Synthetic Studies Toward the Total Synthesis of Azaspiracid-1

by

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Azaspiracid-1, a novel marine toxin that contains 9 rings and 20 stereogenic centers, has drawn considerable attention from synthetic groups worldwide due to its structural complexity, which includes a unique trioxabisspiroketal fused to a tetrahydrofuran ring (ABCD rings), a piperidine-tetrahydrofuran spiroaminal system fused to a 2,9-dioxabicyclo[3.3.1]nonane system (FGHI rings), a connecting six-membered cyclic hemiketal bridge (E ring) and a γ,δ-unsaturated terminal carboxylic acid side chain. Our efforts toward the total synthesis of azaspiracid-1
led to the completion of both C1-C26 northern and C27-C40 southern halves of azaspiracid-1.

Herein, our improved and scalable synthetic studies toward the total synthesis of azaspiracid-1 is described. In particular, an improved and scalable synthesis of sulfone 3.6 with a key one-pot ketalization and methylation of ketone 3.22 to methylated hemiketal 3.24 is illustrated. A total 19 mmol of sulfone 3.6 has been prepared by this approach. An improved and scalable synthesis of aldehyde 3.7 utilizing allyl bromide 3.31 to couple with Evans auxiliary 3.33 has been developed. A total of 10 mmol of aldehyde 3.7 has been prepared by this approach. An improved synthesis toward the ABC ring fragment 3.52 with a high yield Julia coupling step is shown.

Large scale improved syntheses of the linkage fragment 3.2, the aldehyde fragment 4.9 and the azide fragment 4.10 of the southern portion of (−)-azaspiracid-1 have been described.

With an abundant material prepared by this scalable improved approach, we are confident that completing the total synthesis of (−)-azaspiracid-1 will occur in the near future.
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SYNTHETIC STUDIES TOWARD THE TOTAL SYNTHESIS OF

AZASPORACID-1

CHAPTER 1:

Introduction of Spiroketals
1.1 Spiroketal Natural Products

Spiroketals are found in nature as subunits of many natural products isolated from microbes, fungi, plants, insects and marine organisms. In a spiroketal subunit, two rings are joined together by a sp³ carbon atom (spiro center) which makes the faces of these two rings spiro to each other, and there is one oxygen in each ring next to the spiro carbon atom. Since the earliest natural spiroketals (the steroidal saponins¹ and sapogenins)² were isolated in the 1940s, many natural spiroketals showing diverse biological activities have been reported.³ Due to the size of this thesis, only a few natural spiroketals of pharmacological importance will be briefly introduced as followed.

Milbemycin and its closely related avermectin antibiotics (Figure 1.1) show significant insecticidal and acaricidal activity while displaying low mammalian toxicity, therefore this class of spiroketals indicate enormous potential for the treatment of parasitic infections.⁴ Among them, ivermectin is effective for the treatment of onchocerciasis, a parasitic disease that causes permanent blindness of 20-40 million people worldwide.⁵ To date, most of the synthetic effort on spiroketals has been drawn to this series of spiroketals.
Figure 1.1. Structures of milbermycins, avermectins and ivermectin.

Spirolaxine and spirolaxine methyl ether (Figure 1.2) are used for the treatment of gastroduodenal disorders and the prevention of gastric cancer due to their inhibitory activity against the micro-aerophilic Gram-negative bacterium *Helicobacter pylori*.6 The total synthesis of spirolaxine methyl ether have been accomplished by Brimble,7 Dallavalle8 and Phillips.9

Figure 1.2. Structures of spirolaxine and spirolaxine methyl ether.

Reveromycin-A (Figure 1.3) is a potent inhibitor of the mitogenic activity of epidermal growth factor (EGF) in a mouse keratinocyte10 and is a specific
inhibitor of Saccharomyces cerevisiae isoleucyl-tRNA synthetase (IleRS). Rizzacasa, Shimizu and Nakata have reported the total synthesis of reveromycin-A.

![Reveromycin A](image)

**Figure 1.3.** Structure of reveromycin A.

Bistramide A (Figure 1.4) is able to inhibit nucleotide exchange by stabilizing the closed actin conformation and is a potential candidate for anticancer therapy. The total synthesis of bistramide A has been completed by Yadav, Kozmin, Crimmins and Panek.

![Bistramide A](image)

**Figure 1.4.** Structure of bistramide A.

Saponaceolide B (Figure 1.5) was isolated from a Northern Italian mushroom *Tricholoma saponaceum* and it shows antitumor activity toward 60
human cancer lines. The asymmetric synthesis of (+)-saponaceolide B was reported by Trost and coworkers in 1999.

![Structure of (+)-saponaceolide B](image)

**Figure 1.5.** Structure of (+)-saponaceolide B.

Okadaic acid and acanthafolicin (Figure 1.6) are causative agents of diarrhetic shellfish poisoning. These compounds are believed to be produced by symbiotic microorganisms though isolated from marine sponges. Later, pectenotoxin-1 with similar biological activities was isolated from toxic scallops and mussels.
Figure 1.6. Structures of okadaic acid, acanthafolicin and pectenotoxin-1.

1.2 Conformations of Natural Spiroketalts

1.2.1 Anomeric Effect

Due to the 1,3-diaxial steric repulsion, the conformational preference of most substituent groups larger than hydrogen on the cyclohexane ring is in the equatorial position rather than the axial position. However, there are situations where heteroatomic substituents adjacent to a heteroatom within a cyclohexane ring prefer the axial position instead of the less hindered equatorial orientation. This effect is called the “anomeric effect.”²⁵
There are many postulated origins of the anomeric effect, including syn-axial 1,3-repulsions of lone pair orbitals (rabbit ear effect),\textsuperscript{26} electrostatic repulsions,\textsuperscript{27} dipolar interactions,\textsuperscript{28} and n-σ* hyperconjugation stabilizations.\textsuperscript{29} In particular, the n-σ* hyperconjugation stabilizations hypothesis has been believed to be the most important one. As shown in Figure 1.7, compound 1.1 is stabilized by two anomeric effect components, an exo anomeric effect and an endo anomeric effect. In the exo anomeric effect, the lone pair electron of exocyclic oxygen overlap with the σ* orbital of the C–O bond in the ring, which makes the unshared lone pair electron donated into the σ* orbital of the endocyclic C–O bond. This delocalization and hyperconjugation stabilize the axial conformation. Similarly, in the endo anomeric effect, the lone pair of the cyclic oxygen donates into the σ* orbital of the exocyclic C–O bond.\textsuperscript{30} Another stabilizing factor is the dipoles of the two C–O bonds point away in an anomeric conformation to minimize the dipole-dipole repulsion, while the non-anomeric conformation has two dipoles pointed in the same direction.\textsuperscript{31}
Figure 1.7. Exo and endo enomeric effect of compound 1.1

No matter the origin of this effect, a preference (~2.4 kcal/mol) of a C-O substituent in the axial orientation in the 2-position of a tetrahydropyran ring is observed.\(^{30}\) This effect has an important influence in the conformation of natural spiroketalts.

1.2.2 Conformations of Dioxaspiralketals

In 1981, an intriguing cyclization of ketoldiol 1 to the 1,7-dioxaspiro [5.5] undecanes in a single conformation was reported by Deslongchamps and coworkers.\(^{30,32}\)

Scheme 1.8. Enantioselective synthesis of compound 1.3
This exclusive selection of only one single conformer out of three possible conformers might be resulted from the stabilizing anomeric effects. This example demonstrated that the three dimensional space of polycyclic compounds can be defined by stereoelectronic effects and thermodynamic anomerically stabilized polycyclic spiroketals could be synthesized by stereocontrolled self-organization processes. Approximate calculations of the three possible conformers of the 1,7-dioxaspiro [5.5] undecanes by Deslongchamps and coworkers indicate that the lowest energy conformer is the doubly anomeric conformer and the stabilization of each anomeric bond is about 2.4 kcal/mol. Tschumper’s group investigated the systems again using modern molecular dynamic simulations and came to the same conclusion.

![Diagram of possible conformers](image)

**Figure 1.9.** Three possible conformers of the 1,7-dioxaspiro [5.5] undecane

### 1.2.3 Conformations of Trioxaspiralketals

Inspired by the single selectivity of the 1,7-dioxaspiro[5.5]undecanes reaction reported by Deslogchmaps, the McGarvey group investigated the simple 6,6,6 bisspiroketal by a similar cyclization using diketodiol 1.10 as the starting material. The thermodynamically controlled polycyclization gives a cis-
1,7,9-trioxadispiro[5.1.5.3]hexadecane and a trans-1,7,9-
trioxadispiro[5.1.5.3]hexadecane in a roughly 1:2 ratio.

Scheme 1.10. Simple spiroketalization of three dihydroxylketone precursor to
1,7,9-trioxadispiro[5.1.5.3]hexadecane

The trans-isomer predominated in all solvent systems (table 1.11) indicated that the cis-isomer has an energy difference of approximately 0.3-0.7 kcal/mol over the trans-isomer due to the cumulative stereoelectronic and steric effects.35
Table 1.11. Thermodynamic equilibrium between cisoidal and transoidal 1,7,9-
trioxadispiro[5.1.5.3]hexadecane under acidic conditions.\textsuperscript{35}

In the initial analysis, assuming both isomers apply all-chair conformers,
the cis-isomer incorporates four anomic effects but is destabilized by the dipole-
dipole repulsion resulting from the 1,3-diaxial oxygens. In contrast, the trans-
isomer only has three anomic effects, but is relieved of the dipole-dipole
destabilization. It was observed that the preference for the trans-isomer increase to
3.4:1 in hexane, this phenomenon was explained by that the magnitude of the
dipole-dipole repulsion of the cis-isomer become larger in the less polar hexane
solvent. Previous synthetic studies\textsuperscript{36} indicated the presence of a significant
destabilizing effect owing to the dipole-dipole repulsion of these 1,3-diaxial
oxygens, which is in agreement with this explanation.

Further studies based on the \textsuperscript{13}C NMR spectrum of each isomer were
carried out and the peak of the cis-isomer was broadening while the peak simplicity
of the trans-isomer persisted when they were cooled to –83 °C. This observation
reveals that the ground state of the cis-isomer is a rapid interconversion between two conformers while the ground state of the trans-isomer has a C2 symmetry and both isomers apply a twist-boat conformation in the central ring rather than a chair conformation.\textsuperscript{35}

![Ground state conformations of cisoidal and transoidal 1,7,9-trioxadispiro[5.1.5.3]hexadecane](image)

**Figure 1.12.** Ground state conformations of cisoidal and transoidal 1,7,9-trioxadispiro[5.1.5.3]hexadecane

In 2006, Tschumper\textsuperscript{34} revisited this 6,6,6 bispiroketal prototype with more powerful modern computational tools. Interestingly, his result was in agreement with McGarvey’s work in that the twist-boat trans-isomer is the most stable isomer of 1,7,9-trioxadispiro[5.1.5.3]hexadecane. However, in contrast with McGarvey’s work\textsuperscript{35}, an all-chair conformation is found to be the most stable cis-isomer of 1,7,9-trioxadispiro[5.1.5.3]hexadecane. Based on this data, the transoidal bispiroketal has been shown to be the most stable conformer though sometimes the energy
difference between the two most stable of the cisoidal bispiroketal might differ because of the inherent error within the computational calculation methods.

Similar with the studies of the 6,6,6 bispiroketal, the study of the 6,5,6 bispiroketal takes the anomeric stabilizing effect and the dipole-dipole repulsion destabilizing effect into consideration.

![Figure 1.13. Six possible conformers of the 6,5,6 bispiroketal skeleton.](image)

There are six possible conformers, including the doubly anomeric, singly anomeric and non-anomeric bispiroketal of the trans-isomer and the cis-isomer. It is noticed that transoidal bispiroketals are usually more stable over cisodal bispiroketals by \(~1\) kcal/mol\cite{30, 33, 34, 35, 36} due to dipole-dipole repulsion minimization. Therefore, the most stable conformer is the doubly anomeric transoidal spiroketal.
1.2.4 Conformation of Naturally Occuring Spiroketalts

Examination of the structures of naturally occurring spiroketalts reveals most adopt predictable conformations that can maximize the anomeric effects and minimize the steric effects (Figure 1.14). The bisaxial arrangement of spiro C-O bonds is commonly observed in both saturated and unsaturated spiro[5.5] ring systems. For example, the anomerically favored conformation of avermectin B\textsubscript{1a} and B\textsubscript{2a} was revealed by the X-ray crystal structures of avermectin B\textsubscript{1a} and B\textsubscript{2a} aglycones. In the spiroketal conformation of A 204A, the C-O bond in the five-membered ring is axial to the six-membered ring with the other C-O bond in a roughly axial orientation. The monensin-water complex shows an interesting conformation with both the methyl and the hydroxyl axially disposed, which may be stabilized by an intramolecular hydrogen bond. The conformation of hippurin-l monoacetate has the C-O pseudoaxial arrangement as well, though fewer datas are available for spiro [4.4] ring systems.
**Figure 1.14.** Conformations of some natural spiroketals that have C-O bond in axial position.

However, there are two naturally occurring compounds\(^{37}\) (Figure 1.15) that do not reside in a bis-diaxial C-O conformation due to the appreciable conformational influence of the macrocyclic tether connecting the two rings of the speroketals.\(^{41}\)
Conformations of naturally occurring trioxadispiroketalts are much more complex than spiroketalts, and these tricyclic systems are usually heavily substituted. Therefore, general principles applicable to spiroketalts must be examined carefully. For example, 1,6,8-trioxadispiro[4.1.4.3]tetradecanes (Figure 1.16).were studied by Descotes both spectroscopically and crystallographically. The central ring of the syn spiro C-O isomer was revealed by $^1$H and $^{13}$C NMR to reside in a chair conformation while the anti spiro C-O isomer was confirmed by X-ray crystallography to prefer a twist-boat form. This observation was considered as evidence of maximizing anomeric stabilization.
1.2.5 Summary

The conformation of naturally occurring spiriketals is the result of an interplay of the anomeric effect and the steric repulsion. The preference for substituents to reside in axial positions is evident only when the anomeric effect outweighs the 1,3-diaxial steric repulsion, though this is typical in most cases. Therefore, when these two factors are reinforcing (when anomeric effects are maximized and 1,3-diaxial repulsions are minimized), it is possible to predict the molecular conformation. However, it becomes difficult to predict the molecular conformation when these two preferences oppose each other and one of them must be compromised.

1.3 Acid-Catalyzed Spirocyclization and Spiroisomerization.
1.3.1 Conformational Effects on Spiroketal Reactivity.

The preference for axial spiro C-O bonds in the spiro ring systems is apparent in the acid-catalyzed spirocyclizations of dihydroxy ketones or an equivalent.\textsuperscript{33} This inherent thermodynamic bias in the formation of spiro ring systems has been taken advantage of in numerous synthetic studies on the synthesis of complex spiroketalts. Based on the fact that the configuration of the spiro carbon of a natural product corresponds to the thermodynamic most stable form, a generally valid assumption is, if the substitution pattern and other factors are closely mimicked those of the natural product, the acid-promoted spirocyclization of a dihydroxy ketone precursor or an equivalent would proceed to give the correct configuration at the spiro center. Therefore, early work in many spiroketal systems is focused on the assembly of fully functionalized precursors that would cyclize in a thermodynamic acid-catalyzed process to give the same configuration of spiro center with the natural product.

1.3.2 Acid-Catalyzed Spiroisomerization.

There are many examples of spiroisomerization in which one isomer is favored because of the anomeric effects and steric repulsion. A typical example reported by Iwata\textsuperscript{39} in Scheme 1.17 showed that a spiroketal 1.15 containing an axial ethyl group isomerized under strong acidic conditions at the spiro carbon to give a diastereomer 1.16 that has the ethyl group in the equatorial position. In this way, the steric repulsion is minimized and the anomeric effects are maximized.
Scheme 1.17. Isomerization of compound 1.15 to 1.16

In most of the cases, spiroketalts prefer the anomeric conformations. However, the stabilizing influence of the anomeric effect can sometimes be overpowered by severe steric repulsions. An example reported by Ireland in Scheme 1.18 displayed that the anomerically stabilized bis-axial isomer of spiroketal 1.17 underwent isomerization to the mono-anomeric isomer 1.18.

Scheme 1.18. Equilibrium of compound 1.17 and 1.18 under acidic condition.

It is believed that the steric repulsion of the axial spiroketal C-O bond and the axial secondary alkyl group outweight the stability of the doubly anomeric effect in isomer 1.17, therefore, the isomerization proceed from the doubly anomeric isomer to the single anomeric isomer with the relief of steric crowding in isomer 1.17.
1.3.3 Synthesis of Spiroketals by Acid-Catalyzed Spirocyclization.

Although several spiroketal synthesis strategies have been reported, the acid-catalyzed cyclization of dihydroxy ketones or an equivalent is still the most facile and efficient spiroketalization process. The following discussion will focus on some examples of acid-catalyzed spiroketalization.

The enantioselective synthesis of spiroketal 1.23 in Scheme 1.19 started with alkylation of the optically pure lithium reagent 1.19 with the optically pure iodide 1.20 to give a protected trihydroxy ketone 1.21. A Hg(II)-mediated spirocyclization of the triol produced from deprotection of 1.21 affords enantiomerically pure 1.23.

Scheme 1.19. Enantioselective synthesis of spiroketal 1.29

In the synthesis of one of three spiroketal fragments present in okadaic acid, Isobe converted dihydroxy ketone 1.27 to spiroketal 1.28 with catalytic PPTS. (Scheme 1.20)
Scheme 1.20. Synthesis of spiroketal fragment 1.28 in okadaic acid.

The PPTS promoted spiroketalization was used again by Isobe in the synthesis of another spiroketal subunit 1.33 in okadaic acid.\(^1\) (Scheme 1.21) Reductive desulfurization and acid-catalyzed cyclization of 1.31 which was produced by a nucleophilic attach of sulfone 1.30 to lactone 1.29 give spiroketal 1.32 as a single isomer.

Scheme 1.21. Synthesis of single isomer 1.32 in okadaic acid synthesis.

Again, as part of Isobe’s synthesis of okadaic acid, spiroketal 1.37 (Scheme 1.22) comes from acid-catalyzed cyclization of ketone 1.36 which was synthesized
from sulfone 1.34 and aldehyde 1.35 by a nucleophilic addition, Swern oxidation and reductive desulfurization.44

Scheme 1.22. Synthesis of fragment 1.37 in okadaic acid.

In the synthesis of milbemycin β3 reported by Williams,45 (Scheme 1.23) the coupling of the optically active sulfoxide 1.38 with the lactone 1.39 gives a mixture of β-keto sulfoxide 1.40 which was cyclized to spiroketal 1.41 in 75% in two steps with catalytic MsOH in wet benzene.

Scheme 1.23. Synthesis of spiroketal 1.41.

