TOTAL SYNTHESIS OF PUREALIN AND ITS ANALOGUES

SYNTHESIS OF LAGUNAPYRONE B AND ITS ISOMERS WITH FLUOROUS MIXTURE SYNTHESIS

by

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Purealin, a natural product isolated from the sea sponge Psammaplysilla purea is known to inhibit axonemal dynein. A total synthesis of purealin and a small library of purealin analogues are reported herein. These syntheses allowed initial examination of biological properties of purealin and its analogues. The results indicate purealin and some of the analogues inhibited the ATPase activity of isolated cytoplasmic dynein heavy chain. The inhibitory effect of purealin was concentration-dependent. The library of purealidin A showed effective antiproliferative activity against a mouse leukemia cell line, but selective activities against human carcinoma cell lines. These data illustrate small molecule inhibitors of cytoplasmic dynein that could prove to be useful tools for investigation of the cellular function.

Lagunapyrone B, a marine bacteria isolated by Fenical in 1996, possesses an unusual alpha-pyrone functionalized with a highly methyl-branched side chain, a conjugated diene and two skipped dienes. The carbon skeleton of lagunapyrones has not been previously observed. Because of the long distance between the two groups of stereocenters, the absolute configuration of these compounds is difficult to assign using spectroscopic methods. Using fluorous mixture synthesis (FMS), four diastereomers were synthesized in order to determine the absolute configuration of the natural product. Beyond FMS, The approach included Paterson auxiliary anti-aldol, Zirconium-catalyzed and Stille coupling reactions. The longest linear sequence is 23

steps in the synthesis. By comparing the $[\alpha]_D^{25}$ data of final four isomers, compound **2.1c** was determined to be the natural product, whose configuration is 6R, 7S, 19S, 20S, 21R.

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LIST OF ABBREVIATIONS

AD-Mix	Asymmetric dihydroxylation mixture
AIBN	2,2'-Azobisisobutyronitrile
Boc	Butyloxycarbonyl
Cbz	Benzyloxycarbonyl
TBuOK	Potassium tert-butoxide
DBU	1,8-Diazabicyclo[5,4,0]undec-7-ene
DCC	1,3-Dicyclohexylcarbodiimide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL	Diisobutyl aluminum hydride
DMAP	4-Dimethylamino pyridine
DME	Dimethoxyethane
DMF	Dimethyl sulfoxide
Ee	Enantiomeric excess
EDC	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EI	Electron ionization
Equiv	Equivalents
ESI	Electrospray ionization

HMBC	Heteronuclear multiple bond coherence
HMPA	Hexamethylphosphoramide
HMQC	Heteronuclear multiple quantum coherence
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
IR	Infrared spectrometry
KHMDS	Potassium bis(trimethylsilyl)amide
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
Me	Methyl
Mp	Melting point
Ms	Methylsulfonyl
NBS	*n*-Bromosuccinimide
NMR	Nuclear magnetic resonance
PCC	Pyridinium chlorochromate
Ph	Phenyl
PMB	*p*-Methoxybenzyl
Rt	Room temperature
TASF	Tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	Tetrabutylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
TES	Triethylsilyl

TMS	Trimethylsilyl
TFA	Trifluoacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
Ts	4-Toluenesulfonyl

PREFACE

Before one begins the task of reading this document, it is imperative that the contributions of others to the work described within be noted. The author is very grateful to the following individuals and feels indebted to them. The listing, however, is by no means comprehensive and any omission should be considered an oversight on the part of the author.

Professor Dennis Curran, my research advisor, deserves first mention. His steadfast support, encourgement, creativity, and very keen insight have been both inspirational and personally very meaningful. I appreciate all his efforts on my behalf, both in the realm of my graduate studies and in preparation for my life after Pitt.

I would also like to thank Professors Chris Schafmeister, Billy Day, Craig Wilcox for serving on the thesis committee. I would like to thank Professor Theodore Cohen for being the mentor of my proposal defense.

I wish to thank all of the friends and colleagues at Pitt, who have enriched my graduate school experience, including all the past and present members of Curran group. Their assistance is highly valuable for my research and life at Pitt.

I am very appreciative of the help provided to me by Drs Fu-mei Lin, Fu-Tyan Lin, Steve Geib, Kasi Somayajula and John Williams for NMR spectroscopy, crystallography, mass spectroscopy.

Lastly, I would like to thank my family (my parents, my brother and my girl friend Luo suhua) for their support, encourgement, love, sacrifice, patience in dealing with me through the ordeal of my graduate study.

1.0 TOTAL SYNTHESIS OF PUREALIN, PUREALIDIN A AND THEIR ANALOGS

1.1 INTRODUCTION

1.1.1 PUREALIN AND RELATED MARINE NATURAL PRODUCTS

Purealin,[1] a natural product isolated from Okinawan marine sponge *psammaplysilla purea*, is one of hundreds of dibromotyrosine-derived natural products.[2] Its structure, shown in Figure 1.1. consists of a center dibromotyrosine unit attached on the right to a side chain via an amide bond and attached to the left through a three-carbon spacer and another amide bond to aminohistidine ring. The absolute configuration of the naturally occuring enantiomer on C1 and C6 is S, R.

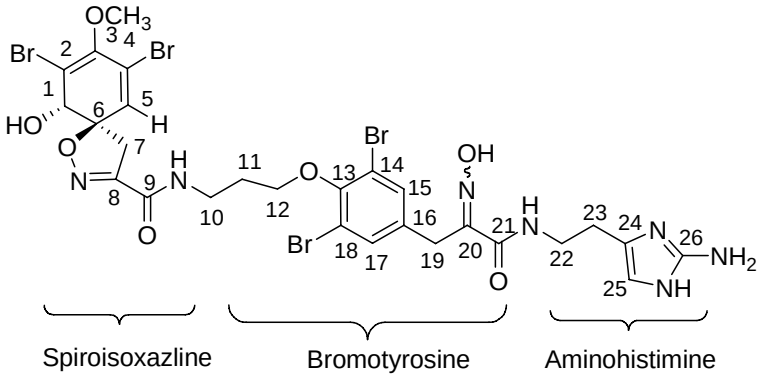


Figure 1.1. Structure of purealin **1.1**

Many other bromotyrosine alkaloids have also been isolated in recent years. A few examples are given in Figure 1.2. Purealidin A[3] was isolated from an Okinawan marine sponge, which was a precusor of purealin. Lipopurealins A, B, C[4] were also isolated from *psammaplysilla purea*. Compared to purealin, lipopurealins A, B, C belong to a new type of bromotyrosine-derived metabolites, which have side chain fatty acids rather than spiroisoxazoline rings.

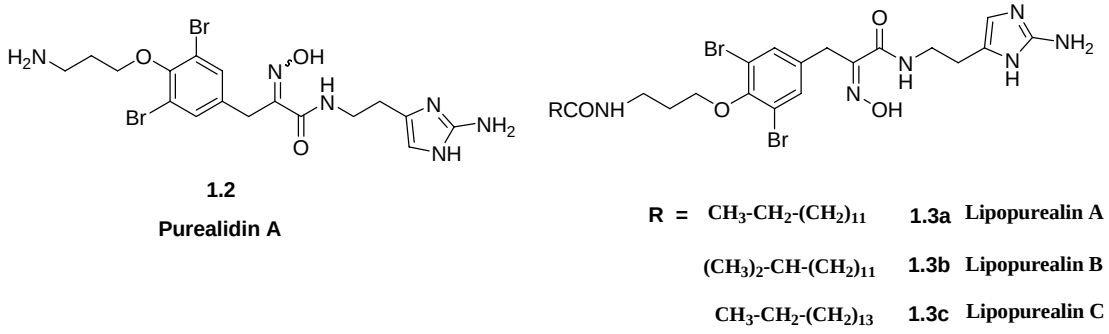


Figure 1.2. Structures of purealidin A and lipopurealins A, B,C

Purealin has an activity for non-ATP mimetic agent in which selectively it inhibits the ATPase activity of dynein and myosin.[5] Those proteins are two different types of molecular motors. Molecular motors[6] are biological machines that are responsible for most forms of movement in the cellular world. Dynein is a motor protein that is involved in many fundamental cellular processes. For example, it can transport many cargos such as membrane organelles, protein complexes and nucleic acids. For example, dynein is responsible for transport of *p53*, the tumor-suppressor protein, to the nucleus in response to DNA damage. *P53*[7] is believed to be among the most frequently mutated genes in human cancer and *p53* mutation can promote tumor progression. Dynein is also responsible for the force necessary to cause the nuclear envelop breakdown. These are some of the reasons to suggest that dynein inhibitor like purealin might be a seminal lead for potential anti-cancer drugs.

Purealidin A has weak inhibitory activity (22% inhibition at 10^{-4} M) against Na, K-ATPase and exhibits some cytotoxicity against L1210 murine leukemia cells in vitro with an IC_{50} value of 1.1 μg/mg. Lipopurealin-A, B, C exhibits inhibitory activities on Na, K-ATPase purified from porcine brain and dog kidney, with lipopurealin-B being the most potent inhibitor (Table 1.1).[4]

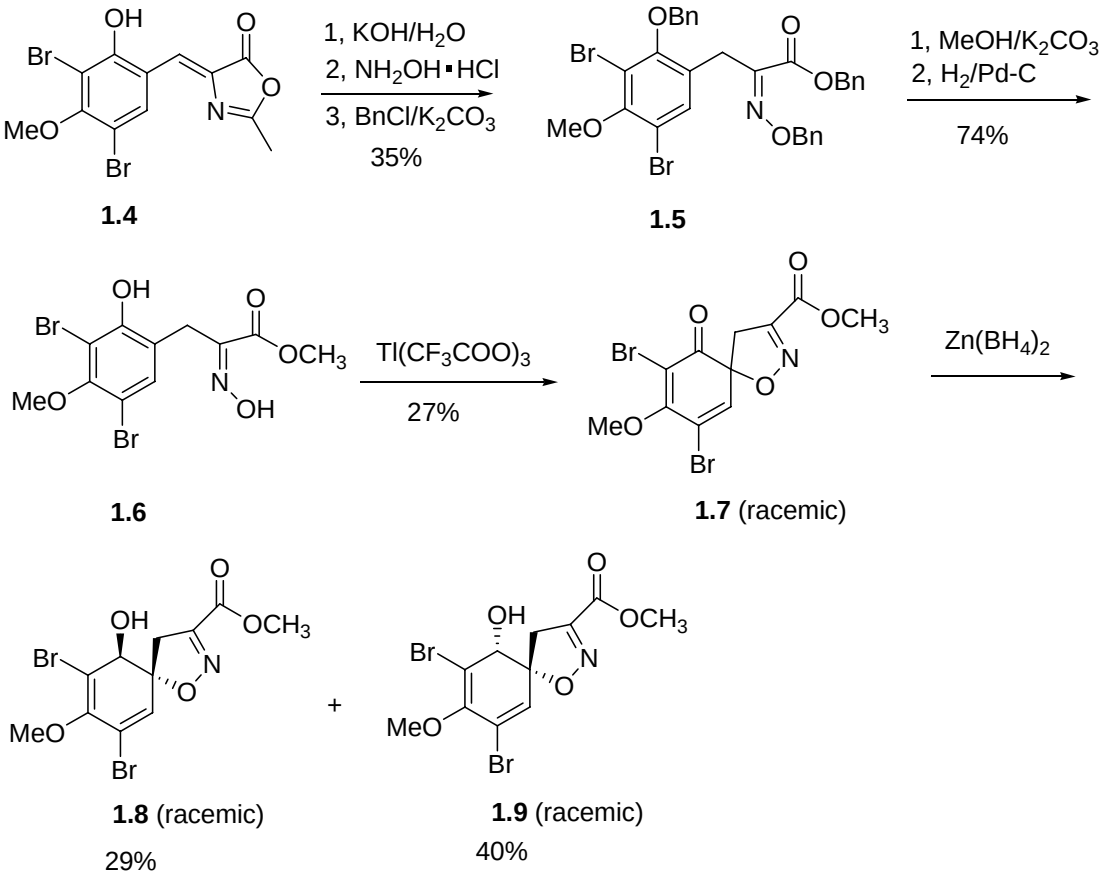
Table 1.1. Biological activities of and lipopurealin A, B,C[4]

Compounds	Na, K-ATPase inhibition IC_{50} (μM)		
	Brain	Kidney	Heart
Lipopurealin-A	30	20	100
Lipopurealin-B	6	10	>100
Lipopurealin-C	60	20	>100

1.1.2 SYNTHESIS OF SPIROISOXAZOLE RINGS.

A central feature of purealin and its relatives is the dibromotyrosine-derived spiroisoxazoline ring. The spiroisoxazoline ester **1.8** and related molecules have been synthesized in several different ways. Yamamura[8] first reported the synthesis of ester **1.5** (Scheme 1.1). When readily accessible azlactone[9] **1.4** was submitted to hydrolysis in 10% KOH followed by oximation and benzylation, the dibenzyl derivative **1.5** was obtained in 35% yield. Transesterification of **1.5** in methanol containing K_2CO_3 afforded the corresponding methyl ester, which on hydrogenolysis led to the desired dihydroxy methyl ester **1.6** in 74% yield. On treatment with thallium(III) trifluoroacetate in CF_3COOH, methyl ester **1.6** was converted to spiroisoxazoline **1.7** in 27% yield. Reduction of the ketone **1.7** was successfully carried out by using excess $Zn(BH_4)_2$ to give the corresponding trans and cis isomers (**1.8** and **1.9**) in 29% and 40% yield. The stereostructure

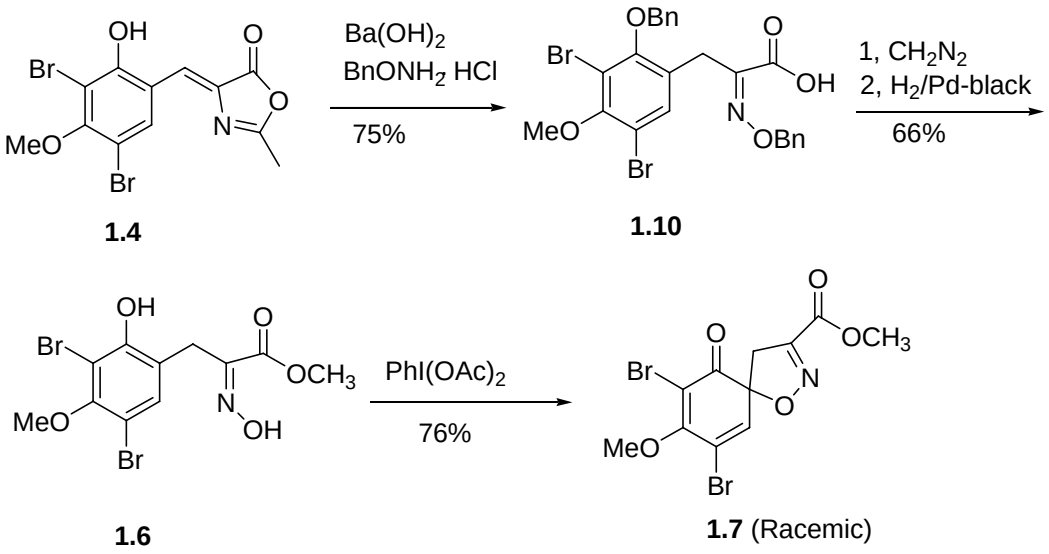
of **1.5** and **1.6** was established on the basis of comparison of ^{1}H NMR spectroscopy with those of aerothionin[10] and *cis*, *cis*-aerothionin.[11] The structure of aerothionin was determined by X-ray analysis.[1]



Scheme 1.1 Synthesis of spiroisoxazole methyl ester

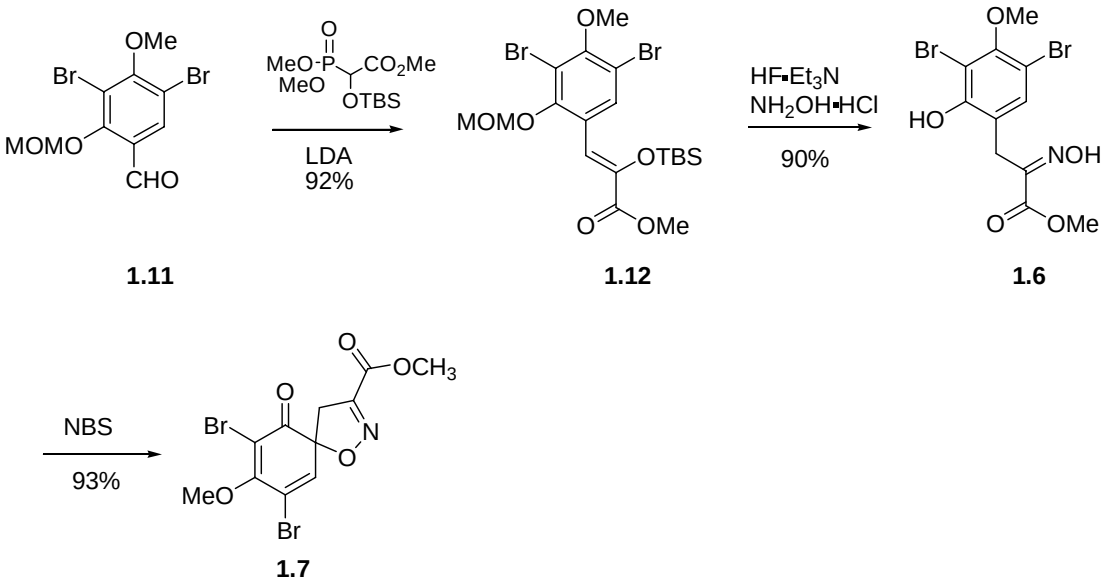
Starting with the same azlactone **1.4**, Hoshino[12] reported the synthesis of spiroisoxazoline **1.7** in much higher yield (Scheme 1.2). The azlactone **1.4** was hydrolyzed with $Ba(OH)_2$ in the presence of *O*-benzylhydroxylamine in aqueous dioxane to give oxime **1.10** in 75% yield. Methylation of acid **1.10** with CH_2N_2 followed by hydrogenolysis over Pd-black afforded dihydroxy methyl ester **6** in 66% yield. The reaction of dihydroxy methyl ester **1.6** with

phenyliodonium diacetate in acetonitrile at 0 °C proceeded smoothly to afford spiroisoxazoline **1.7** in 76% yield.



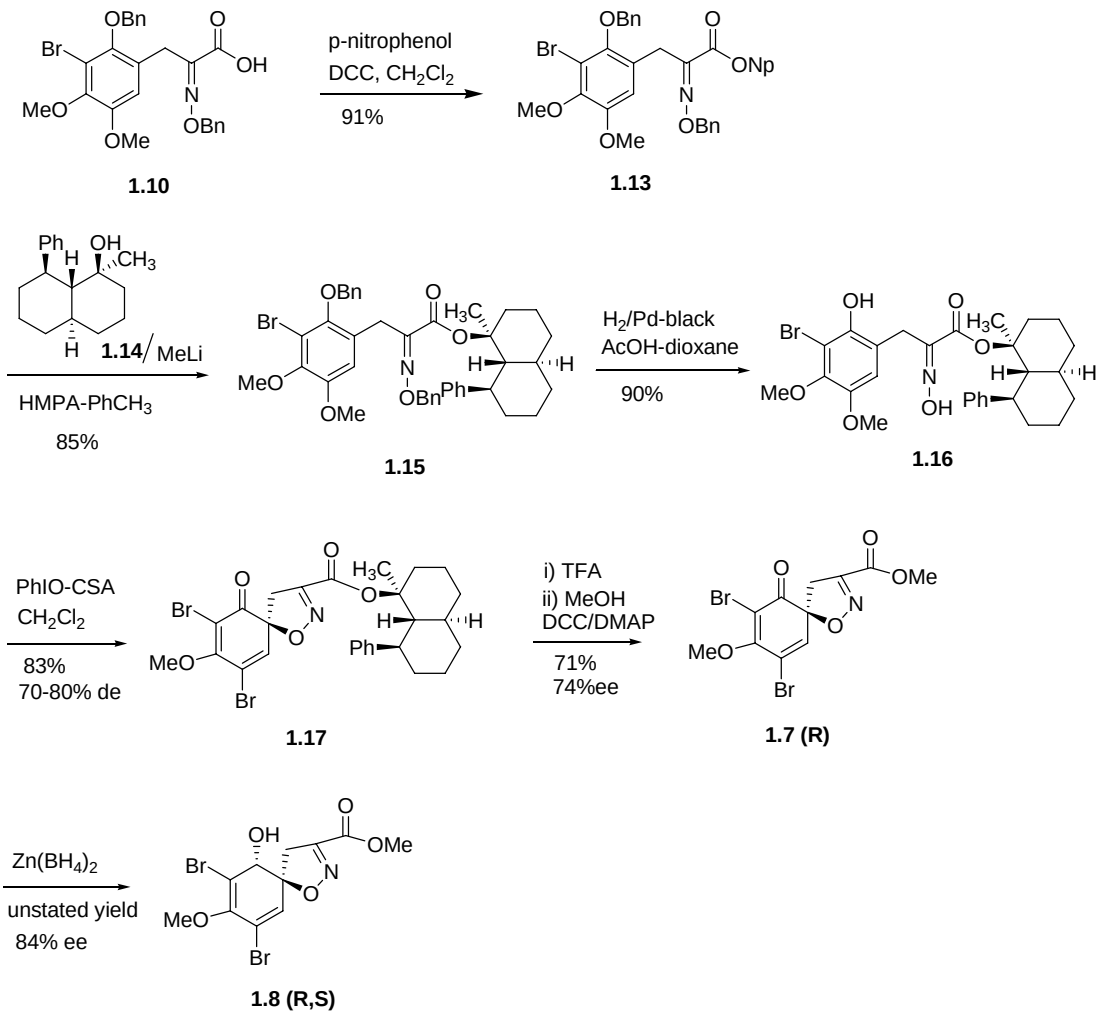
Scheme 1.2 Synthesis of spiroisoxazoline 1.7 with PhI(OAc)2 oxidation

Spilling[13] synthesized spiroisoxazoline **1.7** in a different way (Scheme 1.3). Reaction of the protected aldehyde **1.11** with methyl 2-(*tert*-butyldimethylsilyloxy)-2-(dimethylphosphono) acetate gave the silyl enol ether **1.12** in 92% yield. Deprotection of **1.12** with $Et_3N{\cdot}HF$ in MeOH followed by immediate addition of $NH_2OH{\cdot}HCl$ and Et_3N yielded dihydroxy methyl ester **1.6** in 90% yield. The methyl ester **1.6** was cyclized with NBS in DMF to give the spiroisoxazoline **1.7** in 93% yield. Manganese tris(acetylacetonate)[14] and 2,4,4,6-tetrabromocyclohexa-2,5-dienone (TBCO) [15] were also reported to oxidatively cyclize the phenolic oxime ester **1.7**.



