the FGHI domain, based upon intramolecular heteroauration of embedded alkynes.

Figure 11. Ketal and Spiroaminal in the FGHI Domain of AZA3
3.2.1 Gold-Catalyzed Ketallizations

As early as 2005, Genet and co-workers reported the first example of Au(I) and Au(III) catalyzed cycloisomerization of bis-homopropargylic diols leading to strained dioxabicyclic ketals. Conversion of diol 176 into ketal 177 was achieved efficiently under very mild conditions and in very short time (Scheme 32). The authors also stated that the reaction conditions were compatible with various functional groups. In 2006, the Krause group reported a mild and efficient tandem cycloisomerization-hydroalkoxylation of homopropargylic alcohols to tetrahydrofuranyl ethers. In presence of gold catalyst, silver additives, and a Brønsted acid, the alcohol 177 cyclized into ethoxy ketal 178. The reaction could be carried out in various solvents, including alcohols, with both terminal and internal alkynes as the substrates. Recently, the Apoick group at the University of Florida reported an interesting gold-catalyzed isomerization reaction, which is the gold-catalyzed cyclization of monopropargylic triol 179 to produce the unsaturated spiroketal 180. The reactions are rapid and high yielding with 2 mole % of gold complex and silver additive at low temperature. Due to the excellent activity of Au(I) and Au(III) catalysts, more gold catalyzed transformations are being developed and designed.
As described above, internal and terminal alkynes provide an ideal platform to construct a variety of ketals under the influence of gold catalysts. Compared to ketallization with hydroxy ketone substrates, gold chemistry was shown to be more atom-economic and reliable, especially when the hydroxy ketone substrate bears an α-stereocenter, there could be potential epimerization problems. As such, gold chemistry has become employed increasingly in natural product syntheses. As shown in Scheme 33, four examples were listed for the applications of gold-catalyzed ketalizations in natural products synthesis. As descried in a previous chapter, the Forsyth group reported the construction of trioxadispiroketal system of azaspiracid with the utilization of AuCl/PPTS, which was considered one of the earliest examples for the applications of gold methodology. In the course of the total synthesis of (-)-ushikulide A, a planned Pd-catalyzed spiroketallization of triol derivative of 181 provided only limited reactivity.
While platinum compounds also failed, Trost and co-workers turned their attention to more versatile gold chemistry. After screening a variety of gold catalysts and protecting groups on the C21 alcohol, it was found that benzoate ester 181 successfully avoided the elimination of the propargylic position under AuCl/PPTS conditions. Recently, the Forsyth group reported a formal total synthesis of okadaic acid, highlighting the regiocontrolled gold-catalyzed spiroketallizations. Both the C19 and C34 spiroketals of okadaic acid were assembled under gold conditions. More interestingly, exposure of 183 to AuCl at low temperature (0 °C) triggered the ketalization and elimination of the propargylic alcohol functionality, resulting in the C28-C38 fragment of okadaic acid. This was the first application of Aponick’s method in the natural product synthesis.
Scheme 33. Examples of Applications of Gold-Catalyzed Transformations in Natural Product Synthesis

3.2.2 Gold-Catalyzed Spiroaminal Formation

The gold-catalyzed ketalization has been well-established, while little information, could be found for gold-catalyzed spiroaminal formation. Due to the novel and attractive structure, several methods were explored to construct various spiroaminals. The strategies
to construct spiroaminal moieties were summarized by Sinibaldi and Canet\textsuperscript{70} in three different strategies (Scheme 34). Strategy I involves inter- or intra-molecular ring closure reactions from imidate or aminal compounds as precursors. In strategy II, monocyclization of piperidine or pyran derivatives could be applied to produce spiroaminal core structures. In strategy III, formation of bicyclic cores could also be achieved through double cyclization, in one step, from a ketone linear precursor. Our proposal to construct the C36 spiroaminal moiety through gold catalysis required an initial investigation of new synthetic route to spiroaminal cores, which is the strategy IV. An internal alkyne, instead of a ketone, was prepared to cyclize into spiroaminals under gold conditions.

Scheme 34. Summary of Synthetic Route for Spiroaminals.
A model compound 191 was synthesized in a short manner. The synthesis commenced with silyl protection of 5-hexyn-1-ol followed by nucleophilic opening of propylene oxide. A three-step sequence converted homopropargylic alcohol 188 into acetate 189, which involved acylation, desilylation and sulfonylation. Substitution of sulfonate 189 with sodium azide and clavage of acetate resulted in homopropargylic alcohol 190. Finally, the azide moiety was reduced to amine 191 in gram scale under Staudinger conditions. Different protecting groups were then tested to modify the nucleophilicity of the nitrogen atom.

Scheme 35. Synthesis of Spiroaminal Model Compound

Once the model compounds were addressed, different conditions were tested to reach the spiroaminal structure. Without protecting groups on nitrogen, Au(III) was initially tested with different temperatures, because it was known that hydroamination of alkynes could be achieved with AuCl₃/MeCN. Only the alkyne hydration product was obtained based under these conditions on NMR spectroscopic analysis, which meant gold catalysis did activate the alkyne functionality, but no cyclization occurred while the addition of
water resulted in hydroxy ketone. Addition of Nd(OTf)$_3$ into the systems gave the same result. A commonly used Cbz protecting group was incorporated into the substrate. Treatment of the carbamate with Au(I) catalyst activated with silver triflate still gave the hydration product. Based on the Krause’s study, the solvent was changed to methanol, and it was found that only a hydration product was obtained after careful flash chromatography. Later study showed that the actual product was cyclic mixed methyl ketal, which could transformed into a hydroxy ketone upon silica gel chromatography. Nevertheless, a trace amount of the spiroaminal 194 was produced once changing the solvent to CH$_2$Cl$_2$. The product was confirmed by NMR spectroscopic studies, and we also synthesized the same spiroaminal through a known procedure, which was PPTS-catalyzed methoxy ketal formation followed by cyclization under Nd(OTf)$_3$ conditions. The $^1$H- and $^{13}$C-NMR of two spiroaminal products were identical! The diastereomeric ratio of the resultant spiroaminals was 3:1, based on NMR spectrum. In contrast to the gold-catalyzed spiroketalization, the anomeric effect between N and O atom could not dominate the diastereoselectivity outcome of spiroaminal formation. A high temperature indeed gave us a slightly higher yield. Finally, the protecting group was changed into sulfonamide which started to give us satisfied yield.
Table 1. Conditions Tested to Construct Spiroaminals

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>AuCl₃, MeCN</td>
<td>hydration product</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>AuCl₃, MeCN, 40 °C</td>
<td>hydration product</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>AuCl₃, Nd(OTf)₃, MeCN</td>
<td>hydration product</td>
</tr>
<tr>
<td>4</td>
<td>Cbz</td>
<td>AuCl, AgOTf, MeCN</td>
<td>hydration product</td>
</tr>
<tr>
<td>5</td>
<td>Cbz</td>
<td>AuCl, AgOTf, MeOH</td>
<td>hydration product</td>
</tr>
<tr>
<td>6</td>
<td>Cbz</td>
<td>AuCl, AgOTf, CH₂Cl₂</td>
<td>~ 10% spiroaminal 194</td>
</tr>
<tr>
<td>7</td>
<td>Cbz</td>
<td>AuCl, AgOTf, Toluene, 80 °C</td>
<td>30% spiroaminal 195</td>
</tr>
<tr>
<td>8</td>
<td>Ts</td>
<td>AuCl, AgOTf, CH₂Cl₂</td>
<td>60% spiroaminal 196</td>
</tr>
</tbody>
</table>

The optimization for this newly discovered gold-catalyzed spiroaminal formation is illustrated in Table 2. Different solvents were screened, which showed that the less polar solvents gave higher yields. An 18% yield was obtained with MeCN, while toluene afforded the spiroaminal in 91%. The nitrile of acetonitrile solvent may chelate with the gold catalyst, resulting in a lower efficiency of the catalyst. Gold (III) chloride could also deliver the spiroaminal in moderate yield. The commonly used gold catalyst Ph₃PAuCl did not promote the cyclization. Once some silver additive (AgOTf) was added, the catalyst system became quite efficient for this transformation, while the combination of AuCl/AgOTf consistently gave a lower yield (67%) than that of AuCl without any silver...
additives. These results indicated that it was important to understand the specific details required for the transformation with the specific gold catalyst system.

![Chemical structure](image)

Table 2. Optimization of Gold Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Time</th>
<th>Yield</th>
<th>d.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 mol% AuCl</td>
<td>MeCN</td>
<td>1 h</td>
<td>18%</td>
<td>3 : 1</td>
</tr>
<tr>
<td>2</td>
<td>5 mol% AuCl</td>
<td>CH₂Cl₂</td>
<td>1 h</td>
<td>70%</td>
<td>3 : 1</td>
</tr>
<tr>
<td>3</td>
<td>5 mol% AuCl</td>
<td>THF</td>
<td>1 h</td>
<td>70%</td>
<td>3 : 1</td>
</tr>
<tr>
<td>4</td>
<td>5 mol% AuCl</td>
<td>Toluene</td>
<td>1 h</td>
<td>91%</td>
<td>3 : 1</td>
</tr>
<tr>
<td>5</td>
<td>5 mol% AuCl₃</td>
<td>Toluene</td>
<td>1 h</td>
<td>78%</td>
<td>3 : 1</td>
</tr>
<tr>
<td>6</td>
<td>5 mol% Ph₃PAuCl</td>
<td>Toluene</td>
<td>1 h</td>
<td>NR</td>
<td>3 : 1</td>
</tr>
<tr>
<td>7</td>
<td>5 mol% Ph₃PAuCl</td>
<td>Toluene</td>
<td>1 h</td>
<td>85%</td>
<td>3 : 1</td>
</tr>
<tr>
<td>8</td>
<td>5 mol% AuCl</td>
<td>Toluene</td>
<td>1 h</td>
<td>67%</td>
<td>3 : 1</td>
</tr>
</tbody>
</table>

Protic solvents were also tested for this transformation, which gave very interesting results. On submission of substrate 197 to AuCl/MeOH, no spiroaminal could be obtained after several trials. Isolation with neutralized silica gel chromatography gave the major product as a mixed cyclic methyl ketal, which was consistent with Krause’s result. But interestingly, the difference was that no Brønsted acid was used in the present system. It was clear that the formation of the methoxy ketal required an
intermolecular reaction between the organo-gold intermediate and methanol. From this result, two inferences could be made about the mechanism: (1) the oxygen atom has a much greater cyclization rate than the nitrogen atom under the gold conditions; (2) the intramolecular cyclization of spiroaminals requires much higher activation energy than corresponding intermolecular ketalizations. The solvent was then changed to the more bulky alcohol i-PrO, which gave a mixture of products. One was the desired spiroaminal 198, the other was the corresponding ketal. Thus, the bulky alcohol indeed slowed down the ketalization. The more bulky alcohol t-BuOH was then tested. As postulated, no ketal was isolated, and the desired spiroaminal was obtained in 55% yield.

![Chemical structures](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time</th>
<th>198</th>
<th>199</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeOH</td>
<td>20 min</td>
<td>0%</td>
<td>90% (R^8 = OMe)</td>
</tr>
<tr>
<td>2</td>
<td>i-PrOH</td>
<td>30 min</td>
<td>28%</td>
<td>20% (R^8 = Oi-Pr)</td>
</tr>
<tr>
<td>3</td>
<td>t-BuOH</td>
<td>30 min</td>
<td>55%</td>
<td>0% (R^8 = Ot-Bu)</td>
</tr>
</tbody>
</table>

Table 3. Spiroaminal Formation Using Alcohols as Solvent

Different substrates were synthesized by the author and co-worker Mr. Yong Chen. As shown in Figure 12, more than 10 substrates had been tested, among which moderate to excellent yields of spiroaminal moieties could be obtained under gold conditions. The
efficiency of this gold-catalyzed isomerization is dependent on the ring size and the substitution on the nitrogen atoms. It is quite interesting that no (6,6)-spiroaminal could be synthesized under gold (I) conditions. Further study may be required for a more detailed mechanistic study of this transformation.

Figure 12. Substrate Scope

A spiroaminal forming mechanism was also proposed based on the experimental data (Scheme 35). The gold (I) catalyst may have a dual role in this cyclization process: (1) to activate the alkyne; (2) to facilitate the second cyclization to furnish the spiroaminal. During this process, the alkyne functionality could initially be more electrophilic under gold activation. Then two nucleophilic additions could be possible, which are the 6-exo-dig of nitrogen and 5-endo-dig of oxygen. Based on the observations, the oxygen atom
first cyclizes to form a vinyl ether intermediate, while the 5-endo-dig mode may not be the kinetically favored pathway in accordance with Baldwin’s rules.\textsuperscript{71} A following protiodeauration could liberate the gold (I) catalyst and protonation of the resulting enol ether may lead to an oxocarbenium ions. During the gold-catalyzed ketalization, it is believed that oxocarbenium ion would expeditiously deliver the ketal product, which means that the main function of gold catalyst is to form the oxocarbenium ion intermediate. In this newly discovered gold-catalyzed transformation, gold may have the other function apart from the formation of electrophilic oxocarbenium ion. The Control experiments were also set up for comparison. A corresponding methoxy ketal could not be isomerized into a spiroaminal under PPTS conditions, while it is well known that PPTS can facilitate the formation of oxacarbenium ions. The gold (I) catalyst may act the same way as a lanthanide catalysts\textsuperscript{72} to chelate with an intermediate oxacarbenium ion and nitrogen atom due to the large radius of the gold cation. The catalyst could be finally released to re-enter the next catalytic cycle once the formation of the spiroaminal is complete.
3.2.3 Efforts on FGHI Domain Synthesis

Through a systematic study on model compounds, two ideal platforms were prepared for complex molecule synthesis: one is the well-established gold-catalyzed ketalization and the other is the newly developed gold-catalyzed spiroaminal formation. As noticed in Figure 8, both the C28 bridged ketal and C36 spiroaminal could be possibly set up through gold catalysis. The sequence of gold-catalysis should be considered carefully, that is beginning with FG C28 bridged ketal formation or starting with HI spiroaminal formation. Scheme 36 shows the detailed analysis, which led to clear choice of bridged ketal formation at first, followed by spirominal formation. The first proposed route is FG ring closure with the requisite diol precursor 216. Under gold catalysis, there are at least