When a ketal was synthesized by an intermolecular reaction of a ketone and an alcohol or diol, a Dean-Stark trap and molecular sieves are necessary to remove water from the reaction. However, in most of the intramolecular spiroketalizations, removal of water is not a requirement, since the thermodynamic difference between
dihydroxy ketones and spiroketals is larger than in the intermolecular counterpart. Sometimes, it is difficult to prevent the spiroketal from forming. Such an example (Scheme 1.24) was reported by Burgstahler in the synthesis of 1,6-dioxaspiro[4.4]nonanes.\(^{46}\) Oxidation of triol 1.43 and 1.45 generated spiroketal 1.44 and 1.46 \textit{in situ} respectively without removal of water.

![Scheme 1.24. Synthesis of spiroketal 1.44 and 1.46 in situ without removal of water.](image)

In the monensin synthesis (Scheme 1.25) reported by Still\(^{47}\) and Kishi,\(^{48}\) a single spiroketal isomer 1.49 with the same conformation with that in natural monensin was obtained from the acid-catalyzed cyclization of the common starting hydroxyl ketone 1.48 with different protecting groups.
Scheme 1.25. Enantioselective synthesis of natural spiroketal 1.49.

In a convergent enantioselective synthesis of (+)-phyllanthocin proposed by Burke, the silyl cleavage of hemiacetal 1.53 triggered a concomitant ring closure with complete stereoselectivity at C8.

Scheme 1.26. Enantioselective synthesis of spiroketal 1.54 to the synthesis of (+)-phyllanthocin.
1.4 Conclusion.

In summary, most natural spiroketals prefer a conformation that maximizes the anomeric stabilization and minimizes the steric repulsions and dipole-dipole interactions. In particular, the ground state conformation of dioxaspiroketals and trioxaspiroketals are discussed, which indicates that dioxaspiroketals prefer an all chair diaxial C-O conformation while the trioxaspiroketals favor a twist boat transoidal conformation. Taking advantage of the thermodynamic stabilized ground state conformer, the most facile and efficient synthesis of spiroketals is a simple acid-catalyzed spiroketalization which would equilibrate to afford the thermodynamic isomer.

1.5 References.


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597.


SYNTHETIC STUDIES TOWARD THE TOTAL SYNTHESIS OF AZASPIRACID-1

CHAPTER 2:

Background of Azaspiracid-1
2.1 Discovery, Isolation and Bioactivities of Azaspiracid-1

Azaspiracid-1 is a marine neurotoxin that was discovered in 1995 when at least eight people became ill after consuming mussels harvested from Killary Harbor in Ireland.\(^1\) A subsequent investigation led to the isolation of 2 mg of azaspiracid-1 from 20 kg of mussel meat by Yasumoto, Satake and coworkers.\(^2\) This colorless amorphous solid named azaspiracid-1 was the causative toxin involved in the Killary Harbor poisoning event. After the first reported azaspiracid poisoning, a total of more than 30 azaspiracid analogues (Figure 2.1) have been isolated from some other European locations.\(^3\) Structures of these azaspiracids were determined by tandem MS and NMR spectroscopy, which differs slightly in their methylation and hydroxylation patterns. A marine dinoflagellate that has been discovered in multiple shellfish species including mussels, oysters, scallops, clams, etc. was proposed to be the origin of azaspiracids.\(^4\)
The azaspiracid poisoning symptoms were very similar to diarrhetic shellfish poisoning (DSP) symptoms which is associated with okadaic acid (OA) and dinophysistoxins (DTXs). However, the mouse bioassays of azaspiracid-1 showed clear neutotoxic symptoms including respiratory difficulties, spasms, limb paralysis and death, which are totally different from the typical symptoms of the diarrhetic shellfish poisoning (DSP) bioassay. Azaspiracid-1 is known to possess toxicity in vitro with a lethal dose in mice of 0.2 mg / kg. Although there is no information about toxicity of other azaspiracids to humans, the mechanism by which azaspiracids induce their toxic effects and their biological targets is still unknown. Human consumption of azaspiracid-contaminated shellfish can result in
severe acute symptoms such as nausea, vomiting, diarrhea, and stomach cramps. Other bioactivities of azaspiracid-1 revealed from its effects on in vitro cell cultures include cytoskeletal alterations, caspase activation, cytotoxicity, cytosolic calcium levels modulation, and alteration of neuronal network. The considerable toxicity and the mechanistic elusiveness have made azaspiracids a threat to the shellfish industry and human health. This situation is further complicated by the scarce amount of azaspiracids obtained from natural sources.

2.2 Original Structural and Revised Structure of Azaspiracid-1

The original structure of azaspiracid-1 (Figure 2.2) was proposed by Yasumoto et al. based on mass (HR-FAB MS, FAB MS/MS, CID MS/MS) spectrometry and NMR (\(^1\)H, \(^{13}\)C, HSQC, HMBC, NOE, COSY, TOCSY, ROESY) spectroscopic studies. The molecule was named “azaspir-acid” because it contains an unusual azaspiro ring system (azaspir-) and a carboxylic acid group (-acid). The structural complexity of azaspiracid-1 includes a unique trioxabisspiroketal fused to a tetrahydrofuran ring (ABCD rings), a piperidine-tetrahydrofuran spiroaminal system fused to a 2,9-dioxabicyclo[3.3.1]nonane system (FGHI rings), a connecting six-membered cyclic hemiketal bridge (E ring) and a \(\gamma,\delta\)-unsaturated terminal carboxylic acid side chain. In total, there are 9 rings and 20 stereogenic centers in the molecule. In the originally proposed structure, the functionalization and relative stereochemistries within the ABCDE-ring domain and the FGHI-ring system were assigned individually by the application of NOE correlations and coupling constant
analyses. However, the relative stereochemistry between these two major fragments was undetermined. Furthermore, the absolute stereochemistry of both pieces was also unknown at that time.

![Structures of azaspiracid-1](image)

**Figure 2.2.** The original proposed and the correct structures of azaspiracid-1.

In 2003, the Nicolaou group\textsuperscript{13} claimed to have finished the first total synthesis of the proposed structure of azaspiracid-1 and they noticed that the originally proposed structure was mis-assigned. By degrading the natural material into smaller pieces, the Nicolaou group narrowed down the location of the structural discrepancy between the synthetic and the naturally derived subunits. They confirmed the relative stereochemistry by comparing \textsuperscript{1}H NMR spectroscopic data of synthetic materials with samples derived from the natural product and they determined the absolute configuration by comparing the optical rotation between synthetic products and the fragments derived from natural azaspiracid-1.

In 2004, the reassigned correct structure of azaspiracid-1 (Figure 2.2) was reported by Nicolaou group\textsuperscript{14} and was confirmed by their total synthesis of azaspiracid-1.
As shown in Figure 2.1, the major stereochemical errors were in the ABCD northern portion of the molecule. In the revised structure, the stereochemical configurations of C14, C16, C17, C19 and C20 were inverted, the double bond was relocated between C7 and C8 rather than that originally proposed between C8 and C9, and the southern FGHI ring system was found to be enantiomeric to the proposed structure.

Independently and concurrently, Carter’s group\textsuperscript{15} had converged on the same stereochemical conclusion when they had synthesized the ABCD ring northern half of azaspiracid-1. By contrast, the structural revision by the Carter’s group is based on an independent analysis of the ROSY NMR spectrum of the ABCD bis-spiroketal domain of azaspiracid-1 corroborated by synthesis in 2004. Bispiroketal 2.5 (Scheme 2.3) was synthesized from hemiketal 2.1 by an acid-catalyzed spiroketalization and an acid-catalyzed spiroketal isomerization of cisoidal 2.2 to transoidal 2.3 followed by a debenzylation, an acylation and a chiral rhodium catalysed C–H radical insertion. However, a key NOE (arrowed) was not observed in the 2D-NMR of bispiroketal 2.5, while inverting the C14 methyl gives a compound with the NOE between the C6 hydrogen and the C16 methyl, which led to Carter’s revised structure of azaspiracid-1.
Scheme 2.3. Carter’s synthesis of ABCD ring system that led to the structure revision.

As shown in Figure 2.4, the ABCD ring system of the revised structure benefits from a double anomeric effect while the original proposed structure of this bisspiroketal was thermodynamically less stable with only one anomeric effect at C10. Therefore, the revised structured is thermodynamically favored, which is a significant reference in the subsequent synthetic efforts.
**Figure 2.4.** Conformations of the proposed and revised ABCD bispiroketal.

There are four ketal moieties in azaspiracid-1 (Figure 2.5): the transoidal bispiroketal ABCD ring system 2.7, the bicyclic [3.3.1] FG ring system 2.8, the E ring hemiketal 2.9 and the spiroaminal HI ring system 2.10. The four ketals are fully anomic stabilized and should be available from thermodynamic ketalization and thermodynamic isomerization, which is useful to synthetic studies of azaspiracid-1.

**Figure 2.5.** Ketal subunits in azaspiracid-1.
2.3 Synthetic Efforts Toward Azaspiracid-1

The structural complexity of azaspiracid-1 (20 stereocenters, 9 rings, 3 spirocenters) makes it a challenging synthetic target and has drawn considerable attention from synthetic research groups of Carter, Nicolaou, Nicolaou, Nicolaou, Nicolaou, Nicolaou, Forsyth, Sasaki, and Mootoo. In 2004, Nicolaou group reported the first total synthesis of (−)-azaspiracid-1 and the structural reassignment. An improved total synthesis of (−)-azaspiracid-1 was published by Nicolaou group in 2006. In 2007, the total synthesis of (+)-azaspiracid-1 was accomplished by the Evans group. Besides these two total synthesis of azaspiracid-1, several partial synthetic studies toward azaspiracid-1 have been reported as well.

2.3.1 Nicolaou’s First Generation Total Synthesis of (−)-azaspiracid-1

The first total synthesis of (−)-azaspiracid-1 was accomplished by Nicolaou and coworkers in 2004 following their revision of the originally proposed structure (Figure 2.2). In Nicolaou’s retroanalysis (Scheme 2.6), (−)-azaspiracid-1 is constructed by a dithane coupling between fragment 2.11 and fragment 2.12, and then a Stille coupling of fragment 2.12 and 2.13.
Nicolaou’s synthesis of the ABCD ring system (Scheme 2.7) started from compound 2.14 which derived from L-malic acid and compound 2.23 which comes from D-malic acid. The key step is the TMSOTf catalyzed spiroketalization of triolketone 2.24 to make the ABC ring system in a single step with the desired stereochemistry in 89% yield.
Scheme 2.7. Nicolaou’s synthesis of the ABCD ring system 2.26

Installation of the sidechain of the ABCD ring northern half (Scheme 2.8) features an alkene metathesis using Grubbs 2nd generation catalyst 2.27 with a
good E/Z selectivity. However, the drawback in this synthesis is the laborious fabrication of the C7-C8 double bond in the A ring in five steps, which could have been considered in earlier steps.

Scheme 2.8. Nicolaou’s installing the sidechain of the ABCD ring northern half
Synthesis of fragment 2.12 (Scheme 2.9) begins with a known lactone 2.34 and features an oxidation-reduction protocol to set the desired stereochemistry at C25 of alcohol 2.39 from its epimeric mixture 2.38, which is coupled by aldehyde 2.36 and vinyl iodide 2.37 under the Nozaki–Hiyama–Kishi conditions (CrCl₂, NiCl₂) in 95% yield.

Scheme 2.9. Nicolaou’s synthesis of the linkage fragment 2.12

Synthesis of the GHI ring southern fragment 2.13 (Scheme 2.10) starts from a known lactone and D-isopropylidene glyceraldehydes, which features a boron-mediated aldol reaction of ketone 2.41 and aldehyde 2.43 to afford alcohol 2.44 in 82% with very good stereoselectivity. Another key step is a Yb(OTf)₃- or Nd(OTf)₃-mediated highly stereoselective spiroaminal formation to give compound 2.49.
Scheme 2.10. Nicolaou’s synthesis of the GHI southern fragment 2.13

The first total synthesis of (–)-azaspiracid-1 (Scheme 2.11) was obtained in sequence of 50 longest linear steps with a 0.028% overall yield by combining three fragments together. There are three key steps: the addition of lithio derivative of dithane 2.12 to pentafluorophenol ester 2.11 to form adduct 2.53 in 63% yield, Stille coupling of compound 2.55 and fragment 2.13 to furnish compound 2.56 in
52% yield, and the G ring formation via an intramolecular iodoetherification in the presence of NIS in good yield. This landmark first conquest of (-)-azaspiracid-1 by Nicolaou group in 2004 was achieved by a final step closing the hemiketal E ring under the condition of LiOH and MeOH in 45% yield.
Scheme 2.11. Nicolaou’s first generation total synthesis of (−)-azaspiracid-1
2.3.2 Nicolaou’s Second Generation Total Synthesis of (-)-azaspiracid-1

In 2006, the second generation total synthesis of (-)-azaspiracid-1 was reported by Nicolaou’s group with a major improvement (Scheme 2.12) in the construction of the ABCD ring fragment.\textsuperscript{17g} Instead of installing a dithiane at C9 and laterly converting it into the double bond functionality between C7 and C8, their modified synthesis begins with the C7-C8 double bond already set in the starting material. The vinyl ketone 2.62 prepared from allyl alcohol 2.61 in 8 steps was polycyclized into bispiroketal ABCD ring fragment 2.63 in the presence of a catalyst TMSOTf. And then, (-)-azaspiracid-1 was synthesized via the analogous sequence used in Nicolaou’s first-generation synthesis with a shorter longest linear step (39 steps compared to 50 steps).

Scheme 2.12. Improvement in Nicolaou’s second-generation total synthesis of (-)-azaspiracid-1
2.3.3 Evans’ Total Synthesis of (+)-azaspiracid-1

The total synthesis of (+)-azaspiracid-1 was accomplished by the Evans group in 2007. Evans’ retrosynthesis (Scheme 2.13) dissembled (+)-azaspiracid-1 into a northern ABCD ring fragment 2.64 and a southern EFGHI ring fragment, which could be obtained from spiroketalization of compound 2.66 and 2.67 respectively.
Scheme 2.13. Evans’ retrosynthesis of (+)-azaspiracid-1

Furthermore, compound 2.66 could be synthesized from a Julia coupling of sulfone 2.68 and aldehyde 2.69. Compound 2.67 could be prepared from enolate 2.70, aldehyde 2.71 and aldehyde 2.72 by a Mukaiyama aldol reaction and a boron
aldol addition subsequently. This retrosynthesis disconnected (+)-azaspiracid-1 into five subunits with similar synthetic complexity and shorted the longest linear steps to 26.

The most well-known feature of Evans total synthesis of (+)-azaspiracid-1 is the successful application of a remarkable Cu-catalyzed enantioselective process that have been utilized 3 times in their total synthesis of (+)-azaspiracid-1. As shown in Scheme 2.14, a Cu-catalytic enantioselective glyoxylate-ene reaction was used to set the stereochemistry at the C17 in compound 2.76. A stereoselective reduction of the ketone intermediate that was produced by the addition of metallated iodide 2.78 to Weinreb amide 2.77 gives a single detectable diastereomer 2.79. A careful selective oxidative cleavage of the olefin 2.79 with ozone produced a ketone intermediate in situ, which was then ketalized under acidic PPTS conditions into the D ring fragment 2.80 in good yield.
Scheme 2.14. Evans’ synthesis of subunit 2.69

The synthesis of the A ring subunit 2.68 (Scheme 2.15) features an enantioselective CBS-reduction of ene-ynone 2.82 to afford the desired stereocenter at C6 in alcohol 2.83, a semihydrogenation of alkyne 2.83 under Lindlar conditions to produce the Z-isomer alkene 2.84 in high yield, and a PPTS catalyzed ketalization in MeOH to furnish the desired lactol methyl ether 2.68 in high yield.
Scheme 2.15. Evans’ synthesis of subunit 2.68

As shown in Scheme 2.16, directly based on Carter group’s work, a Julia coupling was utilized to combine sulfone 2.68 and aldehyde 2.69 to give a sulfonyl alcohol intermediate. The intermediate was transformed into ketone 2.66 as a single diastereomer in good yield by a Dess–Martin oxidation and a sodium amalgam excision of the sulfone moiety. A selective deprotection of TES and a PPTS catalyzed spiroketalization constructed the desired bisspiroketal 2.64 as the thermodynamically favored isomer in good yield.
Scheme 2.16. Evans’ synthesis of the northern half fragment 2.64

In Scheme 2.17, a hetero-Diels–Alder reaction catalyzed by a bench-stable copper complex 2.87 developed by Evans group gives methyl-substituted dihydropyran 2.88, which is enantioselectively reduced into tetrahydropyran 2.89 with very high diastereoselectivity. Compound 2.89 was transformed into compound 2.90 with inverse stereocenter at C21, which was epimerized under basic conditions to give epimer 2.91 with the ethylacetate group at C25 in the equatorial position.
Scheme 2.17. Evans’ synthesis of subunit 2.72

The 1,3-syn-dimethyl tetrahydropyran 2.89 (Scheme 2.17) generated in the enantioselective hetero-Diels–Alder reaction can be utilized to synthesize the acyclic fragment 2.70 (Scheme 2.18) with the 1,3-syn-dimethyl in place.

Scheme 2.18. Evans’ synthesis of subunit 2.70

In the synthesis of fragment 2.71 (Scheme 2.19), a highly enantioselective Tin-catalyzed Mukaiyama aldol reaction was applied to furnish an unsaturated
lactone 2.99 featuring a 1,2-anti diol functionality which was reduced to compound 2.100 with high eantioselectivity.

Scheme 2.19. Evans’ synthesis of subunit 2.71

The crucial compound 2.67 in the construction of the southern half fragment 2.65 (Scheme 2.20) was prepared using a chelated-Mukaiyama aldol reaction and a boron aldol reaction to combine the three subunits. This acyclic compound 2.67 underwent an acid-catalyzed polycyclic ketalization to afford compound 2.104 in high yield and selectivity, which could spiroaminalize to desired compound 2.105 simultaneously when the terminal azide was reduced to anime.
Scheme 2.20. Evans’ synthesis of the southern half fragment 2.65

The completion of Evans total synthesis (Scheme 2.21) is elegant by combining the northern aldehyde fragment 2.64 and the southern sulfone fragment 2.65 via a Julia coupling to give two isomers. However, the undesired isomer 2.106 could be transformed to the desired one by a Swern oxidation / LiBH₄ reduction sequence. This total synthesis was finished in 26 longest linear steps with 2.7% overall yield.
Scheme 2.21. Evans’ total synthesis of (+)-azaspiracid-1

2.3.4 The Carter Group synthetic studies toward azaspiracid-1

The total synthesis of azaspiracid-1 has been an ongoing project in our group since our first publication in 2000$^{16a}$ and our group has made significant
contributions\textsuperscript{15,16} to the synthesis of azaspiracid-1. In 2004, the correct structure of
(−)-azaspiracid-1 contained the epimeric stereochemistries at C14, C16, C17 and
C20 was reported independently by our group,\textsuperscript{15} which is concurrent to Nicolaou’s
efforts.\textsuperscript{14} In 2006, we accomplished the synthesis of the C1-C26 northern half of
azaspiracid-1\textsuperscript{16f} (Scheme 2.24), at the same year, we completed the synthesis of the
FGHI ring system of azaspiracid-1\textsuperscript{16g} (Scheme 2.25).