Scheme 1.3 Spilling's approach to the synthesis of spiroisoxazoline 1.7

The fisrt asymmetric synthesis of a spiroisoxazoline ester was achieved by Hoshino and coworkers (Scheme 1.4).[16] Treatment of dibenzyloxime **1.10** with *p*-nitrophenol afforded a *p*-nitrophenyl ester **1.13** in 91% yield, and transesterification of ester **1.13** with lithiated chiral alchohol **1.14** produced 1-methyl-1-decalyl ester **1.15** in 85% yield. Hydrogenolysis of **1.15** gave oxime ester **1.16** in 91% yield. Oxidation of oxime ester **1.16** with PhIO in the presence of CSA at –78 °C afforded spirosioxazoline **1.17** in 83% yield and 70-80% de. The de was estimated on the basis of the resolved methylene proton signals of the isoxazoline ring. Removal of the chiral auxiliary from spiroisoxazoline **1.17** followed by methylation by using DCC and MeOH gave (S) methyl ester **1.7** in 71% yield and 74% ee. The enantiomeric excess (ee) was determined by HPLC using chiral column. Finally the spiroisoxazoline methyl ester **1.7** was reduced to give the trans alcohol **1.8** according to Yamamura method[8] in unstated yield and 84% ee.



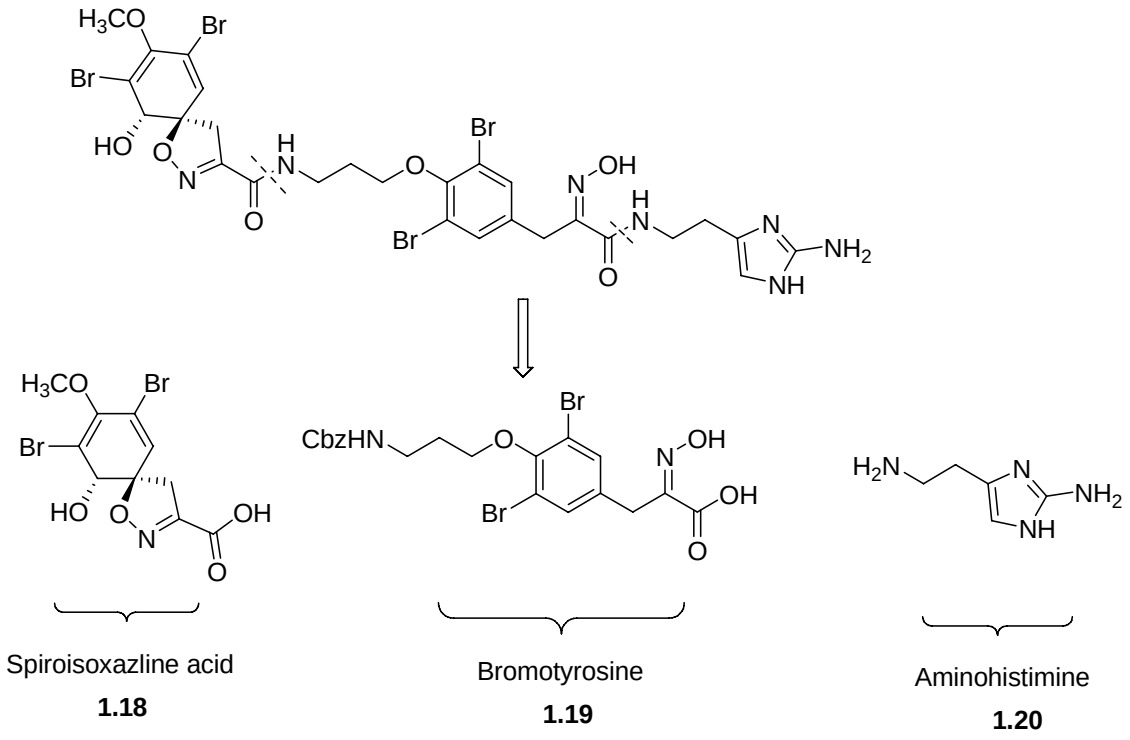
Scheme 1.4 Asymmetric synthesis of spiroisoxazoline ester 1.8

1.2 TOTAL SYNTHESIS OF PUREALIN AND PUREALILIN

1.2.1 RETROSYNTHESIS

According to retrosynthetic analysis shown in Scheme 1.5, purealin can be derived from three fragments: a left side spiroisoxazoline acid **1.18a**, a middle side bromotyrosine spacer **1.19**, a

right side aminohistamine **1.20**. The three fragments are attached to each other through amide bonds. The coupling of middle fragment-bromotyrosine spacer with right fragment-aminohistidine will afford the natural product purealidin A, which can be coupled with the right side spiroisoxazoline acid to afford purealin.

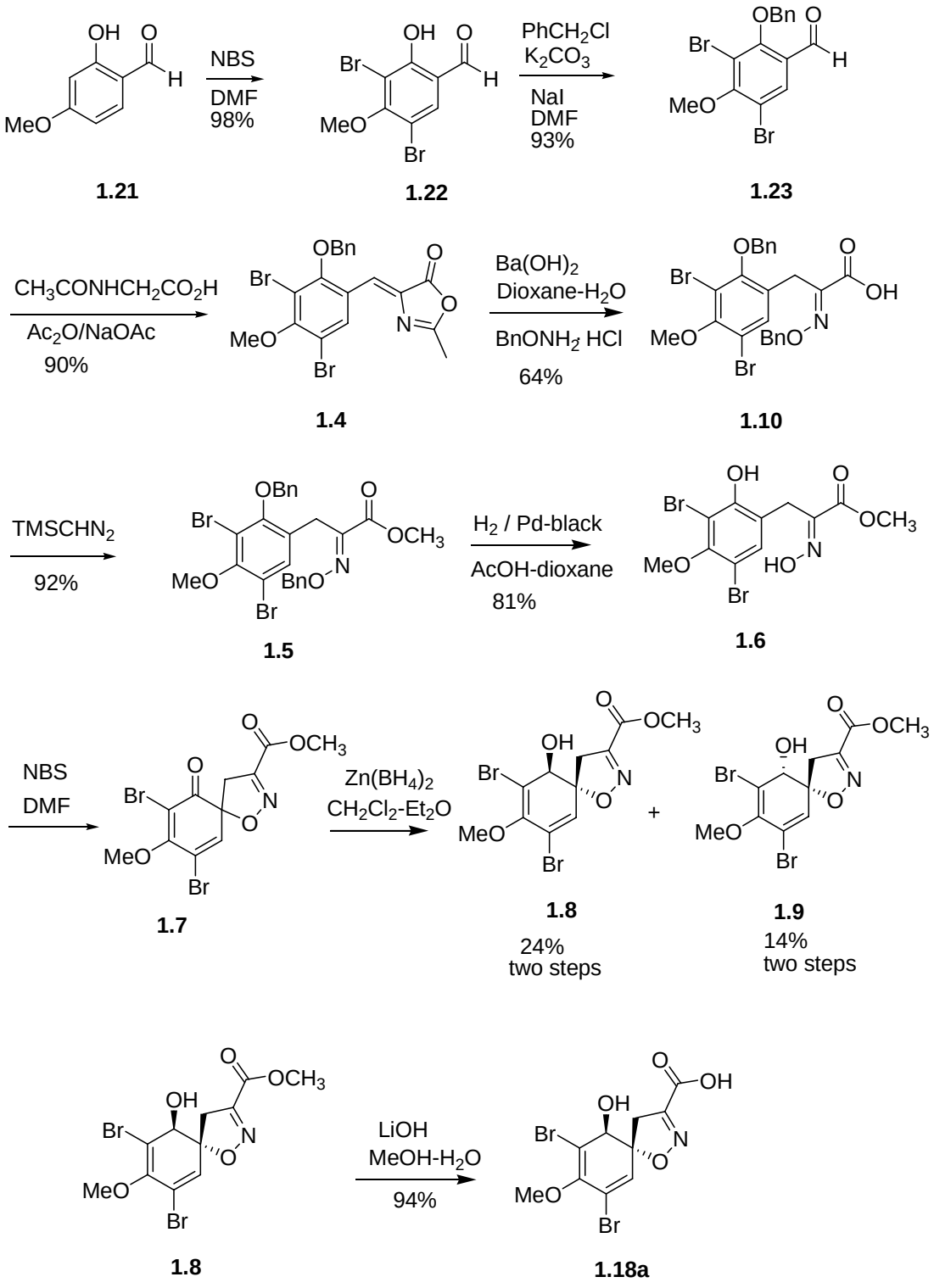


Scheme 1.5 Retrosynthesis of purealin

1.2.2 SYNTHESIS OF SPIROISOXAZOLINE ACID 1.18A

The known spiroisoxazoline methyl esters **1.8** and **1.9** were synthesized according to Hoshino (Scheme 1.6).[12] Commerically available 2-hydroxy-4-methoxybenzaldehyde **1.21** was treated with NBS in DMF to provide the dibromoaldehyde **1.22** in 98% yield. Protection of dibromophenol **1.22** in DMF with benzyl chloride followed by heating with acetylglycine in

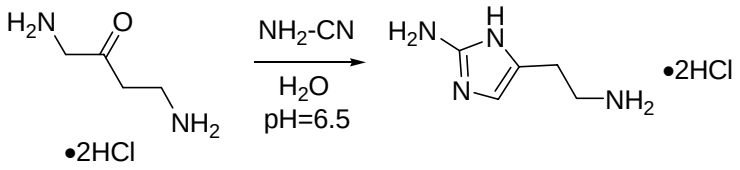
acetic anhydride provided azlactone **1.4** in 90% yield. Azlactone **1.4** was hydrolyzed with $Ba(OH)_2$ in the presence of *O*-benzylhydroxylamine to provide dibenzyl oxime-acid **1.10** in 64% yield. Dibenzyloxime acid **1.10** was treated with $TMSCHN_2$ to provide methyl ester **1.5** in 92% yield. Hydrogenolysis of **1.5** with palladium-black in acetic acid and dioxane afforded *O*-phenolic oxime-methyl ester **1.6** in 81% yield**.** Oxime-methyl ester **1.6** was cyclized with NBS in DMF to afford spirosioxazoline **1.7** in 92% yield (crude). Because spirosioxazoline **1.7** is sensitive to silica gel, it was not purified but was taken directly to the next step. Reduction of spiroisoxazoline **1.7** was carried out by using excess $Zn(BH_4)_2$ to give the corresponding trans and cis isomers (**1.8** and **1.9**) which can be separated by preparative TLC or careful column chromatography. $Zn(BH_4)_2$[17] was prepared with $ZnCl_2$ and $Na(BH_4)_2$ and used as a 0.1 N solution in ether. In these two steps, trans isomer **1.8** was obtained in 24% and cis isomer **1.9** was obtained in 14%. Characterization of isomers **1.8** and **1.9** was based on the literature.[8] Ester **1.8** was easily hydrolyzed to acid **1.18a** in the presence of lithium hydroxide in 94% yield.[18]



Scheme 1.6 Synthesis of spiroisoxazoline acid 1.18a

1.2.3 SYNTHESIS OF AMINOHISTAMINE 1.20

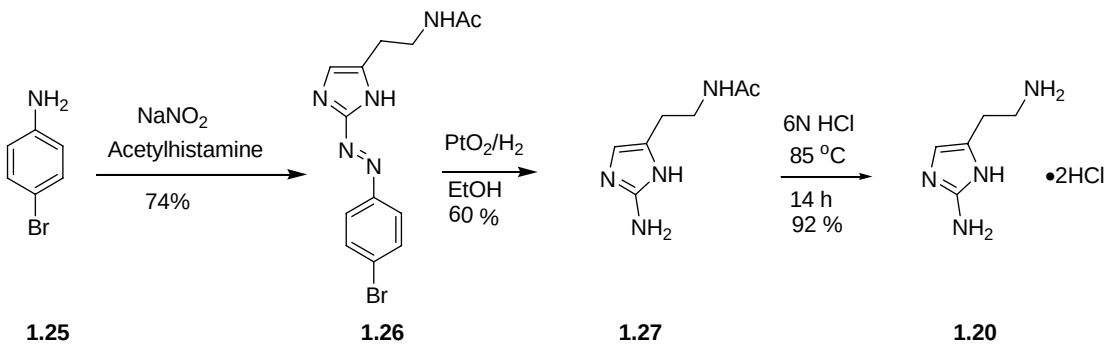
Aminohistamine **1.20** was synthesized according to a known procedure (Scheme 1.7).[19] Heating cyanamide with 1,4-diaminobutanone dihydrochloride **1.24** in aqueous solution for 2 h at pH 6.5 afforded aminohistamine dihydrochloride **1.20,** which was obtained after removing the solvent and was not further purified but was carried on to the next step. In this reaction, pH is very important. If the solution was too acidic, the reaction was incomplete, and if the reaction is too basic, some identified impurities were formed.



1.24 **1.20**

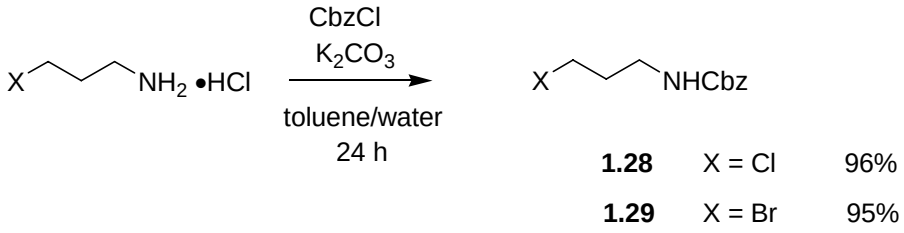
Scheme 1.7 Synthesis of aminohistamine 1.20

An alternative literature route[20] was also used to synthesize aminohistamine **1.20** (Scheme 1.8). Nω-acetylhistamine was treated with the aryldiazonium from *p*-bromoaniline **1.25** and sodium nitrite to afford the 2-arylazo derivative **1.26** in 74% yield. 4-Arylazo derivative and 2,4-diarylazo derivative were also obtained in 12% yield and in 9% yield respectively. Azo **1.26** was converted to 2-aminoimidazole **1.27** by Pd-catalyzed hydrogenolysis of compound in 60% yield. After that, the side-chain acetamido group was cleaved by treatment with 6M HCl at 85 °C in 92% yield. Aminohistamine **1.20** was purified by ion exchange column chromatography. The ^{1}H NMR spectrum of aminohistamine **1.20** from this route was identical to that of from the other route. Compared to the first approach (Scheme 1.7), this route is longer and gives lower yield.



Scheme 1.8 Synthesis of aminohistidine 1.20 from p-bromoaniline

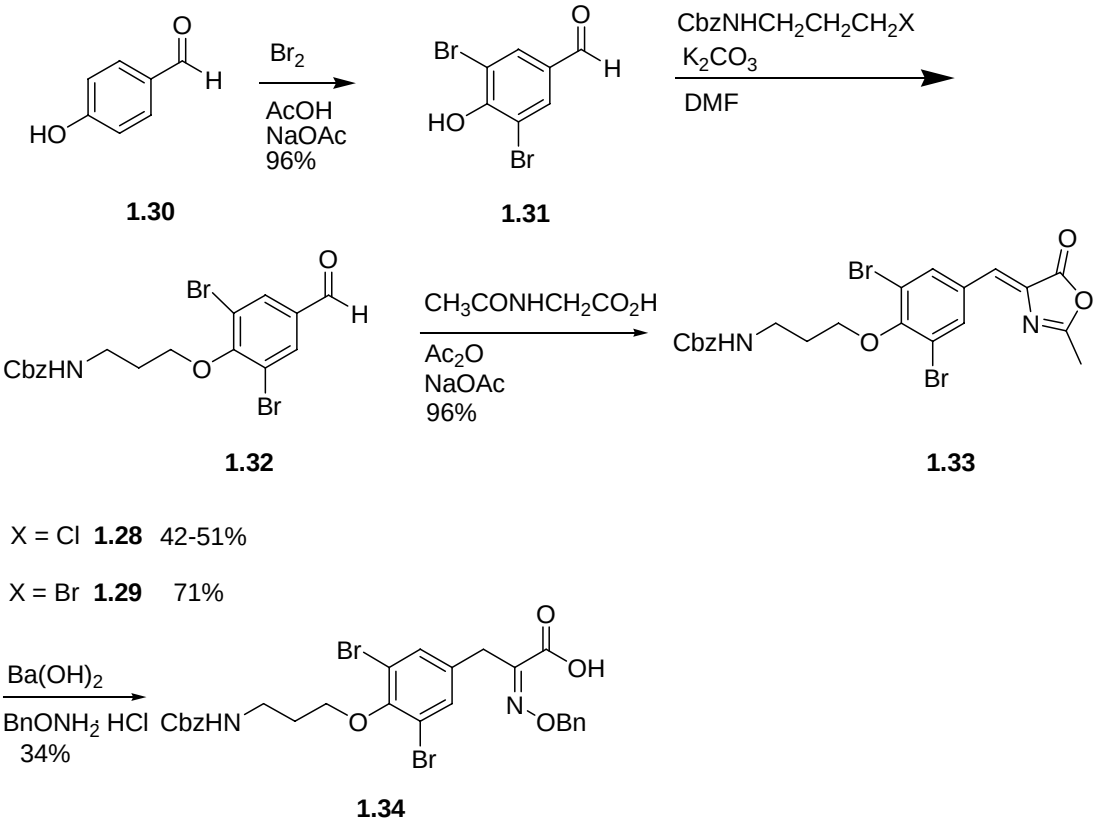
Cbz-protected halopropylamines **1.28** and **1.29** were easily synthesized from 3-chloropropylamine hydrochloride and 3-bromopropylamine hydrobromide (Scheme 1.9).[21] CbzCl was added at 0 °C, then the reaction mixture was stirred for 24 h. After the solvent was removed, **1.28** and **1.29** were obtained in 96% and 95% yields separately.



Scheme 1.9 Cbz protection of 3-halopropylamine

After right fragment–spiroisoxazoline acid **1.18a** was successfully synthesized, the middle fragment-bromotyrosine **1.19** (Scheme 1.10) was the next target. Bromination of 4-hydroxybenzaldehyde **1.30** afforded the dibromoaldehyde **1.31** in 96% yield.[22] Treatment of compound **1.31** with 3-(*N*-benzyloxycarbonylamino)propyl bromide **1.29** afforded aryl ether **1.32** in 71% yield.[23] When a mixture of aldehyde **1.32** and acetylglycine were stirred at 120 ºC in acetic anhydride for 4 h, a yellow solid was obtained after the mixture was cooled to room

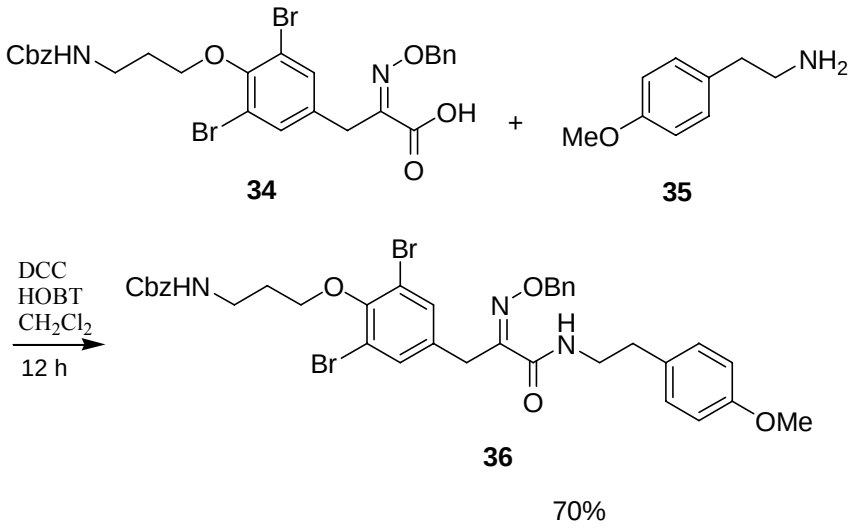
temperature. Filtration afforded azlactone **1.33** in 96% yield. Azlactone **1.33** was hydrolyzed with $Ba(OH)_2$ in the presence of *O*-benzylhydroxylamine in aqueous dioxane (water/dioxane, 1:1) to afford benzyloxime acid **1.34**, but the yield was only 34%. One of the possible reasons for the low yield is the Cbz group in acid **1.34** might remove during hydrolysis under basic conditions. The Cbz-deprotected compound might partition into the aqueous phase during extraction.



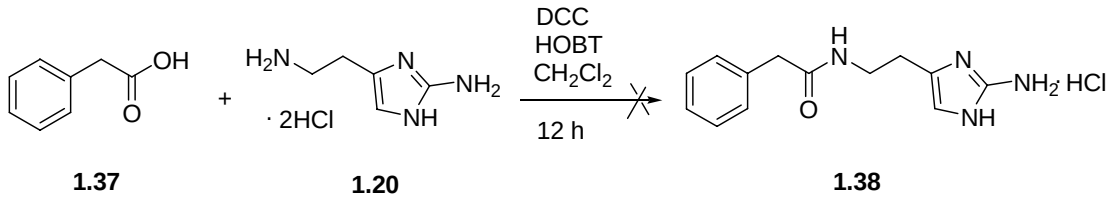
Scheme 1.10 Synthesis of O-benzyloxime acid 1.34

With the acid **1.34** in hand, the coupling reaction of **1.34** with aminohistamine **1.20** was the next target. Before the reaction was conducted, two model reactions were tested. The coupling reaction between amine **1.35** and acid **1.34** with DCC and HOBt as the coupling

reagents and dichloromethane as the solvent proceeded smoothly and the amide **1.36** was obtained in 70% yield after flash chromatography (Scheme 1.11). Amide **1.36** was characterized by ^{1}H NMR and ^{13}C NMR spectroscopic analysis. A model coupling reaction that reacted aminohistamine **1.20** with phenylacetic acid **1.37** in CH_2Cl_2 with DCC and HOBt at room temperature was also conducted (Scheme 1.12). One equiv phenylacetic acid and 2 equiv of aminohistidine were employed in that reaction. After 12 h, the acid was still there from TLC analysis. As determined from the crude ^{1}H NMR spectrum, only the acid was recovered. A variety of coupling reagents (BOP, EDCI, DMAP) and solvent systems (CH_2Cl_2, DMF, THF) were employed, but there was no evidence that amide **1.38** was obtained.