Scheme 36. Proposed Mechanism of Gold-Catalyzed Sprioaminal Formation
two possible nucleophilic addition pathways. The desired one is the C32 hydroxyl to
attack the activated C27-C28 alkyne, while the undesired competing addition is that the
same hydroxyl may also attack the C35-C36 alkyne moiety. The anticipated reaction path
is 6-exo-dig, while the undesired is 5-exo-dig, which is more kinetically favored.
However, after analysis of the intermediate conformation, it was concluded that this route
may deliver the desired product 217. In the transition state, the 6-exo-dig route could
adopt the chair-like conformation for the cyclization, while 5-exo-dig may have a five-
membered ring intermediate under gold catalysis. From the aforementioned Forsyth’s
study on the formal total synthesis of okadaic acid,69 the propargylic hydroxyl and the
bulky R11 may be on the same face of the five-membered ring when the substrate has
such 1,3-anti hydroxyl functionality. The steric repulsion could slow down the
kinetically favored 5-exo-dig cyclization, resulting in the desired 6-exo-dig pathway. The
second proposed route is HI ring closure first. The dialkynyl hydroxy sulfonamide 218
was chosen as the precursor of the designed route. Under the gold catalysis, there are also
two possible reaction patterns, which are the desired 5-endo-dig and undesired 7-exo-dig.
Based on Baldwin’s rules, it is difficult to predict which would be preferable.
Comparison of the above two synthetic plans clearly showed that the first FG ring closure
gives a much higher possibility to reach the final target.
The synthesis commenced with the preparation of the alkyne 224 (Scheme 38). The acetyl alcohol 220 was kindly provided by Mr. Yong Chen. Two-step protecting group manipulations efficiently converted 220 into 221, involving C40-O-silylation and removal of the C36-O-acetyl group. The resultant C36 primary alcohol 221 was then oxidized into aldehyde 222 under Swern conditions. No epimerization was observed at
the α-position during the oxidation process. Finally, a Corey-Fuchs reaction\textsuperscript{73} was applied to convert aldehyde 222 into alkyne 224 with excellent yield. Hünig's base was utilized to buffer the acidic environment, since the primary silyl group was clearly cleaved under abasic Corey-Fuchs conditions.

Scheme 38. Synthesis of the Alkyne 224

Once the HI fragment alkyne 224 was obtained, the assembly of a bridged ketal was addressed (Scheme 39). A mild zinc-mediated coupling between HI alkyne 224 and FG aldehyde 225 stereoselectively produced the propargylic alcohol 226.\textsuperscript{74} The silyl ethers were cleaved under acid conditions. Treatment of resultant triol with 2,2-dimethoxypropane under acidic conditions resulted in the selective protection of the internal 1,3-anti-diol. The \textsuperscript{13}C-NMR chemical shift difference of the two methyl groups on the acetonide protecting group further confirmed the selectivity of Carreira’s protocol.\textsuperscript{75} A Mitsunobu condition\textsuperscript{76} was applied to convert the C40 hydroxyl moiety into a sulfonyl amide functionality. The acetonide was removed under acidic conditions. Exposure of the resultant diol to TBAF solution delivered the free alkyne 228. The following key step for
the construction of the bridged ketal actually successfully delivered the anticipated product with AuCl/PPTS. Here, PPTS bears comment of its importance. Two separable products with 2:1 ratio were initially isolated from flash chromatography without PPTS. Through our analysis, the minor portion should be the kinetic ketalization product. Fortunately, the undesired portion could be cleanly isomerized into the desired thermodynamically favored ketal 222. Finally, the combination of catalytic AuCl and PPTS efficiently delivered 222 as the only ketalization product.
The first gold catalyzed reaction successfully gave the anticipated result. Then we moved forward for the second application of the newly developed gold-catalyzed spiroaminal formation (Scheme 40). Treatment of ketal 229 with TFA/CH₂Cl₂ resulted in the cleavage of the C33 O-PMB ether and C40 N-Boc carbamate. The resultant hydroxy sulfonamide 230 was the precursor for the second key step for this new generation of FGHI domain synthesis. However, submission of 230 to AuCl/Toluene did not give any
desired spiroaminal. Different gold catalyst systems with a variety of solvents and temperatures were then tested, but no spiroaminal product never could be isolated.

Scheme 40. Attempted Construction of the Spioaminal in the FGHI Domain

A recently published result from the Aponick group was then noticed for the possible reactions during the gold catalyzed sprioaminal formation. Under gold catalysis conditions, diol 231 was transformed into furan 232 in an extremely fast fashion (Equation 1). Two furan proton peaks were indeed observed in $^1$H-NMR spectrum from the major isolated product. With the similarity of our substrate to that of Aponick’s report, we postulated that our substrate was transformed into some kind of furan derivative, which could be considered as a thermodynamic sink. However, a more detailed mechanistic study is definitely required for our specific reaction, which may give some hints to avoid the elimination of the propargylic position.
3.3 NHK Route for the Total Synthesis of AZA3

Due to the problems with protecting group manipulations met after the Yamaguchi coupling reactions between carboxylic acid 126 and hydroxyl 127, a new synthetic route was proposed (Scheme 41). The hemiketal E ring moiety could also be synthesized from ynone 233. A copper-mediated reduction and global silyl deprotection is planned to assemble the skeleton of AZA3. A well-known NKH coupling between C1-C21 aldehyde 234 and alkynyl iodide 235 was taken advantage of to deliver the propargylic alcohols, which could be oxidized into ynone 233. Compared with the previous route, only one slight change has been inserted into the C1-C21 domain, changing the C20 O-Piv to O-TIPS, which virtually would not affect the aforementioned ABCD domain synthesis. Based on this revised route, we also have opportunities to access the AZA1 and AZA2 through ultimate alkylation of the C22 α-position of ynone 233. With knowledge of Evans’ and Nicoloau’s late stage syntheses of AZA1, this newly proposed synthetic plan could provide easier manipulations to achieve the total synthesis, especially after the coupling between 234 and 235.
Based on the revised synthetic plan, an alternative synthesis to the E fragment has been achieved. As shown in Scheme 42, the fragment synthesis commences with a Paterson anti-aldol reaction between the aldehyde and lactate derived ketone, yielding the β-hydroxy ketone with excellent yield and stereoselectivity. Silylation of the resultant hydroxyl group followed by reduction of the ketone and benzoate ester functionality delivered the mixture of diols. Sodium periodate efficiently cleaved the diol into an aldehyde intermediate, which was then converted into the TMS-alkyne under Corey-Fuchs conditions. The PMB protecting group was then oxidatively removed with the influence of DDQ. The resultant primary alcohol was then oxidized into aldehyde under Parikh-Doering conditions.
Once the aldehyde 241 was obtained, the synthesis of the EFGHI linear precursor 244 was then addressed (Scheme 43). A reliable NHK reaction was applied to couple the aldehyde 241 and the alkynyl iodide 163, producing mixture of propargylic alcohols 242. The C34 TBS groups was then selectively removed under buffered HF-Py conditions. The resultant diol was then oxidized into aldehyde 243. The MgBr$_2$$\cdot$OEt$_2$ chelate-controlled Mukaiyama aldol reaction gave an excellent yield and high stereoselectivity. The resultant $\beta$-hydroxy ketone was then silylated into 244.
Once the EFGHI linear precursor 244 was efficiently synthesized, the assembly of the C22-C40 complex architecture followed (Scheme 44). The C33 O-PMB group was removed under DDQ conditions. Treatment of the resultant γ-hydroxy ketone with PPTS/MeOH resulted in the cyclization to deliver the cyclic methyl ketal. It is worth mentioning that the products after this cyclization step are extremely sensitive to acidic conditions, including the chromatography. A DIHMA reaction was applied to construct the bridged ketal 246, which consistently gave low yields after different forms of TBAF and temperature were screened. The resultant free C25 hydroxyl was then silylated. The azide group was reduced under modified Staudinger conditions and *in-situ* protected as a Teoc Carbamate. The spiroaminal ring was cyclized with Nd(OTf)$_3$ to furnish the fully functionalized C22-C40 domain of AZA3.
Figure 13 shows a possible reason for the low yield from the key DIHMA process. Under the fluoride conditions, four silyl groups in the 245 were quickly removed. Due to the full dissociation of fluoride with ammonium ion, the strong silicon and fluoride bond would force the desilylation with no selectivity, resulting in a possible tetra anion in the anhydrous THF environment. Because of the repulsion between the same charges, the low yield would result from the DIHMA reactions. Based on this analysis, a modification
on the silyl groups is being tested. A free alkyne is planned to be obtained under the Corey-Fuchs conditions in the E ring fragment synthesis. A smaller TES group was selected for the C32 position, and a more bulkly TBS group is chosen to replace the labile TES group at the C34 position.

Figure 13. DIHMA Process
Experimental Data

General Methods:

Unless otherwise noted, all reactions were carried out under an argon atmosphere in over-dried glassware using standard syringe, cannula, and septa techniques. Dichloromethane, tetrahydrofuran, diethyl ether, toluene, and dimethylformamide were purified with a Pure Solv. MD-6 solvent purification system. Triethylamine, diisopropylethylamine, acetonitrile, methanol were distilled from calcium hydride under nitrogen. All other solvents were used as received.

Analytical thin layer chromatography (TLC) was performed using 0.25 mm Silicycle silica gel 60 F\textsubscript{254} plates. Solvents for chromatography are listed as volume: volume ratios. Optical rotations were measured on a Perkin-Elmer polarimeter. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker DPX 400 spectrometer, operating at 400 MHz for \textsuperscript{1}H NMR and 100 MHz for \textsuperscript{13}C NMR. Chemical shifts were reported in ppm on the \(\delta\) scale relative to residual CHCl\(_3\) (\(\delta = 7.28\) for \textsuperscript{1}H NMR and \(\delta = 77.2\) for \textsuperscript{13}C NMR) as an internal reference. The coupling constant values (\(J\)) are in Hertz (Hz). The following abbreviations have been used for signal multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad. ESI mass spectra were measured on a Bruker MicroOTOF instrument.
(S)-4-((R)-2,2-Dimethyl-1,3-dioxolan-4-y1)-4-((4-methoxybenzyl)oxy)butan-1-ol (135)

To a solution of olefin 134 (10.8 g, 37 mmol) in THF (200 mL) at 0 °C was added drop-wise BH₃ (37.0 mL, 1 M in THF, 37 mmol). After 2 h at rt, the reaction mixture was cooled to 0 °C. Water (4.0 mL), 3 M aqueous NaOH (13.2 mL) and 30% aqueous H₂O₂ (8.7 mL) were successively added. The mixture was stirred for 2 h at rt and was then diluted with water (200 mL). The pH was adjusted to 6-7 with 10% aqueous HCl. The aqueous phase was extracted with diethyl ether (3 x 200 mL) and the combined organic phases were washed with saturated aqueous NaHCO₃ and brine. The organic phases were dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified by flash chromatography (hexanes-ethyl acetate, 3:1, v/v) to provide alcohol 135 (7.94 g, 26 mmol, 70%) as a colorless oil.

Rᵣ = 0.33 (hexanes-ethyl acetate, 1:1, v/v); ¹H NMR (CDCl₃, 400 MHz): δ 7.26 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz), 4.59 (q_AB, Δv = 16 Hz, J_AB = 11 Hz, 2H), 4.12 (q, J = 6.2 Hz, 1H), 4.06 (dd, J = 6.4 Hz, 1.6 Hz, 1H), 3.88 (dd, J = 6.4 Hz, 1.5 Hz, 1H), 3.82 (s, 3H), 3.64 (m, 2H), 3.57 (td, J = 6.0 Hz, 3.2 Hz, 1H), 1.72 (m, 3H), 1.63 (m, 3H), 1.44 (s, 3H), 1.37 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz): δ 159.3, 130.3, 129.5, 113.8, 109.1, 78.58, 77.5, 72.3, 66.6, 62.9, 55.3, 28.1, 27.4, 26.6, 25.23; IR (neat): 3436, 2935, 1612, 1513, 1454, 1370, 1301, 1248, 1069 cm⁻¹; [α]D²⁵ + 17.1 (c 1.56, CHCl₃); HRMS-ESI(m/z) calculated for [M+Na]⁺ 333.1673, found 333.1687.
(S)-4-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-4-((4-methoxybenzyl)oxy)butanal (136)

To a solution of oxalyl chloride (2.3 mL, 26 mmol) in CH$_2$Cl$_2$ (100 mL) at -78 °C was added drop-wise DMSO (3.6 mL, 52 mmol). After 20 min at -78 °C, a solution of 135 (4.0 g, 13 mmol) in CH$_2$Cl$_2$ (30 mL) was added, then the solution was warmed to -60 °C. After 1 h at -60 °C, i-Pr$_2$NEt (13.5 mL, 77.4 mmol) was added. The mixture was stirred for 10 min at –60 °C and 10 min at 0 °C. Cold 1 M aqueous HCl solution (48 mL) was added. The organic phase was mixed with pH = 7 aqueous buffer solution. The aqueous phase was extracted with CH$_2$Cl$_2$ (3 x 50 mL). The combined organic phases were washed with brine and dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated. The residue was purified by flash chromatography (hexanes-ethyl acetate, 5:1, v/v) to provide aldehyde 136 (3.92 g, 12.7 mmol, 99%) as a colorless oil.