In our retrosynthesis (Scheme 2.22), (−)-azaspiracid-1 is dissembled into a
FGHI ring system southern half 2.109 and a C1-C26 northern half 2.108 which is
disconnected into an ABCD ring system fragment 2.110 and a E ring linkage
fragment 2.111 by a Horner–Wadsworth–Emmons reaction.
Scheme 2.22. Carter’s retrosynthesis of (–)-azaspiracid-1

The key step in our synthesis of the ABCD ring system 2.110 (Scheme 2.23) is a PPTS-catalyzed spiroketalization of compound 2.114 with moderate diastereoselectivity. Fortunately, the undesired cisoidal 2.115 is readily converted to the desired transoidal 2.116 quantitatively under thermodynamic acidic equilibrium conditions. Compound 2.114 was synthesized by a Julia coupling of sulfone 2.112 and aldehyde 2.113 in a good yield.
Scheme 2.23. Carter’s synthesis of the ABCD ring system 2.110

As shown in Scheme 2.24, the ABCD ring system 2.110 was connected to the E ring linkage 2.111 via a Horner–Wadsworth–Emmons reaction with good diastereoselectivity to give compound 2.118, which was deprotonated using NaHMDS and oxidized by a large excess of Davis oxaziridine to provide hydroxy-ketone 2.119 as a single stereoisomer. Triflation of 2.119 followed by displacement using the potassium salt of p-nitrobenzoic acid inverted the stereochemistry at C20 to give 2.120, which was transformed to 2.121 by desilylation, selenation and oxidation/elimination subsequently. The northern half fragment 2.108 was produced from 2.120 by anchoring the olefin sidechain using a Grubbs metathesis reaction.
Scheme 2.24. Carter’s synthesis of the northern half fragment 2.108

Carter’s synthesis of the FGHI ring system 2.109 (Scheme 2.25) features a high yielding aldol reaction to make alcohol 2.124, a Mitsunobu-type stereochemistry inversion of compound 2.125 to compound 2.126, a ketalization of compound 2.127 to compound 2.128 with the desired stereochemistry and a Yb-catalyzed spiroaminal formation to give compound 2.109.
Scheme 2.25. Carter’s synthesis of the southern half fragment 2.109

2.3.5 The Forsyth Group synthetic studies toward azaspiracid-1

In 2004, shortly after the revision of the structure of azaspiracid-1, a synthesis (Scheme 2.26) of the ABCD ring trioxadispiroketal 2.140 was reported by Forsyth and coworkers.\textsuperscript{19f} The key step in this strategy is the selective TES deprotection and a following spiroketalization in the presence of TsOH to form the trioxaspiroketal 2.140.
Scheme 2.26. Forsyth’s initial synthesis of the ABCD ring system 2.140

In 2007, a modified synthesis (Scheme 2.27) of the ABCD trioxaspiroketal 2.140 was reported by Forsyth and coworkers,\textsuperscript{19i} which features a cobalt-catalyzed oxyetherification of 2.141 to make the D ring fragment 2.142 and a Au-catalyzed bissiproketalization of enyne 2.145 to yield the desired trioxaspiroketal 2.140.
Scheme 2.27. Forsyth’s modified synthesis of the ABCD ring system 2.146

In 2006, Forsyth and coworkers published a synthesis of the FGHI ring system (Scheme 2.28) of (-)-azaspiracid-1. A Mukaiyama aldol reaction between enolate 2.147 and aldehyde 2.148 was utilized to build C33,34-syn-aldol 2.149. A one-pot Staudinger reduction/intramolecular aza-Wittig reaction-imine capture sequence was highlighted in the treatment of compound 2.150 with Et₃P in benzene to afford compound 2.151. The FGHI ring fragment was accomplished by a fluoride-initiated bis-conjugate addition of the liberated C32 and C34 oxygens to the C28 Michael acceptor.
2.3.6 The Sasaki Group synthetic studies toward azaspiracid-1

In 2006, a synthesis of the EFGHI ring fragment 2.162 (Scheme 2.29) was reported by the Sasaki group. There are two key steps in this strategy, a Yb(OH)$_3$ spiroaminal formation to yield compound 2.157 and a HF-Pyridine mediated intramolecular ketalization to furnish the EFGHI ring fragment 2.162. Sasaki’s synthesis of the EFGHI fragment takes 37 steps for the longest linear step and gives an overall yield of 0.025%.
2.3.7 The Mootoo Group synthetic studies toward azaspiracid-1

In 2007, an unusual spiroketalization strategy was reported in Mootoo’s synthesis of the ABCD trioxadispiroketal 2.173 (Scheme 2.30), which was initiated by iodonium dicollidine perchlorate (IDCP) and AgOTf to produced the desired trioxadispiroketal 2.173 as a single isomer.\textsuperscript{21} A ring-closed metathesis (RCM) catalyzed by Grubbs’ catalyst was used to make compound 2.165, which was
subjected to a subsequent diastereoselective cyclopropanation and opening of the
cyclopropane ring to set the stereochemistry at the C14 stereocenter.

Scheme 2.30. Mootoo’s synthesis of the ABCD ring moiety 2.173
2.4 Conclusion

In summary, the formidable structural complexity and the intriguing bioactivity of marine toxin azaspiracid-1 have attracted considerable attention from synthetic groups worldwide. Synthetic efforts from Carter’s group and Nicolaou’s group led to the structural revision of azaspiracid-1 in 2004. In the same year, the first total synthesis of (−)-azaspiracid-1 was reported by Nicolaou group with 50 longest linear steps. In 2006, Nicolaou’s second-generation total synthesis of (−)-azaspiracid-1 in a 39 longest linear steps was published. In 2007, Evans group reported a total synthesis of (+)-azaspiracid-1 with a 26 longest linear steps. Besides these two total syntheses, several partial syntheses from the research groups including Carter, Forsyth, Sasaki and Mootoo have been published as well.

Despite all these achievements, the biological mechanism of action of azaspiracid-1 still needs further studies, which has been limited by the scarcity of azaspiracid-1 from natural sources. Furthermore, the controlling features in the formation of the polycyclic system is still not understood, and the problem in developing a more efficient coupling of the northern and the southern halves is unsolved. Therefore, azaspiracid-1 deserves more attention from the synthetic community. Herein, our synthetic studies toward the total synthesis of azaspiracid-1 are described in the following chapter.
2.5 Reference


Chapter 3:

Synthetic Studies on the Northern ABCD ring system of Azaspiracid-1:

An Improved Synthesis of the sulfone fragment 3.6, the aldehyde fragment 3.7
and the ABC ring Bisspiroketal Moiety 3.52
3.1 Retrosynthesis of (−)-Azaspiracid-1.

In our retrosynthetic analysis (Scheme 3.1), (−)-azaspiracid-1 can be disassembled into three fragments: the ABCD ring system northern half 3.1, the E ring linkage fragment 3.2 and the FGHI ring system southern half 3.3. The northern portion ABCD ring system 3.1 has nearly the same size and complexity with the southern portion FGHI ring system 3.3, which would shorten the longest linear steps of the total synthesis and benefit the overall yield. The northern portion ABCD ring system 3.1 contains a densely functionalized array with 7 stereocenters and a challenging bisspiroketal functionality while the southern portion FGHI ring system 3.3 has 8 stereocenters with a spiroaminal, a heavily oxidized tetrahydrofuran moiety, and an α-oxy bicyclic ketal, all of them are sensitive labile functional groups.

Scheme 3.1. Retrosynthetic analysis of (−)-azaspiracid-1
In our further retrosynthetic analysis (Scheme 3.2), the northern portion ABCD ring system 3.1 can be synthesized by a Grubbs\(^1\) olefin metathesis from bisspiroketal 3.4, which can be built by a bisspiroketalization of ketone 3.5 as the key step. The functionalized ketone 3.5 is obtained by a Julia\(^2\) coupling of sulfone 3.6 and aldehyde 3.7, both of which have similar size and complexity.

![Scheme 3.2. Retrosynthetic analysis of the ABCD ring northern fragment 3.1](image)

**Scheme 3.2.** Retrosynthetic analysis of the ABCD ring northern fragment 3.1

3.2 Synthetic studies toward the synthesis of the northern portion ABCD ring system 3.1.

Before my arrival in the Carter group, several impressive publications on their synthetic efforts toward the total synthesis of azaspiracid-1 had been reported.\(^3\) In 2006, Carter and Zhou reported a synthesis of the C1-C26 northern
portion of azaspiracid-1 and a synthesis of the southern FGHI ring system of azaspiracid-1 in two important papers.\textsuperscript{3g, 3h} Unfortunately, they ran out of starting material when they are just 5 steps away from the total synthesis of (–)-azaspiracid-1,\textsuperscript{4} which required preparation of more starting material for the total synthesis of (–)-azaspiracid-1. First of all, azaspiracid-1 is still a challenging synthetic target with limited availability from natural resources. Furthermore, the total synthesis of azaspiracid-1 will facilitate the understanding of the controlling factors in polycyclization reactions, coupling reactions of bulky fragments, and sensitive functional group manipulations. Last but not least, an efficient and scaleable synthesis of the northern and southern portions is necessary to afford enough material for a total synthesis of azaspiracid-1. Therefore, my synthetic studies toward the total synthesis of (–)-azaspiracid-1 will follow the initial approach developed by Carter and coworkers,\textsuperscript{3, 4} but will be carried out on large scale (250 mmol scale) and will improve the low yield steps in the original route.

The improved synthetic studies toward the northern portion is described in this chapter as followed, the improved synthetic studies toward the southern portion will be illustrated in next chapter (Chapter 4).

\textbf{3.2.1 Synthesis of sulfone 3.6}

As shown in Scheme 3.3, sulfone 3.10 was synthesized from dibromopropane 3.8 by two subsequent nucleophilic substitution reactions on 300 mmol scale in good yield.
Scheme 3.3. Synthesis of sulfone 3.10

The synthesis of allyl bromide 3.17 started with a borane reduction of D-malic acid 3.11 (Scheme 3.4). A following chemoselective protection of the triol 3.12 gave alcohol 3.13, which was converted into aldehyde 3.14 via Swern oxidation. A Witting reaction of the aldehyde 3.14 in MeOH afforded the α,β-unsaturated ester 3.15$^5$ with an 8:1 Z/E ratio, which was subjected to a DIBAL reduction and a Mitsunobu-type substitution to yield allyl bromide 3.17 on a 200 mmol scale.
Scheme 3.4. Synthesis of allyl bromide 3.17

Ketone 3.22 was synthesized in 5 steps from sulfone 3.10 (Scheme 3.5). Sulfone 3.10 and allyl bromide 3.17 was utilized to make sulfone 3.18 by a nucleophilic attack of the lithio derivative of sulfone 3.10 to allyl bromide 3.17. The reaction mixture was subjected to an acidic deprotection conditions without purification due to the similar polarity of sulfone 3.18 and bromide 3.17 which made chromatographic purification difficult. Precautions should be taken in the acidic deprotection of unpurified sulfone 3.18, the reaction must be quenched in less than 16 hours though TLC shows the presence of starting material. Elongation of the reaction time to more than 16 hours did not increase the yield, because a reaction equilibrium had been reached in 16 hours. Since compound 3.18 was not
purified from the coupling reaction and was used as a crude in the deprotection reaction immediately, further exposure of the reaction to daylight could decompose the trace amount of allyl bromide \textit{3.17} left in the strong acidic mixture and led to the destruction of the diol product \textit{3.19}.

A selective protection of the primary alcohol of diol \textit{3.19} with a bulky TBDPS group gave tertiary alcohol \textit{3.20}, which was transformed into \textit{3.21} by a TES protection in 99% yield. The mild oxidant bis-(trimethylsilyl) peroxide \textsuperscript{6} was utilized in the oxidation of sulfone \textit{3.21} to ketone \textit{3.22} without isomerizing the alkene. However, it was difficult to drive the reaction to completion, 74% yield was obtained based on the consumed starting material. Interestingly, the expensive starting material sulfone \textit{3.21} could be easily recycled. One year later, a procedure based on work by Mr. Subham Mahapatra in our group improved the yield of this oxidation to 99%.
Scheme 3.5. Synthesis of ketone 3.22

The mechanism of oxidation of sulfone 3.21 to ketone 3.22 was illustrated in Scheme 3.6. When (TMSO)$_2$ was used, the last step is an intermolecular nucleophilic attack to initiate the leaving of sulfonyl group and the ketone formation; in contrast, the last step is an intramolecular cleavage when Davis oxaziridine was applied. This might be the cause of different yields in these two reactions.
Scheme 3.6. Oxidation mechanism

An improved one-pot cyclization and methylation reaction was developed to convert ketone 3.22 to compound 3.24 (Scheme 3.7). In the initial approach
developed by Dr. X.T. Zhou,\textsuperscript{3f, 3g} sulfone 3.22 was deprotected to initiate a cyclization to afford hemiketal 3.23 as a crude product in 47% yield, which was unstable and must be converted the methylate hemiketal 3.24 immediately under PPTS/MeOH conditions. Bearing the unstability of hemiketal 3.23 and the overall low yield (less than 50%) in mind, we discovered an improved one-pot procedure to convert ketone 3.22 to the methylated hemiketal 3.24 as a single isomer in 84% yield in one step.

Scheme 3.7. Synthesis of hemiketal 3.24

As shown in Scheme 3.8, it is believed that the TES group in ketone 3.22 falls off readily in PPTS/MeOH conditions, the resulted alcohol cyclized \textit{in situ} to form the anomeric stabilized thermodynamic favored hemiketal 3.23, which was methylated simultaneously in one-pot to furnish methylated hemiketal 3.24.
Scheme 3.8. Mechanism of ketalization

The sulfide 3.24 was oxidized to sulfone\textsuperscript{7} 3.6 by a mild Ley oxidation\textsuperscript{8} reaction (Scheme 3.9). However, the reaction mixture under TPAP/NMO/MS conditions (40 °C, 3 hours) gave 78% of desired sulfone 3.6 and 22% of half-oxidized sulfoxide 3.25. Interestingly, subjected to the same oxidation conditions again, sulfoxide 3.25 could be transformed into sulfone 3.6 in 99% yield. Herein, we have made 27 mmol of sulfone 3.6 by this improved approach.
Scheme 3.9. Synthesis of sulfone 3.6

3.2.2 Synthesis of aldehyde 3.7

As illustrated in Scheme 3.10, the monosubstitution of 1,3-propandiol with PMB only gave 42% yield of alcohol 3.27, because of the competitive PMB disubstituted byproduct. Swern oxidation of alcohol 3.27 gave aldehyde 3.28 in 99% yield, which was converted to α-alkenyl ester 3.29 by a Wittig reaction in 84% yield of the desired E-isomer with an 15:1 E/Z ratio. Subsequent DIBAL reduction and Mitsunobo type substitution give allyl bromide 3.31 in a good yield.
Scheme 3.10. Synthesis of allyl bromide 3.31

Scheme 3.11. Synthesis of allyl bromide 3.30.2 in the original approach

The coupling adduct 3.34 was obtained by an improved procedure to couple allyl bromide 3.31 with Evans auxiliary 3.33, which is easily available by alkylation of Evans oxazolidinone 3.32 (Scheme 3.12). However, in the initial reported procedure, 4 Evans auxiliary 3.33 is reacted with allyl iodide 3.30.2, which was made from the common allyl alcohol 3.30 in 2 steps (Scheme 3.11). Unfortunately, compound 3.30.1 and 3.30.2 are unstable and need to be prepared without exposure to daylight and have to be used in next step immediately. Furthermore, the coupling reaction of allyl iodide 3.30.2 with the Evans auxiliary 3.33 is concentration sensitive. After screening series of starting material concentrations, Dr. D.L. Kuiper 4 found out that when 1.8 equivalent of iodide
3.30.2 was used in a molarity of 0.35 M, the optimized yield is 94% based on Evans auxiliary 3.33 (but 52% based on allyl iodide 3.30.2).

The synthesis of diol 3.41 from compound 3.33 in 8 steps was illustrated in Scheme 3.12. In contrast with previous work, we decided to apply allyl bromide 3.31 in this coupling reaction, which was made from common allyl alcohol 3.30 in one step with 84% yield. Interestingly, allyl bromide 3.31 was found to be very stable and could be recovered from the coupling reaction. Unlike the original procedure conducted at –78 °C during the whole reaction under conventional Evans conditions, we warmed up the reaction to room temperature for 7 hours and was surprised to see that the reaction still gives only one single diastereomer product 3.34 with an improved yield of 94% (based on starting material allyl bromide 3.31).

Learning from our group previous experience that the π stacking interaction between the chiral ligand and the benzyl ester can improve the diastereoselectivity in Sharpless dihydroxylation reactions, a displacement of the oxazolidinone moiety of 3.34 with a benzyl alkoxide gives benzyl ester 3.35, which is transformed to lactone 3.36 via a modified Sharpless asymmetric dihydroxylation to install two hydroxyl stereocenters at the same time. The DDQ-mediated ketal formation was carried out by adding DDQ portionwisely into the reaction to furnish the p-methoxyphynyl ketal 3.37 in 86%, which was reduced by LiBH₄/MeOH to diol 3.38 in 99% yield. Selective protection of the diol 3.38 afforded tertiary alcohol 3.39 in 99% yield, which was further protected with benzyl group to compound
3.40. Deprotection of compound 3.40 under PTSA/MeOH conditions gave diol 3.41 as a glassy product.

Scheme 3.12. Synthesis of diol 3.41
As shown in Scheme 3.13, diol 3.41 was transformed to aldehyde 3.7 in 4 steps. Selective benzyla\-tion of diol 3.41 was optimized by Dr. D.L. Kuiper\(^4\) using 2 equivalent benzylate reagent 3.42 and 10% TfOH to afford alcohol 3.43 in 83% yield. After TES protection of alcohol 3.43, the product 3.44 was selective deprotected by a procedure developed by Dr. R.G. Carter to form terminal alcohol 3.45, which was oxidized to aldehyde 3.7 via a Ley oxidation.\(^8\)

![Scheme 3.13. Synthesis of aldehyde 3.7](image)

**3.2.3 synthesis of the ABC ring Bisspiroketal Moiety 3.52 (Scheme 3.11)**

With sulfone 3.6 and aldehyde 3.7 in hand, we proceeded to prepare the coupling adduct 3.46 by a Julia coupling reaction (Scheme 3.14). As, TLC showed that sulfone 3.6 and adduct 3.46 have similar Rf values, the crude mixture was oxidized using TPAP/NMO to give ketone 3.47. In order to improve this transformation further, we explored using the aldehyde 3.7 as the limiting reagent. Freshly prepared LiTMP key to the success of this reaction. Finally, by using 2.0
equivalent sulfone 3.6 and 2.0 equivalent freshly prepared LiTMP, a 91% yield over 2 steps was obtained and about 1.0 equivalent sulfone 3.6 was recovered.