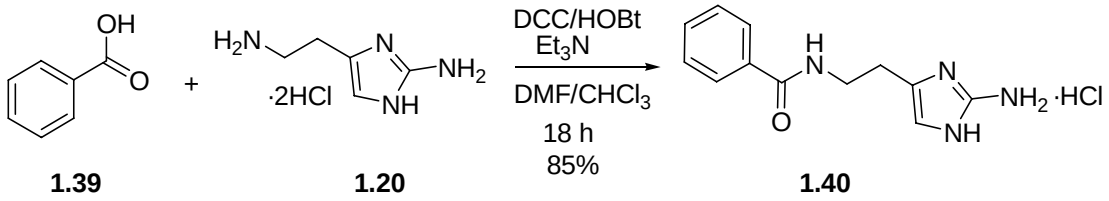


Scheme 1.11 Model coupling of phenylethylamine with O-benzyloxime acid



Scheme 1.12 Attempted coupling reaction of aminohistidine with phenylacetic acid

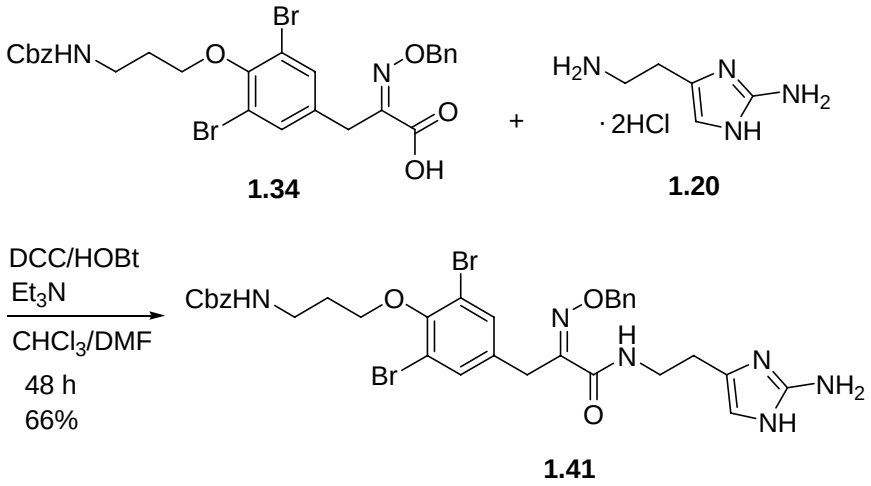
Another model coupling reaction was conducted using different workup (Scheme 1.13). A mixture of benzoyl acid **1.39** and aminohistamine **1.20** was treated with DCC and HOBt in DMF and chloroform (1:1). After 18 h at room temperature, the solvent was removed by vacuum pump. The crude product was chromatographed with methanol and dichloromethane to provide amide **1.40** mixed with HOBt. Fortunately, **1.40** was separated from HOBt by flash chromotagraphy (EtOAc/acetone/formic acid/water = 10: 2: 1: 1) and obtained in 85% yield.



1.39 **1.20** **1.40**

Scheme 1.13 Benzoyl acid coupling with aminohistamine

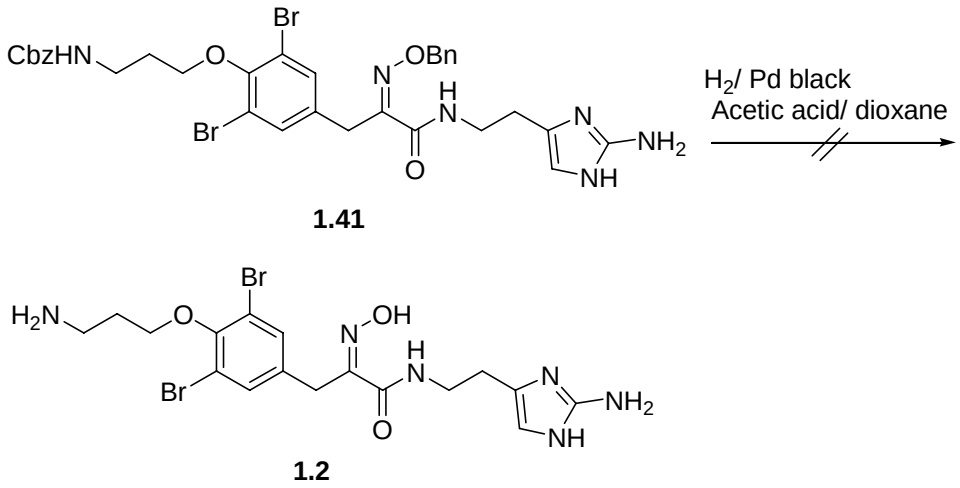
Following the successful model reaction, acid **1.34** and aminohistamine **1.20** were treated with DCC and HOBt in chloroform and DMF (1:1) at room temperature (Scheme 1.14). After 48 h, the solvent was removed by vacuum. TLC analysis with methanol and dichloromethane showed a new spot for amide **1.41** was very close to HOBt. But the crude product was easily purified by flash chromotagraphy with acetone and ethyl acetate and formic acid and water (EtOAc/Acetone/Formic acid/water = 5: 3: 0.3: 0.3) to afford amide **1.41** in 66% yield.



Scheme 1.14 Coupling reaction of aminohistamine 1.20 with acid 1.34

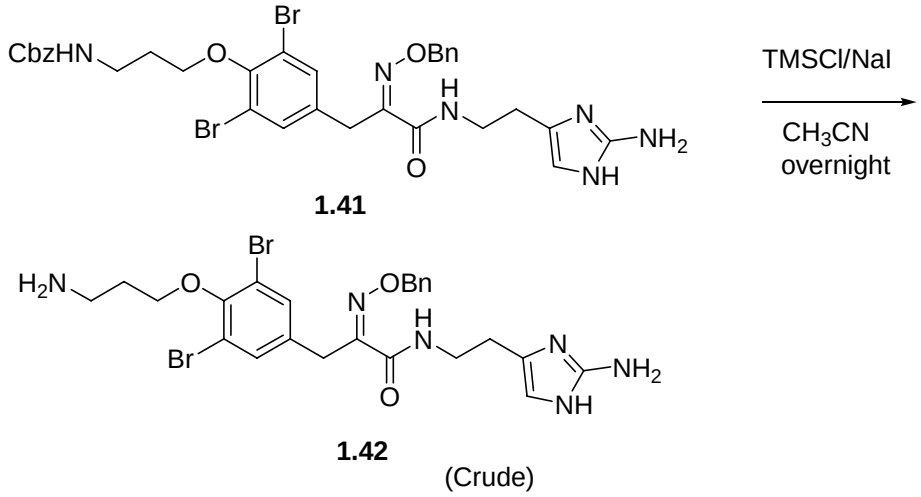
1.2.4 SYNTHESIS OF PUREALIDIN A

With amide **1.41** in hand, removal of the benzyl and Cbz protecting group is the next target. When the amide **1.41** was subjected to hydrogenation with palladium black in acetic and dioxane,[12] only the starting material was obtained (Scheme 1.15). Hydrogenation with palladium on carbon in methanol and ethanol led to a decomposition, and hydrogenation in acetic acid and dioxane returned starting material back. When hydrogenation was done in ethyl acetate, only starting material was obtained, possibly because of the insolubility of amide **1.41.**



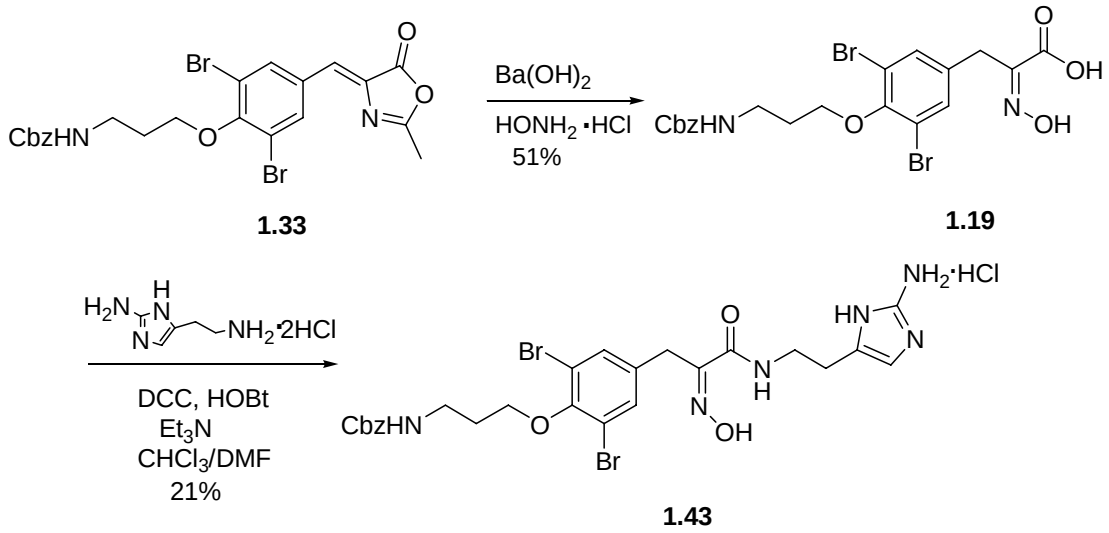
Scheme 1.15 Deprotection of benzyl and Cbz group by hydrogenation

When the amide **1.41** was treated with TMSCl/NaI,[24] the crude ^{1}H NMR and mass spectra showed that only the Cbz group was removed to give amine **1.42** (Scheme 1.16). When **1.41** was exposed to 6M HCl, at room temperature only starting material was obtained; when the mixture was refluxed in methanol, decomposition occurred.



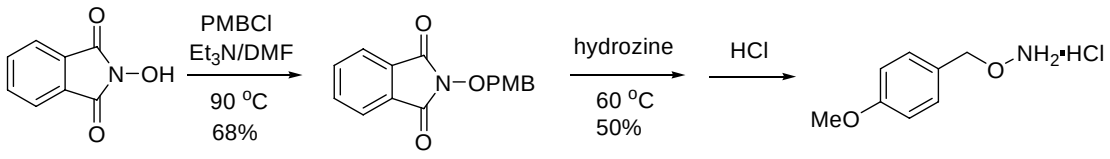
Scheme 1.16 Deprotection of benzyl and Cbz group by TMSCl/NaI

Since removal of the oxime benzyl group was difficult, the unprotected oxime acid **1.19** was then synthesized to couple with aminohistamine **1.20** (Scheme 1.17). Azlactone **1.33** was hydrolyzed in the presence of hydroxyamine under basic conditions to afford oxime-acid **1.19** in 51% yield. Acid **1.19** is poorly soluble in chloroform, and when it was subjected to coupling with aminohistamine **1.20**, amide **1.43** was obtained only in 21% yield.



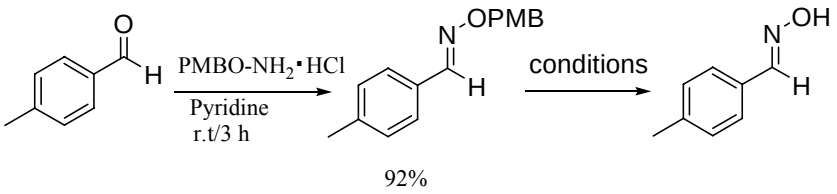
Scheme 1.17 Aminohistamine coupling with oxime-acid 1.19

The benzyl protected group was replaced with a more easily removable *p*-methoxy benzyl (PMB) group. *O*-PMBhydroxyamine **1.46** was synthesized by known procedures[25] (Scheme 1.18). *N*-Hydroxyphthalimide was treated with PMBCl in DMF at 90 °C to afford *N*-benzhydryloxyphthalimide **1.45** in 68% yield. This was hydrolyzed in the presence of hydrazine to give *O*-PMB-hydroxyamine **1.46** in 50% yield.



Scheme 1.18 Synthesis of PMB-hydroxyamine 1.46

Before the coupling reaction between acid **1.50a** and aminohistamine **1.20** was done, a model reaction was conducted (Scheme 1.19). The *O*-PMB protected benzaldoxime **1.48** was treated under a variety of conditions to remove the PMB group. When benzaldoxime **1.48** treated with TMSCl/NaI, decomposition resulted (entry 1). When DDQ was applied to this reaction, most of starting material was recovered and also some of unidentified compound was obtained (entry 3).[26] However, the PMB group on benzadoxime **1.48** was removed with $AlCl_3$ and anisole in CH_2Cl_2 in 82% yield (entry 4).[27] In acetonitrile (entry 5) the yield was less than 10%; in CH_2Cl_2 and CH_3NO_2 (1: 1) (entry 7) the yield was 79%.



92%

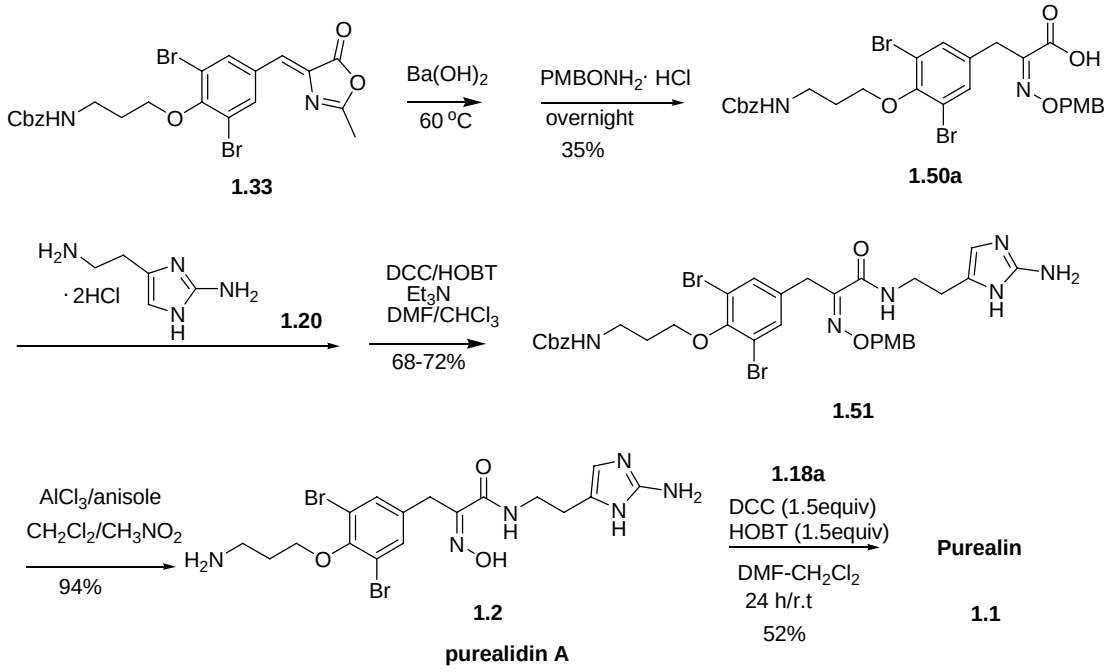
1.47 **1.48** **1.49**

Entry	conditions	yield
1	$TMSCl/NaI/CH_3CN$	Decomposition
2	$TMSCl/NaI/CH_2Cl_2$	Starting Material
3	DDQ/CH_2Cl_2-H_2O	Starting Material+Decomposition
4	**$AlCl_3$/Anisole/CH_2Cl_2/0^0C**	**82%**
5	$AlCl_3$/Anisole/CH_3CN	<10%
6	$AlCl_3$/Anisole/CH_2Cl_2-CH_3CN	Decomposition
7	**$AlCl_3$/Anisole/CH_2Cl_2-CH_3NO_2**	**79%**

Scheme 1.19 Deprotection of PMB group in model system

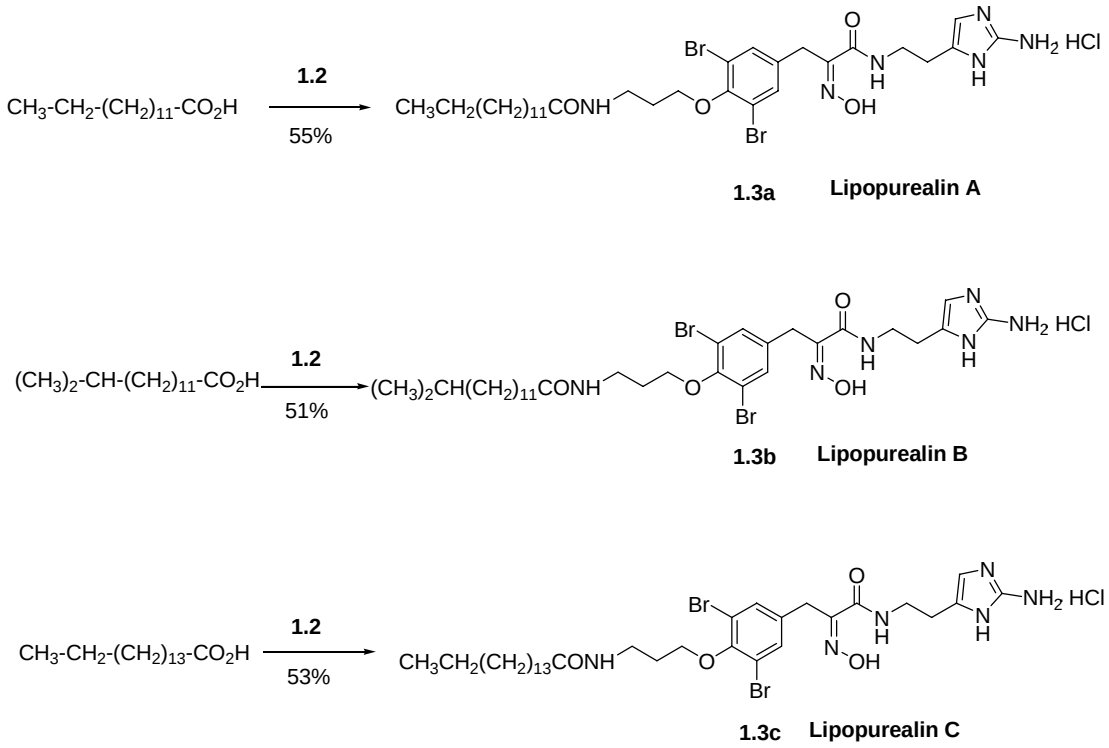
The *O*-PMB protected oxime acid **1.50** was then synthesized to react with aminohistamine **1.20**. When azlactone **1.33** was treated with *O*-PMB protected hydroxyamine under basic conditions, the *O*-PMB oxime acid **1.50a** (Scheme 1.20) was obtained in 35% yield. Acid **1.50a** was treated with aminohistamine **1.20** in the presence of DCC and HOBt to afford amide **1.51** in 68-72% yield. Finally, the PMB and Cbz groups were removed by $AlCl_3$/anisole to afford amine **1.2** in 94% yield. Amine **1.2** is the natural product purealidin A and this work gives its full synthesis for the first time. ^1H and ^{13}C NMR and mass spectra of amine **1.2** were identical to those reported for the compound isolated from its sponges.[3] Purealin was synthesized subsequently by coupling amine **1.2** with spiroisoxazoline acid **1.18a** in 52% yield. The ^1H and

^{13}C NMR and mass spectra of purealin were identical to the literature.[1] The coupling reaction of purealidin A hydrochloride salt with spiroisoxazoline acid **1.18a** in the presence of Et_3N did not give purealin. Only treatment of purealidin A (free amine) with acid **1.18a** in the absence of Et_3N afforded purealin.



Scheme 1.20 Synthesis of purealidin A and purealin

With purealidin A in hand, lipopurealins A, B, C were synthesized with DCC and HOBt as the coupling reagents (Scheme 1.21). The ^{1}H NMR spectra of these three compounds are identical to the literature.[4] The small difference between these derivatives is the side chain-fatty acids. Lipopurealin-A has myristic acid as the side chain; lipopurealin-B has methyl myristic as the side chain; lipopurealin-C has palmitic acid as the side chain.



Scheme 1.21 Synthesis of lipopurealin-A, B, C

1.3 SYNTHESIS OF PUREALILIN A ANALOGS

1.3.1 INTRODUCTION

Modern drug discovery[28] often entails the synthesis and biological testing of molecule collections, referred to as libraries, which arise from the combinations of different building blocks by the same chemical strategy.[29] Over the last decade, combinatorial library synthesis has become a very important field both in academic and industrial research.[29] Combinatorial techniques on the solid and solution-phase have significantly increased the efficiency of the drug

discovery process.[30] Importantly, combinatorial chemistry allows for the high throughput synthesis of drug candidates with broad diversity and/or complexity.[31]

Purealin (Scheme 5) consists of three segments: left segment is the spiroisoxazoline acid building blocks; middle segment is the bromophenyl oxime-acid building blocks; right segment is the aminohistidine building blocks. If we use four different left segments, four different middle segments and four different right segments are used, a 64-compound-library can be made. In the synthesis of the library, first step is coupling middle segments and right segments together. Deprotection of Cbz and PMB group followed by coupling reaction with left segment affords purealin analogs.

1.3.2 SYNTHESIS OF SPIROISOXAZOLINE ACIDS

Cis and trans isomers dibromo (**1.18a** and **1.18b**) and dichloro (**1.18c** and **1.18d**) acids were chosen as the building blocks (Figure 1.3). Synthesis of acid A_1 (**1.18a**) has been illustrated in chapter 2 (Scheme 1.6). Acids **1.18a** and **1.18b** are diastereomers. Acid **1.18a** can stay at room temperature for several weeks without obvious decomposition. Surprisingly, acid **1.18b** was found to be unstable. Hydrolysis of spiroisoxazoline ester **1.9** led to ring opening (Scheme 1.22). When ester **1.9** was treated with NaOD in an NMR tube, ^{1}H NMR analysis shows it was completely hydrolyzed to afford acid **1.18b** in 1 h; but when the solvent (in CD_3OD) was removed, acid **1.18b** changed to ring-opened acid **1.52** immediately. We found spiroisoxazoline ester **1.9** was stable in CD_3OD containing with 1% (v/v) TFA even for one week.