R$_f$ = 0.8 (hexanes-ethyl acetate, 1:1, v/v); $^1$H NMR (CDCl$_3$, 400 MHz): δ 9.75 (t, $J$ = 1.44 Hz, 1H), 7.26 (d, $J$ = 8.7 Hz, 2H), 6.90 (d, $J$ = 8.6 Hz, 2H), 4.54 (q$_{AB}$, $\Delta$$\nu$ = 19 Hz, $J_{AB}$ = 11.1 Hz, 2H), 4.08 (m, 2H), 3.86 (m, 1H), 3.82 (s, 3H), 3.54 (m, 1H), 2.55 (t, $J$ = 7.2 Hz, 2H), 2.01 (m, 1H), 1.85 (m, 1H), 1.42 (s, 3H), 1.36 (s, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz): 202.1, 159.4, 130.1, 129.6, 113.9, 109.2, 77.7, 72.2, 66.6, 55.3, 39.3, 26.6, 25.2, 23.3; IR (neat): 2984.3, 2930.1, 2883.6, 1721.5, 1613.0, 1512.3, 1307.7, 1248.7, 1070.7, 1032.0, 846.0; $[\alpha]_D^{25}$ + 8.14 (c 1.5, CHCl$_3$); HRMS-ESI(m/z) calculated for [M+Na]$^+$: 331.1516, found 331.1521.
(6S)-6-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-6-((4-methoxybenzyl)oxy)-1-(trimethylsilyl)hex-1-yn-3-ol (136a)

To a solution of trimethylsilylacetylene 137 (6.22 mL, 43.8 mmol) in THF (130 mL) at –78 °C was added dropwise n-BuLi (15.7 mL, 2.5 M in THF, 40 mmol). After 30 min in –78 °C, a solution of aldehyde 136 (4.5 g, 15 mmol) in THF (16 mL) was added slowly. The solution was allowed to stir 1 h before saturated aqueous NH₄Cl was added. The aqueous phase was extracted with diethyl ether (3 x 80 mL). The combined organic phases were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified by flash chromatography (hexanes-ethyl acetate, 4:1, v/v) to provide alcohol 136a (5.0 g, 13 mmol, 87%) as a colorless oil.

R_f = 0.43 (hexanes-ethyl acetate, 3:1 v/v); ¹H NMR (CDCl₃, 400 MHz): δ 7.29 (m, 2H), 6.90 (d, J = 8.5 Hz, 2H), 4.57 (m, 2H), 4.40 (q, 1H), 4.08 (m, 2H), 3.88 (m, 1H), 3.82 (s, 3H), 3.57 (m, 1H), 1.90 (m, 5H), 1.43 (d, 3H), 1.36 (d, 3H), 0.19 (d, 9H); ¹³C NMR (CDCl₃, 125 MHz): δ 159.33, 159.27, 130.30, 130.06, 129.66, 129.51, 113.84, 113.82, 109.12, 109.09, 106.76, 106.61, 89.52, 89.42, 78.35, 78.32, 77.29, 71.99, 71.85, 66.86, 66.62, 62.70, 62.55, 55.23, 32.87, 32.44, 26.66, 26.60, 26.23, 25.66, 25.28, 25.26, -0.12, -0.15; IR (neat): 3441.4(broad), 2937.9, 1613.6, 1514.0, 1249.4, 1073.8, 843.5; HRMS-ESI(m/z) calculated for [M+Na]⁺: 429.2068, found 429.2060.
To a solution of **12a** (4.5 g, 11 mmol) in CH$_2$Cl$_2$ (100 mL) and DMSO (20 mL) at 0 °C was added Et$_3$N (9.2 mL, 67 mmol) and SO$_3$·Py (7.6 g, 48 mmol) successively. After 2 h at 0 °C, saturated aqueous NH$_4$Cl (100 mL) was added. The aqueous phase was extracted with diethyl ether (3 x 80 mL). The combined organic phases were washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated. The residue was purified by flash chromatography (hexanes-ethyl acetate, 5:1, v/v) to provide ketone **13** (3.7 g, 9.2 mmol, 83%) as colorless oil.

R$_f$ = 0.57 (hexanes-ethyl acetate, 3:1, v/v); $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.27 (d, $J$ = 8.6 Hz, 2H), 6.90 (d, $J$ = 8.6 Hz, 2H), 4.53 (s, 2H), 4.07 (m, 2H), 3.85 (m, 1H), 3.82 (s, 3H), 3.53 (m, 1H), 2.71 (m, 2H), 2.06 (m, 1H), 1.87 (m, 1H), 1.43 (s, 3H), 1.36 (s, 3H), 0.26 (s, 9H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 187.3, 159.3, 130.3, 129.5, 113.9, 109.2, 102.0, 97.8, 77.6, 72.2, 66.7, 55.3, 40.5, 26.6, 25.3, 24.8, -0.8; IR(neat): 2957.5, 2945.6, 2899.2, 1676.8, 1612.3, 1513.8, 1250.7, 1072.8, 847.1, 761.5; [α]$_D^{25}$ + 9.56 (c 0.5, CHCl$_3$); HRMS (ESI+) calculated for [M+Na]$^+$: 427.1911, found 427.1903.

(S)-6-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-6-((4-methoxybenzyl)oxy)-1-
(trimethylsilyl)hex-1-yn-3-one (138)
To a solution of 138 (3.58 g, 8.86 mmol) in MeOH (30 mL) was added TsOH·H₂O (0.17 g, 0.89 mmol). After 2 h, the solution was diluted by diethyl ether before saturated aqueous NaHCO₃ was added. The aqueous phase was extracted with diethyl ether (3 x 50 mL). The combined organic phases was washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified by flash chromatography (hexanes-ethyl acetate, 8:1, v/v) to provide alcohol 139 (2.2 g, 5.8 mmol, 65%) as a colorless oil.

R_f = 0.37 (hexanes-ethyl acetate, 3:1, v/v); ^1H NMR (CDCl₃, 400 MHz): δ 7.26 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 4.43 (q₁, AB, ð = 64 Hz, J_AB = 11.2 Hz, 2H), 3.82 (s, 3H), 3.75 (m, 2H), 3.57 (m, 1H), 3.44 (td, J = 10.0 Hz, 4.4 Hz, 1H), 3.38 (s, 3H), 3.10 (m, 3H), 1.91 (m, 2H), 0.21 (s, 9H); ^13C NMR (CDCl₃, 100 MHz): δ 159.3, 130.1, 129.3, 113.9, 101.9, 94.1, 89.0, 73.2, 72.5, 70.3, 62.7, 55.2, 50.4, 35.6, 24.3, -0.27; IR (neat): 3502(broad), 2957, 2899, 1612, 1513, 1250, 1152, 1089, 1040, 846, 760; [α]D25 + 6.84 (c 2.1, CHCl₃); HRMS-ESI(m/z) calculated for [M+Na]^+: 401.1755, found 401.1763.
(((2R,5S,6R)-6-((E)-2-Iodovinyl)-2-methoxy-5-((4-methoxybenzyl)oxy)tetrahydro-2H-pyran-2-yl)ethynyl)trimethylsilane (141)

To a solution of 139 (1.0 g, 2.7 mmol) in CH₂Cl₂ (30 mL) and DMSO (6 mL) at 0 °C was added i-Pr₂NEt (2.78 mL, 15.9 mmol), SO₃·Py (1.8 g, 11.4 mmol) sequentially. After 5 min at 0 °C, cold 1M aqueous HCl (10 mL) was added. The organic phase was neutralized by pH = 7 aqueous buffer. The aqueous phase was extracted with CH₂Cl₂ (3 x 30 mL). The combined organic phase was washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified by flash chromatography (hexanes-ethyl acetate, 4:1, v/v) to provide the aldehyde 140 as a colorless oil (0.99 g, 2.6 mmol, 96%).

A suspension of powdered anhydrous CrCl₂ (1.95 g, 15.9 mmol) was stirred in THF (24 mL) at 0 °C. A solution of the aldehyde 140 (0.99 g, 2.64 mmol) and CHI₃ (1.56 g, 3.96 mmol) in 1,4-dioxane (4 mL) was added drop-wise via cannula. The solution was allowed to warm to rt in 3 h. Then after stirring for 9 h, saturated aqueous NaHCO₃ was added. The aqueous phase was extracted with diethyl ether (3 x 30 mL). The combined organic phases were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (hexanes-ethyl acetate, 40:1, v/v) to provide vinyl iodide 141 (0.8 g, 2 mmol, 75%) as a colorless oil.
R_f = 0.60 (hexanes-ethyl acetate, 5:1, v/v); ^1H NMR (CDCl_3, 400 MHz): δ 7.25 (d, J = 8.6 Hz, 2H), 6.92 (d, J = 8.6 Hz, 2H), 6.65 (dd, J = 14.8 Hz, 6.4 Hz, 1H), 6.51 (dd, J = 14.8 Hz, 1.2 Hz, 1H), 4.53 (q_{AB}, J_{AB} = 54 Hz, J_{AB} = 11.3 Hz, 2H), 3.91 (ddd, J = 6.2 Hz, 3.3 Hz, 1.1 Hz, 1H), 3.83 (s, 3H), 3.36 (s, 3H), 3.21 (td, J = 10 Hz, 4.4 Hz, 1H), 2.11 (m, 1H), 1.91 (m, 3H), 0.20 (s, 9H); ^13C NMR (CDCl_3, 100 MHz): δ 159.3, 143.2, 130.1, 129.4, 113.9, 101.7, 94.1, 89.1, 79.8, 75.2, 75.1, 70.8, 55.3, 50.5, 35.5, 24.8, -0.03; IR (neat): 2955, 1513, 1249, 1085, 1043, 944, 859, 844, 760; [α]_D^{25} + 6.57 (c 1.6, CHCl_3); HRMS-ESI(m/z) calculated for [M+Na]^+: 523.0772, found 523.0765.

**tert-Butyl(((E))-5-((2R,3S,6R)-6-methoxy-3-((4-methoxybenzyl)oxy)-6-((trimethylsilyl)ethynyl)tetrahydro-2H-pyran-2-yl)pent-4-en-1-yl)oxy)diphenylsilane (143)**

To a solution of allyl TBDPS ether 142 (720 mg, 2.4 mmol) in THF (13 mL) at 0 °C was slowly added 9-BBN (6.4 mL, 0.5 M in THF, 3.2 mmol). The solution was slowly warmed to rt and then stirred at rt for 2 h. To this solution was added solution of 3 M aqueous K_3PO_4 (1.06 mL, 1.2 mmol) in DMF (1.1 mL). After 30 min at rt, the above solution was added to a solution of vinyl iodide (600 mg, 1.2 mmol) and PdCl_2(dppf)-CH_2Cl_2 (98 mg, 0.12 mmol) via cannula. After 5 min stirring, the solution
was diluted with diethyl ether (10 mL) and H₂O (10 mL). The aqueous phase was extracted with diethyl ether (3 x 10 mL). The combined organic phases were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (hexanes-ethyl acetate, 40:1, v/v) to provide 143 (760 mg, 1.16 mmol, 95%) as a colorless oil.

R_f = 0.62 (hexanes-ethyl acetate, 5:1, v/v); ¹H NMR (CDCl₃, 400 MHz): δ 7.69 (dd, J = 7.8 Hz, 1.6 Hz, 4H), 7.42 (m, 6H), 7.22 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 5.85 (dt, J = 15.4 Hz, 6.8 Hz, 1H), 5.52 (dd, J = 15.2 Hz, 7.6 Hz 1H), 4.50 (q_{AB}, \Delta v = 25 Hz, J_{AB} = 11.3 Hz, 2H), 3.88 (t, J = 8.1 Hz, 1H), 3.79 (s, 3H), 3.71 (t, J = 6.3 Hz, 2H), 3.38 (s, 3H), 3.20 (td, J = 9.5 Hz, 4.5 Hz, 1H), 2.22 (q, J = 6.4 Hz, 2H), 2.10 (m, 1H), 1.97 (m, 2H), 1.87 (m, 1H), 1.71 (m, 2H), 1.08 (s, 9H), 0.20 (s, 9H); ¹³C NMR (CDCl₃, 100 MHz): δ 159.1, 135.6, 134.9, 134.0, 130.5, 129.5, 129.3, 127.9, 127.6, 113.7, 102.3, 94.0, 88.5, 75.7, 74.6, 70.9, 63.5, 55.2, 50.4, 35.9, 31.9, 28.9, 26.9, 25.1, 19.2, -0.2; IR (neat): 2933.1, 2856.8, 1612.0, 1513.0, 1249.5, 1109.9, 844.2, 702.5; [α]D²⁵ + 4.32 (c 1.6, CHCl₃); HRMS-ESI(m/z) calculated for [M+Na]⁺: 693.3402, found 693.3434.

(2R,3S,6R)-2-((E)-5-(((tert-Butyldiphenylsilyl)oxy)pent-1-en-1-yl)-6-methoxy-6-((trimethylsilyl)ethynyl)tetrahydro-2H-pyran-3-ol (143a)
To a solution of 143 (406 mg, 0.6 mmol) in CH₂Cl₂ (10 mL), pH = 7 aqueous buffer (1 mL), and t-BuOH (0.5 mL) was added DDQ (412 mg, 1.8 mmol). After stirring 10 min at rt, the solution was diluted with diethyl ether (10 mL) and saturated aqueous NaHCO₃ (15 mL). The aqueous phase was extracted with diethyl ether (3 x 15 mL). The combined organic phases were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (hexanes-ethyl acetate, 20:1, v/v) to provide 143a (299 mg, 0.54 mmol, 90%) as a colorless oil.

Rᵥ = 0.62 (hexanes-ethyl acetate, 3:1, v/v); ¹H NMR (CDCl₃, 400 MHz): δ 7.69 (dd, J = 7.7 Hz, 1.6 Hz, 4H), 7.42 (m, 6H), 5.87 (dt, J = 15.4 Hz, 6.6 Hz, 1H), 5.50 (dd, J = 15.6 Hz, 8.4 Hz, 1H), 3.71 (m, 1H), 3.40 (m, 4H), 2.23 (q, J = 6.8 Hz 2H), 2.12 (m, 1H), 2.06 (td, J = 13 Hz, 4.3 Hz, 1H), 1.94 (m, 1H), 1.85 (m, 1H), 1.70 (m, 2H), 1.54 (d, J = 3.0 Hz, 1H), 1.07 (s, 9H), 0.21 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): δ 137.2, 135.6, 134.0, 129.6, 127.6, 127.2, 102.1, 94.1, 88.8, 76.7, 68.6, 63.2, 50.5, 35.9, 31.7, 28.8, 26.9, 26.8, 19.2, -0.2; IR (neat): 3420.1 (broad), 3070.8, 2933.8, 2858.0, 1428.2, 1251.1, 1111.3, 1049.6, 944.6, 860.0, 702.1; [α]D²⁵ + 5.48 (c 1.07, CHCl₃); HRMS-ESI(m/z) calculated for [M+Na]⁺: 573.2852, found 573.2827.