Cleavage of the sulfone moiety of compound 3.47 by sodium amalgam furnishes ketone 3.48, which was spiroketalized under PPTS catalyzed conditions to afford a combined 99% yield with a transoidal/cisoidal ratio of about 2.4:1. This unseparable mixture of cisoidal 3.49 and transoidal 3.50 was desilylated by TBAF to cisoidal alcohol 3.51 and transoidal alcohol 3.52. After purification, the cisoidal alcohol 3.51 can be isomerized to the desired transoidal alcohol 3.52 under strong acidic conditions in 99% yield.
Scheme 3.14. Synthesis of the ABC ring bisspiroketal 3.52
3.3 Conclusion

An improved and large scale synthesis of sulfone 3.6 with a key one-pot ketalization and methylation of ketone 3.22 to methylated hemiketal 3.24 have been illustrated. A total 19 mmol of sulfone 3.6 has been prepared by this approach. An improved and scalable synthesis of aldehyde 3.7 utilizing allyl bromide 3.31 to couple with Evans auxiliary 3.33 has been schemed out. A total of 10 mmol of aldehyde 3.7 has been prepared by this approach. An improved synthesis toward the ABC ring fragment 3.52 with a high yield Julia coupling step has been shown.

3.4 Reference


10. Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* 1994, 94, 2483. AD-mix-β* involves 3 mol% K₂OsO₄•2H₂O, 10 mol% DHQD Phal, 2.9 eq. K₂Fe(CN)₆ and 2.7 eq. K₂CO₃ with 1 eq. MeSO₂NMe₂ to enhance catalyst turnover and 5 eq. of NaHCO₃ to buffer the reaction.

SYNTHETIC STUDIES TOWARD THE TOTAL SYNTHESIS OF
AZASPIRACID-1

Chapter 4:

Synthetic Studies on the Southern Half and the Linkage fragment of
Azaspiracid-1:

An Improved Synthesis of the Linkage Fragment 3.2, the Aldehyde Fragment
4.9 and the Azide Fragment 4.10 of Azaspiracid-1
4.1 An Improved Synthesis of the Linkage Fragment 3.2

As shown in the retrosynthetic analysis of azaspiracid-1 (Scheme 3.1), the linkage fragment 3.2 is one of the three main fragments of zaspiraicid-1 with 2 stereocenters and was synthesized in 6 steps in our approach (Scheme 4.1). The stereochemistry of C22 in compound 4.3 was installed by an alkylation of Evans auxiliary 4.2, which was prepared from commercial available oxazolidinone 4.1 via a simple alkylation in 95% yield. Reductive cleavage of the oxazolidinone moiety of compound 4.3 under LiBH₄/MeOH conditions afforded optical pure alcohol 4.4 in 95% yield, which was transformed to iodide 4.5 under Mitsunobo-type substitution conditions. The stereochemistry of C24 was set by a Myers asymmetric alkylation between chiral amide auxiliary 4.6 and iodide 4.5 to furnish amide 4.7,¹ which was reductive cleaved to the linkage fragment 3.2 by borane ammonia complex. A total of 22 mmol of fragment 3.2 has been synthesized by the method.
4.2 Synthetic Studies on the Southern Portion of Azaspiracid-1

4.2.1 Retrosynthetic Analysis of the Southern Portion Fragment 3.3

As one of the three main fragments of azaspiracid-1 (Scheme 3.1), the southern portion fragment 3.3 was synthesized from compound 4.8 in several steps. Compound 4.8 can be disconnected into aldehyde 4.9 and azide 4.10 by an aldol reaction (Scheme 4.2).
4.2.2 An Improved Synthesis of Aldehyde Fragment 4.9 of the Southern Portion

Chiral sulfonamide 4.16\textsuperscript{3} was synthesized in 250 gram scale as a needle-like colorless pure crystal by a modified procedure displayed in Scheme 4.3. Starting with commercial available (+)-camphorsulfonic acid 4.11, sulfonamide 4.13 was obtained as a colorless crystal by a chlorination using dichlorosulfoxide refluxing in dichloromethane for 22 hours and a following one-pot \textit{in situ} reaction with saturated aqueous ammonia. The resulting sulfonamide 4.13 was dehydrated by refluxing in toluene with Amberlyst catalyst under Dean-Stark conditions to form the unsaturated cyclized sulfonamide 4.14, which was reduced to the saturated sulfonamide 4.15 by LiAlH\textsubscript{4} in 99% yield. Acylation of the compound 4.15 with trans-crotonyl chloride afford the desired sulfonamide 4.16. This is a scalable and reliable procedure to prepare sulfonamide 4.16 without using any chromatography column purification, since all the products are recrystalized out of the reaction mother liquid.
Scheme 4.3. Synthesis of sulfamide 4.16

The aldehyde 4.22 (Scheme 4.4) was accessible from a DIBAL reductive cleavage of the sulfonamide adduct 4.20, which was prepared by a highly stereoselective TMSCl-mediated catalytic 1,4-addition\(^4\) to the previous prepared sulfonamide 4.16 using an organocopper reagent that was freshly prepared from Grignard reagent 4.19. This reliable cuprate addition furnishes a high diastereoselectivity (20:1 dr) as has been described by Paquette and Boulet.\(^3\) To get a higher yield of the key Grignard reagent 4.19, the Mg turnings have to be dry stirred for more than 10 days under Argon before the addition of chloride 4.18.
**Scheme 4.4. Synthesis of aldehyde 4.22**

Synthesis of the aldehyde 4.9 was accomplished in ten steps (Scheme 4.5). The first key step is a boron-midiated aldol reaction of the previous prepared aldehyde 4.22 with the Andrus dioxanone\(^5\) that gives the aldol 4.27 in 99% yield (10:1 dr). The Andrus dioxanone can be synthesized in a 50 mmol scale starting from a Sharpless asymmetric dihydroxylation of a symmetric aromatic alkene 4.23 and a following one-pot metellation and substitution.\(^5\) After opening the lactone ring of compound 4.27 to get the methylate ester 4.28, the second key step is a selective protection of the hydroxyl group at C32 in diol 4.27 with TIPSOTf and 2,6-lutidine in DCM, which surprised us by affording compound 4.29 in 83% yield. The ester 4.30.1 was obtained by a TMS protection of alcohol 4.30, which was accessible from a CAN oxidative cleavage of compound 4.29. Finally, a total 48 mmol of ester 4.9 was prepared by the approach and was stored at this stage, which

\[\text{Cl} - \text{Cl} \xrightarrow{\text{BnOH, NaH, THF, DMF, rt, 20 h, 57\%}} \text{Cl} - \text{O} \xrightarrow{\text{Mg dry stirred 20 d, 1,2-dibromoethane, 54\%}} \text{Cl} \text{Mg} - \text{O} \text{Bn} \]

\[\text{4.17} \rightarrow \text{4.18} \rightarrow \text{4.19} \]

\[\text{O} \xrightarrow{\text{CuBr-SMe}_2, \text{LiCl, TMSCl, -78 °C, 2 h, 95\% dr > 20 : 1}} \text{O} \]

\[\text{4.16} \rightarrow \text{4.17} \rightarrow \text{4.20} \]
would be converted easily to aldehyde 4.9 by a DIBAL reduction and a Dess–Martin oxidation in the future usage.

Scheme 4.5. Synthesis of fragment 4.9
4.2.3 An Improved Synthesis of Azide Fragment 4.10 of the Southern Portion

Synthesis of azide 4.10 started from a Myers alkylation adduct 4.31 that was prepared by a reliable procedure illustrated in Scheme 4.1 in 5 steps. Cleavage of the pseudophedrine moiety of amide 4.31 by methyllithium furnishes methyl ketone 4.32 in 88% yield, which was transformed to hemiketal 4.33 via a DDQ oxidative cyclization. Opening of the cyclic hemiketal 4.33 to acyclic sulfonyl protected methyl ketone 4.34 and a following nucleophilic substitution gave azide 4.10 as a highly volatile, transparent liquid.

![Scheme 4.6. Synthesis of fragment 4.10](image)

4.3 Conclusion

Large scale improved syntheses of the linkage fragment 3.2, the aldehyde fragment 4.9 and the azide fragment 4.10 of the southern portion of (−)-azaspiracid-1 have been described. An abundant materials have been prepared by these scalable
improved approaches for the further synthetic efforts toward the total synthesis of 
(−)-azaspiracid-1, which places us in a positive stage to the completion of (−)-
azaspiracid-1.

4.4 Future work

With the preparation of sulfone 3.6, aldehyde 3.7, azide 3.10, aldehyde 3.9
and alcohol 3.2 via our improved large scale approach, we are confident of
completing the total synthesis in the near future with adequate starting materials.
Our future synthetic efforts toward the total synthesis are schemed out as followed.
As displayed in Scheme 4.7, lactol 4.35 will be prepared in 5 established steps from
the Julia coupling adduct of sulfone 3.6 and aldehyde 3.7 as the northern portion
ABCD ring system.

Scheme 4.7. Synthesis of lactol fragment 4.35

As illustrated in Scheme 4.8, azide 4.10 and aldehyde 4.9 will be combined
by an aldol reaction to afford compound 4.8, which will be polycyclized into FGHI
ring system spiroaminal 4.36 in 14 steps. The resulting spiroketal 4.36 will be functionalized to the southern portion EFGHI ring system 4.37 in 11 steps using the previous prepared E ring linkage fragment 3.2. With the northern half 4.35 and the southern half 4.37 in hand, compound 4.39 will be accessible by a Horner–Wadsworth–Emmons reaction and a following Davis Oxidation. All these steps to the preparation of compound 4.39 have been investigated by Carter and coworkers\(^2\):\(^6\) and have been proved to be reliable. After preparation of compound 4.39, (–)-azaspiracid-1 could be available in 5 proposed potential steps.
Scheme 4.8. Proposed synthesis of (−)-azaspiracid-1
4.5 Reference


SYNTHETIC STUDIES TOWARD THE TOTAL SYNTHESIS OF
AZASPIRACID-1

CHAPTER 5:

Experimental Section
**General:** Infrared spectra were recorded neat unless otherwise indicated and are reported in cm$^{-1}$. $^1$H NMR spectra were recorded in deuterated solvents and are reported in ppm relative to tetramethylsilane and referenced internally to the residually protonated solvent. $^{13}$C NMR spectra were recorded in deuterated solvents and are reported in ppm relative to tetramethylsilane and referenced internally to the residually protonated solvent.

Routine monitoring of reactions was performed using EM Science DC-Alufolien silica gel, aluminum-backed TLC plates. Flash chromatography was performed with the indicated eluents on EM Science Gedurian 230-400 mesh silica gel.

Air and/or moisture sensitive reactions were performed under usual inert atmosphere conditions. Reactions requiring anhydrous conditions were performed under a blanket of argon, in glassware dried in an oven at 120°C or by flame, then cooled under argon. Dry THF and DCM were obtained via a solvent purification system. All other solvents and commercially available reagents were either purified via literature procedures$^1$ or used without further purification.
**Bromide 3.9:** To a stirred solution of NaH (13.20 g, 330 mmol, 60% in mineral oil) in DMF (500 mL) at 0 °C was added thiophenol (42 g, 39 mL, 380 mmol). After 1.5 h, this solution was transferred into another flask containing a solution of 1,3-dibromopropane 3.8 (207 g, 100 mL, 985 mmol) in DMF (500 mL) at 0 °C. The reaction was allowed to warm to room temperature and keep stirred for 20 h. the reaction mixture was poured into saturated K$_2$CO$_3$ solution (1.5 L) and extracted with CH$_2$Cl$_2$ (2 x 500 mL). The dried (MgSO$_4$) extract was concentrated *in vacuo* and the excessive 1,3-dibromopropane 3.8 was distilled out from short pass under reduced pressure to give product 3.9 as colorless oil (75 g, 328 mmol, 86%) remained in the flask. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.18-7.40 (m, 5H), 3.56 (t, J = 6.3 Hz, 2H), 3.09 (t, J = 6.9 Hz, 2H), 2.15- 2.22 (m, 2H).

**Sulfone 3.10:** To a solution of bromide 3.9 (3.85 g, 16.67 mmol) in DMF (33 mL) was added sodium benzenesulfinate (13.65 g, 83.30 mmol). After 24 h, the reaction mixture was quenched with NH$_4$Cl (150 mL) and extracted with EtOAc (3 x 50 mL). The extract was washed with water (150 mL) and saturated NaCl (150 mL). The dried (MgSO$_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 10-50% EtOAc / hexanes, to give product 3.10 (1.95 g, 6.68 mmol, 41%) as colorless oil: $^1$H NMR (400 MHz, CDCl$_3$).
CDCl$_3$ $\delta$ 7.90-7.92 (m, 2H), 7.67-7.70 (m, 1H), 7.56-7.60 (m, 2H), 7.21-7.30 (m, 5H), 3.29 (t, J = 7.5 Hz, 2H), 2.99 (t, J = 6.9 Hz, 2H), 2.02-2.09 (m, 2H).

**Allylic alcohol 3.16:** To a stirred solution of ester 3.15 (0.248 g, 1.00 mmol) in CH$_2$Cl$_2$ (6.7 mL) at $-78^\circ$C was added DIBAL-H (2.4 mL, 2.4 mmol, 1.0 M in CH$_2$Cl$_2$). After 3 h, the reaction was allowed to warm to 0$^\circ$C and quenched by addition of aq. potassium sodium tartrate (6 mL, 10%). The solution was stirred at room temperature overnight to dissolved precipitate and extracted with EtOAc (3 x 6 mL). The dried (MgSO$_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 10-50% EtOAc / hexanes, to give product 3.16 (0.22 g, 1.00 mmol, 100%) as colorless oil: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.48-7.53 (m, 2H), 7.34-7.42 (m, 3H), 5.78-5.85 (m, 1H), 5.65-5.70 (m, 1H), 5.61 (s, 1H), 4.70-4.77 (m, 1H), 4.13-4.38 (m, 3H), 4.01-4.08 (m, 1H), 1.98-2.09 (m, 1H), 1.77 (t, J = 6.0 Hz, 1H), 1.56-1.61 (m, 1H).

**Allylic bromide 3.17:** To a solution of alcohol 3.16 (0.22 g, 1.00 mmol) and PPh$_3$ (0.262 g, 1.00 mmol) in CH$_3$CN (5 mL) at 0 $^\circ$C was added CBr$_4$ (0.332 g,
1.00 mmol). After 5 min, the reaction mixture was allowed to warm to room temperature and stirred for 30 min. The reaction was concentrated in vacuo and purified by chromatography over silica gel, eluting with 10-20% EtOAc / hexanes, to give product 3.17 (0.15 g, 0.53 mmol, 53%) as colorless oil: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.50-7.53 (m, 2H), 7.33-7.41 (m, 3H), 5.84-5.92 (m, 1H), 5.69 (dd, $J = 10.7, 7.3$ Hz, 1H), 5.62 (s, 1H), 4.76-4.81 (m, 1H), 4.31-4.35 (m, 1H), 4.03-4.20 (m, 3H), 1.98-2.08 (m, 1H), 1.56-1.65 (m, 1H).

**Sulfone 3.18:** To a solution of sulfone 3.10 (22.39 g, 76.67 mmol) in THF (155 mL) at -78 °C was added $n$-BuLi (47.92 mL, 76.67 mmol, 1.6 M in hexanes). After 1 h, a solution of 3.17 (8.36 g, 29.44 mmol) in THF (9 mL) was added via cannula. After 25 min, the reaction was warmed to 0 °C and quenched with sat. aq. NH$_4$Cl (46 mL) and extracted with EtOAc (3 x 200 mL). The dried (MgSO$_4$) extract was concentrated in vacuo to give crude product 3.18 as colorless oil: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.81-7.87 (m, 2H), 7.45-7.69 (m, 3H), 7.20-7.39 (m, 10H), 5.57-5.62 (m, 1H), 5.52 (s, 1H), 5.32- 5.49 (m, 1H), 4.52-4.56 (m, 1H), 3.94-4.29 (m, 2H), 3.27-3.44 (m, 1H), 2.12-3.11 (m, 6H), 1.87-2.08 (m, 4H).
**Diol 3.19:** To a solution of crude 3.18 in CH$_3$CN (147 mL) at 0°C was added dropwise aq. HCl (147 mL, 2 M). After 16 h, sat. aq. NaHCO$_3$ (471 mL) was added and the aqueous phase was extracted with CH$_2$Cl$_2$ / EtOAc (1:1) (3 x 200 mL). The dried (MgSO$_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 40-100% EtOAc / hexanes, to give diol 3.19 (3.79 g, 9.33 mmol, 63% over two steps) as colorless oil: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.84-7.86 (m, 2H), 7.54-7.70 (m, 3H), 7.19-7.26 (m, 5H), 5.54-5.59 (m, 1H), 5.37-5.46 (m, 1H), 4.60-4.65 (m, 1H), 3.76-3.88 (m, 2H), 3.31-3.39 (m, 1H), 2.35-3.16 (m, 6H), 1.58-2.10 (m, 4H).

**TBDPS ether 3.20:** To a solution of diol 3.19 (4.83 g, 11.90 mmol) and imidazole (0.97 g, 14.27 mmol) in CH$_2$Cl$_2$ (119 mL) at room temperature was added dropwise TBDPSCl (3.60 g, 3.41 mL, 13.09 mmol). After 2.5 h, the reaction was quenched with sat. aq. NH$_4$Cl (64 mL) and the organic phase was washed with sat. aq. NaHCO$_3$ (64 mL) and extracted with EtOAc (3 x 128 mL). The dried (MgSO$_4$) extract was concentrated in vacuo and purified by chromatography over
silica gel, eluting with 10-50% EtOAc / hexanes, to give product 3.20 (7.21 g, 11.19 mmol, 94%) as colorless oil: $^1$H NMR (400 MHz, CDCl₃) $\delta$ 7.77-7.83 (m, 2H), 7.60-7.65 (m, 5H), 7.37-7.54 (m, 8H), 7.12-7.36 (m, 5H), 5.48-5.56 (m, 1H), 5.29-5.41 (m, 1H), 4.56-4.59 (m, 1H), 3.76-3.86 (m, 2H), 3.26-3.37 (m, 1H), 2.98-3.16 (m, 3H), 2.38-2.71 (m, 2H), 2.08-2.23 (m, 1H), 1.74-2.00 (m, 2H), 1.07 (s, 9H).