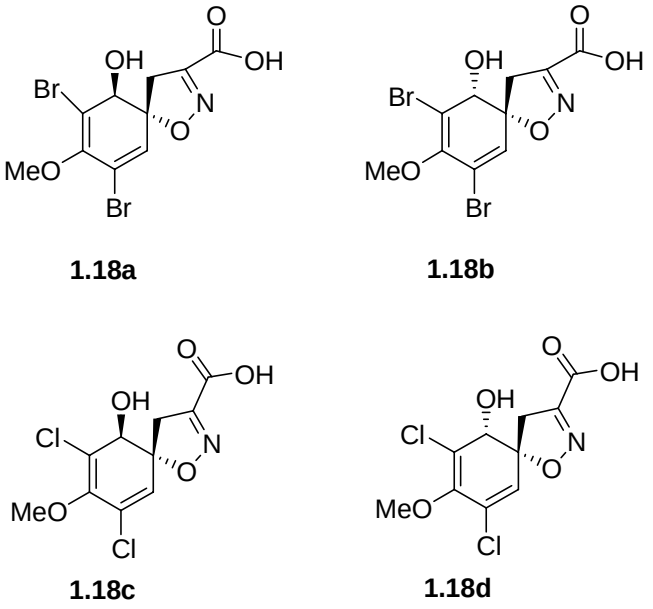
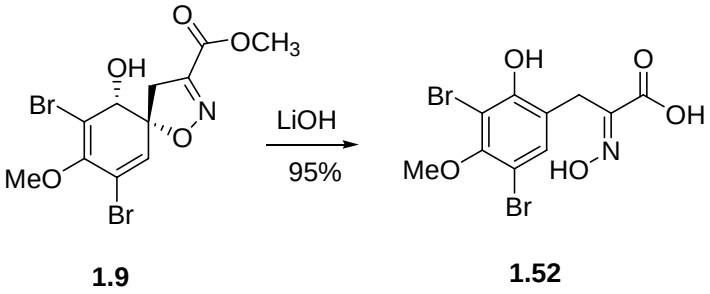


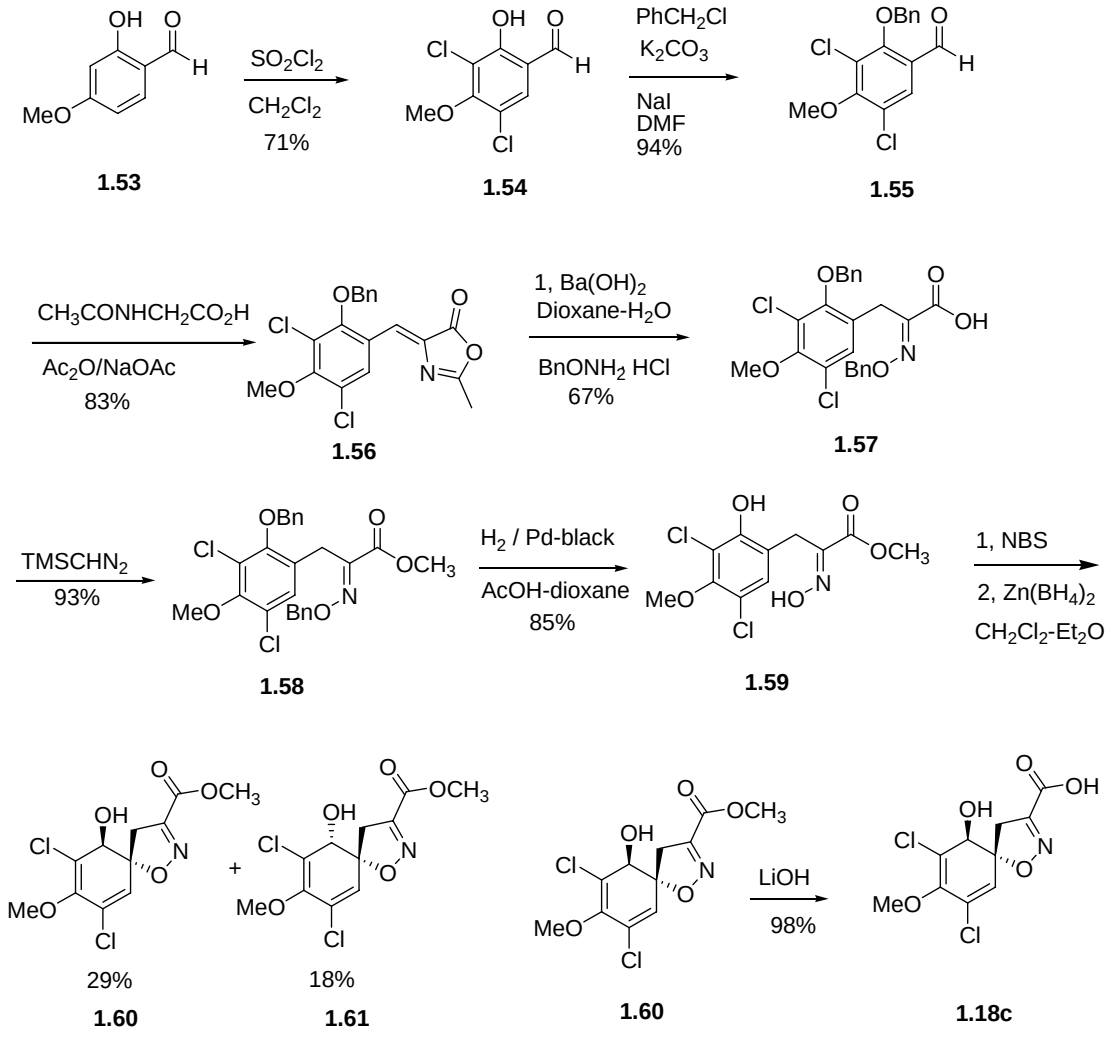
Figure 1.3. Four different spiroisoxazoline acids for library synthesis



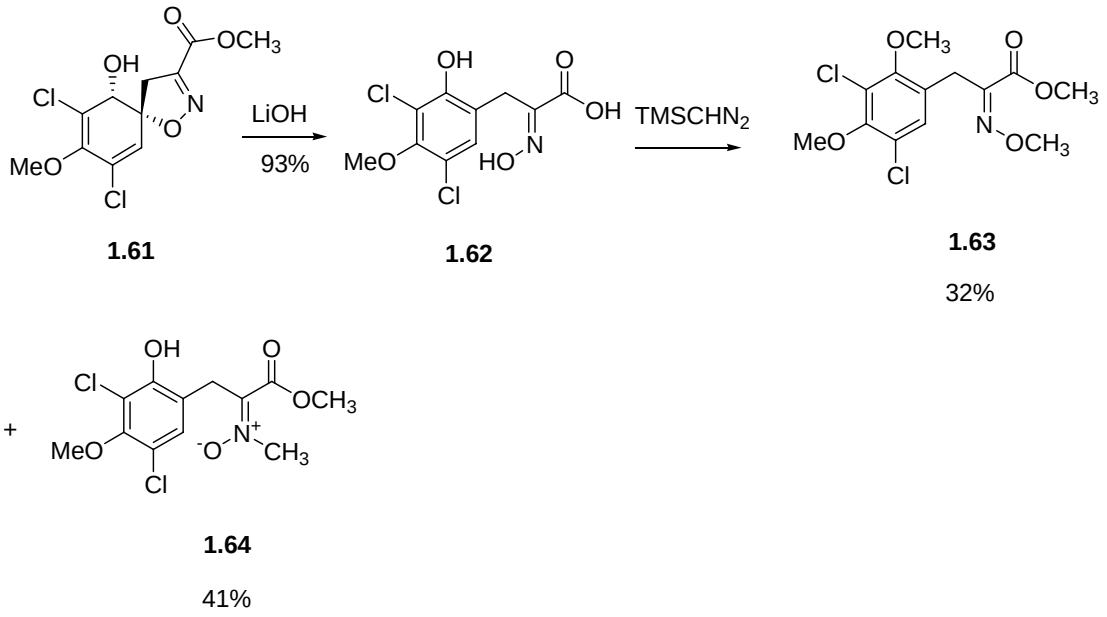
Scheme 1.22 Hydrolysis of spiroisoxaline ester

Synthesis of **1.18c** (Scheme 1.23) was the same as the synthesis of **1.18a**, except for the first step. Commercially available 2-hydroxy-4-methoxy-benzaldehyde **1.53** was treated with SO_2Cl_2 in CH_2Cl_2 under refluxing for 72 h to afford chlorolated aldehyde **1.54** in 71% yield.[32] Aldehyde **1.54** was converted as such to alcohol **1.60** and **1.61**, which were separated by flash chromatography. Hydrolysis of **1.61** gave **1.18c**. Acid **1.18d** is the diastereomer of acid **1.18c**, but just like acid **1.18b**, **1.18d** was found unstable too. Hydrolysis of spiroisoxazoline ester **1.60** did not afford the desired acid **1.18d** but the ring opening acid **1.76** (Scheme 24). Treatment of

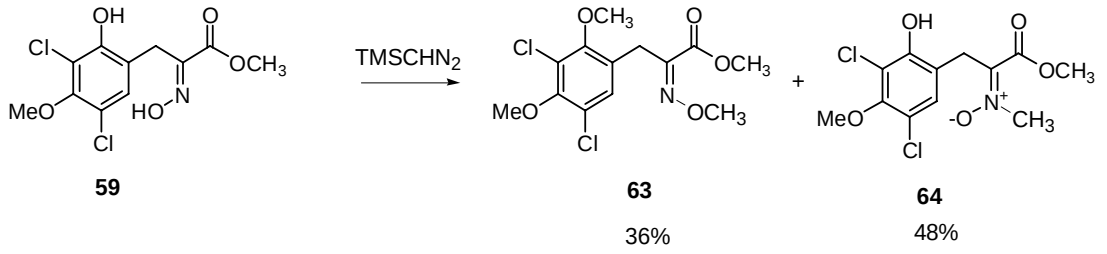
1.76 with $TMSCHN_2$ afforded two products **1.62** and **1.63** in 32% and 41% yield respectively, which have the same molecular weight, very similar ^1H and ^{13}C NMR spectra. Treatment of oxime ester **1.59** with $TMSCHN_2$ also afforded **1.63** and **1.64** in 36% and 48% yields (Scheme 1.25). From ^1H NMR, **1.63** or **1.64** has four methoxy groups, but their structures have not been determined yet. Further study is in progress.



Scheme 1.23 Synthesis of chlorospiroisoxazoline acid 18c



Scheme 1.24 Hydrolysis of spiroisoxazoline ester 1.61



Scheme 1.25 Treatment of oxime ester 1.59 with TMSCHN2

1.3.3 SYNTHESIS OF BROMOPHENYL OXIME ACIDS (1.50A, 1.50B, 1.50D)

Four different bromophenyl oxime acids were chosen as the building blocks for segment B (Figure 1.4). These are 3,5-dibromo-4-butoxyphenyl oxime acid **1.50a**; 3-bromo-4-butoxyphenyl oxime acid **1.50b**; 3,5-dibromo-2-butoxyphenyl oxime acid **1.50c** and 3, 5-dibromo-2-butoxyphenyl oxime acid **1.50d.**

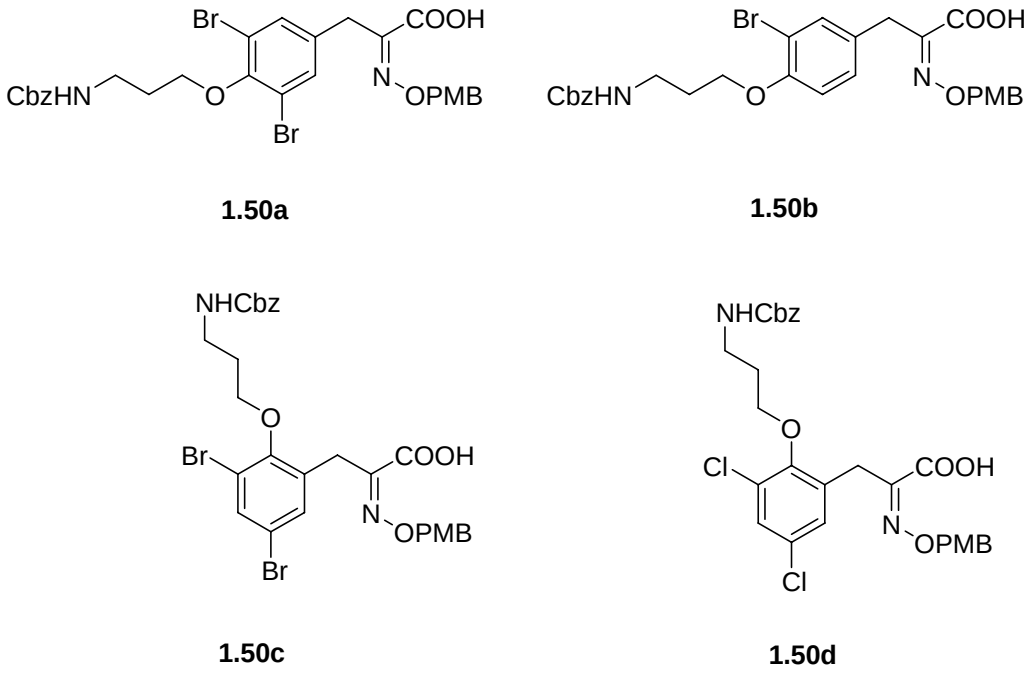
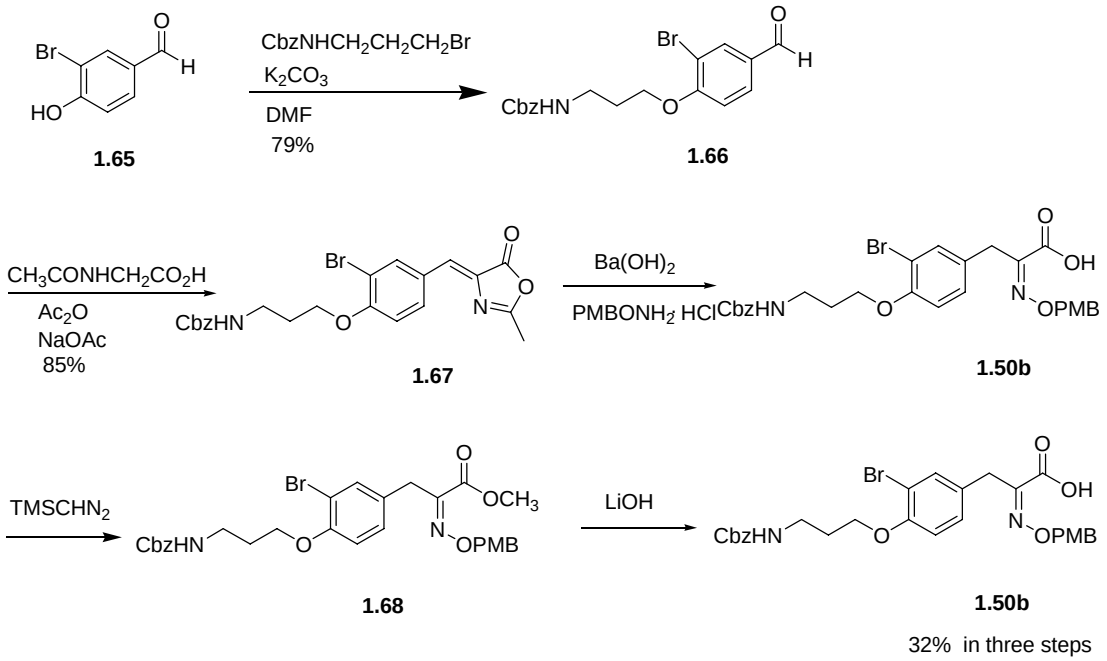


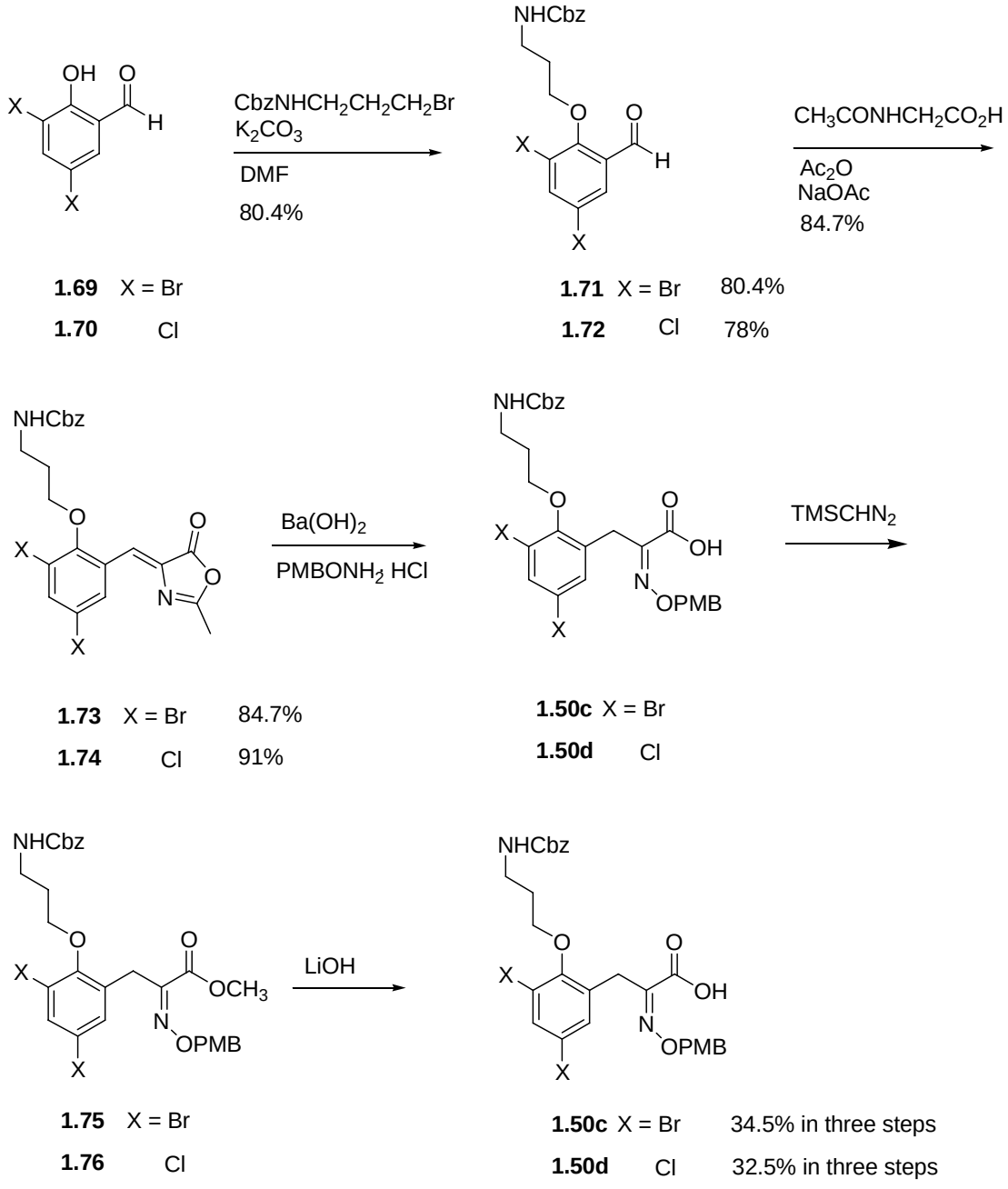
Figure 1.4. Four different bromophenyloxime acids for library synthesis

The synthesis (Scheme 1.26) of acid **1.50b** is analogous to that of acid **1.50a** (Scheme 1.20). 3-Bromo-4-hydroxybenzaldehyde **1.65** was protected by 3-(*N*-benzyloxy-carbonylamino)propyl bromide to afford phenyl ether **1.66** in 79% yield. This was treated with acetylglycine in acetic anhydride at 120 °C for 4 h to give azlactone **1.67** in 85% yield. Treatment of **1.67** with $Ba(OH)_2$ in the presence of $PMBONH_2 \cdot HCl$ provided oxime acid **1.50b**, which is an oil and was difficult to purify. Treatment of oily acid **1.50b** with $TMSCHN_2$ followed by hydrolysis with LiOH afforded acid **1.50b** as a white solid in 32% overall yield in three step.



Scheme 1.26 Synthesis of acid 1.50b

According to the same procedure, acid **1.50c** and acid **1.50d** (Scheme 1.27) were synthesized.



Scheme 1.27 Synthesis of acids 50c and 50d

1.3.4 SYNTHESIS OF PUREALIDIN A ANALOGS

The four amines (Figure 1.5) chosen to for the library synthesis are phenethylamine (**1.77a**), 2-(4-methoxyphenyl) amine (**1.77b**), 2-(4-chlorophenyl) amine (**1.77c**) and tyrosine (**1.77d**). They are all commercially available and have good solubility in dichloromethane.

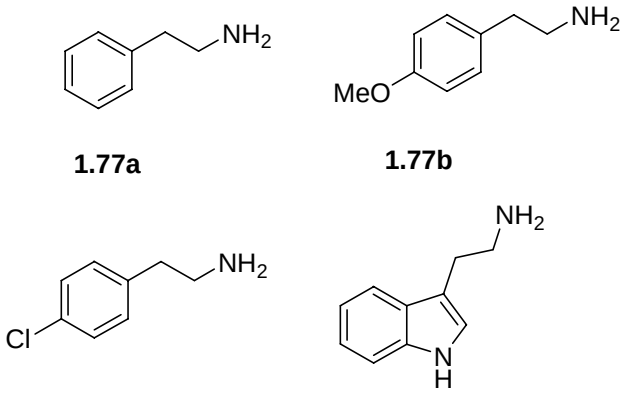
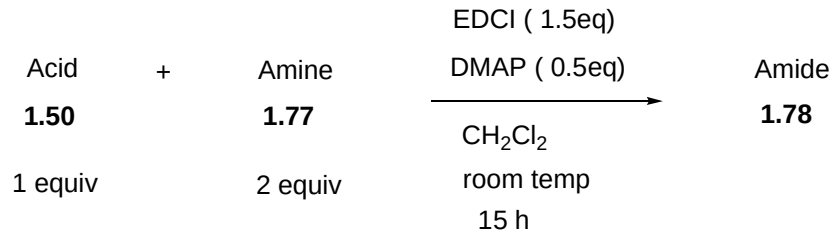


Figure 1.5. Four different amines for the library synthesis

All the 16 coupling reactions were done by the same protocol. In a typical procedure[33] (Scheme 1.28), a mixture of 1 equiv acid, 2 equiv amine, 1.5 eqiuv EDCI and 0.5 equiv DMAP was stirred in CH_2Cl_2 at room temperature for 15 h. After the reaction was finished, 80 mL ether was added. The mixture was washed with 5% HCl to remove EDCI and DMAP. HPLC analysis shows presence of a single peak of all sixteen crude amides by employing isocratic elution with CH_3CN/H_2O (70:30, 1 mL/min) and symmetry C_{18} column. Table 2 shows the yields and retention times of the 16 amides. LC-MS analysis shows that eight amides made from acid **1.77a** and **1.77b** (in the left column at table 2) exhibit not only $[M+1]^+$ peaks, but also $[M+Na]^+$, $[M+2Na]^+$, $[M+2Na+K]^+$, $[M+3Na+K]^+$; Eight amides made from acid **1.77c** and **1.77d** (in the

right column at Table 1.2) exhibit $[M+1]^+$ peaks and $[M+Na]^+$, $[M+2Na+K]^+$. The general structures of 16 amides are shown below (Figure 1.6).