(2R,6R)-2-((E)-5-((tert-Butyldiphenylsilyl)oxy)pent-1-en-1-yl)-6-methoxy-6-((trimethylsilyl)ethynyl)dihydro-2H-pyran-3(4H)-one (144)
To a solution of 143a (410 mg, 0.75 mmol) in CH₂Cl₂ (6 mL) and DMSO (2 mL) at 0 °C was added i-Pr₂NEt (0.77 mL, 4.5 mmol) and SO₃·Py (510 mg, 3.2 mmol) successively. After 10 min at 0 °C, cold 1M aqueous HCl (3 mL) was added. The organic phase was separated and neutralized with pH=7 aqueous buffer. Then the aqueous solution was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic phases were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (hexanes-ethyl acetate, 15:1, v/v) to provide 144 (400 mg, 0.72 mmol, 96%) as a colorless oil.

Rᵥ = 0.72 (hexanes-ethyl acetate, 5:1, v/v); ¹H NMR (CDCl₃, 500 MHz): δ 7.69 (dd, J = 7.7 Hz, 1.4 Hz, 4H), 7.42 (m, 6H), 5.78 (dt, J = 12.3 Hz, 5.3 Hz, 1H), 5.56 (dd, J = 12.4 Hz, 5.4 Hz, 1H), 4.44 (d, J = 6.9 Hz, 1H), 3.69 (t, J = 6.3 Hz, 2H), 3.49 (s, 3H), 2.59 (m, 3H), 2.31 (m, 1H), 2.23 (q, J = 5.6 Hz, 2H), 1.71 (m, 2H), 1.07 (s, 9H), 0.23 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): δ 207.6, 136.7, 135.5, 134.0, 129.5, 127.6, 122.8, 101.0, 94.8, 90.0, 77.1, 63.2, 51.4, 35.6, 33.7, 31.6, 28.8, 26.8, 19.2, -0.3; IR (neat): 3048.1, 2957.1, 2856.7, 1733.7, 1471.8, 1427.7, 1250.9, 1110.8, 1048.2, 932.3, 844.4, 702.5; [α]D²⁵ + 10.8 (c 0.59, CHCl₃); HRMS-ESI(m/z) calculated for [M+Na]+: 571.2666, found 571.2670.
**tert-Butyl((E)-5-((2R,6R)-6-methoxy-6-((trimethylsilyl)ethyl)ynyl)-5,6-dihydro-2H-pyran-2-yl)pent-4-en-1-yl)oxy)diphenylsilane (146)**

To a solution of 17 (420 mg, 0.76 mmol) in THF (8 mL) at -78 °C was added Comins’ reagent (450 mg, 1.14 mmol) and KHMDS (2.3 mL, 0.5 M in THF, 1.14 mmol) sequentially. After 10 min at -78 °C, pH = 7 aqueous buffer (8 mL) was added. The aqueous phase was extracted with diethyl ether (3 x 15 mL). The combined and organic phases were washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered and concentrated. The residue was purified by flash chromatography (hexanes + 0.3% Et$_3$N, v/v) to provide crude product vinyl triflate 145 (477 mg, 0.70 mmol, 92%) as a pale yellow oil.

To a solution of the vinyl triflate 145 (477 mg, 0.70 mmol) in THF (7 mL) was added LiCl (294 mg, 7 mmol) and $n$Bu$_3$SnH (0.55 mL, 2.1 mmol). To the mixture was slowly added Pd(PPh$_3$)$_4$ (81 mg, 0.07 mmol). After stirring 10 min at rt, saturated aqueous NaHCO$_3$ (8 mL) was added. The aqueous phase was extracted with diethyl ether (3 x 10 mL). The combined organic phases were washed with brine, dried over Na$_2$SO$_4$, filtered and concentrated. The residue was purified by flash chromatography (hexanes-ethyl acetate, 200:1, v/v) to provide 146 (289 mg, 0.54 mmol, 77%) as a colorless oil.

R$_f$ = 0.58 (hexanes-ethyl acetate, 10:1, v/v); $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.69 (dd, $J = 7.7$ Hz, 1.5 Hz, 4H), 7.42 (m, 6H), 5.73 (m, 2H), 5.62 (dt, $J = 10.5$ Hz, 1.3 Hz, 1H), 5.48 (dd, $J = 15.3$ Hz, 7.8 Hz, 1H), 4.50 (s-broad, 1H), 3.69 (t, $J = 6.3$ Hz, 2H), 3.52 (s, 3H), 2.72 (m, 1H), 2.34 (m, 1H), 2.18 (q, $J = 7$ Hz, 2H), 1.69 (m, 2H), 1.07 (s, 9H), 0.21 (s, 9H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 135.6, 134.0, 133.9, 129.5, 128.6, 127.6, 127.5, 120.1, 102.2, 94.0, 89.2, 71.0, 63.3, 51.3, 36.1, 31.7, 28.6, 26.9, 19.2, -0.2; IR (neat):
tert-Butyl(((E)-5-((2R,6R)-6-(iodoethynyl)-6-methoxy-5,6-dihydro-2H-pyran-2-yl)pent-4-en-1-yl)oxy)diphenylsilane (129)

To a solution of 146 (87 mg, 0.16 mmol) in DMF (1.5 mL) at rt was added NIS (47 mg, 0.21 mmol) and AgOTf (36.1 mg, 0.16 mmol) sequentially. After stirring at rt, diethyl ether (3 mL) and saturated aqueous Na$_2$S$_2$O$_3$ (3 mL) was added. The aqueous phase was extracted with diethyl ether (3 x 5 mL). The combined organic phases were washed with brine, dried over Na$_2$SO$_4$, filtered and concentrated. The residue was purified by flash chromatography (hexanes-ethyl acetate, 40:1, v/v) to provide 129 (79 mg, 0.13 mmol, 82%) as a colorless oil.

R$_f$ = 0.42 (hexanes-ethyl acetate, 10:1, v/v); $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.69 (dd, $J$ = 7.7 Hz, 1.5 Hz, 4H), 7.42 (m, 6H), 5.73 (m, 2H), 5.62 (dt, $J$ = 10.4 Hz, 1.2 Hz, 1H), 5.48 (dd, $J$ = 15 Hz, 7.8 Hz, 1H), 4.49 (s-broad, 1H), 3.69 (t, $J$ = 6.3 Hz, 2H), 3.52 (s, 3H), 2.72 (m, 1H), 2.39 (m, 1H), 2.18 (q, $J$ = 7.2 Hz, 2H), 1.70 (m, 2H), 1.07 (s, 9H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 135.6, 134.2, 134.0, 129.5, 128.3, 127.6, 127.5, 120.6, 95.0, 92.6, 71.1, 63.2, 51.6, 36.1, 31.7, 28.6, 26.9, 19.2, 3.8; IR (neat): 3069.7, 3042.9, 2930.9, 2855.5, 2180.9, 1660.0, 1588.9, 1470.6, 1427.2, 1232.0, 1182.4, 1110.2, 1016.2, 1036.6,
967.1, 822.9, 702.2, 505.5; $[\alpha]_{D}^{25} + 10.4$ ($c$ 0.85, CHCl$_3$); HRMS-ESI (m/z) calculated for [M+Na]$^+$: 609.1298, found 609.1294.

A typical procedure of gold-catalyzed spiroaminal formation: To a flask of gold (I) chloride (2 mg, 8 µmol) was added the solution of hydroxy sulfonamide 197 (45 mg, 0.16 mmol) in toluene (1.5 mL) through cannula. The reaction was stirred for 1 h before Et$_3$N (0.1 mL). The reaction mixture was directly separated by flash chromatography (hexanes-ethyl acetate, 40:1, v/v) to provide spiroaminal 198 (40 mg, 0.15 mmol, 91%) as colorless oil.

\[
\begin{align*}
\text{Tosyl} & \quad \text{197} & \quad \text{202} (85\%) \\
\end{align*}
\]

6-Tosyl-1-oxa-6-azaspiro[4.4]nonane (202)

$R_f = 0.80$ (hexanes-ethyl acetate, 1:1, v/v); $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.81 (d, $J =$ 8.3 Hz, 2H), 7.27 (d, $J = 7.9$ Hz, 2H), 4.18 (q$_{AB}$, $J = 6.8$ Hz, 1H), 3.77 (m, 1H), 3.46 (m, 1H), 3.31 (m, 1H), 2.93 (m, 1H), 2.43 (s, 3H), 2.27 (m, 1H), 2.05 (m, 3H), 1.78 (m, 2H);

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 142.8, 137.6, 129.2, 127.8, 103.5, 68.5, 49.1, 41.9, 37.0, 25.6, 22.1, 21.5; HRMS-ESI (m/z) calculated for [M+Na]$^+$: 304.0978, found: 304.0979
6-Tosyl-1-oxa-6-azaspiro[4.5]decane (208)

R<sub>f</sub> = 0.47 (hexanes-ethyl acetate, 3:1, v/v); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 7.78 (d, <i>J</i> = 8.3 Hz, 2H), 7.27 (d, <i>J</i> = 8.0 Hz, 2H), 4.04 (m, 1H), 3.72 (m, 1H), 3.56 (m, 1H), 3.36 (m, 1H), 2.54 (m, 1H), 2.41 (s, 3H), 1.72 (m, 5H), 1.51 (m, 4H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ 142.3, 140.8, 129.1, 127.0, 97.8, 68.2, 45.6, 36.7, 35.8, 25.0, 24.6, 22.5, 21.4; HRMS-ESI (<i>m/z</i>) calculated for [M+Na<sup>+</sup>]: 318.1134, found: 318.1132

1-Tosyl-6-oxa-1-azaspiro[4.5]decane (212)

R<sub>f</sub> = 0.43 (hexanes-ethyl acetate, 3:1, v/v); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 7.85 (d, <i>J</i> = 8.3 Hz, 2H), 7.27 (d, <i>J</i> = 8.0 Hz, 2H), 3.82 (m, 1H), 3.50 (m, 2H), 3.35 (m, 1H), 2.88 (td, <i>J</i> = 13.2 Hz, 4.4 Hz, 1H), 2.42 (s, 3H), 2.25 (m, 1H), 1.89 (m, 1H), 1.76 (m, 3H), 1.67 (m, 2H), 1.54 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ 142.6, 137.8, 128.9, 128.3, 96.3, 64.6, 49.4, 34.7, 34.5, 25.0, 22.1, 21.5, 21.3; HRMS-ESI (<i>m/z</i>) calculated for [M+Na<sup>+</sup>]: 318.1134, found: 318.1135
7-Methyl-1-tosyl-6-oxa-1-azaspiro[4.5]decane (214)

R_f = 0.50 (hexanes-ethyl acetate, 3:1, v/v); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta \) 7.87 (d, \(J = 8.2\) Hz, 2H), 7.23 (d, \(J = 8.1\) Hz, 2H), 3.56 (m, 1H), 3.49 (m, 1H), 3.31 (m, 1H), 2.76 (td, \(J = 13.3\) Hz, 4.6 Hz, 1H), 2.41 (s, 3H), 2.15 (m, 1H), 1.86 (m, 2H), 1.78 (m, 2H), 1.67 (m, 1H), 1.51 (m, 2H), 1.05 (d, \(J = 6.1\) Hz, 3H); \(^1\)C NMR (CDCl\(_3\), 100 MHz): \(\delta \) 142.4, 137.6, 128.7, 128.5, 96.7, 70.5, 49.3, 35.2, 34.1, 32.4, 22.2, 21.8, 21.5, 21.4; HRMS-ESI \((m/z)\) calculated for [M+Na\(^+\)]: 332.1291, found: 332.1293

2,2-Dimethyl-6-tosyl-1-oxa-6-azaspiro[4.4]nonane (204)

R_f = 0.75 (hexanes-ethyl acetate, 2:1, v/v); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta \) 7.88 (d, \(J = 8.3\) Hz, 2H), 7.26 (d, \(J = 8.0\) Hz, 2H), 3.38 (m, 1H), 3.27 (m, 1H), 3.02 (m, 1H), 2.41 (s, 3H), 2.19 (m, 2H), 2.02 (m, 2H), 1.82 (m, 3H), 1.40 (s, 3H), 1.21 (s, 3H); \(^1\)C NMR (CDCl\(_3\), 100 MHz): \(\delta \) 142.7, 137.8, 129.1, 127.7, 103.1, 82.3, 49.0, 43.5, 37.3, 37.1, 28.9, 28.3, 21.9, 21.5; HRMS-ESI \((m/z)\) calculated for [M+Na\(^+\)]: 332.1291, found: 332.1290
**tert-Butyl(((2R,4S)-2,4-dimethylhex-5-yn-1-yl)oxy)dimethylsilane (224)**

To a solution of vinyl bromide 223 (1.6 g, 4.0 mmol) in THF (50 mL) at -78 °C was added drop-wise n-BuLi (3.3 mL, 2.5 M in Hexane, 8.1 mmol). After 30 min, water (0.7 mL, 40 mmol) was added drop-wise. The mixture was allowed to stir for 30 min before saturated aqueous NH₄Cl (40 mL) was added. The aqueous was extracted with diethyl ether (3 x 40 mL). The combined organic phases were dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified by flash chromatography (hexanes-ethyl acetate, 80:1, v/v) to provide alkyne 217 (0.96 g, 4.0 mmol, 99%) as a colorless oil. 