TES ether 3.21: To a solution of 3.20 (7.21 g, 11.19 mmol) in CH₂Cl₂ (112 mL) at –78 °C was sequentially added 2,6-lutidine (1.79 g, 1.94 mL, 16.79 mmol) and TESOTf (3.59 g, 3.07 mL, 13.43 mmol). After 20 min, the reaction was quenched with NH₄Cl (60 mL) and extracted with EtOAc (3 x 113 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 10-50% EtOAc / hexanes, to give product 3.21 (8.48 g, 11.18 mmol, 100%) as colorless oil: $^1$H NMR (400 MHz, CDCl₃) $\delta$ 7.78-7.84 (m, 2H), 7.37-7.70 (m, 14H), 7.17-7.28 (m, 4H), 5.40-5.48 (m, 1H), 5.14-5.20 (m, 1H), 4.44-4.54 (m, 1H), 3.58-3.75 (m, 2H), 3.22-3.33 (m, 1H), 3.02-3.11 (m, 2H), 1.37-2.66 (m, 6H), 1.09 (s, 9H of a diastereomer), 1.07 (s, 9H of a diastereomer), 0.86-0.97 (m, 9H), 0.46-0.57 (m, 6H).
Ketone 3.22: To a solution of 3.21 (0.90 g, 1.19 mmol) in THF (7.9 mL) at –78 °C was added NaHMDS (1.42 mL, 1.42 mmol, 1.0 M in THF). After 20 min, the TMSOTMS$_2$ (0.43 g, 0.514 mL, 2.38 mmol) was added. After 20 min, the reaction mixture was quenched with sat. aq. NH$_4$Cl (26 mL) and extracted with EtOAc (3 x 40 mL). The organic phase was washed with saturated NaHCO$_3$ (80 mL). The dried (MgSO$_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 10-30% EtOAc / hexanes, to give product 3.22 (385 mg, 0.61 mmol, 51%) and recovered ether 3.21 (334 mg, 0.44 mmol, 37%) as colorless oil: $^1$H NMR (400 MHz, CDCl$_3$) δ 7.63-7.67 (m, 4H), 7.28-7.44 (m, 10H), 7.19-7.23 (m, 1H), 5.56-5.58 (m, 2H), 4.65-4.72 (m, 1H), 3.76-3.83 (m, 1H), 3.62-3.68 (m, 1H), 3.05-3.33 (m, 4H), 2.65-2.76 (m, 2H), 1.75-1.83 (m, 1H), 1.57-1.61 (m, 1H), 1.08 (s, 9H), 0.96 (t, J = 8.0 Hz, 9H), 0.60 (q, J = 8.0 Hz, 6H).

Alcohol 3.23: To a solution of ketone 3.22 (0.85 g, 1.34 mmol) in MeOH (10.5 mL) and CH$_2$Cl$_2$ (2.7 mL) at room temperature was added NH$_4$F (51.5 mg, 1.34 mmol). After 16 h, the reaction mixture was concentrated in vacuo and
purified by chromatography over silica gel, eluting with 10-40% EtOAc / hexanes, to give crude product 3.23 (0.32 g, 0.63 mmol, 47%) as colorless oil: $^1$H NMR (400 MHz, CDCl$_3$) δ 7.37-7.81 (m, 4H), 7.15-7.46 (m, 11H), 5.60-5.76 (m, 2H), 4.40-4.56 (m, 1H), 3.79-3.91 (m, 2H), 2.98-3.06 (m, 2H), 1.60-2.26 (m, 6H), 1.07 (s, 9H).

Sulfide 3.24: To a solution of 3.23 (0.32 g, 0.63 mmol) in MeOH (18 mL) at room temperature was added PPTS (0.16 g, 0.63 mmol). After 1 h, the reaction was quenched with sat. aq. NaHCO$_3$ (6 mL) and extracted with EtOAc (3 x 20 mL). The dried (MgSO$_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 20-40% EtOAc / hexanes, to give product 3.24 (0.32 g, 0.61 mmol, 97%) as colorless oil: $^1$H NMR (400 MHz, CDCl$_3$) δ 7.69-7.74 (m, 4H), 7.18-7.48 (m, 11H), 5.70-5.71 (m, 2H), 4.35-4.37 (m, 1H), 3.87-3.94 (m, 1H), 3.75-3.81 (m, 1H), 3.21 (s, 3H), 2.85-2.96 (m, 2H), 1.67-2.26 (m, 6H), 1.08 (s, 9H).

Sulfide 3.24: To a solution of ketone 3.22 (3.47 g, 5.49 mmol) in MeOH (44 mL) and CH$_2$Cl$_2$ (11 mL) at room temperature was added PPTS (208 mg, 0.83
mmol). After 5 min, the reaction mixture was quenched with sat. aq. NaHCO₃ (50 mL) and extracted with EtOAc (3 x 100 mL), the dried (MgSO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 40% EtOAc / hexanes, to give crude product 3.24 (2.45 g, 4.60 mmol, 84%) as colorless oil: [α]D₂₃ +28.7° (c = 1.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.69-7.74 (m, 4H), 7.18-7.48 (m, 11H), 5.70-5.71 (m, 2H), 4.35-4.37 (m, 1H), 3.87-3.94 (m, 1H), 3.75-3.81 (m, 1H), 3.21 (s, 3H), 2.85-2.96 (m, 2H), 1.67-2.26 (m, 6H), 1.08 (s, 9H).

**Sulfone 3.6:** To a solution of sulfide 3.24 (3.03 g, 5.69 mmol) in CH₃CN (30 mL) with powdered 4 Å mol. sieves (6.10 g) was sequentially added NMO (3.37 g, 28.46 mmol) and TPAP (103 mg, 0.285 mmol). The reaction mixture was warmed to 40 °C. After 4 h, the reaction was diluted with 25% EtOAc / hexanes (40 mL), filtered through a small plug of silica gel (25% EtOAc / hexanes rinse), concentrated in vacuo and purified by chromatography over silica gel, eluting with 10-40% EtOAc / hexanes, to give a crude sulfoxide 3.25 (0.75 g, 1.37 mmol, 22%) and the desired product 3.6 (2.52 g, 4.47 mmol, 78%) as colorless oil: [α]D₂₃ = +28.5° (c = 1.00, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.90-7.96 (m, 2H), 7.55-7.71 (m, 7H), 7.38-7.47 (m, 6H), 5.61-5.70 (m, 2H), 4.36 (br, 1H), 3.85-3.91 (m,
1H), 3.73-3.79 (m, 1H), 3.17 (s, 3H), 3.05-3.15 (m, 2H), 1.68-2.24 (m, 6H), 1.06 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 138.9, 135.6, 135.5, 133.8, 129.7, 129.4, 128.9, 128.1, 127.7, 120.7, 97.6, 65.8, 59.9, 51.4, 48.3, 37.8, 32.8, 29.2, 26.9, 19.2.

**Sulfone 3.6:** To a solution of the recovered crude sulfide 3.25 (1.53 g, 2.78 mmol) in CH$_3$CN (14 mL) with powdered 4 Å mol. sieves (2.59 g) was sequentially added NMO (2.69 g, 22.26 mmol) and TPAP (150 mg, 0.417 mmol). The reaction mixture was warmed to 40 °C. After 10 h, the reaction was diluted with 25% EtOAc / hexanes (40 mL), filtered through a small plug of silica gel (25% EtOAc / hexanes rinse), concentrated in vacuo and purified by chromatography over silica gel, eluting with 10-40% EtOAc / hexanes, to give product 3.6 (1.19 g, 2.11 mmol, 76%) as colorless oil: $[\alpha]_D^{23} = +28.5^\circ$ (c = 1.00, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.90-7.96 (m, 2H), 7.55-7.71 (m, 7H), 7.38-7.47 (m, 6H), 5.61-5.70 (m, 2H), 4.36 (br, 1H), 3.85-3.91 (m, 1H), 3.73-3.79 (m, 1H), 3.17 (s, 3H), 3.05-3.15 (m, 2H), 1.68-2.24 (m, 6H), 1.06 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 138.9, 135.6, 135.5, 133.8, 129.7, 129.4, 128.9, 128.1, 127.7, 120.7, 97.6, 65.8, 59.9, 51.4, 48.3, 37.8, 32.8, 29.2, 26.9, 19.2.
PMB ether propyl alcohol 3.27: To a stirred solution of 1, 3-propanediol 3.26 (21 g, 20 mL, 278 mol) in THF (825 mL) at 0 °C was added NaH (12.8 g, 319 mmol, 60% dispersion in mineral oil). After 20 min at rt, the reaction was cooled to 0 °C and paramethoxybenzyl chloride (50 g, 43.5 mL, 319 mmol) and tetrabutyl ammonium iodide (11.8 g, 32 mmol) were added sequentially. After 5 min, the reaction was warmed to rt. After 11 h, the reaction was quenched with H₂O (500 mL) and extracted with EtOAc/Et₂O (1:1) (4 x 1 L). The dried (MgSO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 10-40% EtOAc / hexanes, to give PMB ether propyl alcohol 3.27 (21.64 g, 110.3 mmol, 44%) as a colorless oil: ¹H NMR (400 MHz, CDCl₃) δ 7.27–7.31 (m, 2H), 6.89–6.94 (m, 2H), 4.49 (s, 2H) 3.86 (s, 3H), 3.81 (t, J = 5.6 Hz, 2H), 3.68 (t, J = 5.8 Hz, 2H), 1.90 (q, J = 5.7 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 159.3, 130.2, 129.3, 113.9, 72.9, 69.0, 61.7, 52.3, 32.1.

Aldehyde 3.28: A solution of oxalyl chloride (6.53 g, 4.42 mL, 51.4 mmol) in CH₂Cl₂ (116 mL) at -78 °C was charged carefully with DMSO (8.40 g, 7.63 mL, 107.5 mmol). After 15 min, a solution of alcohol 3.27 (9.17 g, 46.73 mmol) in CH₂Cl₂ (58 mL, 2 x 5 mL rinses) was added via cannula. After 15 min, triethylamine (23.64 g, 32.59 mL, 233.7 mmol) was added dropwise. After 10 min,
the reaction was warmed to 0°C by ice bath. After 15 min, the ice bath was removed and the reaction was allowed to rt. After 1 h at rt, the reaction was quenched with water (150 mL) and extracted with CH$_2$Cl$_2$ (3 x 100 mL). The dried (MgSO$_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 5-25% EtOAc / hexanes, to give ester aldehyde 3.28 (9.03 g, 46.5 mmol, 99%) as a colorless oil: $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 9.81 (d, $J$ = 1.4 Hz, 1H), 7.27-7.29 (m, 2H), 6.90-6.91 (m, 2H), 4.49 (s, 2H), 3.80-3.82 (m, 2H), 1.28-1.30 (m, 3H); $^{13}$C NMR (700 MHz, CDCl$_3$) $\delta$ 159.3, 129.4, 113.9, 72.9, 63.5, 55.3, 43.9, 29.8.

Ester 3.29: Crude aldehyde 3.28 (32.39 g, 166.2 mmol) was diluted in CH$_2$Cl$_2$ (900 mL) and then charged with Ph$_3$P=CHCO$_2$Me (63.90 g, 191.1 mmol). After 48 h, the reaction was concentrated in vacuo purified by chromatography over silica gel, eluting with 5-30% EtOAc / hexanes, to give ester 3.29 (28.89 g, 115.6 mmol, 70%, E/Z=15:1) as a colorless oil: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.25–7.39 (m, 2H), 7.01 (dt, $J$ = 15.7, 6.9 Hz, 1H) 6.89–6.94 (m, 2H), 5.89 (d, $J$ = 5.9 Hz, 1H), 4.49 (s, 2H), 3.85 (s, 3H), 3.76 (s, 3H), 3.59 (t, $J$ = 6.4 Hz, 2H), 2.53 (dq, $J$ = 6.4, 0.6 Hz, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 166.9, 159.2, 146.6, 130.2, 129.3, 122.4, 113.8, 72.4, 68.0, 55.3, 51.5, 32.7.
Alcohol 3.30: A stirred solution of ester 3.29 (7.24 g, 28.9 mmol) in CH₂Cl₂ (170 mL) at -78°C was charged with DIBAL-H (70 mL, 70 mmol, 1.0 M in CH₂Cl₂). After 1 h, the reaction was allowed to warm to rt. After 1 h, the reaction was quenched with aq. sodium tartrate solution (170 mL, 10%) and stirred vigorously. After 3 h, the aqueous layer was extracted with CH₂Cl₂ (4 x 50 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 20-50% EtOAc / hexanes, to give known allylic alcohol 3.30 (5.71 g, 25.7 mmol, 89%) as a colorless oil: ¹H NMR (400 MHz, CDCl₃) δ 7.27–7.32 (m, 2H), 6.89- 6.94 (m, 2H), 5.73-5.78 (m, 2H), 4.48 (s, 2H), 4.13 (m, 2H), 3.84 (s, 3H), 3.52 (t, J = 6.7 Hz, 2H), 2.37-2.43 (m, 2H), 1.46 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 159.2, 131.0, 130.4, 129.4, 129.2, 72.6, 69.3, 63.5, 55.3, 32.7.

Bromide 3.31: A stirred solution of alcohol 3.30 (5.71 g, 25.7 mmol) in CH₂Cl₂ (213 mL) at 0 °C was added sequentially CBr₄ (10.22 g, 30.8 mmol) and Ph₃P (8.09 g, 30.8 mmol). After 30 min at 0 °C, MeOH (0.3 ml) was added. After 45 min at 0 °C, the reaction was concentrated in vacuo and run through a silica gel plug, eluting with 30-50% EtOAc / hexanes, to give allyl bromide 3.31 (6.18 g, 21.7 mmol, 84%) as a colorless oil: ¹H NMR (700 MHz, CDCl₃) δ 7.28-7.30 (m,
1H, 6.91-6.92 (m, 2H) 5.80-5.83 (m, 2H), 4.47 (s, 2H) 3.98 (d, J = 6.3 Hz, 2H), 3.84 (d, J = 0.7 Hz , 3H), 3.51-3.53 (m, 2H) 2.39-2.42 (m, 2H); $^{13}$C NMR (700 MHz, CDCl$_3$) $\delta$ 159.2, 132.8, 130.3, 129.4, 128.1, 113.8, 72.6, 68.9, 55.3, 33.3, 32.6.

Alkylation adduct 3.34: To a stirred solution of oxazolidinone 3.33 (13.53 g, 58.0 mmol) in THF (124 mL) at -78 °C was charged with NaHMDS (30 mL, 60 mmol, 2.0 M in THF). After 30 min, bromide 3.31 (33.50 g, 116 mmol) was added via cannula as a solution in THF (50 mL solution, 2 x 4 mL rinse). After 1 h, the reaction was warmed to rt and after 7 h, the reaction was quenched with sat. aq. ammonium chloride (200 mL) and was extracted with EtOAc (3 x 200 mL). The dried (MgSO$_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 10–40% EtOAc / hexanes, to give recovered allyl bromide 3.31 (17.08 g, 59.9 mmol, 52%) followed by product 3.34 (11.37 g, 26.0 mmol, 45%, 99% BRSM) as a colorless oil: [$\alpha$]$_D^{23}$ = +22.2° (c = 1.00, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.20- 7.40 (m, 7H), 6.86-6.92 (m, 2H), 5.56-5.58 (m, 2H), 4.6-4.74 (m, 1H), 4.42-4.49 (m, 2H), 4.16- 4.24 (m, 2H), 3.83 (s, 3H), 3.48 (t, J = 6.9 Hz, 2H) 3.31 (dd, J = 13.2, 3.1 Hz, 1H), 2.70 (dd, J = 9.1, 7.5 Hz, 1H) 2.46-
2.54 (m, 1H), 2.30-2.38 (m, 2H), 2.17-2.26 (m, 2H), 1.20 (d, $J = 6.8$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 176.7, 159.1, 153.1, 135.4, 130.6, 129.5, 129.45, 129.42, 129.3, 129.0, 128.6, 127.3, 113.8, 72.5, 69.7, 66.0, 55.4, 55.3, 38.1, 37.6, 36.9, 33.0, 16.4.