Scheme 1.28 Coupling reaction of phenylethylamine with bromophenyloxime acid

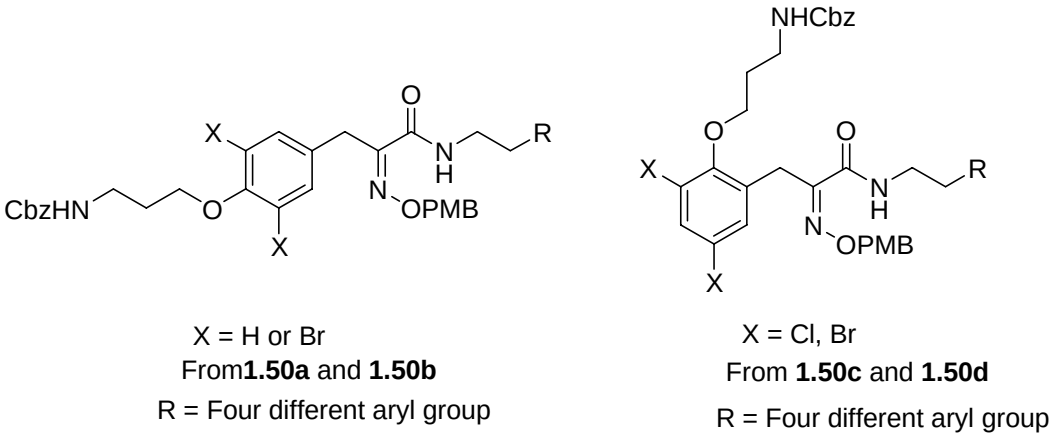


Figure 1.6. General structures of amides **1.78**

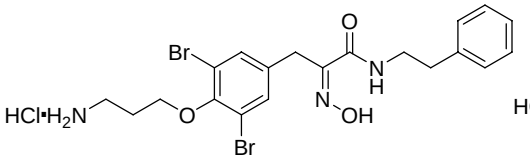
Table 1.2. Yields and retention time of 16 different amides

Amides	Yield	Retention Time (min)	Amides	Yield	Retention Time(min)
1.78 {**1.50a**, **1.77a**}	92.5%	9.8	**1.78** {**1.50c**, **1.77a**}	82%	12.8
1.78 {**1.50a**, **1.77b**}	92.8%	9.0	**1.78** {**1.50c**, **1.77b**}	90%	11.5
1.78 {**1.50a**, **1.77c**}	96%	12.6	**1.78** {**1.50c**, **1.77c**}	79%	16.8
1.78 {**1.50a**, **1.77d**}	90.5%	8.2	**1.78** {**1.50c**, **1.78d**}	81%	9.9
1.78 {**1.50b**, **1.77a**}	89%	7.0	**1.78** {**1.50d**, **1.77a**}	91%	11.2
1.78 {**1.50b**, **1.77b**}	95%	6.4	**1.78** {**1.50d**, **1.77b**}	88%	10.0
1.78 {**1.50b**, **1.77c**}	91%	8.7	**1.78** {**1.50d**, **1.77c**}	87%	14.5
1.78 {**1.50b**, **1.77d**}	88%	5.7	**1.78** {**1.50d**, **1.77d**}	86%	8.6

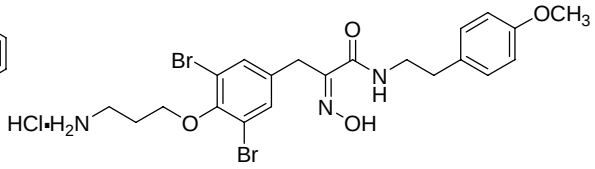
Conditions for HPLC : CH_3CN/H_2O = 70/30, 1 mL/min

Symmetry-C_{18} column was used

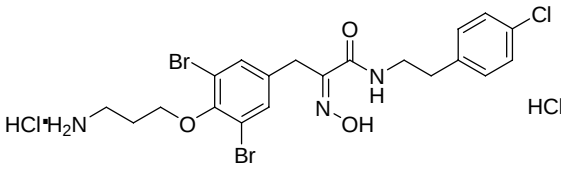
Deprotection of the PMB and Cbz groups of the 16 amides was done according to a standard procedure. A mixture of the amide (Table 1.2), $AlCl_3$ (10 equiv) and anisole (10 equiv) in CH_2Cl_2/CH_3NO_2 (1:1) was stirred at room temperature for 3 h. After the solvent was removed, the crude product was purified by flash chromatography with a eluent of ethyl acetate : acetone : formic acid : water = 10 : 6: 1: 1 to afford 16 purealidin A analogs **1.79** (Figure 1.7).



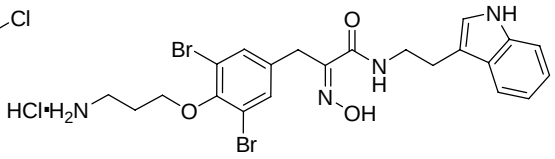
1.79 {1.50a, 1.77a}



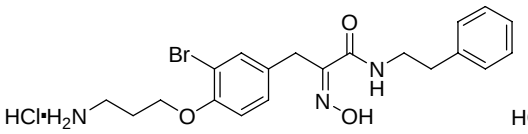
1.79 {1.50a, 1.77b}



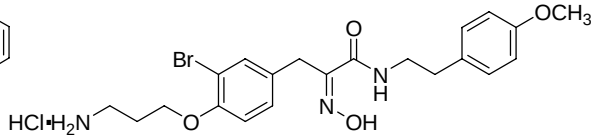
1.79 {1.50a, 1.77c}



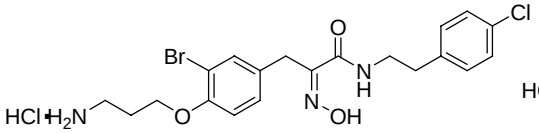
1.79 {1.50a, 1.77d}



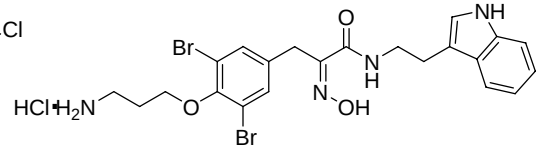
1.79 {1.50b, 1.77a}



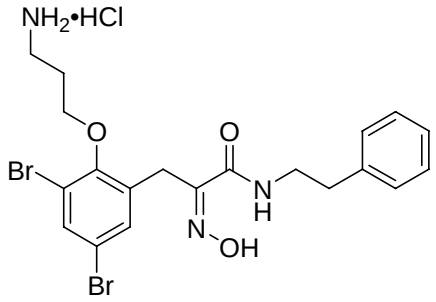
1.79 {1.50b, 1.77b}



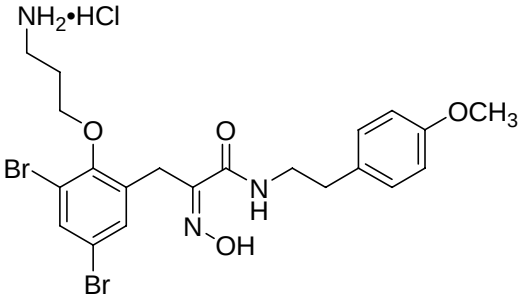
1.79 {1.50b, 1.77c}



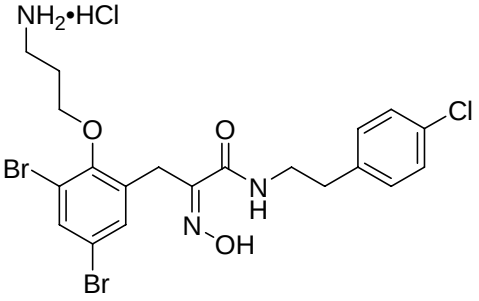
1.79 {1.50b, 1.77d}



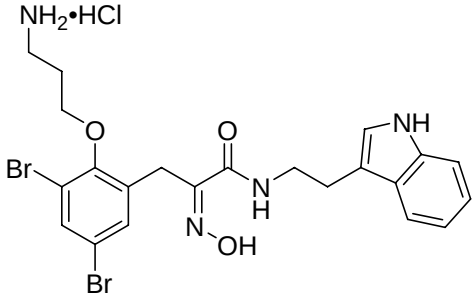
1.79 {1.50c, 1.77a}



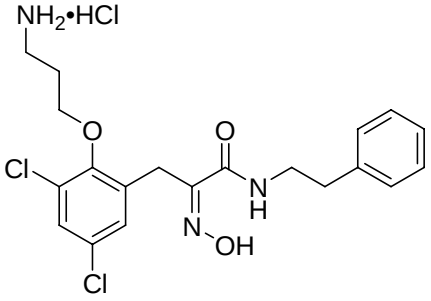
1.79 {1.50c, 1.77b}



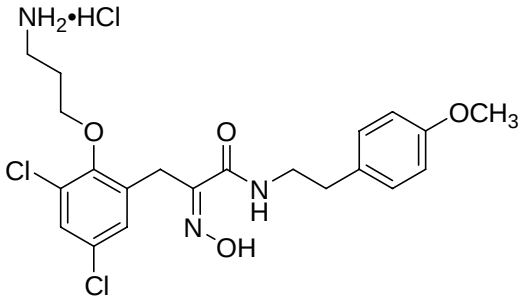
1.79 {1.50c, 1.77c}



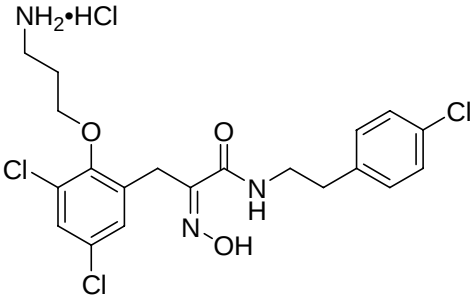
1.79 {1.50c, 1.77d}



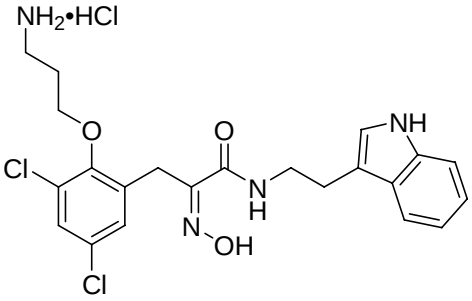
1.79 {1.50d, 1.77a}



1.79 {1.50d, 1.77b}



1.79 {1.50d, 1.77c}



1.79 {1.50d, 1.77d}

Figure 1.7. Structures of 16 analogs of purealidin A

Each library member was obtained in about 25-50 mg scale and was characterized by LC-MS. Most spectra showed the presence of a single peak, which confirmed the identity of prepared analogs of purealidin A. The yields and retention time are shown in Table 3. However, **1.79 {1.50a, 1.77d}, 1.79** {1.**50b**, **1.77d**}, library members showed more than one peak and **1.79** {**1.50d**, **1.77c**} and **1.79** {**1.50d**, **1.77d**} did not show $[M+H]^+$ or $[M+Na]^+$ peak. These four amines will be repurified again in the future. In addition, **1.79** {**1.50b**, **1.77c**}, **1.79** {**1.50a**, **1.77a**}, **1.79** {**1.50a**, **1.77c**}, **1.79** {**1.50c**, **1.77d**}, **1.79** {**1.50c**, **1.77a**} library members were characterized by ^{1}H NMR spectroscopy.

Table 1.3. Yields and retention time of 16 analogs of purealidin A

Product	Yields	Retention Time (min)	Product	Yields	Retention Time (min)
1.79 {**1.50a**, **1.77a**}	95%	7.0	**1.79** {**1.50c**, **1.77a**}	82%	15.2
1.79 {**1.50a**, **1.77b**}	92.8%	7.5	**1.79** {**1.50c**, **1.77b**}	90%	13.8
1.79 {**1.50a**, **1.77c**}	89%	13.7	**1.79** {**1.50c**, **1.77c**}	79%	2.2
1.79 {**1.50a**, **1.77d**}	50%	8.5	**1.79** {**1.50c**, **1.77d**}	87%	13.6
1.79 {**1.50b**, **1.77a**}	89%	6.0	**1.79** {**1.50d**, **1.77a**}	91%	12.4
1.79 {**1.50b**, **1.77b**}	95%	5.7	**1.79** {**1.50d**, **1.77b**}	88%	11.4
1.79 {**1.50b**, **1.77c**}	91%	9.4	**1.79** {**1.50d**, **1.77c**}	87%	2.4
1.79 {**1.50b**, **1.77d**}	87%	6.3	**1.79** {**1.50d**, **1.77d**}	64%	13.6

Conditions for HPLC: CH_3CN (0.1% TFA)/H_2O (0.1%TFA) = 65/35, Rate = 0.5ml/min, Symmetry C_{18} column was used

1.3.5 BIOLOGICAL ACTIVITIES OF PUREALIN AND RELATED COMPOUNDS

The 21 purealidins and purealin were assessed for antiproliferative activity against a small panel of human carcinoma cells [MDA-MB231 (breast), PC-3 (prostate), 2008 (ovarian)] as well as against the mouse L1210 leukemia cell line. The L1210 cells were used to compare data obtained here against that reported in the literature for purealin.[22] The 50% growth inhibitory (GI_{50}) values obtained (Table 1.4) show that although purealin **1.1** and purealidin A **1.2** were not active against the human cell lines, some of the purealidin A analogues, e.g., **1.79** {**1.50d**, **1.77c**} and **1.79** {**1.50d**, **1.77d**} showed low micromolar antiproliferative activity. The mouse leukemia cells, on the other hand, were uniformly sensitive to the individual library components.

The abilities of library components to inhibit the ATPase activity of cytoplasmic dynein heavy chain purified from bovine brain (bDyHC)[39] were examined (Table 1.5). Three compounds, purealin **1.1**, purealidin A **1.2** and the purealidin analog **1.79**{**1.50b**, **1.77c**}, gave IC_{50} values of 0.24, 10.9 and 43 μM, respectively. Although purealin **1** and purealidin A **5** were inactive as human cancer cell antiproliferative agents, their inhibition of cytoplasmic dynein ATPase activity supported the hypothesis that purealin/purealidin and analogs are good seminal leads for finding small molecules to inhibit this target.

Table 1.4. Antiproliferative activities of purealidin A analogs

Compounds	IC_{50} (μM)			
	2008	L1210	MB231	PC-3
1.79 {**1.50a**, **1.77a**}	29 ± 2	6.4 ± 2.2	27 ± 0	31 ± 3
1.79 {**1.50a**, **1.77b**}	24 ± 2	2.8 ± 2.8	17 ± 2	21 ± 5
1.79 {**1.50a**, **1.77c**}	29 ± 1	7.8 ± 2.5	27 ± 2	30 ± 4
1.79 {**1.50a**, **1.77d**}	27 ± 1	5.8 ± 1.2	24 ± 2	26 ± 9
1.79 {**1.50b**, **1.77a**}	30 ± 5	6.2 ± 0.9	>50	31 ± 6
1.79 {**1.50b**, **1.77b**}	31 ± 12	9.9 ± 6.1	48 ± 14	39 ± 4
1.79 {**1.50b**, **1.77c**}	27 ± 3	6.5 ± 2.0	26 ± 1	33 ± 4
1.79 {**1.50b**, **1.77d**}	26 ± 2	7.6 ± 1.9	25 ± 1	32 ± 6
1.79 {**1.50c**, **1.77a**}	19 ± 5	6.3 ± 0.4	5.7 ± 0.8	19 ± 6
1.79 {**1.50c**, **1.77b**}	25 ± 2	6.2 ± 0.9	8.8 ± 0.6	35 ± 15
1.79 {**1.50c**, **1.77c**}	5.6 ± 0.9	6.3 ± 0.8	5.6 ± 0.7	15 ± 7
1.79 {**1.50c**, **1.77d**}	7.5 ± 0.4	5.4 ± 0.9	6.7 ± 1.0	31 ± 6
1.79 {**1.50d**, **1.77a**}	8.8 ± 2.7	7.5 ± 0.9	7.6 ± 3.2	31 ± 7
1.79 {**1.50d**, **1.77b**}	29 ± 1	6.9 ± 0.5	24 ± 2	32 ± 11
1.79 {**1.50d**, **1.77c**}	5.4 ± 0.6	5.9 ± 0.5	5.2 ± 0.9	7.8 ± 0.9
1.79 {**1.50d**, **1.77d**}	5.7 ± 0.1	5.8 ± 1.1	5.3 ± 0.0	5.0 ± 1.1
Purealin	>50	3.2 ± 1.2	>50	>50
Purealidin A	>50	4.7 ± 1.6	>50	>50
Lipopurealin A	28 ± 3	9.0 ± 1.9	28 ± 1	30 ± 4
Lipopurealin B	29 ± 1	12 ± 4	28 ± 3	25 ± 9
Lipopurealin C	5.7 ± 1.2	9.7 ± 1.6	7.0 ± 0.4	32 ± 3

Table 1.5. Dynein activities of purealin and related compounds

Compounds	IC_{50}	Compounds	IC_{50}
1.79{**1.50a**, **1.77a**}	>50	**1.79**{**1.50c**, **1.77d**}	>50
1.79{**1.50a**, **1.77b**}	>50	**1.79**{**1.50d**, **1.77a**}	>50
1.79{**1.50a**, **1.77c**}	>50	**1.79**{**1.50d**, **1.77b**}	>50
1.79{**1.50a**, **1.77d**}	>50	**1.79**{**1.50d**, **1.77c**}	>50
1.79{**1.50b**, **1.77a**}	>50	**1.79**{**1.50d**, **1.77d**}	>50
1.79{**1.50b**, **1.77b**}	>50	**Lipopurealin A**	>50
1.79{**1.50b**, **1.77c**}	43 ± 36	**Lipopurealin B**	>50
1.79{**1.50b**, **1.77d**}	>50	**Lipopurealin C**	>50
1.79{**1.50c**, **1.77a**}	>50	**Purealin**	0.24 ± 0.06
1.79{**1.50c**, **1.77b**}	>50	**Purealidin A**	10.9 ± 5.9
1.79{**1.50c**, **1.77c**}	>50		

1.3.6 SUMMARY

This chapter described the first synthesis of purealin, lipopurealin A, B, C and purealidin A. A 16-membered library of purealidin A has also been synthesized. Biological evaluation of some of the purealidin A analogues, e.g., **1.79** {**1.50d**, **1.77c**} and **1.79** {**1.50d**, **1.77d**} showed low micromolar antiproliferative activity to all the test cell lines. The mouse leukemia cells, on the other hand, were uniformly sensitive to these compounds. As we expected, purealin **1** and purealidin A **5** showed excellent inhibition of cytoplasmic dynein ATPase activity.

1.4 EXPERIMENTAL

Procedures:

All reactions were performed under an atmosphere of argon unless the reaction solvent contained water. Reaction solvents were freshly dried either by distillation or by passing through an activated alumina column. Benzene was distilled from Na/benzophenone. Methylene chloride, THF, ether, toluene were dried by activated alumina according to Pangborn, A.; Giardello, M. A.; Grubbs, R, H.; Rosen, R. K.; Timmers, F.; *J. Organometallics*, **1996**, *15*, 1518.

^{1}H and ^{13}C NMR spectra were taken on Bruker models Avance DPX 300 (300MHz) and Avance 300 (300 MHz) spectrometers. Chemical shifts are reported in parts per million (ppm) downfield relative to TMS using the residual solvent proton resonance of $CDCl_3$ (7.27 ppm) or central $CDCl_3$ carbon peak (77.0 ppm) as the internal standard. In reporting spectral data, the following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintuplet, m = multiplet, dd = doublet doublet, dt = doublet triplet.

Infrared spectra were taken on a Mattson Genesis Series FTIR using thin film on NaCl plate or in KBr pellets. Peaks are reported in wavenumbers (cm^{-1}). High resolution mass spectra were obtained on a V/G 70/70 double focusing machine and were reported in units of *m/z*.

Compounds **1.4**[9b], **1.5**[12], **1.6**[12], **1.7**[12], **1.8**[12], **1.9**[12], **1.10**[12], **1.20**[19, 20], **1.22**[9b], **1.23**[9b], **1.26**[20, 22], **1.27**[20, 22], **1.28**[21], **1.29**[21], **1.31**[22], **1.45**[25], **1.46**[25], **1.49**[35], **1.54**[33] have been reported before.

Purealin (1.1)

A mixture of acid **1.18a** (11.5 mg, 0.03 mmol), purealidin A **1.2** (22 mg, 0.04 mmol, free amine), DCC (9.3 mg, 0.045 mmol), HOBt (6.1 mg, 0.045 mmol) in CH_2Cl_2 (3 mL) and DMF (3 mL) was stirred at room temperature for 20 h. After solvent was removed under reduced pressure, the crude product was purified by flash chromatography (EtOAc/Acetone/Formic acid/water = 5: 3: 0.3: 0.3). After the flash column chromatography, the product was dissolved in methanol and acidified with 0.5 N HCl. Solvents were removed to afford **1.1** as a pale yellow solid (14 mg, 54%): mp 139-141 ºC; IR (KBr, cm^{-1}) 3450 (broad), 1655, 1541; ^1H NMR (300 MHz, CD_3OD): δ 7.47 (s, 2H), 6.51 (s,1H), 6.42 (d, *J* = 0.6 Hz, 1H), 4.08 (d, *J* = 0.6 Hz, 1H), 4.04 (t, *J* = 6.0 Hz, 2H), 3.83 (s, 2H), 3.78 (d, *J* = 18.3 Hz, 1H), 3.72 (s, 3H), 3.58 (t, *J* = 6.9 Hz, 2H), 3.46 (t, *J* = 6.9 Hz, 2H), 3.09 (t, *J* = 18.3 Hz, 1H), 2.70 (t, *J* = 6.9 Hz, 2H), 2.10 (quin, *J* = 6.6 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.12, 158.90, 154.46, 150.78, 150.75, 147.07, 146.79, 136.19, 132.82, 131.24, 124.13, 120.72, 117.21, 113.06, 109.04, 90.15, 73.49, 71.23, 59.56, 37.28, 36.16, 29.34, 27.84, 24.3; MS (ESI) *m/z* $[M + H]^+$, 880 (6), 882 (16), 884 (17), 886 (13), 888 (5); HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{29}Br_4N_7O_7$ 879.8884, found 879.8935. HPLC analysis: 8:17, t_R = 19.9 min, 98% purity.