R<sub>f</sub> = 0.85 (Hexanes-Ethyl acetate, 10:1, v/v); <sup>1</sup>H NMR (CDCl₃, 400 MHz): δ 3.47 (m, 2H), 2.54 (m, 1H), 2.04 (d, J = 2.4 Hz, 1H), 1.88 (m, 1H), 1.62 (m, 1H), 1.22 (d, J = 6.8 Hz, 3H), 1.15 (m, 1H), 0.92 (m, 12H), 0.06 (s, 6H); <sup>13</sup>C NMR (CDCl₃, 100 MHz): δ 88.89, 68.61, 68.20, 40.57, 33.88, 25.95, 23.46, 21.69, 18.35, 16.17, -5.36; IR (neat): 3312, 2929, 2856, 1471, 1255, 1093, 836, 774, 628; [α]<sub>D</sub><sup>25</sup> + 16.4 (c 1.91, CHCl₃); HRMS-ESI (m/z) calculated for [M+ Na<sup>+</sup>]: 263.1802, found: 263.1801.
(5R,6S,7R,10S,12R)-6-((4-methoxybenzyl)oxy)-2,2,3,3,10,12,15,15,16,16-decamethyl-5-((R)-2-methyl-5-(trimethylsilyl)pent-4-yn-1-yl)-4,14-dioxa-3,15-disilaheptadec-8-yn-7-ol (226)

To a flask of Zn(OTf)$_2$ (0.8 g, 2.2 mmol, pre-dried overnight 120 °C under house vacuum) was added ligand (0.37 g, 2.2 mmol). The mixture was then dried under house vacuum at rt for 30 min before toluene (3 mL) and Et$_3$N (0.3 mL, 2.2 mmol) was added. The resulting slurry was then stirred for 2 h. The solution of Alkyne 224 (0.49 g, 2.2 mmol) in toluene (1 mL) was added drop-wise. The mixture was allowed to stirred for 1 h before the solution of aldehyde 225 (0.17 g, 0.42 mmol) in toluene (1 mL) was added through cannula. The mixture was stirred for 48 h before saturated aqueous NaHCO$_3$ (5 mL) was added. The aqueous phase was extracted with diethyl ether (3 x 5 mL). The combined organic phases were dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated. The residue was purified by flash chromatography (hexanes-ethyl acetate, 20:1, v/v) to provide alkyne 226 (0.2 g, 0.28 mmol, 69%) as a colorless oil.

R$_f$= 0.4 (Hexanes-Ethyl acetate, 5:1, v/v); $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.34 (d, $J$ = 8.6 Hz, 2H), 6.90 (d, $J$ = 8.6 Hz, 2H), 4.86 (q$_{AB}$, $\Delta v$ = 72 Hz, $J$ = 10.8 Hz, 2H), 4.39 (m, 1H), 4.05 (m, 1H), 3.83 (s, 3H), 3.55 (dd, $J$ = 6.3 Hz, 3.1 Hz, 1H), 3.47 (m, 2H), 2.90 (d, $J$ = 3.8 Hz, 1H), 2.63 (m, 1H), 2.24 (m, 2H), 1.91 (m, 1H), 1.61 (m, 3H), 1.24 (d, $J$ = 6.7 Hz, 3H), 1.17 (m, 1H), 1.04 (d, $J$ = 6.7 Hz, 3H), 0.92 (m, 21H), 0.16 (m, 15H), 0.06 (s, 6H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 159.35, 130.46, 129.61, 113.86, 113.81, 105.41, 90.79, 85.89, 78.94, 74.26, 71.29, 68.56, 62.02, 55.25, 40.67, 39.26, 33.72, 28.67, 26.53, 25.95, 25.91, 23.67, 21.61, 20.42, 18.33, 17.98, 16.32, 0.15, -4.03, -4.60, -5.39; IR (neat): 3460,
To a solution of 226 (120 mg, 0.16 mmol) in MeOH (1 mL) was added TsOH•H₂O (3 mg, 0.02 mmol). The mixture was allowed to stir 3.5 h before diethyl ether (4 mL) and saturated aqueous NaHCO₃ (4 mL) was added. The aqueous phase was extracted by diethyl ether (3 x 5 mL). The combined organic phases were dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified by flash chromatography (hexanes-ethyl acetate, 1:1, v/v) to provide triol 226a (72 mg, 0.15 mmol, 90%) as a colorless oil.

Rf = 0.5 (Hexanes-Ethyl acetate, 1:1, v/v); ¹H NMR (CDCl₃, 400 MHz): δ 7.31 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 4.78 (qAB, Δν = 52 Hz, J = 11.1 Hz, 2H), 4.46 (br, 1H), 4.06 (m, 1H), 3.81 (s, 3H), 3.61 (m, 4H), 3.03 (br, 1H), 2.61 (m, 3H), 1.97 (m, 1H), 1.69 (m, 2H), 1.41 (m, 1H), 1.21 (d, J = 6.8 Hz, 3H), 1.13 (m, 1H), 1.04 (d, J = 6.7 Hz, 3H), 0.91 (d, J = 6.7 Hz, 3H), 0.16 (s, 9H); ¹³C NMR (CDCl₃, 100 MHz): δ 159.40, 130.07, 129.64, 113.86, 106.22, 90.65, 85.90, 83.69, 79.60, 73.61, 69.69, 68.11, 62.68, 55.26, 40.72, 39.59, 34.26, 29.12, 25.97, 24.05, 21.75, 20.79, 16.30, 0.11; IR (neat): 3373, 2956, 2914, 1714, 1514, 1462, 1249, 1097, 1035, 839, 775; [α]D ²⁵ - 1.68 (c 1.41, CHCl₃); HRMS-ESI (m/z) calculated for [M + Na⁺]: 739.4580, found: 739.4578.

(2R,4S,7R,8R,9R,11R)-8-((4-Methoxybenzyl)oxy)-2,4,11-trimethyl-14-(trimethylsilyl)tetradeca-5,13-diyn-1,7,9-triol (226a)
2872, 2171, 1514, 1458, 1247, 1089, 1035, 842; \([\alpha]_{D}^{25} + 28.1\) (c 1.0, CHCl\(_3\)); HRMS-ESI (m/z) calculated for [M + Na\(^+\)]: 511.2850, found: 511.2851.

![Image of compound 226b]

\((2R,4S)-6-((4R,5R,6R)-5-((4\text{-methoxybenzyl})\text{oxy})-2,2\text{-dimethyl}-6-((R)-2\text{-methyl}-5-(\text{trimethylsilyl})\text{pent}-4\text{-yn-1-yl})-1,3\text{-dioxan-4-yl})-2,4\text{-dimethylhex}-5\text{-yn-1-ol} \) (226b)

To a solution of 226a (0.18 g, 0.37 mmol) in CH\(_2\)Cl\(_2\) (4 mL) was added PPTS (2 mg, 3.7 \(\mu\)mmol) and Dimethoxy propane (0.45 mL, 3.7 mmol). The mixture was allowed to stir 12 h before saturated aqueous NaHCO\(_3\) (4 mL) was added. The aqueous phase was extracted by diethyl ether (3 x 5 mL). The combined organic phases were dried over anhydrous Na\(_2\)SO\(_4\), filtered, and concentrated. The residue was dissolved in MeOH (1 mL), and the solution was added PPTS (2 mg, 3.7 \(\mu\)mmol). The mixture was stirred 5 min before saturated aqueous NaHCO\(_3\) (4 mL) was added. The aqueous phase was extracted by diethyl ether (3 x 5 mL). The combined organic phases were dried over anhydrous Na\(_2\)SO\(_4\), filtered, and concentrated. The residue was purified by flash chromatography (hexanes-ethyl acetate, 8:1, v/v) to provide 226b (160 mg, 0.31 mmol, 83%) as a colorless oil.

R\(_f\) = 0.3 (Hexanes-Ethyl acetate, 3:1, v/v); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.26 (d, \(J = 8.6\) Hz, 2H), 6.87 (d, \(J = 8.6\) Hz, 2H), 4.75 (q\(_{AB}\), \(\Delta\nu = 105\) Hz, \(J = 11.4\) Hz, 2H), 4.73 (m, 1H), 3.84 (m, 1H), 3.79(s, 3H), 3.42 (d, \(J = 5.9\) Hz, 2H), 3.32 (dd, \(J = 8.1\) Hz, 4.7 Hz, 1H), 2.59
(m, 1H), 2.25 (m, 2H), 1.87 (m, 1H), 1.63 (m, 3H), 1.54 (s, 3H), 1.32 (s, 3H), 1.28 (m, 1H), 1.21 (d, J = 6.8 Hz, 3H), 1.13 (m, 1H), 1.01 (d, J = 6.7 Hz, 3H), 0.91 (d, J = 6.7 Hz, 3H), 0.13 (s, 9H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 159.23, 130.18, 129.38, 113.66, 105.95, 100.49, 92.37, 85.60, 78.64, 76.75, 72.07, 68.74, 68.05, 63.60, 55.22, 40.33, 38.75, 34.23, 29.01, 27.10, 26.17, 24.10, 23.41, 21.54, 20.12, 16.33, 0.13; IR (neat): 3464, 2958, 2171, 1610, 1514, 1458, 1379, 1247, 1037, 842; [α]$_D^{25}$ + 68.7 (c 1.0, CHCl$_3$); HRMS-ESI (m/z) calculated for [M+ Na$^+$]: 551.3163, found: 551.3162.

**tert-Butyl((2R,4S)-6-((4R,5R,6R)-5-((4-methoxybenzyl)oxy)-2,2-dimethyl-6-((R)-2-methyl-5-(trimethylsilyl)pent-4-yn-1-yl)-1,3-dioxan-4-yl)-2,4-dimethylhex-5-yn-1-yl)(tosyl)carbamat (227)**

To a solution of 226b (0.16 g, 0.31 mmol) in THF (4 mL) was added Ph$_3$P (357 mg, 1.4 mmol), NHTsBoc (328 mg, 1.24 mmol), and DIAD (0.2 mL, 1.1 mmol) sequentially. The mixture was allowed to stir 1h before saturated aqueous NH$_4$Cl (4 mL) was added. The aqueous phase was extracted by diethyl ether (3 x 5 mL). The combined organic phases were dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated. The residue was purified by flash chromatography (hexanes-ethyl acetate, 15:1, v/v) to provide 227 (210 mg, 0.31 mmol, 89%) as a colorless oil.
R_f= 0.6 (Hexanes-Ethyl acetate, 3:1, v/v); ^1H NMR (CDCl_3, 400 MHz): δ 7.81 (d, J = 8.3 Hz, 2H), 7.31 (m, 4H), 6.88 (d, J = 8.6 Hz, 2H), 4.81 (q_{AB}, Δν = 122 Hz, J = 11.4 Hz, 2H), 4.77 (m, 2H), 3.80 (m, 4H), 3.73 (m, 2H), 3.33 (dd, J = 7.9 Hz, 4.6 Hz, 1H), 2.66 (m, 1H), 2.43 (s, 3H), 2.34 (m, 1H), 2.23 (m, 1H), 2.07 (m, 1H), 1.85 (m, 1H), 1.62 (m, 2H), 1.54 (s, 3H), 1.33 (m, 13H), 1.23 (d, J = 6.8 Hz, 3H), 1.01 (d, J = 6.7 Hz, 3H), 0.95 (d, J = 6.7 Hz, 3H), 0.15 (s, 9H); ^13C NMR (CDCl_3, 100 MHz): δ 159.22, 151.26, 143.90, 137.53, 130.33, 129.55, 129.21, 127.92, 113.66, 106.05, 100.56, 91.80, 85.52, 83.95, 79.08, 76.96, 72.29, 69.06, 63.55, 55.24, 52.49. 41.09, 38.91, 31.72, 31.55, 29.15, 27.82, 26.74, 26.29, 23.81, 23.52, 21.54, 21.31, 20.12, 16.90, 14.08, 0.16; IR (neat): 2960, 1728, 1514, 1355, 1249, 1155, 1089, 842; [α]_D^{25} + 20.1 (c 1.33, CHCl_3); HRMS-ESI (m/z) calculated for [M+ Na^+] 804.3936, found: 804.3938.


To a solution of **227** (60 mg, 76 µmmol) in MeOH (1.5 mL) was added TsOH•H_2O (1.2 mg, 7.6 µmmol). The mixture was allowed to stir 10 min before diethyl ether (4 mL) and saturated aqueous NaHCO_3 were added. The aqueous phase was extracted by diethyl ether (3 x 5 mL). The combined organic phases were dried over anhydrous Na_2SO_4,
filtered, and concentrated. The residue was purified by flash chromatography (hexanes-ethyl acetate, 8:1, v/v) to provide \(227a\) (60 mg, 7.6 \(\mu\)mol, 99%) as a colorless oil.

\[ R_f = 0.44 \text{ (Hexanes-Ethyl acetate, 2:1, v/v); } ^1H \text{ NMR (CDCl}_3, 400 \text{ MHz): } \delta 7.79 (d, J = 8.4 \text{ Hz, 2H}), 7.32 (m, 4H), 6.88 (d, J = 8.6 \text{ Hz, 2H}), 4.74 (q_{AB}, \Delta v = 24 \text{ Hz, } J = 11.2 \text{ Hz, 2H}), 4.54 (m, 1H), 4.01 (m, 1H), 3.81 (s, 3H), 3.73 (m, 2H), 3.47 (t, J = 5.2 \text{ Hz, 1H}), 3.18 (br, 1H), 2.88 (br, 1H), 2.59 (m, 1H), 2.44 (s, 3H), 2.38 (m, 2H), 2.27 (m, 1H), 2.18 (m, 1H), 1.97 (m, 1H), 1.61 (m, 2H), 1.48 (m, 1H), 1.33 (s, 9H), 1.25 (d, J = 6.8 \text{ Hz, 3H}), 1.03 (d, J = 6.8 \text{ Hz, 3H}), 0.98 (d, J = 6.8 \text{ Hz, 3H}), 0.15 (s, 9H); ^{13}C \text{ NMR (CDCl}_3, 100 \text{ MHz): } \delta 159.32, 151.31, 144.15, 137.38, 130.33, 129.66, 129.24, 127.82, 113.83, 106.09, 90.14, 85.73, 84.36, 84.10, 79.71, 73.69, 69.91, 62.78, 55.24, 52.98, 41.59, 39.19, 32.20, 28.93, 27.82, 26.04, 23.96, 21.68, 21.57, 20.70, 16.77, 0.14; IR (neat): 3527, 2958, 1728, 1514, 1354, 1249, 1153, 1087, 842; [\alpha]_D^{25} + 19.0 \text{ (c 1.33, CHCl}_3); \text{ HRMS-ESI (m/z) calculated for [M+ Na}^+]: 764.3623, found: 764.3625.}

![Diagram of tert-Butyl((2R,4S,7R,8R,9R,11R)-7,9-dihydroxy-8-((4-methoxybenzyl)oxy)-2,4,11-trimethyltetradeca-5,13-diyn-1-yl)(tosyl)carbamate (228)](image)


To a solution of \(227a\) (80 mg, 0.1 mmol) in THF (2 mL) was added TBAF (0.4 mL, 0.3 mmol, 1 M solution in THF). The reaction was allowed to stir 10 min before saturated aqueous \(\text{NH}_4\text{Cl}\) (3 mL) was added. The aqueous phase was extracted by diethyl ether (3 x
5 mL). The combined organic phases were dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified by flash chromatography (hexanes-ethyl acetate, 8:1, v/v) to provide 228 (60 mg, 86 μmol, 86%) as a colorless oil.