Benzyl Ester 3.35: A stirred solution of benzyl alcohol (9.5 g, 9.1 mL, 87.7 mmol) in THF (150 mL) at 0 °C was charged with n-butyl lithium (33.4 mL, 83.3 mmol, 2.5 M in hexanes). After 10 min, alkylate 3.34 (19.19 g, 43.9 mmol) in THF (40 mL, 10 mL rinse) was added via cannula. After 2 h, the reaction was quenched with sat. aq. ammonium chloride (130 mL). The solution was extracted with EtOAc (3 x 100 mL). The dried (MgSO$_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 10-20% EtOAc / hexanes, to give benzyl ester 3.35 (11.95 g, 32.43 mmol, 74%) as a colorless oil: $[\alpha]_D^{23} = -3.3^\circ$ (c = 1.00, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.41 –7.27 (m, 7H), 6.89-6.94 (m, 2H), 5.44- 5.51 (m, 2H), 5.13 (s, 2H), 4.45 (s, 2H), 3.84 (s, 3H), 3.45 (t, $J = 6.9$ Hz, 2H), 2.50-2.55 (m, 1H), 2.40-2.50 (m, 2H), 2.28-2.35 (m, 2H), 2.18-2.25 (m, 1H), 1.85 (d, $J = 6.8$ Hz, 3H) $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 176.0, 159.2, 130.6, 129.3, 128.7, 128.6, 128.2, 128.1, 128.0, 113.8, 72.5, 66.1, 55.3, 39.6, 36.7, 33.0, 31.3, 28.0, 16.5.
**Lactone 3.36:** To a vigorously stirred solution of ester 3.35 (13.46 g, 36.53 mmol) in t-butanol / H₂O (1:1, 160 mL) were added sequentially NaHCO₃ (15.34 g, 182.65 mmol), methane sulfonamide (3.48 g, 36.53 mmol), K₂CO₃ (13.63 g, 98.63 mmol), K₃Fe(CN)₆ (34.9 g, 105.94 mmol), (DHQD)₂PHAL (1.14 g, 1.46 mmol) and K₂OsO₄-2H₂O (0.135 g, 0.37 mmol). After 60 h at rt, the reaction was quenched with sat. aq. Na₂S₂O₃ (200 mL) until effervescence stopped (~ 10 min). The solution was then diluted in brine (300 mL) and extracted with EtOAc (4 x 150 mL). The dried (MgSO₄) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 10-60% EtOAc / hexanes, to give lactone 3.36 (8.54 g, 29.01 mmol, 79%, dr 10:1) as a colorless oil: [α]D²³ = −8.0° (c = 1.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.25-7.40 (m, 2H), 6.88-6.94 (m, 2H), 4.49 (s, 2H), 4.25-4.35 (m, 1H), 3.83 (s, 3H), 3.76-3.67 (m, 2H), 2.65-2.75 (m, 1H), 2.39-2.45 (m, 1H), 1.88-1.78 (m, 3H) 1.31 (d, J = 7.0Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 179.5, 159.2, 130.1, 129.4, 113.9, 113.8, 81.0, 72.9, 71.1, 67.1, 55.3, 43.3, 32.5, 32.3, 15.1.
**PMP Acetal 3.37:** To a stirred suspension of lactone 3.36 (6.82 g, 23.17 mmol), powdered 4Å molecular sieves (6.5 g) in CH₂Cl₂ (156 mL) at 0 °C was added DDQ (5.53 g, 24.33 mmol) in three portions over 25 min. After 2 h, the reaction was filtered through a pad of Celite® and rinsed with CH₂Cl₂ (3 x 20 mL) then quenched with deionized water (200 mL) and extracted with CH₂Cl₂ (6 x 100 mL). The dried (MgSO₄) extract was concentrated *in vacuo* and purified by triteration with Et₂O to give acetal 3.37 (5.80 g, 19.84 mmol, 86% single diastereomer) as a white solid: \( [\alpha]_D^{23} = -35.0^\circ \) (c = 1.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃) \( \delta 7.35-7.45 \text{ (m, 2H)}, 6.88-6.95 \text{ (m, 2H)}, 5.51 \text{ (s, 1H)}, 4.40-4.49 \text{ (m, 1H)}, 4.28-4.39 \text{ (m, 1H)}, 3.95-4.05 \text{ (m, 1H)} 3.83 \text{ (s, 3H)}, 2.60-2.78 \text{ (m, 1H)}, 2.41 \text{ (dq, } J = 8.9, 6.2 \text{ Hz, 1H)}, 2.05 \text{ (dq, } J = 12.3, 5.1 \text{ Hz 1H)}, 1.83 \text{ (dq, } J = 10.4, 1.1 \text{ Hz, 3H)}, 1.45-1.55 \text{ (m, 1H)}, 1.31 \text{ (d, } J = 7.0 \text{ Hz, 3H}); ¹³C NMR (100 MHz, CDCl₃) \( \delta 179.0, 160.0, 130.7, 127.5, 113.6, 101.2, 78.9, 77.4, 55.3, 35.1, 31.6, 26.0, 15.2. \)
Diol 3.38: A stirred suspension of LiBH₄ (2.44 g, 100.74 mmol) in THF (154 mL) was charged with methanol (3.17 g, 4.0 mL, 98 mmol). After 30 min, the suspension was cooled to -10°C and acetal 3.37 (9.82 g, 33.58 mmol) in THF (154 mL, 2 x 48 mL rinse) was added via cannula and the reaction was warmed to rt. After 4 h, the reaction was quenched with the addition of a pH 7 buffer solution (520 mL) and extracted with Et₂O (4 x 300 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 20-50% EtOAc / hexanes, to give diol 3.38 (10.17 g, 34.31 mmol, 99%) a white solid: [α]D²³ = +4.2° (c=1.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.32-7.42 (m, 2H), 6.88-6.96 (m, 2H), 5.49 (s, 1H), 4.31(dd, J = 12.6 Hz, 1H), 3.99 (dt, J = 12.2 Hz, 1H), 3.99 (dt, J = 12.2 Hz, 1H) 3.80 (s, 3H), 3.60-3.80 (m, 2H), 3.55 (dd, J = 10.9, 4.6 Hz, 1H), 3.45 (dd, J = 10.9, 7.0Hz, 1H), 3.05 (brS, 1.2H), 1.79-1.93 (m, 2H), 1.45-1.58 (m, 2H), 1.35-1.45 (m, 1H), 0.98 (d, J = 5.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 160.5, 130.8, 127.4, 113.6, 101.2, 80.4, 72.7, 68.6, 66.5, 55.1, 37.0, 33.8, 27.0, 17.5.
Pivalate 3.39: To a stirred solution of diol 3.38 (4.14 g, 13.97 mmol) in CH$_2$Cl$_2$ (88 mL) was sequentially added DMAP (0.17 g, 1.40 mmol) and Et$_3$N (1.81 g, 2.5 mL, 17.46 mmol). The solution was cooled to -78 °C and PivCl (2.06 g, 2.1 mL, 17.04 mmol) was added. After 30 min, the reaction was allowed to warm to 0°C over a period of 1 h. The reaction was then quenched with sat. aq. ammonium chloride (500 mL) and extracted with EtOAc (3 x 300 mL). The dried (MgSO$_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 20-60% EtOAc / hexanes, to give pivalate 3.39 a colorless oil (5.08 g, 13.34 mmol, 95%): $[\alpha]_D^{23} = -2.2^\circ$ (c=1.00, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.42-7.43 (m, 2H), 6.91-6.92 (m, 2H), 5.51 (s, 1H), 4.30 (dd, $J = 4.2$ Hz, 1H), 3.93-4.02 (m, 3H) 3.83 (s, 3H), 3.68-3.83 (m, 2H), 2.21-2.22 (m, 1H), 1.93-1.95 (m, 1H), 1.63-1.64 (m, 1H), 1.50 (d, $J = 12.6$ Hz, 1H), 1.23-1.29 (m, 13H), 1.00 (d, $J = 6.3$ Hz, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 178.5, 160.1, 131.0, 127.4, 113.6, 101.1, 80.5, 71.3, 69.6, 66.5, 55.3, 38.8, 35.7, 29.2, 27.2, 27.1, 16.2.
Benzylate acetal 3.40: To a stirred solution of pivolate 3.39 (7.23 g, 19.00 mmol) in DMF (48 mL) was added benzyl bromide (33 g, 23 mL, 190 mmol), then NaH (1.52 g, 38 mmol, 60% dispersion in mineral oil) was added at −78 °C and the reaction was allowed to rt. After 8 h at rt, the reaction was quenched with addition of sat. aq. ammonium chloride (270 mL) and was extracted with Et₂O (4 x 300 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 8-50% EtOAc / hexanes, to give compound 3.40 (8.00 g, 17.00 mmol, 89%) as a colorless oil: [α]D²³ = +8.1° (c=1.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.35-7.45 (m, 2H), 7.20-7.30 (m, 5H), 6.89-6.94 (m, 2H), 5.53 (s, 1H), 4.6-4.9 (m, 2H), 4.30-4.34 (dd, J = 11.3 Hz and 3.8 Hz, 1H), 4.05 (ddd, J = 11.4, 5.8, and 2.3 Hz, 1H), 3.9-4.0 (m, 3H), 3.30 (s, 3H), 3.66-6.70 (m, 1H), 2.1-2.2 (m, 1H) 1.89 (qd J = 4.7 and 12.3Hz, 1H), 1.64-1.71 (ddd J = 24 Hz, 14 Hz and 4 Hz, 1H) 1.50-1.55 (m, 1H) 1.37-1.43 (ddd, J = 12.8, 9.8, and 2.8 Hz, 1H) 1.24 (s, 6H), 0.92 (d, J = 6.7 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 178.5, 159.9, 138.7, 131.2, 128.3, 127.9, 127.8, 127.6, 127.3, 113.5, 101.1, 79.4, 78.3, 73.3, 69.6, 66.9, 55.3, 38.9, 22.7, 29.2, 27.2, 26.5, 16.0.
**Diol 3.41:** To a stirred solution of acetal 3.40 (2.12 g, 4.50 mmol) in methanol (43 mL) was added PTSA monohydrate (860 mg, 4.50 mmol). After 21 h, the reaction was quenched with addition of NaHCO₃ (1.90 g). The slurry was stirred for 10 min, filtered, concentrated *in vacuo*, and purified by chromatography over silica gel, eluting with 0-60% EtOAc / hexanes giving diol 3.41 (1.32 g, 3.75 mmol, 83%).

**Benzylate alcohol 3.43:** To a stirred solution of alcohol 3.41 (1.62 g, 4.61 mmol) in CH₂Cl₂ (33 mL) was added benzyl 2,2,2-trichloroacetimidate (4.84 mL, 4.84 mmol, 1.0 M in CH₂Cl₂) and trifluromethanesulfonic acid (9.20 mL, 1.84 mmol, 0.2 M in CH₂Cl₂) sequentially at 0 °C. The reaction was allowed to rt. After 21 h, the reaction was quenched with sat. aq. NaHCO₃ (200 mL), and extracted with CH₂Cl₂ (5 x 50 mL). The dried (MgSO₄) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 0-60% EtOAc / hexanes, to give known alcohol 3.43 (1.70 g, 3.84 mmol, 83%) as a colorless oil:
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.30–7.38 (m, 10H), 4.63 (s, 2H), 4.55 (s, 2H), 3.88–3.99 (m, 3H), 3.73–3.78 (m, 1H), 3.65–3.68 (m, 1H), 3.49–3.55 (m, 1H), 2.88 (d, $J$ = 4.0 Hz, OH), 2.01–2.06 (m, 1H), 1.81–1.86 (m, 2H), 1.65–1.72 (m, 1H), 1.43–1.49 (m, 1H), 1.23 (s, 9H), 0.96 (d, $J$ = 6.8 Hz, 3 H).

**TES Ether 3.44**: To a stirred solution of 3.43 (215 mg, 0.48 mmol) in CH$_2$Cl$_2$ (2.5 mL) at 0°C were sequentially added DMAP (6 mg, 0.048 mmol), Et$_3$N (73 mg, 0.10 mL, 0.73 mmol), and TESCl (88 mg, 98.4 µL, 0.59 mmol). After 50 min, the reaction was quenched with sat. aq. NH$_4$Cl (3.5 mL) and extracted with Et$_2$O (4 x 35 mL). The dried (MgSO$_4$) extract was concentrated *in vacuo* and purified chromatography over silica gel, eluting with 5 – 20% EtOAc / hexanes, to give product 3.44 (231 mg, 0.41 mmol, 86%) as a colorless oil: [$\alpha$]$_D$$^{23}$ = +28.1° (c 1.00, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.38 – 7.29 (m, 10 H), 4.66 (d, $J$ = 11.6 Hz, 1 H), 4.53 (s, 2 H), 4.51 (d, $J$ = 11.6 Hz, 1 H), 4.18 – 4.14 (m, 1 H), 4.00 (dd, $J$ = 10.8, 5.6 Hz, 1 H), 3.92 (dd, $J$ = 10.8, 5.6 Hz, 1 H), 3.62 – 3.58 (m, 2 H), 3.51 – 3.47 (m, 1 H), 2.09 – 2.03 (m, 2 H), 1.66 – 1.43 (m, 3 H), 1.23 (s, 9 H), 0.98 (t, $J$ = 8.0 Hz, 9 H), 0.90 (d, $J$ = 6.8 Hz, 3 H), 0.61 (q, $J$ = 8.0 Hz, 6 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 179.0, 139.1, 128.7, 128.3, 128.0, 127.8, 79.5, 73.2, 72.3, 70.2, 68.6, 67.7, 39.3, 32.4, 31.7, 29.9, 27.7, 16.7, 7.4, 5.4.
Alcohol 3.45: To a stirred solution of 3.44 (449 mg, 0.81 mmol) in THF (4.4 mL) at 0°C were added MeOH (55.4 mg, 70 µL, 3.69 mmol) and LiBH₄ (0.87 mL, 1.73 mmol, 2.0 M in THF). The reaction was warmed to r.t. and sat. aq. NH₄Cl (46 µL) was added dropwise. After 2.5 h, the reaction was quenched with sat. aq. NH₄Cl (30 mL) and extracted with Et₂O (4 x 25 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified chromatography over silica gel, eluting with 10 – 40% EtOAc / hexanes, to give product 3.45 (328 mg, 0.69 mmol, 86%) as a colorless oil: [α]D²³ = +33.6° (c 1.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.29 – 7.38 (m, 10 H), 4.69 (d, J = 11.2 Hz, 1 H), 4.53 (s, 2 H), 4.50 (d, J = 11.2 Hz, 1 H), 4.20 – 4.24 (m, 1 H), 3.45 – 3.62 (m, 5 H), 2.30 (br, OH), 2.02 – 2.10 (m, 1 H), 1.77 – 1.83 (m, 1 H), 1.60 – 1.66 (m, 2 H), 1.44 – 1.50 (m, 1 H), 0.98 (t, J = 8.0 Hz, 9 H), 0.92 (d, J = 6.8 Hz, 3 H), 0.61 (q, J = 8.0 Hz, 6 H); ¹³C NMR (100 MHz, CDCl₃) δ 139.1, 138.4, 128.8, 128.7, 128.5, 128.2, 127.9, 127.8, 81.0, 73.1, 72.3, 69.0, 68.0, 67.5, 34.3, 32.8, 31.4, 17.8, 7.3, 5.4.

Aldehyde 3.7: To a stirred solution of 3.45 (1.15 g, 2.43 mmol) in CH₂Cl₂ (42 mL) with powdered 4 Å mol. sieves (3.0 g) were sequentially added NMO
(0.51 g, 4.38 mmol) and TPAP (0.10 g, 0.29 mmol) at room temperature. After 1.5 h, the reaction was filtered through a small plug of silica gel (25% EtOAc /hexanes rinse) and concentrated in vacuo to give 3.7 (1.03 g, 2.19 mmol, 90%) as a colorless oil: $[\alpha]_{D}^{23} = +21.0^\circ$ (c 1.00, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.56 (d, $J = 2.4$ Hz, 1 H), 7.29 – 7.36 (m, 10 H), 4.59 (d, $J = 11.2$ Hz, 1 H), 4.52 (s, 2 H), 4.43 (d, $J = 11.2$ Hz, 1 H), 4.16 – 4.17 (m, 1 H), 3.58 – 3.61 (m, 2 H), 3.44 – 3.46 (m, 1 H), 2.47 – 2.48 (m, 1 H), 2.06 – 2.08 (m, 1 H), 1.87 – 1.89 (m, 1 H), 1.60 – 1.68 (m, 2 H), 1.05 (d, $J = 7.2$ Hz, 3 H), 0.97 (t, $J = 7.6$ Hz, 9 H), 0.59 (q, $J = 7.6$ Hz, 6 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 205.0, 138.7, 138.2, 128.4, 128.3, 128.1, 127.8, 127.6, 127.5, 79.7, 72.8, 72.0, 67.9, 67.1, 44.4, 31.2, 30.4, 13.6, 7.0, 5.0.

Ketone Sulfone 3.47: To a stirred solution of sulfone 3.6 (48 mg, 0.085 mmol) in THF (0.57 mL) at $-78^\circ$C was added freshly prepared transparent lithium 2,2,6,6-tetramethylpiperidine (85 µL, 0.085 mmol, 1.0 M in THF) dropwise. After 25 min, a solution of the aldehyde 3.7 (20 mg, 0.0425 mmol) in pre-cooled THF (0.10 mL) was added via cannula to the sulfone solution. After 60 min, the reaction was removed from the cooling bath and allowed to rt, quenched with sat. aq. NH$_4$Cl
(3 mL) and extracted with EtOAc (4 X 10 mL). The dried (MgSO4) extract was concentrated in vacuo to give crude hydroxy sulfone 3.46. The crude hydroxy sulfone 3.46 was used next step immediately.

To a stirred solution of crude hydroxy sulfone 3.46 in CH2Cl2 (0.42 mL) were sequentially added powdered 4 Å mol. sieves (27 mg), TPAP (15 mg, 0.0425 mmol) and NMO (15 mg, 0.128 mmol). After 3 h, the reaction was diluted with 25% EtOAc / hexanes, filtered through a small plug of silica gel, concentrated in vacuo and purified by chromatography over silica gel, eluting with 10-40% EtOAc / hexanes, to give ketone sulfone 3.47 (40 mg, 0.039 mmol, 91% over two steps) as a colorless oil: 1H NMR (300 MHz, CDCl3); 7.26-7.77 (m, 25H), 5.49-5.63 (m, 2H), 4.17-4.72 (m, 7H), 3.76-3.84 (m, 1H), 3.41-3.71 (m, 4H), 3.2 2-3.30 (m, 1H), 3.15 (s, 3H of a diastereomer), 2.90 (s, 3H of a diastereomer), 2.41-2.50 (m, 1H), 1.46-2.22 (m, 12H), 1.04 (s, 9H of a diastereomer), 1.01 (s, 9H of a diastereomer), 0.92-0.96 (m, 9H), 0.56-0.62 (m, 6H); 13C NMR (75 MHz, CDCl3) δ 205.2, 139.2, 136.0, 134.5, 134.2, 130.0, 129.4, 129.1, 129.0, 128.9, 128.7, 128.4, 128.2, 128.1, 127.9, 127.8, 121.2, 98.1, 79.8, 73.1, 73.0, 72.7, 69.0, 68.0, 67.4, 66.0, 60.2, 48.8, 45.2, 38.2, 31.6, 30.7, 27.2, 19.6, 15.0, 7.4, 5.4.
Spiroketal 3.51 and 3.52: To a stirred solution of ketosufone 3.47 (11.3 mg, 0.011 mmol) in THF (0.20 mL) and MeOH (0.72 mL) at –10°C was added Na₂HPO₄ (11.2 mg, 0.080 mmol). After 5 min, 5% Na / Hg amalgam (31 mg, 0.068 mmol, 5% in Hg) was added. After 1 h, the reaction was diluted with 20% EtOAc / hexanes, filtered through a small plug of silica gel and concentrated in vacuo to give crude ketone 3.48 (10.9 mg) which was used next step without further purification.

To a stirred solution of ketone 3.48 (10.9 mg) in THF/H₂O (0.60 mL, 4 : 1) was added PPTS (3 mg, 0.012 mmol). After 18 h, the solution was quenched with saturated NaHCO₃ (5 mL) and extracted with EtOAc (3 x 5 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified chromatography over
silica gel, eluting with 5-20% EtOAc / hexanes, to give two bisspiroketals 3.49 and 3.50 (11.2 mg, 99%, 2.5:1 transoidal/cisoidal) as a colorless oil.

Cis spiroketal 3.51 and trans spiroketal 3.52: To a solution of 3.49 and 3.50 (11.2 mg) in THF (0.1 mL) was added TBAF (0.3 mL, 0.3 mmol, 1.0 M in THF). After 1.5 h, the reaction was quenched with sat. aq. NH₄Cl (0.3 mL) and extracted with EtOAc (5 x 5 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified chromatography over silica gel, eluting with 5-20% EtOAc / hexanes, to give a mixture of trans spiroketal 3.52 and cis-spiroketal 3.51 (9.7 mg, 94%) as a colorless oil.