Purealidin A (1.2)

A mixture of amide **1.51** (130 mg, 0.168 mmol)**,** $AlCl_3$ (335 mg, 2.52 mmol) and anisole (272 mg, 2.52 mmol) in CH_3NO_2 (6 mL) and CH_2Cl_2 (6 mL) was stirred for 4 h at room temperature, then water was added. The solvents were removed under reduced pressure and the crude product was subjected to column chromatography (CH_2Cl_2: CH_3OH = 2: 1) to provide **1.2** as a pale yellow solid (84 mg, 94%): IR (KBr, cm^{-1}) 3387(broad), 1679, 1661, 1529, 1458; ^1H

NMR (300 MHz, DMSO-d_6) δ 12.11 (s, 1H), 12.09 (s, 1H), 8.18 (brs, 1H), 7.45 (s, 2H), 7.36 (s, 2H), 6.56 (s, 1H), 3.99 (t, *J* = 6.6 Hz, 2H), 3.75 (s, 2H), 3.04-3.01 (m, 2H), 2.60 (t, *J* = 6.6 Hz, 2H), 2.09 (quin, *J* = 6.6 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.12, 150.81, 150.50, 146.78, 136.39, 132.85, 124.21, 117.20, 109.10, 70.48, 37.28, 36.28, 27.87, 27.65, 24.34; MS (ESI) *m/z* $[M+H]^+$, 517 (14), 519 (25), 462 (8), 280 (8), 260 (100); HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{22}Br_2N_6O_3$ 517.0174, found 517.0198. HPLC: C_{18}, 91%, 3:17 CH_3CN(0.1% TFA)/H_2O(0.1% TFA), t_R = 11.5 min.

Lipopurealin A (1.3a)

A mixture of methyl myristic acid (9.7 mg, 0.04 mmol), purealidin A **1.2** (21 mg, 0.05 mmol), DCC (12.5 mg, 0.08 mmol), HOBt (8.1 mg, 0.08 mmol) and Et_3N (0.1 mL) in CH_2Cl_2 (3 mL) and DMF (3 mL) was stirred at room temperature for 20 h. After solvent was removed under reduced pressure, the crude product was purified by flash chromatography (EtOAc/Acetone/Formic acid/water = 5: 3: 0.3: 0.3). The product was dissolved in methanol and acidified with 0.5 N HCl. The solvents were removed to afford **1.3a** as a pale yellow solid (15 mg, 52%): mp 93-95 ºC; IR (KBr, cm^{-1}) 3310 (broad), 2922, 2851, 1677, 1541, 1456; ^{1}H NMR (300 MHz, CD_3OD) δ 7.47 (s, 2H), 6.51 (s, 1H), 4.01 (t, *J* = 6.2 Hz, 2H), 3.83 (s, 2H), 3.47 (t, *J* = 7.0 Hz, 2H), 3.45 (t, *J* = 7.1 Hz, 2H), 2.70 (t, *J* = 6.9 Hz, 2H), 2.20 (t, *J* = 7.4 Hz, 2H), 2.04 (quin, *J* = 6.6 Hz, 2H), 1.61 (quin, *J* = 6.9 Hz, 2H), 1.28 (brs, 20H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 176.49, 165.64, 152.91, 152.11, 148.65, 137.36, 134.52, 126.15, 118.77, 110.78, 72.39, 38.97, 37.80, 37.20, 33.06, 30.91, 30.83, 30.73, 30.68, 30.59, 30.52, 30.44, 30.42, 30.28, 28.84, 27.08, 25.85, 23.71, 14.41; MS (ESI) *m/z* $[M+H]^+$, 727 (50), 729

(100), 472 (5), 365 (5), 239 (18); HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{31}H_{49}Br_2N_6O_4$ 727.2151, found 727.2182. HPLC: 93%, C_{18}, 3:2 CH_3CN(0.1% TFA)/H_2O(0.1% TFA), t_R = 31.1 min.

Lipopurealin B (1.3b)

According to the similar procedure as **1.3a**, **1.3b** was obtained as a pale yellow solid (12 mg, 53%): mp 91-93 ºC; IR (KBr, cm^{-1}) 3416 (broad), 2924, 1674, 1642, 1543, 1457; ^1H NMR (300 MHz, CD_3OD) δ 7.47 (s, 2H), 6.51 (s,1H),4.01 (t, *J* = 6.2 Hz, 2H), 3.83 (s, 2H), 3.47 (t, *J* = 6.9 Hz, 2H), 3.44 (t, *J* = 6.9 Hz, 2H), 2.70 (t, *J* = 6.8 Hz, 2H), 2.20 (t, *J* = 7.2 Hz, 2H), 2.04 (quin, *J* = 6.6 Hz, 2H), 1.61 (quin, *J* = 6.9 Hz, 2H), 1.54-1.49 (m, 1H), 1.28 (brs, 16H), 1.19-1.15 (m, 2H), 0.87 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 176.43, 165.63, 152.90, 152.10, 148.64, 137.34, 134.50, 126.14, 118.76, 110.77, 72.39, 40.24, 38.96, 37.87, 37.74, 37.23, 31.01, 30.91, 30.76, 30.71, 30.66, 30.57, 30.40, 30.27, 29.17, 29.13, 28.84, 28.49, 27.06, 25.83, 23.03; MS (ESI) *m/z* $[M+H]^+$, 741 (46), 743 (100), 472 (5), 239 (40). HPLC: 92%, C_{18}, 3:2 CH_3CN (0.1% TFA) /H_2O(0.1% TFA), t_R = 17.9 min.

Lipopurealin C (1.3c)

According to the similar procedure as **1.3a**, **1.3c** was obtained as a pale yellow solid (16 mg, 55%): mp 104-105 ºC; IR (KBr, cm^{-1}) 3310 (broad), 2916, 2849, 1679, 1642, 1543, 1457; ^1H NMR (300 MHz, CD_3OD) δ 7.47 (s, 2H), 6.51 (s, 1H),4.01 (t, *J* = 6.2 Hz, 2H), 3.83 (s, 2H), 3.47 (t, *J* = 7.0Hz, 2H), 3.44 (t, *J* = 7.0 Hz, 2H), 2.70 (t, *J* = 6.9 Hz, 2H), 2.19 (t, *J* = 7.4 Hz, 2H), 2.04 (quin, *J* = 6.6 Hz, 2H), 1.61 (quin, *J* = 6.7 Hz, 2H), 1.28 (brs, 24H), 0.90 (t, *J* = 6.9Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 176.49, 165.64, 152.91, 152.11, 148.65, 137.36, 134.52, 126.15, 118.77, 110.78, 72.39, 38.97, 37.80, 37.20, 33.06, 30.91, 30.83, 30.73, 30.68, 30.59, 30.52,

30.44, 30.42, 30.28, 28.84, 27.08, 25.85, 23.71, 14.41; MS (ESI) *m/z* $[M+H]^+$ 755 (16), 757 (32), 379 (3), 239 (100); HRMS (ESI) *m/z* calcd for $C_{33}H_{53}Br_2N_6O_4$ 755.2525, found 755.2495. HPLC: 95%, C_{18}, 3:2 CH_3CN(0.1% TFA)/H_2O(0.1% TFA), t_R = 12.2 min.

4-(2-Benzyloxy-3,5-dibromo-4-methoxybenzylidene)-2-methyl-4H-oxazol-5-one (1.4)

A mixture of aldehyde **1.23** (12 g, 30 mmol) and sodium acetate (2.46 g, 30 mmol) and *N*-acetylglycine (3.51 g, 30 mmol) in Ac_2O (60 mL) was stirred at 120 °C for 4 h. A yellow solid precipitated after the reaction mixture was cooled to room temperature. After filtration, the solid was washed with cold pentane and ethyl ether (1:1) to yield **1.4** (12.8 g, 89%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.84 (s, 1H), 7.38-7.32 (m, 5H), 7.24 (s, 1H), 4.99 (s, 2H), 3.95 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.06, 166.88, 157.14, 156.43, 135.16, 134.74, 133.34, 128.96, 128.74, 126.34, 122.86, 114.76, 113.88, 77.21, 60.85, 15.69.

3-(2-Benzyloxy-3,5-dibromo-4-methoxyphenyl)-2-benzyloxyiminopropionicacidmethylester (1.5)

$TMSCHN_2$ (12 mL, 2.0 N in hexane) was added to a solution of acid **1.10** (9.0 g, 16 mmol) in benzene (120 mL) and absolute methanol (40 mL) at 0 °C. The reaction mixture was stirred for 45 min at room temperature. 5% HCl (10 mL) was added at 0 °C. A yellow solid precipitated after most of organic solvents were removed. After filtration, the solid was washed with cold pentane and ethyl ether (1:1) to yield **1.5** (8.03 g, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49-7.46 (m, 2H), 7.39-7.29 (m, 6H), 7.21-7.17 (m, 2H), 7.19 (s, 1H), 5.23 (s, 2H), 4.93 (s, 2H), 3.89 (s, 2H), 3.86 (s, 3H), 3.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.64, 154.16, 153.82,

149.89, 136.51, 135.95, 132.00, 128.60, 128.51, 128.37, 128.37, 128.24, 128.13, 127.88, 114.47, 112.73, 77.98, 74.40, 60.58, 52.83, 26.38.

3-(3,5-Dibromo-2-hydroxy-4-methoxyphenyl)-2-hydroxyiminopropionic acid methyl ester (1.6)

A solution of benzyl ester **1.5** (7.4 g, 12.8 mmol) in AcOH (90 mL) and dioxane (90 mL) was hydrogenated over Pd-black (1.21 g) under H_2 (1 atm) at room temperature for 24 h. After filtration, the solvent was removed under reduced pressure. Then EtOAc (200 mL) was added. The solution was washed with water and dried over $MgSO_4$. The crude product was purified by column chromatography (hexane/EtOAc = 2: 1) to afford **1.6** (4.19 g, 82%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (s, 1H), 3.94 (s, 2H), 3.91 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.47, 153.73, 151.50, 149.87, 133.37, 119.36, 107.63, 60.55, 53.49, 25.50.

7,9-Dibromo-8-methoxy-10-oxo-1-oxa-2-aza-spiro[4.5]deca-2,6,8-triene-3-carboxylicacid methyl ester (1.7)

A mixture of NBS (940 mg, 5.29 mmol) and *O*-phenolic oxime acid derivative **1.6** (1.40 g, 3.53 mmol) in DMF (15 mL) was stirred at room temperature for 3 h. After addition of ethyl ether (200 mL), the solution was washed successively with water, 5% NaS_2O_3 and water and dried over $MgSO_4$. The solvent was removed under reduced pressure, spiroisoxazoline **1.7** (1.29 g, 92%) was obtained as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 (s, 1H), 4.18 (s, 3H), 3.91 (s, 3H), 3.61 (d, J = 18 Hz, 1H), 3.30 (d, J = 18 Hz, 1H).

7,9-Dibromo-10-hydroxy-8-methoxy-1-oxa-2-azaspiro[4.5]deca-2,6,8-triene-3-carboxylic acid methyl ester (1.8)

$Zn(BH_4)_2$ (0.1 N solution in ethyl ether, 35 mL) was added to a solution of crude spiroisoxazoline **1.7** (1.1 g, 2.78 mmol) in CH_2Cl_2 (35 mL) at 0 °C in 10 min. The reaction mixture was stirred for another 5 min at room temperature. After addition of saturated aq NH_4Cl, the mixture was extracted with ethyl ether (3×100 mL). The extracts were washed with water and dried over $MgSO_4$. The crude product was purified by column chromatography (hexane/EtOAc = 2: 1) to afford **1.8** (290 mg, 26.3%) and **9** as pale yellow solids (170 mg, 15.5%): ^{1}H NMR (300 MHz, acetone-d_6) δ 6.53 (s, 1H), 5.42 (d, *J* = 8.1 Hz, 1H), 4.21 (d, *J* = 8.1 Hz, 1H), 3.84 (d, *J* = 18.0 Hz, 1H), 3.83 (s, 3H), 3.72 (s, 3H), 3.20 (d, *J* = 18.0 Hz, 1H), 2.83 (s, 1H); ^{13}C NMR (75 MHz, acetone-d_6) δ 161.16, 152.52, 148.84, 132.17, 122.21, 113.83, 92.50, 75.22, 60.24, 52.80, 39.95.

7,9-Dibromo-10-hydroxy-8-methoxy-1-oxa-2-azaspiro[4.5]deca-2,6,8-triene-3-carboxylic acid methyl ester (1.9)

^{1}H NMR (300 MHz, acetone-d_6) δ 6.31 (s, 1H), 5.07 (brs, 1H), 4.55 (brs, 1H), 3.82 (s, 3H), 3.73 (s, 3H), 3.46 (d, *J* = 18.0 Hz, 1H), 3.39 (d, *J* = 18.0 Hz, 1H); ^{13}C NMR (75 MHz, acetone-d_6) δ 161.30, 152.31, 146.20, 131.70, 127.64, 123.98, 90.48, 74.47, 60.46, 52.85, 43.43.

3-(2-Benzyloxy-3,5-dibromo-4-methoxyphenyl)-2-benzyloxyiminopropionic acid (1.10)

A mixture of azlactone **1.4** (12 g, 25 mmol) and $Ba(OH)_2$ (30 g, 175 mmol) in dioxane (180 mL) and water (180 mL) was stirred for 1 h at 60 °C. *O*-Benzyl hydroxylamine hydrochloride (12 g, 75 mmol) was added at 60 °C, and the mixture was stirred vigorously at the

same temperature for 14 h. The reaction mixture was cooled to 0 °C, A yellow solid precipitated after the solution was acidified with 15% HCl. After filtration, the solid was washed with cold pentane and ethyl ether (1:1) to yield **1.10** as pale yellow solid (10.5 g, 74.6%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62-7.59 (m, 2H), 7.52-7.45 (m, 6H), 7.34-7.30 (m, 2H), 7.37 (s, 1H), 5.33 (s, 2H), 5.12 (s, 2H), 4.02 (s, 2H), 4.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.28, 154.45, 154.25, 149.34, 136.53, 135.57, 131.99, 128.79, 128.75, 128.53, 128.34, 128.18, 127.91, 114.72, 112.88, 78.60, 74.86, 60.69, 25.20.

7,9-Dibromo-10-hydroxy-8-methoxy-1-oxa-2-azaspiro[4.5]deca-2,6,8-triene-3-carboxylic acid (1.18a)

The mixture of spiroisoxazoline acid **1.8** (198 mg, 0.5 mmol) and $LiOH{\cdot}H_2O$ (63 mg, 1.5 mmol) in methanol (15 mL) and water (15 mL) was stirred for 30 min at room temperature. After addition of 5% HCl (3 mL), methanol was removed under reduced pressure. Then EtOAc (50 mL) was added. The mixture was washed with water and dried over $MgSO_4$. Solvent was removed under reduced pressure to afford **1.18a** (189 mg, 98%) as a pale yellow solid: mp 110-112 ºC; IR (KBr, cm^{-1}) 3500 (broad), 1723, 1589; ^{1}H NMR (300 MHz, CD_3OD) δ 6.44 (s, 1H), 4.91 (s, 3H), 4.11 (s, 1H), 3.75 (d, *J* = 18.0 Hz, 1H), 3.73 (s, 3H), 3.10 (d, *J* = 18.0 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 162.72, 153.87, 149.31, 132.17, 122.79, 114.16, 93.07, 75.47, 60.38, 40.17; MS (EI) *m/z* $[M]^+$ 381 (12), 365 (34), 351 (57); HRMS (EI) *m/z* $[M]^+$ calcd for $C_{10}H_9Br_2NO_5$ 380.8847, found 380.8865.

7,9-Dibromo-10-hydroxy-8-methoxy-1-oxa-2-azaspiro[4.5]deca-2,6,8-triene-3-carboxylic acid (1.18c)

A mixture of spiroisoxazoline ester **1.60** (215 mg, 0.7 mmol) and $LiOH \cdot H_2O$ (88 mg, 2.1 mmol) in methanol (15 mL) and water (5 mL) was stirred for 1 h at room temperature. After addition of 5% HCl (5 mL), most of methanol was removed under reduced pressure. Then EtOAc (50 mL) was added and the mixture was washed with water and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford **1.18c** (196 mg, 95%) as a pale yellow solid. mp 97-99 ºC IR (KBr, cm^{-1}) 3265, 2942, 1720, 1589; ^1H NMR (300 MHz, CD_3OD) δ 6.13 (d, *J* = 0.7 Hz, 1H), 4.04 (s, 1H), 3.76 (d, *J* = 18 Hz, 1H), 3.75 (s, 3H), 3.10 (d, *J* = 18 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 162.58, 153/72, 147.20, 133.19, 126.96, 123.57, 91.95, 74.29, 60.63, 40.15; MS (EI) *m/z* [M^+] 293 (26), 276 (35), 259 (25), 208 (50), 193 (100); HRMS (EI) m/z [M - 17]$^+$ calcd for $C_{10}H_8Cl_2NO_4$ 275.9830, found 275.9833.

3-[4-(3-Benzyloxycarbonylaminopropoxy)-3,5-dibromophenyl]-2-hydroxyiminopropionic acid (1.19)

A mixture of azlactone **1.33** (1.1 g, 2 mmol) and $Ba(OH)_2$ (2.4 g, 14 mmol) in dioxane (40 mL) and water (40 mL) was stirred at 60 °C for 1 h. Hydroxylamine hydrochloride (414 mg, 6 mmol) was added at 60 °C, and the mixture was stirred vigorously at the same temperature for 12 h. The reaction mixture was cooled to 0 °C and acidified with 10% HCl. The reaction mixture was extracted with EtOAc. The extracts were washed with water and dried over $MgSO_4$. The crude product was purified by column chromatography (EtOAc/MeOH = 5: 1) to afford **1.19** as a pale yellow solid (560 mg, 51%): ^1H NMR (300 MHz, CD_3OD) δ 7.47 (s, 2H), 7.31 (brs, 5H), 5.07 (s, 2H), 3.95 (brs, 2H), 3.83 (s, 2H), 3.43 (t, *J* = 6.6 Hz, 2H), 2.05-2.00 (m, 2H).

5-(2-Aminoethyl)-1H-imidazol-2-ylamine (1.20)

NaOH (0.5 mL 0.1 N solution) was added to a solution of 1, 4 di-aminobutanone dihydrochloride (875 mg, 5 mmol) and NH_2CN in H_2O (10 mL) to adjust pH to 6.5. The mixture was stirred at 60 °C for 2 h. After cooling to 0 °C, 0.5 N HCl was added to adjust the pH to 2. After evaporating the solvent, ethanol (10 mL) was added. Then the solvent was removed again to afford as a pale yellow solid. The solid was dried in vacuum desiccator with P_2O_5 overnight to afford **1.20** (1.01 g): ^{1}H NMR (300 MHz, CD_3OD) δ 6.71 (t, *J* = 1.0 Hz, 1H), 3.21 (t, *J* = 7.2 Hz, 2H), 2.91 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, CD_3OD) 149.05, 123.55, 112.02, 39.21, 23.79; MS (EI) *m/z* 126 (55), 111 (65), 96 (100), 83(65).

3,5-Dibromo-2-hydroxy-4-methoxybenzaldehyde (1.22)

NBS (8.9 g, 50 mmol) in DMF (20 mL) was added to a solution of 2-hydroxy-4-methoxybenzaldhyde (3.8 g, 25 mmol) in DMF (10 mL) in 30 min at 0 °C. After the reaction was stirred at 0 °C for 20 min, ether (200 mL) was added. The reaction mixture was washed with successively with water and 5% NaS_2O_3, dried with $MgSO_4$. After the solvent was removed under reduced pressure, dibromobenzadehyde **1.22** (7.47 g, 96.4%) was obtained as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.75 (s, 1H), 9.77 (s, 1H), 7.76 (s, 1H), 3.98 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.07, 161.03, 159.42, 136.24, 118.61, 107.80, 60.90.

2-Benzyloxy-3,5-dibromo-4-methoxybenzaldehyde (1.23)

A mixture of dibromobenzadehyde **1.22** (7.75 g, 25 mmol)**,** NaI (3.75 g, 25 mmol), K_2CO_3 (8.3 g, 60 mmol), $PhCH_2Cl$ (3.16 g, 25 mmol) in DMF (40 mL) was stirred at room temperature for 24 h, then diluted with water (100 mL), extracted with ether, dried with $MgSO_4$.

The solvent was removed under reduced pressure, and benzyl ether **1.23** (9.8 g, 98%) was obtained as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.93 (s, 1H), 7.99 (s, 1H), 7.41-7.40 (m, 5H), 5.12 (s, 2H), 3.98 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.01, 160.27, 159.15, 134.78, 131.46, 129.09, 128.83, 128.32, 115.35, 114.39, 78.00, 60.89.