Rf = 0.1 (Hexanes-Ethyl acetate, 3:1, v/v); ¹H NMR (CDCl₃, 400 MHz): δ 7.78 (d, J = 8.4 Hz, 2H), 7.31 (m, 4H), 6.88 (d, J = 8.6 Hz, 2H), 4.76 (q, JAB = 29 Hz, J = 11.2 Hz, 2H), 4.53 (d, J = 3.5 Hz, 2H), 4.01 (m, 1H), 3.81 (s, 3H), 3.73 (d, J = 7.6 Hz, 2H), 3.47 (t, J = 5 Hz, 1H), 3.26 (br, 1H), 2.91 (br, 1H), 2.66 (m, 1H), 2.45 (s, 3H), 2.38 (m, 1H), 2.28 (m, 1H), 2.15 (m, 1H), 1.97 (m, 1H), 1.93 (t, J = 2.6 Hz, 1H), 1.63 (m, 2H), 1.46 (m, 1H), 1.33 (s, 9H), 1.25 (d, J = 6.8 Hz, 3H), 1.05 (d, J = 6.8 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H);
¹³C NMR (CDCl₃, 100 MHz): δ 159.3, 151.3, 144.2, 137.4, 130.3, 129.7, 127.8, 113.8, 90.2, 84.4, 83.9, 79.6, 73.6, 70.0, 69.4, 62.9, 55.2, 53.0, 41.6, 38.9, 32.2, 28.6, 27.8, 24.5, 24.0, 21.7, 21.6, 20.6, 16.7; IR (neat): 3527, 2962, 2929, 1728, 1514, 1352, 1249, 1155, 1087, 842; [α]D₂⁵ + 20.0 (c 1.0, CHCl₃); HRMS-ESI (m/z) calculated for [M+ Na⁺]: 692.3228, found: 692.3229.

tert-butyl((2R,4S)-6-((1R,3R,4R,5R,7S)-4-((4-methoxybenzyl)oxy)-1,7-dimethyl-2,9-dioxabicyclo[3.3.1]nonan-3-yl)-2,4-dimethylhex-5-yn-1-yl)(tosyl)carbamate (229)
To a flask of AuCl (1.4 mg, 6 μmol) was added the solution of 228 (40 mg, 59 μmol) and PPTS (1.5 mg, 6 μmol) in CH₂Cl₂ (2 mL). The mixture was allowed to stir 10 min before Et₃N (0.02 mL) was added. The mixture was purified by flash chromatography (hexanes-ethyl acetate, 8:1, v/v) to provide 229 (34 mg, 51 μmol, 85%) as a colorless oil.

Rᵣ= 0.62 (Hexanes-Ethyl acetate, 3:1, v/v); ¹H NMR (CDCl₃, 400 MHz): δ 7.83 (d, J = 8.4 Hz, 2H), 7.31 (m, 4H), 6.89 (d, J = 8.6 Hz, 2H), 4.88 (dd, J = 6.5 Hz, 1.6 Hz, 1H), 4.45 (q_AB, Δν = 80 Hz, J = 11.5 Hz, 2H), 4.19 (t, J = 2.5 Hz, 1H), 3.81 (s, 3H), 3.76 (m, 2H), 3.59 (dd, J = 6.5 Hz, 2.5 Hz, 1H), 2.70 (m, 1H), 2.43 (s, 3H), 2.38 (m, 1H), 1.98 (m, 1H), 1.75 (dd, J = 13.2 Hz, 4.0 Hz, 1H), 1.59 (m, 1H), 1.49 (m, 4H), 1.34 (m, 10H), 1.25 (m, 5H), 0.97 (d, J = 6.7 Hz, 3H), 0.88 (d, J = 6.5 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 159.2, 151.3, 143.8, 137.6, 130.2, 129.3, 129.2, 127.9, 113.7, 97.9, 90.0, 83.9, 78.5, 75.9, 73.7, 70.7, 61.4, 55.3, 52.6, 43.3, 41.2, 35.8, 31.8, 28.2, 27.8, 23.8, 22.4, 22.1, 21.6, 21.5, 16.8; IR (neat): 2954, 1726, 1354, 1514, 1249, 1153, 1087, 842; [α]D²⁵ + 40 (c 0.5, CHCl₃); HRMS-ESI (m/z) calculated for [M+ Na⁺]: 692.3228, found: 692.3226.

N-((2R,4S)-6-(((1R,3R,4R,5R,7S)-4-hydroxy-1,7-dimethyl-2,9-dioxabicyclo[3.3.1]nonan-3-yl)-2,4-dimethylhex-5-yn-1-yl)-4-methylbenzenesulfonamide (230)
To a cooled (0 °C) solution of 229 (140 mg, 0.21 mmol) in CH₂Cl₂ (3 mL) was added TFA (0.6 mL) slowly. The mixture was allowed to warm up to rt. After stirring 2.5 h, the reaction was added saturated aqueous NaHCO₃ (5 mL) and diethyl ether (5 mL). The aqueous phase was extracted by diethyl ether (3 x 5 mL). The combined organic phases were dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified by flash chromatography (hexanes-ethyl acetate, 3:1, v/v) to provide 230 (90 mg, 190 μmol, 93%) as a colorless oil.

Rᵣ = 0.2 (Hexanes-Ethyl acetate, 2:1, v/v); ¹H NMR (CDCl₃, 400 MHz): δ 7.77 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 4.66 (br, 1H), 4.61 (dd, J = 9.5 Hz, 1.9 Hz, 1H), 4.34 (t, J = 3.7 Hz, 1H), 4.11 (m, 1H), 2.88 (m, 3H), 2.51 (m, 1H), 2.44 (s, 3H), 2.13 (m, 1H), 1.88 (m, 3H), 1.47 (m, 5H), 1.31 (m, 1H), 1.16 (m, 4H), 0.95 (d, J = 6.6 Hz, 3H), 0.89 (d, J = 6.7 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 143.4, 136.9, 129.7, 127.1, 108.8, 90.8, 83.4, 78.1, 76.0, 61.6, 49.3, 43.3, 41.0, 32.7, 31.9, 24.9, 24.7, 23.9, 21.9, 21.54, 21.50, 17.2; IR (neat): 3481, 3410, 2956, 1448, 1327, 1159, 843; [α]D²⁵ + 38 (c 0.5, CHCl₃); HRMS-ESI (m/z) calculated for [M+ Na⁺]: 472.2128, found: 472.2129.

(2S,4R,5S)-5-hydroxy-6-((4-methoxybenzyl)oxy)-4-methyl-3-oxohexan-2-yl benzoate (238)
To a cooled (-78 °C) solution of c-Hex₂BCl (0.32 g, 1.5 mmol) in Et₂O (4 ml) was added Me₂Net (0.2 g, 1.8 mmol), followed by ketone 237 (0.2 g, 1.0 mmol) in Et₂O (4 mL). The reaction mixture was warmed to 0 °C and stirred for 2 h before cooling to –78 °C. The aldehyde 236 (0.7 g, 4.0 mmol) in Et₂O (2 mL) was added and the stirring continued for another 2 h, before being transferred to a freezer (-20 °C) for 14 h. The reaction was quenched at 0 °C by addition of MeOH (4 mL), and pH = 7 aqueous buffer (4 mL). H₂O₂ (4 mL, 30%) was then added and the stirring continued for 1 h before the addition of H₂O (30 mL) and CH₂Cl₂ (30 mL). The aqueous phase was then extracted by CH₂Cl₂ (3 x 30 mL). The organic phases were dried over anhydrous MgSO₄, filtered, and concentrated. The residue was purified by flash chromatography (hexanes-ethyl acetate, 5:1, v/v) to provide alcohol 238 (0.38 g, 0.98 mmol, 98%) as a colorless oil.

R_f = 0.2 (Hexanes-Ethyl acetate, 3:1, v/v); ¹H NMR (CDCl₃, 400 MHz): δ 8.07 (m, 2H), 7.54 (t, J = 7.4 Hz, 1H), 7.42 (t, J = 7.8 Hz, 2H), 7.21 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 5.43 (q, J = 7.0 Hz, 1H), 4.46 (qAB, Δν = 24 Hz, J = 11.5 Hz, 2H), 3.95 (m, 1H), 3.75 (s, 3H), 3.50 (m, 2H), 3.32 (br, 1H), 3.09 (m, 1H), 1.54 (d, J = 7.0 Hz, 3H), 1.17 (d, J = 7.1 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 210.3, 165.4, 159.0, 132.9, 129.6, 129.4, 129.2, 129.1, 128.1, 113.5, 74.5, 72.7, 72.0, 71.3, 54.9, 44.4, 15.1, 13.5; IR (neat): 3527, 2935, 1717, 1514, 1250, 1114, 1002, 819, 714; [α]D²⁵ + 12.1 (c 2.1, CHCl₃); HRMS-ESI (m/z) calculated for [M+ Na⁺]: 409.1622, found: 409.1621.
(2S,4R,5S)-5-((tert-butyldimethylsilyl)oxy)-6-((4-methoxybenzyl)oxy)-4-methyl-3-oxohexan-2-yl benzoate (238a)

To a cooled (-78 °C) solution of β-hydroxy ketone 238 (0.38 g, 0.98 mmol) in CH₂Cl₂ (10 mL) was added 2,6- lutidine (0.46 ml, 3.92 mmol) and TBSOTf (0.68 mL, 2.94 mmol) sequentially. The mixture was allowed to stir 1 h before saturated aqueous NaHCO₃ (10 mL) was added. The aqueous phase was then extracted by diethyl ether (3 x 10 mL). The combined organic phases were washed with brine. The organic phases were dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified by flash chromatography (hexanes-ethyl acetate, 30:1, v/v) to provide 238a (0.43 g, 0.86 mmol, 89%) as a colorless oil.

Rₓ = 0.68 (Hexanes-Ethyl acetate, 3:1, v/v); ¹H NMR (CDCl₃, 400 MHz): δ 8.09 (m, 2H), 7.59 (m, 1H), 7.46 (m, 2H), 7.24 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 5.48 (q, J = 7.0 Hz, 1H), 4.47 (qAB, Δν = 31 Hz, J = 11.6 Hz, 2H), 4.14 (m, 1H), 3.82 (s, 1H), 3.48 (m, 2H), 3.48 (m, 2H), 3.24 (m, 1H), 1.52 (d, J = 7.0 Hz, 3H), 1.13 (d, J = 7.0 Hz, 3H), 0.86 (s, 9H), 0.05 (s, 3H), -0.01 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 208.4, 165.7, 159.2, 133.1, 130.2, 129.8, 129.7, 129.3, 128.3, 113.7, 74.7, 73.0, 72.8, 71.7, 55.2, 46.2, 25.8, 18.0, 15.3, 12.9, -4.7, -4.9; IR (neat): 2930, 1720, 1612, 1513, 1452, 1249, 1114, 835, 712; [α]D₂⁵ -4.24 (c 2.2, CHCl₃); HRMS-ESI (m/z) calculated for [M+ Na⁺]: 523.2486, found: 523.2489.
(2R,3S)-3-((tert-butyldimethylsilyl)oxy)-4-((4-methoxybenzyl)oxy)-2-methylbutanal (239a)

To a cooled (-78 °C) solution of ketone 238a (0.2 g, 0.4 mmol) in THF (5 mL) was added LiBH₄ (176 mg, 8 mmol). The mixture was allowed to warm up to rt slowly and stir 24 h before slow addition of H₂O (5 mL) and diethyl ether (5 mL). The aqueous phase was extracted by diethyl ether (3 x 10 mL). The organic phases were dried over anhydrous MgSO₄, filtered, and concentrated. The residue was purified by flash chromatography (hexanes-ethyl acetate, 4:1, v/v) to provide alcohol 239 (153 g, 0.38 mmol, 96%) as a colorless oil.

To a solution of 239 (110 mg, 0.28 mmol) in MeOH (1.5 mL) and H₂O (0.7 mL) was added NaIO₄ (354 mg, 1.68 mmol). The reaction mixture was stirred at rt for 30 min before the addition of H₂O (5 mL) and diethyl ether (5 mL). The aqueous phase was extracted by diethyl ether (3 x 5 mL). The organic phases were dried over anhydrous MgSO₄, filtered, and concentrated. The residue was purified by flash chromatography (hexanes-ethyl acetate, 12:1, v/v) to provide alcohol 239a (95 mg, 0.27 mmol, 96%) as a colorless oil.

Rᵣ = 0.61 (Hexanes-Ethyl acetate, 3:1, v/v); ¹H NMR (CDCl₃, 400 MHz): δ 9.75 (d, J = 1.9 Hz, 1H), 7.23 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 4.44 (s, 2H), 4.14 (m, 1H),
3.81 (s, 3H), 3.48 (dd, $J = 6.2$ Hz, 1.4 Hz, 1H), 2.61 (m, 1H), 1.11 (d, $J = 7.0$ Hz, 3H), 0.89 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 203.7, 159.2, 129.9, 129.3, 113.7, 73.0, 72.6, 71.6, 55.2, 49.9, 25.7, 18.0, 9.9, - 4.5, - 5.1; IR (neat): 2953, 1724, 1612, 1513, 1463, 1249, 1102, 836, 777; $\left[\alpha\right]_{D}^{25}$ - 43.7 (c 1.9, CHCl$_3$); HRMS-ESI (m/z) calculated for [M+ Na$^+$]: 375.1962, found: 375.1962.

tert-butyl((2S,3S)-5,5-dibromo-1-((4-methoxybenzyl)oxy)-3-methylpent-4-en-2-yl)oxy)dimethylsilane (239b)

To a cooled (0 °C) solution of CBr$_4$ (2.51 g, 7.56 mmol) in CH$_2$Cl$_2$ (25 mL) was added Ph$_3$P (3.96 g, 15.1 mmol). The mixture was allowed to stir 30 min before the addition of aldehyde 239a (1.33 g, 3.77 mmol) and i-Pr$_2$Net (1.32 mml, 7.56 mmol) in CH$_2$Cl$_2$ (12 mL). The reaction was stirred another 20 min and was then added saturated aqueous NaHCO$_3$ (20 mL). The aqueous phase was extracted by CH$_2$Cl$_2$ (3 x 5 mL) and the combined organic phases were washed with brine. The organic phases were dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated. The residue was purified by flash chromatography (hexanes-ethyl acetate, 50:1, v/v) to provide alcohol 239b (1.6 g, 3.16 mmol, 84%) as a colorless oil.