Propanamide 4.2: To a solution of the oxazolidinone 4.1 (26.58 g, 150 mmol) in THF (450 mL) at -78 °C was added n-BuLi (60.60 mL, 151.5 mmol, 2.5 M in Hexane). After 5 min, EtCOCl (14.16 g, 13.36 ml, 153 mmol) was added, and the reaction was warmed to 0°C and then rt over 45 min. After 30 min at rt, the reaction was quenched with aq. NH₄Cl (90 mL) and extracted with DCM (300 mL), the organic extract was washed with aq NaHCO₃ (120 mL) and brine (120 mL) and dried over MgSO₄. The dried extract was condensed and recrystalized from hexane in freezer (–30 °C) to give 4.2 (35.19 g, 150 mmol, 99%) as a transparent needle
liked crystal: 1H NMR (400 MHz, CDCl$_3$) $\delta$ 7.26-7.38 (m, 5H), 4.67-4.73 (m, 1H), 4.18-4.25 (m, 2H), 3.31-3.35 (m, 1H), 2.92-3.05 (m, 2H), 2.77-2.82 (m, 1H), 1.19-1.25 (m, 3H).

\[\text{Alkylation product 4.3: To a solution of the propanamide 4.2 (10.81 g, 46.3 mmol) in CH$_2$Cl$_2$ (225 mL) at 0 °C were added TiCl}_4 (9.23 g, 5.35 mL, 48.7 mmol) and DIPEA (6.71 g, 9.04 mL, 51.9 mmol) to give an intense purple solution. After 60 min, BOMCl (13.56 g, 12.00 mL, 92.7 mmol) was added dropwise and stirring continued over 14 h from 0°C to rt over which time the color slowly faded. The reaction was quenched with pH 7 buffer (14 mL) and extracted with Et$_2$O (3 X 140 mL). The organic phase was washed with water (140 mL) and sat. aq. NaCl (140 mL), The dried extract (MgSO$_4$) was concentrated in vacuo and purified by chromatography over silica gel, eluting with 20-30% EtOAc / Hexanes, to give 4.3 (16.21 g, 45.9 mmol, 99%) as a colorless oil: 1H NMR (400 MHz, CDCl$_3$) $\delta$ 7.16-7.38 (m, 10H), 5.64-5.82 (m, 1H), 4.56 (s, 2H), 4.06-4.27 (m, 3H), 3.81 (dd, J = 9.1, 7.9 Hz, 1H), 3.59 (dd, J = 9.1, 5.3 Hz, 1H), 3.24 (dd, J = 13.5, 3.2 Hz, 1H), 2.73 (dd, J = 13.5, 9.2 Hz, 1H), 1.19 (d, J = 6.9 Hz, 3H), 13C NMR (100 MHz, CDCl$_3$) $\delta$ 175.4, 153.1, 138.2, 135.2, 129.5, 128.9, 128.3, 127.6, 127.5, 127.2, 73.1, 72.3, 65.9, 55.1, 38.3, 37.7, 13.9.]
Alcohol 4.4: To a solution of 4.3 (16.21 g, 45.9 mmol) and MeOH (1.77 g, 2.23 mL, 55.0 mmol) in THF (306 mL) at 0°C was added LiBH₄ (28 mL, 55.0 mmol, 2.0 M in THF). After 13 h, the reaction was quenched by the addition of MeOH (15 mL) and sat. aq. NH₄Cl (15 mL) and extracted with ether (3 X 150 mL). The dried extract (MgSO₄) was concentrated in vacuo and purified by chromatography over silica gel, eluting with 10-50% EtOAc / Hexanes, to give 4.4 (7.87 g, 43.7 mmol, 95%) as a colorless oil: ¹H NMR (400 MHz, CDCl₃) δ 7.28-7.38 (m, 5H), 4.53 (s, 2H), 3.59-3.65 (m, 2H), 3.56 (dd, J = 9.0, 4.6 Hz, 1H), 3.43 (dd, J = 9.0, 8.1 Hz, 1H), 2.52 (dd, J = 6.8, 4.6 Hz, 1H), 2.01-2.15 (m, 1H), 0.87 (d, J = 7.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 138.5, 128.9, 128.1, 128.0, 75.9, 73.8, 68.3, 36.0, 13.9.

Iodide 4.5: To a solution of PPh₃ (13.75 g, 52.4 mmol) in CH₂Cl₂ (152 mL) at 0°C were added sequentially imidazole (4.46 g, 65.6 mmol), I₂ (14.97 g, 59.0 mmol) and a solution of alcohol 4.4 (7.87 g, 43.7 mmol) in CH₂Cl₂ (26 mL). The reaction was then warmed to rt. After 2.5 h, the solvent was removed and the reaction mixture washed with sat. aq. sodium thiosulfate (110 mL), extracted with
ether (3 X 200 mL), water (200 mL) and sat. aq. NaCl (200 mL). The dried extract (MgSO₄) was concentrated in vacuo and purified by chromatography over silica gel, eluting with 20%-60% EtOAc / Hexanes, to give 4.5 (10.20 g, 35.2 mmol, 80%) as a slightly yellow oil: ¹H NMR (400 MHz, CDCl₃) δ 7.25-7.39 (m, 5H), 4.55 (s, 2H), 3.43 (dd, J = 9.3, 5.2 Hz, 1H), 3.30-3.40 (m, 3H), 1.78-1.87 (m, 1H), 1.03 (d, J = 6.7 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 138.8, 128.8, 128.1(2), 74.6, 73.6, 35.6, 18.1, 14.4.

Amide 4.7: To a stirred suspension of anhydrous LiCl (18.93 g, 446.5 mmol) and i-Pr₂NH (15.26 g, 21.3 mL, 150.8 mmol) in THF (82 mL) at –78 °C was added n-BuLi (56.3 mL, 140.6 mmol, 2.5 M in hexanes). After 10 min, the solution was briefly warmed to 0 °C before the addition of propionyl amide 4.6 (16.34 g, 73.84 mmol) in THF (326 mL) at -78 °C. After 1 h, the reaction was warmed to 0 °C. After 15 min, the reaction was warmed to rt. After 5 min, the reaction was cooled to 0 °C and a solution of 4.5 (10.20 g, 35.16 mmol) in THF (245 mL) was added via cannula. After 24 h, the reaction was quenched with sat. aq. NH₄Cl (160 mL) and extracted with ether (3 X 400 mL). The organic phase was washed with water (400 mL) and sat. aq. NaCl (400 mL). The dried extract (MgSO₄) was concentrated in vacuo and purified by chromatography over silica gel, eluting with
30-80% EtOAc / Hexanes, to give known compound 4.7\(^5\) (13.39 g, 34.9 mmol, 99%)
as a viscous colorless oil containing a mixture of rotamers (minor resonances are denoted by an asterisk): \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.21-7.41 (m, 10H), 4.60 (t, \(J = 7.2\) Hz, 2.5H), 4.48 (2.5H), 4.40 (br s, 1H), 3.36-3.41 (m, 0.2H), 3.22-3.34 (m, 2H), 3.08-3.13* (m, 0.2H), 2.87* (s, 0.75H), 2.81 (s, 2.5H), 2.73-2.77 (m, 1H), 2.58* (d, \(J = 1.9\) Hz, 0.2H), 1.98-2.05* (m, 0.2H), 1.81-1.86* (m, 0.2H), 1.67-1.80 (m, 2H), 1.07-1.19 (m, 7H), 0.99* (d, \(J = 6.5\) Hz, 1H), 0.94* (d, \(J = 6.5\) Hz, 1H), 0.88 (d, \(J = 6.5\) Hz, 3H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 179.5, 143.0, 139.1, 129.4*, 129.1*, 128.7 (2), 128.1*, 127.9 (2), 127.85, 127.4*, 126.9*, 126.7, 76.2, 73.4, 38.6, 34.6, 31.6, 18.2, 18.0, 14.9.

**Alcohol 3.2:** To a 0 °C stirred solution of LDA (105 mL, 104.7 mmol, 1.0 M solution in THF / hexanes) was added BH\(_3\)•NH\(_3\) (3.23 g, 104.7 mmol). After 15 min, the reaction was warmed to rt. After an additional 10 min, the reaction was cooled back to 0 °C and a solution of amide 4.7 (13.39 g, 34.9 mmol) in THF (40 mL) was added slowly via cannula. After 5 min, the reaction was then warmed to rt. After 2 h, the reaction was quenched with HCl (100 mL, 3 M). After 30 min, the reaction was extracted with Et\(_2\)O (3 x 200 mL). The dried extract (MgSO\(_4\)) was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with
eluting with 10-50% EtOAc / hexanes to afford alcohol 3.2 (4.88 g, 21.9 mmol, 63%) as a mixture of rotamers in a colorless oil. $[\alpha]_D^{23} = -6.6$ (c = 1.00 CHCl$_3$); $^1$H NMR (400 MHz; CDCl$_3$) $\delta$ 7.20-7.40 (m, 5H), 4.45-4.60 (m, 2H), 3.22-3.50 (m, 4H), 2.38 (s, 1H), 1.86-1.96 (m, 1H), 1.67-1.76 (m, 1H), 1.47-1.54 (m, 1H), 0.79-1.30 (m, 7H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 138.6, 128.3, 127.6, 75.9, 73.1, 67.7, 37.7, 33.1, 31.0, 18.18, 17.6.

Sulfamide 4.13: To a solution of (+)-CSA 4.11 (70 g, 301.4 mmol) in DCM (600 mL) under reflux conditions was added thionyl chloride (43.22 g, 26.5 mL, 361.6 mmol) dropwise. After 19 h, the reaction was cooled to 0°C and was added dropwise into a flash containing concentrated NH$_4$OH (750 mmol, sat. aq.) at 0°C via addition funnel. The reaction was warmed to rt and stirred for 15 h, then the reaction was extracted with DCM and dried over MgSO$_4$, the filtrate was concentrated under vacuo to give sulfamide 4.13 (61.48 g, 265.8 mmol, 88% in 2 steps) as colorless solid: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.36 (s, 2H), 3.47-3.51 (m, 1H), 3.13-3.22 (m, 1H), 2.43-2.49 (m, 1H), 2.27 (s, 6H), 2.10-2.19 (m, 4H), 1.47-1.53 (m, 2H).
**Compound 4.14:** To a solution of sulfamide **4.13** (65.92 g, 285.0 mmol) in toluene was added Amberlyst Cat. (8.94 g), the reaction was refluxed for 20 h under Dean-Stark condition. Then, the reaction was cooled to rt and DCM (250 mL) was added to dissolve all the product and the mixture was filtered. The filtrate was concentrated and dried under vacuo to give product **4.14** (59.93 g, 281.0 mmol, 99%) as colorless solid: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.18-3.21 (m, 1H), 2.97-3.00 (m, 1H), 2.76-23.82 (m, 1H), 2.38-2.43 (m, 1H), 2.28-2.29 (m, 1H), 2.05-2.19 (m, 2H), 1.78-1.83 (m, 1H), 1.52-1.64 (m, 1H), 1.13 (s, 3H), 0.92 (s, 3H).

**Compound 4.15:** To a solution of **4.14** (58.05 g, 266.0 mmol) in THF (950 mL) at 0 °C was added LiAlH$_4$ (11.10 g, 293 mmol). After 30 min, the reaction was allowed to rt by removal of the ice bath. After 24 h at rt, the reaction was cooled to 0°C using ice bath, and a small amount of H$_2$O was added dropwisely to quench the reaction slowly until the reaction turned to a turbid gelatous mixture. MgSO$_4$ and DCM was added to dried the mixture and get a clear solution with precipitate at the bottom. After filtration, the precipitate was washed with DCM 10 times. The elute
and filtrate was combined and condensed to give product 4.15 (57.07 g, 265 mmol, 99%) as colorless solid: $^1$H NMR (400 MHz, CDCl$_3$) δ 4.03 (s, 1H), 3.42-3.48 (m, 1H), 3.10-3.18 (m, 2H), 1.86-2.01 (m, 4H), 1.44-1.51 (m, 1H), 1.31-1.33 (m, 1H), 1.14 (s, 3H), 0.95 (s, 3H).

**Alkylation product 4.16**: To a solution of 4.15 (57.07 g, 265 mmol) in toluene (930 mL) at 0 °C was added NaH (15.9 g, 397.5 mmol, 60% in mineral oil). The reaction was allowed to rt and stirred for 3 h, then trans-crotonylchloride (37.44 g, 36 mL, 344.5 mmol) was added. The reaction was stirred at rt for 22 h and quenched with H$_2$O (500 ml). The mixture was extracted with EtOAc (3 X 300 ml), the dried extract was condensed to give a crude product, which was recrystallized in boiling MeOH (150 mL) to give a colorless crystal product 4.16 (49.32 g, 174 mmol, 66%): $^1$H NMR (400 MHz, CDCl$_3$) δ 7.08-7.17 (m, 1H), 6.58-6.63 (m, 1H), 3.93-3.97 (m, 1H), 3.44-3.55 (m, 2H), 2.08-2.19 (m, 2H), 1.90-1.98 (m, 6H), 1.35-1.47 (m, 2H), 1.21 (s, 3H), 1.04 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 164.0, 146.2, 122.3, 65.2, 53.2, 48.5, 47.8, 44.7, 38.5, 32.9, 26.5, 20.9, 19.9, 18.4.
Allyl chloride 4.18: To a slurry of pentane-washed NaH (16.42 g, 408 mmol, 60% in mineral oil) in THF (480 mL) was added BnOH (43.85 g, 42 mL, 400 mmol) with effervescence. After 30 min, DMF (100 mL) was added and the reaction mixture was raised to reflux. After 30 min, the reaction was allowed to cool to rt. This solution was then transferred to an addition funnel via syringe and added slowly dropwise to a solution of 3-chloro-2-chloromethyl-1-propene 4.17 (50.00 g, 46.3 mL, 400 mmol) in THF (250 mL) at rt over 30 min. After 16 h, the reaction mixture was quenched with H₂O (500 mL) and extracted with ether-pentane (1:1, 3 X 500 mL). The organic phase was washed with water (500 mL) and sat. aq. NaCl (500 mL). The dried extract (MgSO₄) was concentrated in vacuo and purified by chromatography over silica gel, eluting with 2-10% Et₂O / Hexanes, to give the known allyl chloride 4.18 (44.36 g, 226.0 mmol, 57%) as a colorless oil: ¹H NMR (400 MHz, CDCl₃) δ 7.28-7.36 (m, 5H), 5.33 (d, J = 0.7 Hz, 1H), 5.28 (d, J = 1.2 Hz, 1H), 4.53 (s, 2H), 4.14 (d, J = 0.7 Hz, 2H), 4.13 (s, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 142.4, 138.4, 128.8, 128.1(2), 117.3, 72.8, 70.7, 45.6.
**Sultam 4.20**: Following the similar procedure described by Paquette, 1,2-dibromoethane (7.16 g, 3.3 mL, 38.4 mmol) was added to a slurry of Mg (dry-stirred 23 d, 36 g, 1500 mmol) in degassed THF (900 mL). After 30 min, a solution of chloride 4.18 (21.85 g, 111.1 mmol) in THF (85 mL) was added slowly and the grey reaction mixture was stirred at rt overnight to give Grinard reagent 4.19 (about 60 mmol, 54%, the concentration was determined by a titration using menthol in the presence of 1,10-phenanthroline). Separately, CuBr•SMe₂ (16.67 g, 81.1 mmol) and LiCl (3.67 g, 86.5 mmol) were dissolved in THF (120 mL) and added to the solution of 4.19 at –78 °C via cannula. TMSCl (8.81 g, 10.29 mL, 81.1 mmol) was then added followed by a solution of compound 4.16 (15.32 g, 54.1 mmol) in THF (120 mL) after which the clear brown reaction mixture was stirred at –78 °C. After 2 h, the reaction was quenched with aq. NH₄Cl/NH₄OH (9:1, pH 9, 125 mL), warmed to rt and partitioned between ether (1000 mL) and water (500 mL). The aqueous layer was extracted with EtOAc (3 X 500 mL). The organic phase was washed with sat. aq. NaCl (500 mL). The dried extract (MgSO₄) was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 5%-20% EtOAc / Hexanes, to give the sultam 4.20 (22.85 g, 51.3 mmol, 95%) as a colorless oil: ¹H NMR (400 MHz, CDCl₃) δ 7.33-7.44 (m, 5H), 5.15 (s, 1H), 4.99 (s, 1H),
4.53 (dd, $J = 13.4$, 12.1 Hz, 2H), 4.00 (dd, $J = 17.1$, 12.9 Hz, 2H), 3.90 (t, $J = 6.3$ Hz, 1H), 3.48 (dd, $J = 26.0$, 13.9 Hz, 2H), 2.79 (dd, $J = 16.1$, 5.8 Hz, 1H), 2.53 (dd, $J = 16.1$, 7.6 Hz, 1H), 2.30-2.40 (m, 1H), 2.02-2.17 (m, 4H), 1.86-1.98 (m, 3H), 1.35-1.46 (m, 2H), 1.00 (d, $J = 6.3$ Hz, 3H), 0.99 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 171.8, 144.4, 138.9, 128.7, 128.0, 127.9, 114.1, 73.1, 72.4, 65.6, 53.4, 48.7, 48.1, 45.0, 42.9, 41.2, 39.0, 33.3, 28.4, 26.9, 21.2, 20.3.

**Aldehyde 4.22:** To a solution of sultam 4.20 (11.64 g, 26.12 mmol) in CH$_2$Cl$_2$ (135 mL) at $-78$ °C was added DIBAL-H (54 mL, 53.8 mmol, 1.0 M in CH$_2$Cl$_2$) dropwise over 1.5 h. After 2 h, the reaction was carefully quenched with methanol (200 mL) and poured into aq. sodium potassium tartrate (300 mL, 10%) at rt (150 mL CH$_2$Cl$_2$ rinse). After 5 h, the aqueous layer was extracted with CH$_2$Cl$_2$ (3 X 200 mL). The dried extract (MgSO$_4$) was concentrated _in vacuo_. The oil was dissolved in a solution of 10% EtOAc / hexanes solution (35 mL) and placed in the refrigerator to induce crystallization. After 16 h, the crystals were filtered (5% EtOAc / hexanes rinse) to yield the recovered auxiliary 4.21 (4.83 g, 22.40 mmol, 86%) and the mother liquor was concentrated _in vacuo_ and purified by chromatography over silica gel, eluting with 10-80% EtOAc / Hexanes, to give the aldehyde 4.22 (5.66 g, 24.40 mmol, 93%): $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.74 (dd,
$J = 2.4, 1.6 \text{ Hz, 1H}$), 7.28-7.40 (m, 5H), 5.14 (s, 1H), 4.94 (s, 1H), 4.50 (s, 2H), 3.95 (s, 2H), 2.53 (ddd, $J = 15.3, 4.0$ and $1.7 \text{ Hz, 1H}$), 2.16-2.32 (m, 2H), 2.00-2.13 (m, 2H), 0.96 (d, $J = 6.4 \text{ Hz, 3H}$); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 203.0, 144.2, 138.7, 128.8, 128.1, 128.0, 114.5, 73.1, 72.5, 51.0, 41.4, 26.7, 20.5.