N-{2-[2-(4-Bromophenylazo)-3H-imidazol-4-yl]ethyl}acetamide (1.26)

Sodium nitrite (1.44 g, 21 mmol in 20 mL H_2O) was added to a mixture of *p*-bromoaniline (3.44 g, 20 mmol) in 2.3 N HCl (100 mL) at 0 °C – 2 °C in 50 min. The solution of diazonium salt was stored at 0 °C for 40 min then it was added to a mixture of *N*ω-acetylhistimine (3.06 g, 20 mmol) in sodium carbonate solution (1.6 N, 250 mL). It is very important to keep the temperature at 0 °C – 2 °C. After the addition, the reaction mixture was stored in the freezer for 0.5 h. The red solid precipitated. After filtration, the crude product was obtained as a dark red solid. The crude product was purified by column chromatography ($CHCl_3$/MeOH = 7: 1) to afford 2-arylzao derivative **1.26** (4.98 g, 74%) as a yellow solid and 4-arylzao derivative **1.26b** (0.85 g, 12.5%) and 2,4-diarylzao derivative **1.26c** (0.42 g, 9%). **1.26**: ^{1}H NMR (300 MHz, CD_3OD) δ 7.83 (d, *J* = 8.7 Hz, 2H), 7.20 (d, *J* = 8.7 Hz, 2H), 7.16 (s, 1H), 3.49 (t, *J* = 6.9 Hz, 2H), 2.87 (t, *J* = 6.9 Hz, 2H), 1.93 (s, 3H). **1.26b**: ^{1}H NMR (300 MHz, CD_3OD) δ 7.82-7.64 (m, 5H), 3.55 (t, *J* = 6.9 Hz, 2H), 3.21 (t, *J* = 6.9 Hz, 2H), 1.84 (s, 3H). **1.26c**: ^{1}H NMR (300 MHz, CD_3OD) δ 7.91 (d, *J* = 8.7 Hz, 2H), 7.86 (d, *J* = 8.7 Hz, 2H), 7.76 (d, *J* = 8.7 Hz, 2H), 7.69 (d, *J* = 8.7 Hz, 2H), 3.60 (t, *J* = 7.0 Hz, 2H), 3.25 (t, *J* = 7.0 Hz, 2H), 1.81 (s, 3H).

N-[2-(2-Amino-3H-imidazol-4-yl)ethyl]acetamide (1.27)

A solution of **1.26** (3.36 g, 10 mmol) in 10mL absolute ethanol was hydrogenated over PtO_2 (400 mg) under H_2 atmosphere (35-40 psi) at room temperature. After 18 h, PtO_2 (400 mg) was added again. The reaction was stirred for another 18 h. After filtration, ethanol was removed under reduced pressure from the filtrate. The crude product was obtained as a yellow oil and purified by ion exchange resin Dowex 50w with 5% $NH_3 \cdot H_2O$ as the eluent to afford **1.27** as a pale yellow solid (1.1 g, 60%): ^{1}H NMR (300 MHz, CD_3OD) δ 6.27 (s, 1H), 3.31 (t, J = 7.2 Hz, 2H), 2.55 (t, J = 7.2 Hz, 2H), 1.88 (s, 3H); ^{13}C NMR (75MHz, $CDCl_3$) 173.40, 150.82, 131.79, 112.15, 40.46, 28.03, 22.67.

(3-Chloropropyl)carbamic acid benzyl ester (1.28)

CbzCl (9mL, 62 mmol) was added to a mixture of 3-chloropropylamine hydrochloride (7.8 g, 60 mmol) and K_2CO_3 (25 g, 180 mmol) in toluene (120 mL) and water (120 mL) at 0 °C. The mixture was stirred for 24 h at room temperature. After addition of ether (250 mL), the mixture was washed with water and dried over $MgSO_4$. Solvent was removed under reduced pressure to afford **1.28** as an oil (13.1 g, 96%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (brs, 5H), 5.20 (brs, 1H), 5.07 (s, 2H), 3.54 (t, J = 6.3 Hz, 2H), 3.30 (q, J = 6.3 Hz, 2H), 1.92 (quin, J = 6.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.40, 136.30, 128.38, 127.99, 66.56, 42.12, 38.16, 32.22.

(3-Bromopropyl)carbamic acid benzyl ester (1.29)

CbzCl (9 mL, 62 mmol) was added to a mixture of 3-bromopropylamine hydrochloride (13.2 g, 60 mmol) and K_2CO_3 (24.8 g, 180 mmol) in toluene (120 mL) and water (120 mL) at 0

°C. The mixture was stirred for 24 h at room temperature. After addition of water (100 mL), the mixture was extracted with ethyl ether (4×80 mL) and dried over $MgSO_4$. the solvent was removed under reduced pressure to afford **1.29** as an oil (16.0 g, 98%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 5H), 5.14 (brs, 1H), 5.08 (s, 2H), 3.39 (t, *J* = 6.2 Hz, 2H), 3.30 (q, *J* = 6.3 Hz, 2H), 2.02 (quin, *J* = 6.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.45, 136.48, 128.46, 128.07, 128.00, 66.70, 39.47, 32.54, 30.47.

3,5-Dibromo-4-hydroxybenzaldehyde (1.31)

Bromine (30.2 g, 190 mmol in 50mL acetic acid) was added to a mixture of 4-hydroxybenzaldehyde (11 g, 90 mmol) and sodium acetate (22.9 g, 279 mmol) in acetic acid (200 mL) at room temperature in 20 min. The reaction mixture was stirred for 1 h at room temperature. Solid precipitated after water (200 mL) was added. After filtration, the solid was washed with water and dried in the vacuum desiccator with P_2O_5 overnight to afford **1.31** as a pale yellow solid (24.1 g, 95.6%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.80 (s, 1H), 8.00 (s, 2H), 6.43 (s, 1H); ^{13}C NMR (75 MHz, acetone-d_6) δ 189.75, 157.01, 134.95, 132.67, 112.39.

[3-(2,6-Dibromo-4-formylphenoxy)propyl]carbamic acid benzyl ester (1.32)

A mixture of 3,5-dibromo-4-hydroxybenzaldehyde **1.31** (2.8 g, 10 mmol), K_2CO_3 (3.45 g, 25 mmol), **1.29** (3.0 g, 11 mmol) in DMF was stirred at 100 °C for 4 h. Then the reaction mixture was extracted with ether (5 × 40 mL). The extracts were washed with water and dried over $MgSO_4$. The crude product was purified by column chromatography (hexane: EtOAc = 2: 1) to afford **1.32** as a white solid (3.32 g, 70.5%): IR (KBr, cm^{-1}) 3311, 3063, 1693, 1544; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.86 (s, 1H), 8.03 (s, 2H), 7.38-7.35 (m, 5H), 5.16 (brs, 1H), 5.13 (s,

2H), 4.15 (t, J = 5.8 Hz, 2H), 3.56 (q, J = 6.3 Hz, 2H), 2.12 (quin, J = 6.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.31, 157.81, 156.38, 136.49, 134.18, 133.84, 128.40, 128.03, 119.31, 71.58, 66.59, 38.35, 29.92; MS (EI) *m/z* $[M+2]^+$ 471 (8), 365 (27), 279 (30), 223 (19); HRMS (EI) *m/z* $[M^+]$calcd for $C_{18}H_{16}Br_2NO_4$ 467.9446, found 467.9464.

[3-(2,6-Dibromo-4-formylphenoxy)propyl]carbamic acid benzyl ester (1.33)

A mixture of aldehyde **1.32** (3.02 g, 6.28 mmol) and sodium acetate (515 mg, 6.28 mmol) and *N*-acetylglycine (735 mg, 6.28 mmol) in Ac_2O (12.5 mL) was stirred at 120 °C for 4 h. Yellow solid precipitated after the reaction mixture was cooled down. After filtration, the solid was washed with cold pentane and ethyl ether (1:1) to yield **1.33** as a yellow solid (3.35 g, 97%): IR (KBr, cm^{-1}) 3316, 3066, 1807, 1772, 1682; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (s, 2H), 7.38-7.33 (m, 5H), 6.92 (s, 1H), 5.21 (brs,1H), 5.13 (s, 2H), 4.12 (t, J = 5.7 Hz, 2H), 3.55 (q, J = 6.3 Hz, 2H), 2.44 (s, 3H), 2.11 (quin, J = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.32, 167.00, 156.43, 154.65, 136.56, 135.83, 133.74, 131.80, 128.48, 128.06, 126.96, 118.62, 71.53, 66.61, 38.50, 29.91, 15.71; MS (ESI) *m/z* $[M + Na]^+$ 573 (50), 575 (100), 553 (35), 551 (15); HRMS (ESI) *m/z* calcd for $C_{22}H_{20}Br_2N_2O_5$ 572.9614, found 572.9565.

3-[4-(3-Benzyloxycarbonylaminopropoxy)-3,5-dibromophenyl]-2-benzyloxyiminopropionic acid (1.34)

A mixture of azlactone **1.33** (2.2 g, 4 mmol) and $Ba(OH)_2$ (4.8 g, 28 mmol) in dioxane (28 mL) and water (28 mL) stirred at 60 °C for 1 h. *O*-Benzylhydroxylamine hydrochloride (2.05 g, 12.8 mmol) was added at 60 °C, and the mixture was stirred vigorously at the same temperature for 6 h. The reaction mixture was cooled to 0 °C and acidified with 10% HCl. The

reaction mixture was extracted with EtOAc. The extracts were washed with water and dried over $MgSO_4$. The crude product was purified by column chromatography (EtOAc/MeOH = 10: 1) to afford **1.34** (850 mg, 34%) as a pale yellow solid: mp 118-120 °C; IR (KBr, cm^{-1}) 3437, 2933, 1763, 1721, 1513, 1455, 1369, 1231; ^{1}H NMR (300 MHz, $CDCl_3$-CD_3OD 1:2) δ 7.47 (s, 2H), 7.35 (brs, 10H), 5.31 (s, 2H), 5.10 (s, 2H), 4.02 (t, *J* = 5.7 Hz, 2H), 3.82 (s, 2H), 3.27 (t, *J* = 6.6Hz, 2H), 2.07 (quin, *J* = 6.0, 2H); ^{13}H NMR (75 MHz, $CDCl_3$-CD_3OD 1:2) δ 164.15, 156.77, 151.17, 149.65, 136.25, 135.66, 134.46, 132.96, 128.28, 128.00, 127.56, 127.37, 117.37, 77.66, 70.77, 66.14, 37.98, 29.37; MS (ESI) *m/z* $[M + Na]^+$ 655(15), 635(10), 591(100), 547(20), 439(15); HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{27}H_{26}Br_2N_2O_6$ 655.0021, found 655.0055.

[3-(4-{2-Benzyloxyimino-2-[2-(4-methoxyphenyl)ethylcarbamoyl]-ethyl}-2,6-dibromo phenoxy)propyl]carbamic acid benzyl ester (1.36)

A mixture of the acid **1.34** (32 mg, 0.05 mmol), 2-(4-methoxyphenyl)ethylamine (7 mg, 0.05 mmol), HOBt (7 mg, 0.05 mmol) and DCC (9.6 mg, 0.05 mmol) in CH_2Cl_2 (5 mL) was stirred for 12 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and then washed with saturated aq NH_4Cl and dried over $MgSO_4$. The crude product was purified by column chromatography (hexane/EtOAc = 3: 1) to afford **1.36** as an oil (28 mg, 70%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (s, 2H), 7.37-7.26 (m, 10H), 7.08 (d, *J* = 8.5Hz, 2H), 6.84 (d, *J* = 8.5Hz, 2H), 6.69 (t, *J* = 6.0Hz, 1H), 5.26 (brs, 1H), 5.16 (s, 2H), 5.11 (s, 2H), 4.01 (t, *J* = 5.7 Hz, 2H), 3.54 (t, *J* = 5.7 Hz, 2H), 3.50 (t, *J* = 6.6 Hz, 2H), 2.77 (t, *J* = 6.9 Hz, 2H), 2.08-2.02 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.91, 158.27, 156.42, 151.31, 151.16, 136.64, 136.32, 135.18, 134.94, 133.47, 130.60, 129.68, 128.63, 128.47, 138.38, 128.27, 128.05, 128.02, 71.17,

66.55, 55.24, 40.86, 38.67, 34.68, 29.80, 28.62. MS (ESI) *m/z* $[M + H]^+$ 766 (37), 768 (71), 724 (100), 722 (53), 225 (23).

N-[2-(2-Amino-3H-imidazol-4-yl)ethyl]benzamide (1.40)

A mixture of the benzoic acid (12.2 mg, 0.1 mmol), aminohistidine **1.20** (30 mg, 0.15 mmol), HOBt (20 mg, 0.15 mmol), DCC (29 mg, 0.15 mmol), and Et_3N in DMF (3 mL) and $CHCl_3$ (3 mL) was stirred for 24 h at room temperature. The solvent was removed under reduced pressure. The crude product was subjected to column chromatography (EtOAc/Acetone/Formic acid/water = 5: 3: 0.5: 0.5). After flash chromatography, the product was dissolved in methanol and acidified with 1 N HCl. The solvent was removed to afford **1.40** as an pale yellow solid (22.5 mg, 85%): ^{1}H NMR (300 MHz, CD_3OD) δ 7.81 (d, *J* = 7.4 Hz, 2H), 7.53 (t, *J* = 7.0 Hz, 1H), 7.45 (t, *J* = 7.0 Hz, 2H), 6.58 (s, 1H), 3.63 (t, *J* = 6.3 Hz, 2H), 2.83 (t, *J* = 6.3 Hz, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 170.36, 148.54, 135.33, 132.71, 129.53, 128.24, 126.14, 110.82, 39.54, 25.83; MS (ESI) *m/z* $[M + H]^+$ 231(100), 110 (25)

[3-(4-{2-[2-(2-Amino-3H-imidazol-4-yl)ethylcarbamoyl]-2-benzyloxyiminoethyl}-2,6-dibromophenoxy)propyl]carbamic acid benzyl ester (1.41)

A mixture of the acid **1.34** (320 mg, 0.5 mmol), aminohistidine **1.20** (200 mg, 1 mmol), HOBt (135 mg, 1 mmol), DCC (192 mg, 1 mmol), and Et_3N (2.8 mL) in DMF (15 mL) and $CHCl_3$ (15 mL) was stirred for 48 h at room temperature. The solvent was removed under reduced pressure and crude product was purified by column chromatography (EtOAc/Acetone/Formic acid/water = 5: 3: 0.3: 0.3) to afford amide **1.41** as an pale yellow solid: ^{1}H NMR (300 MHz, CD_3OD) δ 7.39 (s, 2H), 7.37-7.29 (m, 10H), 6.48 (s, 1H), 5.25 (s, 2H),

5.07 (s, 2H), 3.98 (t, *J* = 6.0 Hz, 2H), 3.79 (s, 3H), 3.48 (t, *J* = 6.1 Hz, 2H), 3.40 (t, *J* = 6.1 Hz, 2H), 2.70 (t, *J* = 6.1 Hz, 2H), 2.00 (quin, *J* = 6.1 Hz, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 164.69, 158.87, 152.98, 152.69, 148.69, 138.42, 138.02, 136.67, 134.50, 129.64, 129.45, 129.39, 128.94, 128.75, 126.21, 78.71, 72.13, 67.36, 39.04, 31.25, 29.70, 25.83; MS (ESI) *m/z* $[M + H]^+$ 741 (40), 743 (100), 371(9); HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{32}H_{35}Br_2N_6O_5$ 741.1018, found 741.1030.

N-[2-(2-Amino-1H-imidazol-4-yl)ethyl]-3-[4-(3-aminopropoxy)-3,5-dibromophenyl]-2-benzyloxyiminopropionamide (1.42)

TMSCl (15 μL, 0.12 mmol) was added to solution of **1.41** (11 mg, 0.015 mmol) and NaI (18 mg, 0.12 mmol) in acetonitrile at room temperature. The reaction mixture was stirred for 12 h at room temperature. The solvent was removed under reduced pressure to afford crude amine **1.42** as an pale yellow solid: ^{1}H NMR (300 MHz, CD_3OD) δ 7.42 (s, 2H), 7.35-7.29 (m, 5H), 6.52 (s, 1H), 5.26 (s, 2H), 4.09 (t, *J* = 5.7 Hz, 2H), 3.80 (s, 2H), 3.49 (t, *J* = 6.9 Hz, 2H), 2.72 (t, *J* = 6.9 Hz, 2H), 2.20 (quin, *J* = 6.3 Hz, 2H); MS (ESI) *m/z* $[M+ H]^+$ 607 (45).

[3-(4-{2-[2-(2-Amino-3H-imidazol-4-yl)ethylcarbamoyl]-2-hydroxyiminoethyl}-2,6-dibromophenoxy)propyl]carbamic acid benzyl ester (1.43)

A mixture of the acid **1.19** (16 mg, 0.03 mmol), aminohistidine **1.20** (12 mg, 0.06 mmol), HOBt (4 mg, 0.03 mmol), DCC (12 mg, 0.06 mmol), and Et_3N (0.1 mL) in DMF (2 mL) and $CHCl_3$ (2 mL) was stirred for 15 h at room temperature. The solvent was removed under reduced pressure. The crude product was subjected to column chromatography (EtOAc/Acetone/Formic acid/water = 5: 3: 0.4: 0.4). After flash chromatography, the product was dissolved in methanol

and acidified with 1 N HCl. The solvent was removed under reduced pressure to afford amide **1.43** (4.2 mg, 21%): ^{1}H NMR (300 MHz, CD_3OD) δ 7.46 (s, 2H), 7.34-7.29 (m, 5H), 6.50 (s, 1H), 5.07 (s, 2H), 3.99 (t, *J* = 6.0 Hz, 2H), 3.82 (s, 2H), 3.47 (t, *J* = 6.7 Hz, 2H), 3.39 (t, *J* = 6.8 Hz, 2H), 2.70 (t, *J* = 6.7 Hz, 2H), 2.04-2.00 (m, 2H); MS (ESI) *m/z* $[M+ H]^+$ 651 (25).

2-(4-Methoxybenzyloxy)isoindole-1,3-dione (1.45)

A mixture of *N*-hydroxyphthalimide (26.1 g, 160 mmol), PMBCl (25 g, 160mmol) and Et_3N (53 mL, 384 mmol) in DMF (400 mL) was stirred for 40 min at 90 °C. A solid precipitated after the mixture was poured into ice-water (500 mL). The solid was collected by filtration. The product thus obtained was washed with water and dried under vacuum to yield **1.45** as a pale yellow solid (30.8 g, 68%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80-7.78 (m, 2H), 7.73-7.70 (m, 2H), 7.44 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.14 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.42, 160.29, 134.28, 131.53, 128.72, 125.70, 123.31, 113.77, 79.35, 55.11.

***O*-(4-Methoxybenzyl)hydroxylamine HCl salt (1.46)**

A mixture of Compound **1.45** (18.7 g, 66 mmol) in DMF (120 mL) and MeOH (250 mL) was added hydrazine (10 mL) at 60 °C. After the mixture was stirred for 5 min at the same temperature, it was cooled to room temperature. Water (100 mL) was added and most of methanol was removed under reduced pressure. The solution then was extracted with EtOAc (4 × 100 mL), washed with water and dried over $MgSO_4$. The crude product was purified by column chromatography (hexane/EtOAc = 2: 1) to provide an oil. Then methanol (30 mL) and concentrated HCl (6 mL) were added to the oil at 0 °C, and solvent was removed under reduced

pressure to afford **1.46** as a white solid (6.2 g, 50%): ^{1}H NMR (300 MHz, CD_3OD) δ 7.37 (d, *J* = 6.9 Hz, 2H), 6.98 (d, *J* = 6.9 Hz, 2H), 4.95 (s, 2H), 3.82 (s, 3H).

4-Methylbenzaldehyde O-(4-methoxybenzyl)oxime (1.48)

A mixture of amine **1.47** (379 mg, 2 mmol) and 4-methylbenzaldehyde (180 mg, 1.5 mmol) in pyridine (20 mL) was stirred for 3 h at room temperature. EtOAc (50 mL) was added after the solvent was removed under reduced pressure. The solution was washed successively with water, saturated aq $CuSO_4$, water and dried over $MgSO_4$. The crude product was purified by column chromatography (hexane/EtOAc = 20: 1) to afford **1.48** as a white solid (350 mg, 92%): IR (KBr, cm^{-1}) 2931, 1612, 1584, 1511, 1441; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 5.12 (s, 2H), 3.78 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.40, 148.85, 139.90, 130.13, 129.51, 129.44, 129.33, 126.95, 113.77, 75.98, 55.20, 21.40;MS (EI) *m/z* 255 (M^+, 30), 122 (100), 91 (46), 77 (65); RMS (EI) *m/z* (M^+) calcd for $C_{16}H_{17}NO_2$ 255.1257, found 255.1259.

4-Methylbenzaldehyde oxime (1.49)

A mixture of hydroxylamine (105 mg, 1.5 mmol) and 4-methylbenzaldehyde (120mg, 1 mmol) in pyridine (10 mL) was stirred for 1 h at room temperature. EtOAc (50 mL) was added after solvent was removed under reduced pressure. The solution was washed successively with water, saturated aq $CuSO_4$, water, dried with $MgSO_4$. The crude product was purified by column chromatography (hexane/EtOAc = 10: 1) to afford **1.49** as a white solid (127 mg, 94%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (s, 1H), 8.02 (s, 1H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 8.1 Hz, 2H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.35, 140.24, 129.46, 129.12, 127.01, 21.34.

3-[4-(3-Benzyloxycarbonylaminopropoxy)-3,5-dibromophenyl]-2-(4-methoxybenzyloxy imino)propionic acid (1.50a)

A mixture of azlactone **1.33** (2.2 g, 4 mmol) and $Ba(OH)_2$ (4.8 g, 28 mmol) in dioxane (28 mL) and water (28 mL) was stirred at 60 °C for 1 h. *O*-PMBhydroxylamine hydrochloride (1.51 g, 8 mmol) was added at 60 °C, and the mixture was stirred vigorously at the same temperature for 13 h. The reaction mixture was cooled to 0 °C and acidified with 10% HCl. The reaction mixture was extracted with EtOAc. The extracts were washed with water and dried over $MgSO_4$. The crude product was purified by column chromatography (CH_2Cl_2/MeOH = 6 : 1) to afford **1.50a** (934 mg, 33.5%) as a oil: IR (KBr, cm^{-1}) 3320(broad), 2946, 1698, 1688, 1612, 1543, 1514, 1456, 1257. ^{1}H NMR (300 MHz, CD_3OD:$CDCl_3$ =3:1) δ 7.39 (s, 2H), 7.38-7.35 (m, 5H), 7.24 (d, *J* = 7.5 Hz, 2H), 6.86 (d, *J* = 7.5 Hz, 2H), 5.11 (brs, 1H), 5.06 (s, 2H), 4.86 (s, 2H), 3.96 (t, *J* = 5.9 Hz, 2H), 3.77 (s, 3H), 3.40 (t, *J* = 6.7 Hz, 2H), 2.02 (quin, *J* = 6.3 Hz, 2H); ^{13}C NMR (75 MHz, CD_3OD:$CDCl_3$ =3:1) δ 160.74, 158.49, 152.31, 137.97, 137.22, 134.32, 130.88, 129.99, 129.23, 128.73, 128.54, 118.38, 114.76, 77.70, 71.87, 67.23, 55.66, 39.02, 31.29, 30.92. MS (ESI) *m/z* $[M+ Na]^+$ 685 (43), 687 (100), 621 (35), 211 (46). HRMS (ESI) *m/z* $[M+ Na]^+$ calcd for $C_{28}H_{28}Br_2N_2O_7$ 685.0175, found 685.0161.