$R_f$ = 0.37 (Hexanes-Ethyl acetate, 10:1 , v/v); $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.26 (d, $J = 8.7$ Hz, 2H), 6.91 (d, $J = 8.7$ Hz, 2H), 6.45 (d, $J = 9.5$ Hz, 1H), 4.45 (s, 3H), 3.83 (s,
3H), 3.77 (m, 1H), 3.34 (m, 1H), 2.78 (m, 1H), 1.06 (d, \( J = 7.0 \) Hz, 2H), 0.91 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \( \delta \) 159.2, 140.0, 130.2, 129.3, 113.8, 88.2, 73.8, 73.1, 72.8, 55.3, 41.7, 25.9, 18.1, 16.1, -4.2, -4.9; IR (neat): 2953, 1612, 1513, 1620, 1248, 1102, 1035, 837, 776; \([\alpha]_{D}^{25} -11.6 \) (c 1.6, CHCl\(_3\)); HRMS-ESI (\( m/z \)) calculated for [M+ Na\(^+\)]: 529.0380, found: 529.0381.

![240]

tert-butyl((2S,3S)-1-((4-methoxybenzyl)oxy)-3-methyl-5-(trimethylsilyl)pent-4-yn-2-yl)oxy)dimethylsilane (240)

To a cooled (-78 °C) solution of 239b (1.1 g, 2.2 mmol) in THF (20 mL) was added \( n \)-BuLi (2.0 mL, 4.8 mmol, 2.5 M in Hexane) slowly. After stirring 30 min, TMSCl (0.85 mL, 6.6 mmol) was added. The mixture was allowed to stir another 1 h before saturated aqueous NH\(_4\)Cl (20 mL) was added. The aqueous phase was extracted by diethyl ether (3 x 20 mL) and the combined organic phases were washed with brine. The organic phases were dried over anhydrous Na\(_2\)SO\(_4\), filtered, and concentrated. The residue was purified by flash chromatography (hexanes-ethyl acetate, 100:1, v/v) to provide alcohol 240 (1.0 g, 2.0 mmol, 93%) as a colorless oil.

R\(_f\) = 0.37 (Hexanes-Ethyl acetate, 10:1, v/v); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \( \delta \) 7.27 (d, \( J = 8.7 \) Hz, 2H), 6.90 (d, \( J = 8.7 \) Hz, 2H), 4.48 (s, 2H), 3.80 (s, 3H), 3.77 (m, 1H), 3.63 (m, 1H), 3.45 (m, 1H), 2.76 (m, 1H), 1.18 (d, \( J = 7.0 \) Hz, 2H), 0.92 (s, 9H), 0.15 (s, 9H), 0.08
(s, 3H), 0.07 (s, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 159.3, 130.8, 129.4, 113.9, 108.9, 85.8, 73.9, 73.2, 72.8, 55.5, 31.7, 26.0, 18.3, 16.9, 0.4, -4.0, -4.7; IR (neat): 2930, 1612, 1513, 1249, 1096, 840, 776; $[\alpha]_D^{25}$ -14.6 (c 2.5, CHCl$_3$); HRMS-ESI ($m/z$) calculated for [M+ Na$^+$]: 443.2408, found: 443.2406.

(2S,3S)-2-((tert-Butyldimethylsilyl)oxy)-3-methyl-5-(trimethylsilyl)pent-4-yn-1-ol (240a)

To a solution of 240 (1.4 g, 3.3 mmol) in CH$_2$Cl$_2$ (20 mL), $t$-BuOH (4 mL), pH = 7 aqueous buffer (4 mL) was added DDQ (1.52 g, 6.6 mmol). The reaction mixture was allowed to stir 1 h before saturated aqueous NaHCO$_3$ (20 mL) was added. The aqueous phase was extracted by diethyl ether (3 x 40 mL) and the combined organic phases were washed with brine. The organic phases were dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated. The residue was purified by flash chromatography (hexanes-ethyl acetate, 25:1, v/v) to provide alcohol 240a (1.0 g, 3.3 mmol, 99%) as a colorless oil.

$R_f$ = 0.5 (Hexanes-Ethyl acetate, 5:1, v/v); $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 3.78 (m, 2H), 3.64 (m, 1H), 2.73 (m, 1H), 1.81 (br, 1H), 1.19 (d, $J = 7.0$ Hz, 3H), 0.93 (s, 9H), 0.16 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H); $^{13}$C NMR(CDCl$_3$, 100 MHz): $\delta$ 108.83, 86.48, 74.81, 64.20, 31.20, 26.00, 18.30, 16.06, 0.28, -4.34, -4.38; IR (neat): 3426, 2957, 1250, 1097,
1045, 840, 776; \[\alpha\]_D^{25} -3.20 (c 1.86, CHCl_3); HRMS-ESI (m/z) calculated for [M+ Na^+]: 323.1833, found: 323.1831.

(2S,3S)-2-((tert-butyldimethylsilyl)oxy)-3-methyl-5-(trimethylsilyl)pent-4-ynal (241)

To a cooled (0 °C) solution of 240a (1.0 g, 3.3 mmol) in CH_2Cl_2 (24 mL) and DMSO (6 mL) was added \textit{i}-Pr_2Net (3.5 mL, 19.8 mmol) and SO_3·Py (2.28 g, 14.2 mmol) sequentially. The reaction mixture was allowed to stir 5 min before cold 1 M HCl (14 mL) was added. The aqueous phase was extracted by CH_2Cl_2 (3 x 15 mL) and the combined organic phases were washed with pH = 7 aqueous buffer and brine. The organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexanes-ethyl acetate, 40:1, v/v) to provide alcohol aldehyde 241 (1.0 g, 3.3 mmol, 99%) as a colorless oil.

R_f = 0.7 (Hexanes-Ethyl acetate, 5:1, v/v); \textsuperscript{1}H NMR (CDCl_3, 400 MHz): \textsuperscript{\delta} 9.69 (d, J = 1.8 Hz, 1H), 3.94 (dd, J = 5.2 Hz, 1.8 Hz, 1H), 2.83 (m, 1H), 1.21 (d, J = 7.0 Hz, 3H), 0.95 (s, 9H), 0.16 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); \textsuperscript{13}C NMR(CDCl_3, 100 MHz): \textsuperscript{\delta} 202.5, 106.2, 87.4, 79.3, 30.8, 25.7, 18.3, 18.2, - 0.01, - 4.6, - 5.1; IR (neat): 3947, 2857, 1739, 1250, 1215, 841, 758; \[\alpha\]_D^{25} + 4.42 (c 1.2, CHCl_3); HRMS-ESI (m/z) calculated for [M+ Na^+]: 321.1677, found: 321.1675.

To a flask of CrCl$_2$ (1.6 g, 13 mmol) and NiCl$_2$ (40 mg, 0.31 mmol) was added the solution of alkynyl iodide 163 (2.6 g, 4 mmol) and aldehyde 241 (1.0 g, 3.4 mmol) in THF (40 mL). The reaction was allowed to stir 14 h before 1 M aqueous serine saturated with NaHCO$_3$ (60 mL) and diethyl ether (60 mL) was added. The mixture was stirred for 2 h to fully separate the aqueous and organic phases. The aqueous phase was then extracted by diethyl ether (3 x 80 mL) and the combined organic phases were washed with brine. The residue was purified by flash chromatography (hexanes-ethyl acetate, 60:1 to 20:1, v/v) to provide alcohol 242 (2.7 g, 3.3 mmol, 97%) as a colorless oil.

To a solution of 242 (1.3 g, 1.6 mmol) in THF (8 mL) was added Py (0.6 mL, 7.2 mmol) and HF-Py (0.21 mL, 2.4 mmol) sequentially. The mixture was stirred for 12 h before saturated aqueous NaHCO$_3$ (10 mL) was slowly added. The aqueous phase was then extracted by diethyl ether (3 x 10 mL) and the combined organic phases were washed with brine. The residue was purified by flash chromatography (hexanes-ethyl acetate, 8:1, v/v) to provide alcohol 242a (0.85 g, 1.2 mmol, 75%) as a colorless oil.
To a solution of 242a (0.41 g, 0.58 mmol) in CH$_2$Cl$_2$ (6 mL) and DMSO (2 mL) was added i-Pr$_2$NEt (1.2 mL, 7.0 mmol) and SO$_3$·Py (0.74 g, 4.6 mmol) sequentially. The mixture was stirred 10 min before saturated aqueous NH$_4$Cl (10 mL) was added. The aqueous phase was then extracted by diethyl ether (3 x 10 mL) and the combined organic phases were washed with brine. The residue was purified by flash chromatography (hexanes-ethyl acetate, 12:1, v/v) to provide aldehyde 243 (0.36 g, 0.51 mmol, 88%) as a colorless oil.

R$_f$ = 0.7 (Hexanes-Ethyl acetate, 5:1, v/v); $^1$H NMR (CDCl$_3$, 400 MHz): δ 9.64 (d, J = 2.2 Hz, 1H), 7.27 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 4.58 (s, 2H), 4.07 (m, 1H), 3.93 (d, J = 7 Hz, 1H), 3.83 (s, 3H), 3.65 (m, 1H), 2.95 (m, 1H), 2.46 (m, 1H), 2.22 (m, 1H), 1.88 (m, 1H), 1.58 (m, 2H), 1.17 (d, J = 7.1 Hz, 3H), 1.05 (d, J = 6.8 Hz, 3H), 0.95 (s, 9H), 0.89 (s, 9H), 0.15 (s, 9H), 0.11 (m, 12H); $^{13}$C NMR(CDCl$_3$, 100 MHz): δ 203.3, 187.9, 159.5, 129.7, 129.2, 113.9, 107.2, 95.8, 86.3, 86.1, 81.8, 80.4, 72.6, 72.0, 55.3, 40.3, 32.1, 28.3, 26.1, 25.8, 25.7, 20.2, 18.3, 18.1, 16.7, 0.1, - 4.4, - 4.7, - 4.8, - 4.9; IR (neat): 2924, 1725, 1612, 1513, 1462, 1250, 1098, 838; [α]$_D$$^{25}$ - 20.5 (c 1.2, CHCl$_3$); HRMS-ESI (m/z) calculated for [M+ Na$^+$]: 723.3903, found: 723.3905.

To a flask of MgBr₂·OEt₂ (1.4 g, 5.4 mmol) was added the solution of 243 (0.38 g, 0.54 mmol) in CH₂Cl₂ (5 mL) at –78 °C. After stirring 15 min, the mixture was added solution of silyl enol ether (1.1 g, 4.3 mmol) in CH₂Cl₂ (3 mL). The reaction was allowed to stir for 5 h, before slowly warming up to –40 °C in 1 h. pH = 7 aqueous buffer (10 mL) and diethyl ether (10 mL) was added. The aqueous phase was then extracted by diethyl ether (3 x 10 mL) and the combined organic phases were washed with brine. The residue was purified by flash chromatography (hexanes-ethyl acetate, 10:1, v/v) to provide alcohol 243a (0.4 g, 0.46 mmol, 85%) as a colorless oil.

Rf = 0.6 (Hexanes-Ethyl acetate, 3:1, v/v); ¹H NMR (CDCl₃, 400 MHz): δ 7.27 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 4.68 (q_AB, Δν = 119 Hz, J = 11.5 Hz, 2H), 4.09 (m, 1H), 3.92 (d, J = 7.0 Hz, 1H), 3.82 (s, 3H), 3.59 (br, 1H), 3.31 (t, J = 2.4 Hz, 1H), 3.18 (m, 1H), 3.11 (m, 1H), 2.96 (m, 1H), 2.77 (m, 1H), 2.54 (m, 3H), 2.29 (m, 1H), 1.94 (m, 1H), 1.68 (m, 4H), 1.16 (d, J = 7.0 Hz, 3H), 1.07 (m, 6H), 0.94 (m, 21H), 0.12 (m, 21H); ¹³C NMR (CDCl₃, 100 MHz): δ 213.0, 187.9, 159.4, 130.0, 129.7, 113.9, 107.1, 95.9, 86.4, 81.8, 80.5, 80.4, 72.6, 71.9, 67.0, 57.6, 55.3, 44.6, 44.3, 40.7, 37.1, 32.1, 31.4, 28.6, 25.8, 25.7, 20.1, 18.3, 18.0, 17.9, 17.0, 16.9, 0.1, -4.3, -4.6, -4.7, -4.9; IR (neat): 3487, 2956, 2998, 1674, 1514, 1462, 1249, 1103, 839, 777; [α]D²⁵ = 37.5 (c 1.2, CHCl₃); HRMS-ESI (m/z) calculated for [M+ Na⁺]: 892.5118, found: 892.5118.
(3S,4S,9R,11R,12R,13R,16S,18R)-19-azido-4,11-bis((tert-butyldimethylsilyl)oxy)-12-
((4-methoxybenzyl)oxy)-3,9,16,18-tetramethyl-13-((triethyldimethylsilyl)oxy)-1-
(trimethylsilyl)nonadeca-1,6-diyne-5,15-dione (244)

To a cooled (-55 °C) solution of 243a (0.72 g, 0.83 mmol) in CH$_2$Cl$_2$ (10 mL) was added
2,6-lutidine (0.41 mL, 3.3 mmol), TESOTf (0.5 mL, 2.1 mmol) successively. The
reaction mixture was allowed to stir 20 min before pH = 7 aqueous buffer (10 mL) and
diethyl ether (10 mL) was added. The aqueous phase was then extracted by diethyl ether
(3 x 10 mL) and the combined organic phases were washed with brine. The residue was
purified by flash chromatography (hexanes-ethyl acetate, 30:1, v/v) to provide alcohol
244 (0.8 g, 0.82 mmol, 98%) as a colorless oil

R$_f$ = 0.63 (Hexanes-Ethyl acetate, 5:1, v/v); $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.27 (d, $J =$
8.6 Hz, 2H), 6.89 (d, $J = 8.6$ Hz, 2H), 4.51 (q$_{AB} , \Delta
\nu = 68$ Hz, $J = 11.3$ Hz, 2H), 4.41 (m, 1H), 4.01 (m, 1H), 3.91 (d, $J = 7.1$ Hz, 1H), 3.82 (s, 3H), 3.49 (m, 1H), 3.21 (m, 1H),
3.08 (m, 1H), 2.95 (m, 1H), 2.87 (m, 1H), 2.71 (m, 2H), 2.49 (m, 1H), 2.18 (m, 1H), 1.99
(m, 1H), 1.74 (m, 3H), 1.51 (m, 1H), 1.17 (d, $J = 7.1$ Hz, 3H), 1.07 (d, $J = 7.1$ Hz, 6H),
0.94 (m, 27H), 0.56 (m, 6H), 0.15 (s, 9H), 0.11 (m, 12H); $^{13}$C NMR(CDCl$_3$, 100 MHz):
$\delta$ 212.0, 187.8, 159.1, 130.9, 129.2, 113.6, 107.2, 96.5, 86.3, 83.9, 81.9, 80.2, 73.0, 71.5,
68.4, 57.6, 55.2, 45.6, 44.3, 40.0, 37.0, 32.1, 31.4, 28.8, 26.0, 25.7, 20.8, 18.2, 18.1, 18.0,
17.0, 16.9, 7.0, 4.9, 0.1, - 3.6, - 4.7, - 4.9, -5.0; IR (neat): 2956, 2098, 1716, 1514, 1458, 1249, 1107, 833, 775; [α]D25 - 19.0 (c 1.2, CHCl3); HRMS-ESI (m/z) calculated for [M+ Na+]: 1006.5983, found: 1006.5981.