**Diol 4.24:** To a solution of compound 4.23 (28.47 g, 118.5 mmol) in t-BuOH (50 mL) at rt were added sequentially NMO (36 ml, 154.0 mmol, 50% w/v H$_2$O), K$_2$OsO$_2$(OH)$_4$ (87.3 mg, 0.237 mmol) and (DHQD)$_2$PHAL (230.8 g, 0.296 mmol). The reaction was stirred at rt for 24 h and was quenched with Sat. aq. Na$_2$S$_2$O$_3$ (250 mL). The mixture was filtered and washed with H$_2$O (100 mL) and hexane (100 mL) to give diol 4.24 (25.62 g, 93.4 mmol, 79%) as a white powder: $^1$H NMR (400 MHz, CDCl$_3$) δ 7.25-7.39 (m, 5H), 4.55 (s, 2H), 3.43 (dd, $J = 9.3, 5.2 \text{ Hz, 1H}$), 3.30-3.40 (m, 3H), 1.78-1.87 (m, 1H), 1.03 (d, $J = 6.7 \text{ Hz, 3H}$); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 138.8, 128.8, 128.1(2), 74.6, 73.6, 35.6, 18.1, 14.4.
**Dioxalone 4.26:** To a solution of diol **4.24** (2.74 g, 10.0 mmol) in toluene was added Bu₂SnO (2.74 g, 11.0 mmol), the reaction was refluxed for 18 h and cooled down to rt. TBAI (5.80 g, 15.7 mmol) and t-butyl-bromoacetate (3.90 g, 2.95 ml, 20 mmol) was added, the reaction was refluxed for 5 h and was cooled to rt and quenched with sat. aq. Na₂S₂O₃ (90 mL). The mixture was extracted with EtOAc (3 X 100 mL) and washed with brine (100 mL). The dried extract (MgSO₄) was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 15-70% EtOAc / Hexanes, to give dioxalone **4.26** (2.66 g, 8.5 mmol, 85 %) as a solid: ¹H NMR (400 MHz, CDCl₃) δ 7.21-7.41 (m, 10H), 4.60 (t, J = 7.2 Hz, 2.5H), 4.48 (2.5H), 4.40 (br s, 1H), 3.36-3.41 (m, 0.2H), 3.22- 3.34 (m, 2H), 3.08-3.13* (m, 0.2H), 2.87* (s, 0.75H), 2.81 (s, 2.5H), 2.73-2.77 (m, 1H), 2.58* (d, J = 1.9 Hz, 0.2H), 1.98-2.05* (m, 0.2H), 1.81-1.86* (m, 0.2H), 1.67-1.80 (m, 2H), 1.07-1.19 (m, 7H), 0.99* (d, J = 6.5 Hz, 1H), 0.94* (d, J = 6.5 Hz, 1H), 0.88 (d, J = 6.5 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 179.5, 143.0, 139.1, 129.4*, 129.1*, 128.7 (2), 128.1*, 127.9 (2), 127.85, 127.4*, 126.9*, 126.7, 76.2, 73.4, 38.6, 34.6, 31.6, 18.2, 18.0, 14.9.
Andrus aldol adduct 4.27: To a solution of dioxalone \((R, R)-4.26\) (10.12 g, 32.2 mmol) in \(CH_2Cl_2\) (32 mL) at \(-78\) °C was added \(Et_3N\) (5.18 g, 7.14 mL, 51.2 mmol). After 3 min, a solution of \(Chx_2BOTf\) (45.4 mL, 45.4 mmol, 1.0 M in hexanes)\(^\text{11}\) was added dropwise over 15 min. After 140 min, a solution of the aldehyde 4.22 (8.67 g, 37.3 mmol) in \(CH_2Cl_2\) (8.2 mL, precooled) was added via cannula. The aldehyde flask was rinsed with an additional portion of \(CH_2Cl_2\) (2 X 1.7 mL, precooled). After 10 min, the reaction flask was transferred to the freezer (approximately \(-30\)°C). After 23 h, the reaction was quenched by the addition of \(MeOH\) (24 mL). The solution was then poured into a stirring solution of aq. pH = 7 phosphate buffer (160 mL) at rt. (75 mL \(CH_2Cl_2\) rinse). To the stirring solution was then added \(H_2O_2\) (32 mL, 30% aqueous). After 90 min, the reaction mixture was diluted with sat. aq. \(NaCl\) (160 mL) and \(CH_2Cl_2\) (160 mL) and extracted with \(CH_2Cl_2\) (3 X 160 mL). The organic layer was then washed with \(NaCl\) (200 mL) and the aqueous layer was back extracted with \(CH_2Cl_2\) (2 X 100 mL). The dried extract (MgSO\(_4\)) was concentrated \textit{in vacuo} and purified by chromatography over silica gel, eluting with 20-50% EtOAc / Hexanes to give aldol adduct 4.27 (14.69 g, 26.9 mmol, 84%) as a colorless oil: \([\alpha]_D^{23} = +68.8\ (c\ 1.00,\ CH_3CN)\); \(^1\)H NMR (400
MHz, CDCl$_3$) $\delta$ 7.27-7.36 (m, 5H), 6.96 (dd, $J = 8.7$, 6.9 Hz, 4H), 6.75 (d, $J = 8.1$ Hz, 4H), 5.35 (d, $J = 9.3$ Hz, 1H), 5.07 (s, 1H), 4.96 (d, $J = 9.3$ Hz, 1H), 4.93, (s, 1H), 4.47 (m, 3H), 4.26 (br s, 1H), 3.94 (dd, $J = 22.0$, 12.6 Hz, 2H), 3.75 (s, 3H), 3.74 (s, 3H), 3.54-3.62 (m, 1H), 3.26 (br s, 1H), 2.30 (dd, $J = 13.6$, 4.6 Hz, 1H), 1.66-1.98 (m, 6H), 1.49-1.58 (m, 1H), 1.21-1.31 (m, 2H), 0.94 (d, $J = 6.6$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 170.3, 160.4, 160.2, 145.0, 138.7, 129.2, 129.0, 128.8, 128.4, 128.1, 128.0, 127.1, 114.2, 114.1, 113.8. 85.6, 78.2, 76.9, 73.3, 72.5, 72.0, 55.6, 41.4, 40.7, 27.8, 21.1.

**Methyl ester 4.28:** To a stirred solution of aldol product 4.27 (8.39 g, 15.4 mmol) in dry MeOH (142 mL) at 0°C was added NaH (65 mg, 1.62 mmol, 60% in mineral oil). After 30 min, the reaction was quenched with saturated NH$_4$Cl (9 mL). The MeOH was then removed *in vacuo* and the residue was diluted with sat. aq. NaCl (175 mL), extracted with EtOAc (3 X 140 mL). The dried extract (MgSO$_4$) was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 20-80% EtOAc / Hexanes to give 4.28 (6.93 g, 11.98 mmol, 78%) as a glassy semi-solid: $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.40-7.30(m, 5H), 7.01-6.96 (m, 4H), 6.80-6.76 (m, 4H), 5.10 (s, 1H), 4.95 (s, 1H), 4.94 (d, $J = 9.3$ Hz, 1H),
4.50-4.48 (m, 3H), 4.30-4.26 (m, 1H), 3.96 (dd, J = 19.2, 12.6 Hz, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 3.66 (d, J = 1.7 Hz, 1H), 3.52 (s, 3H), 3.01 (d, J = 4.8 Hz, 1H), 2.32 (dd, J = 13.8, 4.8 Hz, 1H), 2.05-1.65 (m, 4H), 0.97 (d, J = 6.6 Hz, 3H); ^13^C (75 MHz, CDCl$_3$): δ 171.3, 159.7, 159.5, 145.0, 138.6, 132.0, 129.7, 129.6, 128.8, 128.7, 128.2, 128.1, 114.0, 113.8, 113.7, 89.7, 82.2, 78.7, 73.3, 72.5, 70.8, 55.6, 52.1, 40.9, 40.0, 28.0, 21.3.

**TIPS ether 4.29**: To a stirred solution of methyl ester 4.28 (17.23 g, 29.8 mmol) in CH$_2$Cl$_2$ (260 mL) at -78 °C was sequentially added 2,6-lutidine (7.12 g, 7.7 mL, 66.1 mmol) followed by TIPSOTf (10.95 g, 9.64 mL, 35.7 mmol). After an additional 35 min, the reaction was quenched with MeOH (9 mL) followed by sat. aq. NaHCO$_3$ (350 mL) and warmed to rt. The aqueous layer was diluted with sat. aq. NaCl (180 mL) and extracted with CH$_2$Cl$_2$ (3 X 180 mL). The dried (MgSO$_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 5%-30% EtOAc / hexanes, to give 4.29 (18.09 g, 24.6 mmol, 83%) as a colorless oil: [α]$_D^{23}$ = +18.0 (c 1.00, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$) δ 7.37-7.35 (m, 5H), 6.95-6.91 (dd, J = 2.1, 8.7 Hz, 4H), 6.71-6.67 (dd, J = 2.1, 8.7 Hz, 4H), 5.17 (s, 1H), 4.98 (s, 1H), 4.71 (d, J = 8.4 Hz, 1H), 4.52 (s, 2H), 4.45 (d, J =
8.7 Hz, 2H), 4.17 (d, \( J = 1.8 \) Hz, 1H), 3.97 (s, 2H), 3.92 (s, 1H), 3.75 (s, 3H), 3.74 (s, 3H), 3.50 (s, 3H), 2.15-2.05 (m, 2H), 1.97-1.90 (m, 1H), 1.70-1.60 (m, 1H), 1.44-1.37 (m, 1H), 1.13 (s, 21H), 0.90 (d, \( J = 6.6 \) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 170.8, 159.2, 158.9, 144.3, 138.5, 131.5, 129.5, 129.4, 128.5, 128.4, 127.6, 127.5, 113.3, 113.2, 113.1, 89.6, 81.7, 78.5, 73.0, 72.9, 71.9, 55.2, 55.1, 51.5, 42.1, 41.1, 27.1, 19.8, 18.2, 12.6.

**Alcohol 4.30:** To a solution of 4.29 (12.44 g, 16.9 mmol) in CH\(_3\)CN/H\(_2\)O (560 mL, 10 : 1) at 0 °C was added CAN (23.20 g, 42.3 mmol). After 1 h, the reaction was quenched with H\(_2\)O (600 mL) and extracted with Et\(_2\)O (3 x 400 mL). The dried (MgSO\(_4\)) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 10-20% EtOAc / hexanes, to give product 4.30 (6.81 g, 14.22 mmol, 84%) as colorless oil: \([\alpha]_D^{23} = -38.8 \) (c 1.00, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.28 – 7.37 (m 5H), 5.14 (s, 1H), 4.94 (s, 1H), 4.52 (s, 2H), 4.23 – 4.27 (m, 2H), 3.96 – 3.98 (m, 2H), 3.73 (s, 3H), 3.04 (d, \( J = 7.2 \) Hz, 1H), 2.01-2.07 (m, 1H), 1.95-1.99 (m, 1H), 1.78-1.82 (m, 2H), 1.28-1.34 (m, 2H), 1.09 (m, 24H), 0.94-0.98 (m, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 172.6,
TMS ether 4.30.1: To a solution of 4.30 (6.81 mg, 14.22 mmol) in CH₂Cl₂ (140 mL) at −78 °C was sequentially added 2, 6-lutidine (6.11 g, 6.6 mL, 56.9 mmol) and TMSOTf (6.39 g, 5.2 mL, 28.4 mmol). After 30 min, the reaction was quenched with sat. aq. NH₄Cl (150 mL) and extracted with EtOAc (3 x 200 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 10-20% EtOAc / hexanes, to give product 4.30.1 (6.17 g, 11.20 mmol, 79%) as colorless oil: \([\alpha]_D^{23} = −13.0 \text{ (c 1.00, CHCl}_3)\); \(^1\)H NMR (300 MHz, CDCl₃) \(\delta 7.28 – 7.38 \text{ (m 5H)}, 5.14 \text{ (s, 1H)}, 4.97 \text{ (s, 1H)}, 4.52 \text{ (s, 2H)}, 4.24 – 4.26 \text{ (m, 2H)}, 3.97 – 3.99 \text{ (m, 2H)}, 3.70 \text{ (s, 3H)}, 1.74 – 2.05 \text{ (m, 4H)}, 1.27 – 1.31 \text{ (m, 1H)}, 1.09 \text{ (m, 21H)}, 0.91 \text{ (d, } J= 6.6 \text{ Hz, 3H)}, 0.14 \text{ (s, 9H)}; \(^{13}\)C NMR (75 MHz, CDCl₃) \(\delta 172.3, 144.2, 138.5, 128.3, 127.6, 127.4, 113.0, 76.0, 73.7, 72.9, 71.9, 51.5, 42.1, 41.5, 27.4, 19.7, 18.1, 12.6, -0.11.

Methyl ketone 4.32: To a solution of 4.31 (5.76 g, 13.9 mmol) in Et₂O (55 mL) at −78 °C was added MeLi (21 mL, 33.4 mmol, 1.6 M in Et₂O). The solution
was warmed to room temperature over 2.5 h. The reaction was quenched by addition of sat. aq. NH₄Cl (30 mL) and the resulting mixture was extracted with Et₂O (4 x 60 mL). The dried (MgSO₄) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 10% - 50% EtOAc / hexanes, to give product 4.32 (2.47 g, 9.34 mmol, 67%, 99% BRSM) as colorless oil, and recovered SM 4.31 (1.83 g, 4.43 mmol, 32%): [α]D₂₃ = −6.4 (c 1.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.25 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 4.41 (s, 2H), 3.80 (s, 3H), 3.20 – 3.30 (m, 2H), 2.60 – 2.67 (m, 1H), 2.11 (s, 3H), 1.70 – 1.87 (m, 2H), 1.11 – 1.19 (m, 1H), 1.09 (d, J = 6.9 Hz, 3H), 0.94 (d, J = 6.6 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 212.8, 159.0, 130.7, 129.0, 113.7, 75.2, 72.5, 55.2, 45.0, 37.2, 31.5, 27.7, 17.6, 17.2.

**Tosylate 4.34:** To a solution of 4.32 (2.91 g, 11.0 mmol) in CH₂Cl₂ (210 mL) at 0 °C was sequentially added phosphate buffer (21 mL, pH = 7) and DDQ (3.0 g, 13.21 mmol). The reaction mixture was warmed to room temperature. After 1 h, the reaction was quenched by addition of sat. aq. NaHCO₃ (200 mL) and the resulting mixture was extracted with CH₂Cl₂ (3 x 200 mL). The dried (MgSO₄) extract was concentrated *in vacuo* and the solvent volume reduced to approximately 14 mL. The resultant solution of volatile hemiacetal 4.33 was used in the next reaction without further purification.
To a solution of the crude hemiketal 4.33 in CH$_2$Cl$_2$ was added Et$_3$N (1.67 g, 2.3 mL, 16.4 mmol), TsCl (2.31 g, 12.11 mmol) and DMAP (0.14 mg, 1.1 mmol). After 10 h, the reaction was quenched with sat. aq. NH$_4$Cl (50 mL) and the resulting mixture was extracted with CH$_2$Cl$_2$ (3 x 100 mL). The organic layer was washed with water (100 mL) and sat. aq. NaCl (100 mL). The dried (MgSO$_4$) extract was concentrated \textit{in vacuo} and purified by chromatography over silica gel, eluting with 10 - 40% EtOAc / hexanes, to give product 4.34 (1.95 g, 6.53 mmol, 59 % over two steps) as colorless oil. [$\alpha$]$_D^{23}$ = $-9.7$ ($c$ 1.00, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.71 (d, $J$ = 8.4 Hz, 2H), 7.29 (d, $J$ = 8.4 Hz, 2H), 3.72 – 3.82 (m, 2H), 2.47 – 2.54 (m, 1H), 2.39 (s, 3H), 2.04 (s, 3H), 1.62 – 1.74 (m, 2H), 1.11 – 1.19 (m, 1H), 1.00 (d, $J$ = 7.2 Hz, 3H), 0.84 (d, $J$ = 6.6 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 212.4, 145.2, 133.4, 130.3, 128.3, 75.1, 44.9, 36.3, 31.2, 28.3, 22.1, 17.6, 17.1.

Azide 4.10: To a solution of tosylate 4.34 (1.95 g, 6.53 mmol) in DMF (26 mL) was added NaN$_3$ (5.74 g, 88.3 mmol). The slurry was heated to 70 °C. After 3 h, the reaction was cooled to rt and quenched with water (55 mL). The solution was extracted with Et$_2$O /Pentane (1:1, 3 x 100 mL). The dried (MgSO$_4$) extract was concentrated \textit{in vacuo} and purified by chromatography over silica gel, eluting with 10% - 20% EtOAc / hexanes, to give 4.10 (0.94 g, 5.55 mmol, 85%) as colorless
oil: $[\alpha]_D^{23} = -5.6 \ (c \ 1.00, \ \text{CHCl}_3); \ \text{H} \text{NMR} \ (400 \text{ MHz}, \ \text{CDCl}_3) \ \delta \ 3.13 - 3.20 \ (m, \ 2H), \ 2.60 - 2.62 \ (m, \ 1H), \ 2.13 \ (s, \ 3H), \ 1.62 - 1.83 \ (m, \ 2H), \ 1.06 - 1.15 \ (m, \ 1H), \ 1.09 \ (d, \ J = 6.9 \text{ Hz}, \ 3H), \ 0.94 \ (d, \ J = 6.6 \text{ Hz}, \ 3H); \ \text{C} \text{NMR} \ (75 \text{ MHz}, \ \text{CDCl}_3) \ \delta \ 212.1, \ 57.6, \ 44.6, \ 37.2, \ 31.4, \ 27.8, \ 17.8, \ 17.3.$

References


4. Preparation of LiTMP: To a solution of 2,2,6,6-tetramethylpiperidine (282.8 mg, 340 µL, 2.0 mmol) in THF (0.86 mL) was added n-BuLi (0.8 mL, 2.0 mmol, 2.5 M in hexanes). The reaction was warmed to −10 °C and stirred for 30 min prior to use.


9. Titration of Grignard reagent: in a typical titration, performed under an Argon atmosphere, 1.0 mL Grignard reagent was added to a 2.0 mL solution of o-phenanthroline in anhydrous benzene (0.2 mg/mL). The resulting purple solution is titrated with a standard solution (1.00 M) of menthol in anhydrous benzene until the purple color disappeared. In this procedure the number of millimoles of menthol added is equal to the number of millimoles of the Grignard reagent. For the references, see: (a) Lin, H.; Paquette, L. A. *Synth. Comm.* **1994**, 24, 2503. (b) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, 9, 165.


11. To a solution of cyclohexene (3.28 g, 4.05 mL, 40 mmol) in anhydrous ethyl ether (12 mL) at 0 °C was added BH$_3$$\cdot$SMe$_2$ (1.60 g, 2.00 mL, 20 mmol) dropwisely via syringe pump. After 1 h, the reaction was warmed to rt. After 2 h, removal of the solvent under vacuum gave a white solid, which was dissolved by addition of dry n-hexane (12 mL). The reaction was cooled to 0 °C and TfOH (3.01 g, 1.76 mL, 20 mmol) was added dropwisely. The reaction was allowed to rt. After stirring at rt for 2 h, the reaction was kept still for 3 h to give a transparent upper layer of solution, which was transferred into a dry preweight sealed roundbottom flask. Removal of the solvent under high vacuum gave a colorless solid (5.91 g, 18.12 mmol, 91%), which was used to prepare an approximately 1.0 M solution by
addition of dry n-hexane (15mL). The freshly prepared solution was stored in –30 °C freezer for use. For the reference, see: Brown, H. C.; Ganesan, K.; Dhar, R. K. 