To a solution of 244 (0.16 g, 0.16 mmol) in CH2Cl2 (2 mL), pH = 7 aqueous buffer (0.4 mL) and i-BuOH (0.2 mL) was added DDQ (93 mg, 0.4 mmol). The reaction was allowed to stir for 10 min before pH = 7 aqueous buffer (4 mL) and diethyl ether (8 mL) was added. The aqueous phase was then extracted by diethyl ether (3 x 8 mL) and the combined organic phases were washed with brine. The residue was purified by flash chromatography (hexanes-ethyl acetate, 30:1, v/v) to provide alcohol 244a (0.14 g, 0.16 mmol, 98%) as a colorless oil.

Rf = 0.60 (Hexanes-Ethyl acetate, 5:1, v/v); 1H NMR (C6D6, 400 MHz): δ 4.53 (q, J = 5.6 Hz, 1H), 4.06 (d, J = 6.6 Hz, 1H), 3.93 (m, 1H), 3.59 (q, J = 5.4 Hz, 1H), 3.19 (m, 1H), 2.88 (m, 1H), 2.77 (m, 1H), 2.65 (m, 2H), 2.51 (d, J = 6 Hz, 1H), 2.43 (m, 1H), 2.27 (m, 1H), 2.15 (m, 2H), 1.78 (m, 4H), 1.51 (m, 1H), 1.19 (d, J = 7.1 Hz, 3H), 1.05 (m, 24H), 0.93 (m, 3H), 0.73 (m, 9H), 0.15 (m, 27H); 13C NMR (C6D6, 125 MHz): δ 210.7, 187.0, 109.2, 107.7, 95.5, 86.7, 82.4, 81.1, 77.1, 71.9, 69.3, 57.4, 15.9, 44.8, 39.3, 37.0, 32.6,
31.5, 28.7, 26.1, 26.0, 20.7, 18.6, 18.3, 17.9, 17.3, 17.1, 7.2, 5.6, 0.2, - 3.8, -4.35, - 4.83; IR (neat): 3487, 2929, 2098, 1676, 1458, 1249, 1103, 839, 777; [α]D25 -25.6 (c 1.0, Benzene); HRMS-ESI (m/z) calculated for [M+ Na+]: 886.5408, found: 886.5405.

(3R,4R)-1-((2S,3aR,5S,7S,9R,9aR)-2-((2S,4R)-5-azido-4-methylpentan-2-yl)-2-methoxy-7-methyloctahydro-5H-5,9-epoxyfuro[3,2-b]oxocin-5-yl)-3-hydroxy-4-methylhex-5-yn-2-one (246)

To a solution of 244a (0.11 g, 0.13 mmol) in MeOH (1.5 mmol) was added PPTS (0.3 mg, 1.3 µmol). The reaction was stirred for 10 min in rt. To the reaction mixture was added pH = 7 aqueous buffer (5 mL) and diethyl ether (3 mL). The aqueous phase was then extracted by diethyl ether (3 x 5 mL) and the combined organic phases were washed with brine. The residue was purified by flash chromatography (hexanes-ethyl acetate, 80:1, v/v) to provide alcohol 245 (0.11 g, 0.13 mmol, 99%) as a colorless oil.

To a solution of 245 (0.11 g, 0.13 mmol) in THF (2 mL) was added TBAF (0.65 mL, 0.65 mmol, 1 M in THF) in rt. The mixture was allowed to stir for 20 min before pH = 7 aqueous buffer (5 mL) and diethyl ether (3 mL) was added. The aqueous phase was then extracted by diethyl ether (3 x 5 mL) and the combined organic phases were washed with
brine. The residue was purified by flash chromatography (hexanes-ethyl acetate, 8:1, v/v) to provide alcohol 246 (12 mg, 26 µmol, 20%) as a colorless oil.

R_f = 0.4 (Hexanes-Ethyl acetate, 3:1, v/v); \(^1\)H NMR (C_6D_6, 400 MHz): δ 4.24 (m, 4H), 3.26 (d, J = 3.8 Hz, 1H), 3.13 (s, 3H), 3.11 (m, 1H), 2.92 (s, 2H), 2.84 (m, 1H), 2.71 (m, 1H), 2.11 (m, 1H), 2.01 (m, 2H), 1.78 (m, 2H), 1.64 (m, 3H), 1.43 (m, 1H), 3.38 (d, J = 7.1 Hz, 3H), 1.14 (m, 1H), 1.06 (m, 4H), 0.79 (m, 4H), 0.58 (d, J = 7.1 Hz, 3H); \(^13\)C NMR (C_6D_6, 125 MHz): δ 206.9, 111.2, 95.9, 84.0, 80.1, 75.2, 73.8, 71.3, 70.2, 56.5, 50.9, 47.6, 42.8, 41.8, 36.4, 34.4, 33.1, 31.1, 30.3, 35.1, 23.0, 19.6, 17.8, 15.1; IR (neat): 3466, 2929, 2096, 1701, 1450, 1249, 1103, 1047, 839, 777; [\(\alpha\)]_D\(^{25}\) + 1.2 (c 0.3, Benzene); HRMS-ESI (m/z) calculated for [M+ Na\(^+\): 486.2575, found: 486.2573.

![2,2,2-trichloroethyl ((2R,4S)-4-((2S,3aR,5S,7S,9R,9aR)-2-methoxy-7-methyl-5-((3R,4R)-4-methyl-2-methylene-3-((triethylsilyl)oxy)hex-5-yn-1-yl)octahydro-2H-5,9-epoxyfuro[3,2-b]oxocin-2-yl)-2-methylpentyl)carbamate (247)](image)

To a cooled (-78 °C) solution of 246 (12 mg, 26 µmol) in CH_2Cl_2 (1 mL) was added 2,6-lutidine (0.01 mL, 78 µmol) and TESOTf (0.01 mL, 39 µmol) successively. The reaction was allowed to stir 30 min before pH = 7 aqueous buffer (3 mL) and diethyl ether (2 mL)
was added. The aqueous phase was then extracted by diethyl ether (3 x 3 mL) and the combined organic phases were washed with brine. The residue was purified by flash chromatography (hexanes-ethyl acetate, 12:1, v/v) to provide alcohol 246a (14 mg, 20 µmol, 92%) as a colorless oil.

To a solution of 246a (35 mg, 61 µmol) in MeCN (0.2 mL) and MeOH (0.2 mL) was added Ph$_3$P (48 mg, 0.18 mmol). The mixture was stirred for 12 h before TeocOSU (49 mg, 0.18 mmol) was added. After another 12 h, the reaction mixture was concentrated. The residue was purified by flash chromatography (hexanes-ethyl acetate, 8:1, v/v) to provide alcohol 246b (37 mg, 53 µmol, 87%).

To a stirred suspension of methyl triphenyl phosphonium iodide (0.3 g, 0.74 mmol) in PhMe (1 mL) was added KHMS (1.3 mL, 0.67 mmol, 0.5 M solution in PhMe) in rt. The mixture was warmed up to 80 °C. After stirring 30 min, the yellow solution was allowed to slowly cool back to rt. 1 mL of the ylide solution was added to a solution of 246b (37 mg, 53 µmol) in PhMe (1 mL). The solution was stirred at rt for 30 min, before pH = 7 aqueous buffer (3 mL) and diethyl ether (2 mL) was added. The aqueous phase was then extracted by diethyl ether (3 x 3 mL) and the combined organic phases were washed with brine. The residue was purified by flash chromatography (hexanes-ethyl acetate-Et$_3$N, 8:1:0.09, v/v/v) to provide alcohol 247 (20 mg, 28 µmol, 54%) as a colorless oil.

$R_f = 0.4$ (Hexanes-Ethyl acetate, 3:1, v/v); $^1$H NMR (C$_6$D$_6$, 400 MHz): $\delta$ 5.53 (q, $J = 1.2$ Hz, 1H), 5.26 (d, $J = 1.7$ Hz, 1H), 4.51 (t, $J = 6.0$ Hz, 1H), 4.47 (d, $J = 4.3$ Hz, 1H), 4.42 (t, $J = 3.8$ Hz, 1H), 4.43 (m, 3H), 3.39 (d, $J = 3.8$ Hz, 1H), 3.29 (m, 1H), 3.04 (s, 3H), 2.91 (m, 2H), 2.51 (q$_{AB}$, $J = 14.6$ Hz, 2H), 2.26 (m, 1H), 2.11 (m, 2H), 1.92 (d, $J = 2.5$ Hz, 1H), 1.88 (m, 2H).
1.72 (m, 4H), 1.31 (m, 6H), 1.23 (m, 1H), 1.17 (d, J = 6.7 Hz, 3H), 1.08 (t, J = 8.0 Hz, 9H), 1.01 (m, 2H), 0.87 (d, J = 6.5 Hz, 3H), 0.73 (m, 9H), - 0.05 (s, 9H); $^{13}$C NMR (C$_6$D$_6$, 125 MHz): δ 156.9, 145.3, 129.7, 116.2, 115.6, 111.7, 97.0, 86.2, 77.8, 76.2, 73.5, 70.5, 701, 62.6, 47.9, 45.9, 42.6, 40.2, 37.0, 34.8, 32.1, 31.8, 25.1, 23.3, 19.6, 18.1, 18.0, 15.7. 7.3, 5.4, - 1.5; IR (neat): 3054, 2955, 1718, 1437, 1189, 1121, 883, 742, 695; [α]$_D^{25}$ - 6.2 (c 0.5, Benzene); HRMS-ESI (m/z) calculated for [M+ Na$^+$]: 716.4348, found: 716.4349.

2,2,2-trichloroethyl (2S,3S,3a'R,5R,5'S,7'S,9'R,9a'R)-3,5,7'-trimethyl-5'-((3R,4R)-4-methyl-2-methylene-3-((triethylsilyl)oxy)hex-5-yn-1-yl)octahydrospiro[piperidine-2,2'-[5,9]epoxyfuro[3,2-b]oxocine]-1-carboxylate (248)

To a solution of 247 (20 mg, 28 µmol) in MeCN (1 mL) was added Nd(OTf)$_3$ (0.2 mg). The reaction was allowed to stir 10 min before Et$_3$N (0.01 mL) was added. The mixture was directly filtered through a pad of silica gel and washed with ethyl acetate (5 mL). The combined organic phase was concentrated. The residue was purified by flash chromatography (hexanes-ethyl acetate-Et$_3$N, 15:1:0.8, v/v/v) to provide alcohol 248 (13 mg, 20 µmol, 70%) as a colorless oil.

R$_f$ = 0.4 (Hexanes-Ethyl acetate, 5:1, v/v); $^1$H NMR (C$_6$D$_6$, 400 MHz): δ 5.62 (q, J = 1.4 Hz, 1H), 5.17 (d, J = 1.6 Hz, 1H), 4.59 (d, J = 3.2 Hz, 1H), 4.37 (m, 2H), 4.31 (m, 2H), 4.11 (d, J = 4.7 Hz, 1H), 4.05 (dd, J = 13.2 Hz, 4.2 Hz, 1H), 3.46 (dd, J = 13.1 Hz, 12.0 Hz, 1H).
Hz, 1H), 3.22 (m, 1H), 3.14 (d, \( J = 4.6 \) Hz, 1H), 2.64 (q\(_{AB}\), \( J = 14.1 \) Hz, 2H), 2.25 (m, 1H), 1.92 (m, 2H), 1.75 (m, 1H), 1.59 (m, 2H), 1.47 (m, 5H), 1.26 (m, 2H), 1.17 (m, 2H), 1.11 (t, \( J = 8.0 \) Hz, 9H), 0.84 (m, 6H), 0.75 (m, 9H), - 0.04 (s, 9H); \(^{13}\)C NMR (C\(_6\)D\(_6\), 125 MHz): \( \delta \) 156.0, 145.9, 115.5, 97.4, 96.6, 85.9, 78.2, 77.5, 73.8, 70.9, 70.4, 62.9, 49.0, 45.9, 40.8, 39.61, 39.57, 36.3, 34.6, 32.0, 31.8, 24.7, 23.2, 19.1, 18.9, 18.2, 16.7, 7.4, 5.5, - 1.6; IR (neat): 2953, 1697, 1458, 1252, 1169, 1121, 883, 742; \([\alpha]_D^{25}\) + 9.2 (c 0.6, Benzene); HRMS-ESI (m/z) calculated for [M + Na\(^+\)]: 684.4086, found: 684.4084.
References


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Appendix A: Selected NMR Spectra