General procedure **A**: synthesis of *O*-PMB oxime-acids.

A mixture of the ester **1.68** (520 mg, 0.87 mmol) and $LiOH·H_2O$ (104 mg, 2.48 mmol) in methanol (30 mL) and water (10 mL) was sonicated for 3 h at room temperature. The reaction mixture was acidified with 5% HCl (2 mL). A white solid precipitated after most of methanol was removed under reduced pressure. Filtration afforded acid **1.50b** (538 mg, 98%).

3-[4-(3-Benzyloxycarbonylaminopropoxy)-3-bromophenyl]-2-(4-methoxybenzyloxyimino) propionic acid (1.50b)

Using the general procedure of **A**, 497 mg the title compound was prepared in 98% yield as a white solid: mp: 80-82 °C; IR (KBr, cm^{-1}) 3321, 2940, 1701, 1681, 1533, 1514, 1456, 1254; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, *J* = 2.0 Hz, 1H), 7.36-7.30 (m, 5H), 7.29 (d, *J* = 8.6 Hz, 2H), 7.13 (d, *J* = 8.3 Hz, 1H), 6.92 (d, *J* = 8.6 Hz, 2H), 6.73 (d, *J* = 8.3 Hz, 1H), 5.56 (brs, 1H), 5.24 (s, 2H), 5.12 (s, 2H), 4.03 (t, *J* = 5.7, 2H), 3.82 (s, 2H), 3.80 (s, 2H), 3.47 (q, *J* = 5.7, 2H), 2.06-2.02 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.19, 159.97, 156.64, 153.87, 136.67, 133.94, 130.23, 129.33, 129.17, 128.43, 127.95, 127.87, 127.79, 78.20, 67.79, 66.57, 55.27, 39.06, 29.24, 29.20. MS (ESI) *m/z* $[M+ Na]^+$607 (40), 609 (40); HRMS (ESI) *m/z* $[M+ Na]^+$ calcd for $C_{28}H_{29}BrN_2O_7Na$ 607.1056, found 607.1078.

3-[2-(3-Benzyloxycarbonylaminopropoxy)-3,5-dibromophenyl]-2-(4-methoxybenzyloxy imino)propionic acid (1.50c)

Using the general procedure of **A**, 538 mg the title compound was prepared in 98% yield as a white solid: IR (KBr, cm^{-1}) 3422, 3312, 1706, 1684, 1611, 1546, 1514, 1450; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, *J* = 1.9 Hz, 1H), 7.36-7.30 (m, 5H), 7.13 (d, *J* = 8.7 Hz, 2H), 7.11 (d, *J* = 1.9 Hz, 1H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.26 (brs, 1H), 5.15 (s, 2H), 5.10 (s, 2H), 3.94 (t, *J* = 5.7 Hz, 2H), 3.86 (s, 2H), 3.80 (s, 3H), 3.42 (q, *J* = 6 Hz, 2H), 1.99 (quin, *J* = 6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.10, 159.98, 156.69, 153.30, 149.09, 136.59, 134.45, 132.93, 132.59, 130.15, 128.50, 128.09, 127.58, 118.14, 117.06, 114.14, 78.29, 71.23, 66.75, 55.30, 38.43, 30.05, 26.13. MS (ESI) *m/z* $[M+ Na]^+$ 685 (60), 687 (100), 689 (60); HRMS (ESI) *m/z* $[M+ Na]^+$ calcd for $C_{28}H_{28}Br_2N_2O_7Na$ 685.0161, found 685.0176.

3-[2-(3-Benzyloxycarbonylaminopropoxy)-3,5-dichlorophenyl]-2-(4-methoxybenzyloxy imino)propionic acid (1.50d)

Using the general procedure **A**, 433mg title compound was prepared in 98% yield as a white solid: IR (KBr, cm^{-1}) 3312, 2949, 1705, 1684, 1611, 1543, 1514, 1455, 1257; ^1H NMR (300 MHz, $CDCl_3$): δ 7.35-7.30 (m, 5H), 7.22 (d, *J* = 2.0, 1H), 8.3 (d, *J* = 8.3 Hz, 2H), 6.93 (brs, 1H), 8.3 (d, *J* = 8.3 Hz, 2H), 5.23 (brs, 1H), 5.14 (s, 2H), 5.11 (s, 2H), 3.96 (t, *J* = 5.6 Hz, 2H), 3.85 (s, 2H), 3.81 (s, 3H), 3.42 (quin, *J* = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.75, 160.04, 156.70, 151.82, 149.14, 136.62, 132.41, 130.16, 129.26, 129.07, 128.85, 128.56, 128.51, 128.10, 127.57, 114.13, 78.31, 71.26, 66.78, 55.31, 38.43, 30.11, 26.04. MS (ESI) *m/z* $[M+ Na]^+$ 597 (100), 599(75); HRMS (ESI) *m/z* $[M+ Na]^+$ calcd for $C_{28}H_{28}Br_2N_2O_7Na$ 597.1171, found 597.1201.

(3-{4-[2-[2-(2-Amino-3H-imidazol-4-yl)ethylcarbamoyl]-2-(4-methoxybenzyloxyimino) ethyl]-2,6-dibromophenoxy}propyl)carbamic acid benzyl ester (1.51)

A mixture of the acid **1.50a** (220 mg, 0.33 mmol), aminohistidine **1.20** (135 mg, 0.66 mmol), HOBt (89 mg, 0.66 mmol), DCC (192 mg, 1 mmol), and Et_3N (2.8 mL) in DMF (15 mL) and $CHCl_3$ (15 mL) was stirred for 26 h at room temperature. The solvent was removed under reduced pressure and the crude product was subjected to column chromatography (Ethyl acetate: Acetone: Formic acid: Water = 5: 3: 0.3: 0.3) to provide **1.51** as a pale yellow solid (152 mg, 68%): IR (KBr, cm^{-1}) 3387(broad), 1676, 1527, 1455, 1256. ^1H NMR (300 MHz, CD_3OD) δ 7.34 (s, 2H), 7.32-7.23 (m, 5H), 7.24 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 6.51 (s, 1H), 3.96 (t, *J* = 5.8 Hz, 2H), 3.77 (s, 3H), 3.75 (s, 2H), 3.49 (t, *J* = 6.6 Hz, 2H), 3.39 (t, *J* = 6.9 Hz, 2H), 2.72 (t, *J* = 6.6 Hz, 2H), 2.01 (quin, *J* = 6.5 Hz, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 164.78,

161.28, 158.81, 152.92, 152.48, 148.95, 138.37, 136.71, 134.47, 131.19, 129.98, 129.44, 128.93, 128.73, 126.05, 118.75, 115.07, 110.74, 39.17, 39.04, 31.27, 29.71, 25.79; MS (ESI) *m/z* [M+ H]$^+$ 741 (20), 773 (100), 239 (80); HRMS (ESI) *m/z* [M+ H]$^+$ calcd for $C_{33}H_{37}Br_2N_6O_6$ 741.1110, found 741.1141.

3,5-Dichloro-2-hydroxy-4-methoxybenzaldehyde (1.54)

To a solution of the aldehyde **1.53** (7.6 g, 50 mmol) in CH_2Cl_2 (50 mL) was added SO_2Cl_2 (10 mL, 125 mmol) at 0 °C. The mixture was stirred at 40 °C for 24 h, another portion of SO_2Cl_2 (4 mL) was added and the mixture was stirred for another 48 h at the same temperature. The solvent was removed under reduced pressure and the crude product was subjected to column chromatography (hexane/EtOAc = 10: 1) to afford **1.54** as a white solid (7.85 g, 71%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.60 (s, 1H), 9.79 (s, 1H), 7.54 (s, 1H), 4.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.30, 159.13, 157.79, 132.08, 120.02, 117.73, 117.59, 61.08.

2-Benzyloxy-3,5-dichloro-4-methoxybenzaldehyde (1.55)

A mixture of **1.54** (7.1 g, 32 mmol)**,** NaI (4.8 g, 32 mmol), K_2CO_3 (11 g, 80 mmol), $PhCH_2Cl$ (3.68 g, 32 mmol) and DMF (50 mL) was stirred at room temperature for 24 h, diluted with 50 mL water, extracted with ether, washed with water, dried with $MgSO_4$. The solvent was removed under reduced pressure, the product **1.55** (9.38 g, 94.2%) was obtained as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.94 (s, 1H), 7.75 (s, 1H), 7.38 (s, 5H), 5.13 (s, 2H), 3.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.06, 158.28, 157.32, 134.79, 129.08, 128.83, 127.42, 127.19, 125.81, 124.27, 77.72, 61.03.

4-(2-Benzyloxy-3,5-dichloro-4-methoxybenzylidene)-2-methyl-4H-oxazol-5-one (1.56)

A mixture of aldehyde **1.55** (12 g, 30 mmol) and *N*-acetylglycine (3.51 g, 30 mmol) and sodium acetate (2.46 g, 30 mmol) in Ac_2O (60mL) was stirred at 120 °C for 4 h. A yellow solid precipitated after the reaction mixture was cooled to room temperature. The yellow solid was washed with cold pentane and ethyl ether (1:1) to yield **1.56** (12.8 g, 89%) as a yellow solid: mp 137 °C; IR (KBr, cm^{-1}) 1805, 1658, 1561; ^1H NMR (300 MHz, $CDCl_3$) δ 8.63 (s, 1H), 7.44-7.35 (m, 5H), 7.23 (s, 1H), 5.01 (s, 2H), 3.97 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.00, 166.89, 155.26, 154.71, 135.26, 133.32, 130.83, 128.96, 128.78, 128.74, 125.49, 125.21, 124.37, 122.88, 77.12, 60.98, 15.64; MS (EI) *m/z* 391 (M^+, 12), 349 (41); HRMS (EI) *m/z* (M^+) calcd for $C_{19}H_{15}Cl_2NO_4$ 391.0378, found 391.0393.

4-(2-Benzyloxy-3,5-dichloro-4-methoxybenzylidene)-2-methyl-4H-oxazol-5-one (1.57)

A mixture of azlactone **1.56** (9.0 g, 23 mmol) and $Ba(OH)_2$ (27.5 g, 161 mmol) in dioxane (46 mL) and water (46 mL) was stirred 60 °C for 1 h. *O*-Benzyl hydroxylamine hydrochloride (11 g, 69 mmol) was added at 60 °C, and the mixture was stirred vigorously at the same temperature for 14 h. The reaction mixture was cooled to 0 °C, a yellow solid precipitated after the solution was acidified with 15% HCl. The solid was washed with cold pentane and ethyl ether (1:1) to yield **1.57** (7.3 g, 67%) as a pale yellow solid: mp 147-148 °C IR (KBr, cm^{-1}) 3454, 1704, 1009; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48-7.45 (m, 2H), 7.38-7.32 (m, 6H), 7.21-7.19 (m, 2H), 694 (s, 1H), 5.22 (s, 2H), 4.99 (s, 2H), 3.90 (s, 3H), 3.85 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.85, 152.64, 152.23, 149.34, 136.54, 135.59, 128.74, 128.53, 128.35, 128.23, 128.20, 128.15, 127.11, 124.28, 78.57, 74.91, 60.78, 25.20; MS (EI) *m/z* 473 (M^+, 12), 428 (14),

321 (48), 181 (49), 91 (100); HRMS (EI) *m/z* (M^+) calcd for $C_{24}H_{21}Cl_2NO_5$ 473.0797, found 473.0815.

3-(2-Benzyloxy-3,5-dichloro-4-methoxyphenyl)-2-benzyloxyiminopropionic acid methyl ester (1.58)

To a solution of **1.57** (6.6 g, 14 mmol) in benzene (120 mL) and absolute methanol (40 mL) was added $TMSCHN_2$ (11 mL in hexane, 22 mmol) at 0 °C. The reaction mixture was stirred for 45 min at room temperature. 5% HCl (10mL) was added after the reaction was cooled to 0 °C. A yellow solid precipitated after most of methanol and benzene was removed. The solid was washed with cold pentane and ethyl ether (1:1) to yield **1.58** (6.35 g, 93%) as a pale yellow solid: mp 87-89 °C; IR (KBr, cm^{-1}) 1723, 1470, 1209; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48-7.45 (m, 2H), 7.39-7.39 (m, 6H), 7.22-7.19 (m, 2H), 6.97 (s, 1H), 5.24 (s, 2H), 4.94 (s, 2H), 3.88 (s, 3H), 3.87 (s, 2H), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.66, 152.45, 151.88, 149.92, 136.58, 136.02, 128.46, 128.37, 128.30, 128.24, 128.15, 127.97, 127.78, 124.10, 124.00, 77.97, 74.53, 60.65, 52.75, 26.31.

3-(3,5-Dichloro-2-hydroxy-4-methoxyphenyl)-2-ydroxyiminopropionic acid methyl ester (1.59)

A solution of benzyl ester **1.58** (3.9 g, 8 mmol) in AcOH (50 mL) and dioxane (50 mL) was hydrogenated over Pd-black (0.8 g) under H_2 atmosphere (1 atm) at room temperature for 24 h. After filtration, solvent was removed under reduced pressure, EtOAc (200 mL) was added. The solution was washed with water and dried over $MgSO_4$. The crude product was purified by column chromatography (hexane/EtOAc = 2: 1) to afford **1.59** (2.11 g, 85%) as a pale yellow

solid: mp 139-140 °C; IR (KBr, cm^{-1}) 3299, 1733, 1481, 1433, 1451, 1304; ^1H NMR (300 MHz, acetone-d_6) δ 11.81 (brs, 1H), 8.45 (brs, 1H), 7.11 (s, 1H), 3.92 (s, 2H), 3.83 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ 165.72, 152.24, 151.79, 150.59, 129.49, 122.07, 119.28, 117.50, 60.92, 52.92, 26.13; MS (EI) *m/z* 307 (M^+, 50), 290 (48), 230 (100); HRMS (EI) *m/z* (M^+) calcd for $C_{11}H_{11}Cl_2NO_5$ 307.0014, found 307.0027.

7,9-Dichloro-10-hydroxy-8-methoxy-1-oxa-2-azaspiro[4.5]deca-2,6,8-triene-3-carboxylic acid methyl ester (1.60)

A mixture of *O*-phenolic oxime acid derivative **1.59** (1.02 g, 3.31 mmol) and NBS (884 mg, 4.97 mmol) in DMF (15 mL) was stirred for 3 h at room temperature. After addition of ethyl ether (250 mL), the solution was washed successively with water, 5% aq NaS_2O_3 and water, and dried over $MgSO_4$. The organic solvent was removed under reduced pressure, and the crude product (954 mg) was obtained as yellow oil. To a solution of crude ketone (800 mg, 2.61 mmol) in CH_2Cl_2 (35 mL) was added to $Zn(BH_4)_2$ (0.1 N in ethyl ether, 35 mL) at 0 °C in 10 min. The reaction mixture was stirred for another 5 min at room temperature. After addition of saturated aq NH_4Cl, the mixture was extracted with ethyl ether (3×100 mL). The extracts were washed with water and dried over $MgSO_4$. The crude product was purified by column flash chromatography (hexane: EtOAc = 2: 1) to afford **1.60** (290 mg, 29%) and **1.61** as pale yellow solids (152 mg, 18%): mp 100-111 °C; IR (KBr, cm^{-1}) 3376 (broad), 1743, 1604, 1441, 1348, 1270; ^1H NMR (300 MHz, acetone-d_6) δ 6.27 (d, *J* = 1.2 Hz, 1H), 5.50 (d, *J* = 8.0 Hz, 1H), 4.18 (d, *J* = 8.0 Hz, 1H), 3.89 (d, *J* = 18.0 Hz, 1H), 3.88 (s, 3H), 3.80 (s, 3H), 3.25 (d, *J* = 1H); ^{13}C NMR (75 MHz, acetone-d_6) δ 161.11, 152.47, 146.74, 132.49, 126.97, 123.16, 91.29, 74.00,

60.49, 52.83, 39.96; MS (EI) *m/z* 307(M^+,58), 292 (20), 162 (30), 230 (68), 192 (66), 59 (100); HRMS (EI) *m/z* (M^+) calcd for $C_{11}H_{11}Cl_2NO_5$ 307.0014, found 307.0024.

7,9-Dichloro-10-hydroxy-8-methoxy-1-oxa-2-aza-spiro[4.5]deca-2,6,8-triene-3-carboxylic acid methyl ester (1.61)

Mp 109 °C; IR (KBr, cm^{-1}) 3387, 1740, 1438, 1305; ^1H NMR (300 MHz, Acetone-d_6) δ 6.32 (s, 1H), 4.56 (s, 1H), 3.82 (s, 3H), 3.73 (s, 3H), 3.46 (d, *J* = 18 Hz, 1H), 3.40 (d, *J* = 18 Hz, 1H); ^{13}C NMR (75 MHz, acetone-d_6) δ 161.27, 152.28, 146.19, 131.67, 127.62, 123.94, 90.45, 74.44, 60.42, 52.80, 43.40; MS (EI) *m/z* 307(M^+, 8), 292 (45), 290 (65), 262 (25), 230 (100), 192 (86), 59 (24); HRMS (EI) *m/z* (M^+) calcd for $C_{11}H_{11}Cl_2NO_5$ 307.0014, found 307.0007.

(*Z*)-Methyl 3-(3,5-dichloro-2,4-dimethoxyphenyl)-2-(methoxyimino)propanoate (1.63)

IR (film, cm^{-1}) 2943, 1725, 1473; ^1H NMR (300 MHz, $CDCl_3$) δ 7.00 (s, 1H), 4.08 (s, 3H), 3.91 (s, 2H), 3.88 (s, 3H), 3.87 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.63, 153.85, 151.84, 149.39, 128.12, 127.19, 124.00, 123.84, 63.55, 60.65, 52.96, 25.76; MS (EI) *m/z* 335 (M^+, 68), 303 (5), 268 (20), 244 (100). HRMS (EI) *m/z* (M^+) calcd for $C_{13}H_{15}Cl_2NO_5$ 335.0327, found 335.0316.

(*E*)-N-(3-(3,5-Dichloro-2-hydroxy-4-methoxyphenyl)-1-methoxy-1-oxopropan-2-ylidene) methanamine oxide (1.64)

IR (film, cm^{-1}) 2949, 1716, 1472; ^1H NMR (300 MHz, $CDCl_3$) δ 7.07 (s, 1H), 4.21 (s, 3H), 4.00 (s, 2H), 3.87 (s, 3H), 3.86 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.65, 153.94,

151.82, 138.80, 128.34, 127.31, 123.97, 123.63, 60.63, 60.59, 54.05, 25.77; MS (EI) *m/z* 335 (M^+, 100), 318 (24), 303 (5), 283 (55).

General procedure **B**: synthesis of phenol ethers.

A mixture of 3,5-dibromo-4-hydroxybenzaldehyde **1.31** (5.03 g, 25 mmol), K_2CO_3 (8.3 g, 60 mmol), **1.29** (7.1 g, 26 mmol) in DMF was stirred for 4 h at 100 °C. Then the reaction mixture was extracted with ether (5 × 40 mL). The extracts were washed with water, dried with $MgSO_4$. The crude product was purified by column chromatography (hexane: EtOAc = 2: 1) to afford **1.32** as a white solid (7.8 g, 78.6%).

General procedure **C**: synthesis of azlactones.

A mixture of aldehyde **1.32** (6.47 g, 16.05 mmol) in Ac_2O (40 mL) and sodium acetate (1.32 mg, 16.05 mmol) and *N*-acetylglycine (1.88 mg, 16.05 mmol) was stirred at 120 °C for 4 h. A yellow solid precipitated after the reaction mixture was cooled down. The product was washed with cold pentane and ethyl ether (1:1) to yield **1.33** (6.4 g, 84.5%) as a yellow solid.

General procedure **D**: synthesis of *O*-PMB oxime methyl esters

A mixture of azlactone **1.33** (1.89 g, 4 mmol) and $Ba(OH)_2$ (4.8 g, 28 mmol) in dioxane (28 mL) and water (28 mL) was stirred at 60 °C for 1 h. *O*-PMBhydroxylamine hydrochloride (1.52 g, 8 mmol) was added at 60 °C, and the mixture was stirred vigorously at the same temperature for 13 h. The reaction mixture was cooled to 0 °C and acidified with 10% HCl. The reaction mixture was extracted with EtOAc. The extracts were washed with water, dried with $MgSO_4$. To the crude product in dry benzene (40 mL) and absolute methanol (15 mL)

$TMSCHN_2$ (3 mL, 2.0 N in hexane) was added at 0 °C. The mixture was stirred for 40min at room temperature. The organic solvents were removed after addition of saturated aq NH_4Cl. The residue was extracted with ether and the extracts were dried over $MgSO_4$. The crude product was purified by column chromatography (hexane/EtOAc = 2: 1) to afford the ester **1.34** (752 mg, 31.5%) as a white solid.

[3-(2-Bromo-4-formylphenoxy)propyl]carbamic acid benzyl ester (1.66)

Using the general procedure of **B**, 7.8 g the title compound was prepared in 78.6% yield as a white solid: mp 70 °C; IR (KBr, cm^{-1}) 3423, 3310, 1684, 1595, 1542; ^1H NMR (300 MHz, $CDCl_3$) δ 9.81 (s, 1H), 8.04 (d, *J* = 1.9 Hz, 1H), 7.77 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.34 (brs, 5H), 6.97 (d, *J* = 8.4 Hz, 1H), 5.49 (brs, 1H), 5.10 (s, 2H), 4.18 (t, *J* = 5.7 Hz, 2H), 3.48 (q, *J* = 6.0 Hz, 2H), 2.10 (quin, *J* = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.45, 159.98, 156.41, 136.48, 134.27, 131.05, 130.61, 128.36, 127.92, 127.81, 112.72, 112.08, 67.71, 66.43, 38.51, 28.90; MS (EI) *m/z* 391 (M^+, 0.2), 300 (0.3), 192 (30), 91 (100).

{3-[2-Bromo-4-(2-methyl-5-oxo-oxazol-4-ylidenemethyl)phenoxy]propyl}carbamic acid benzyl ester (1.67)

Using the general procedure of **C**, 6.4 g the title compound was prepared in 84.5% yield as a white solid: ^1H NMR (300 MHz, CD_3OD) δ 8.41 (d, *J* = 1.8 Hz, 1H), 7.94 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.37-7.32 (m, 5H), 7.00 (s, 1H), 6.91 (d, *J* = 8.6 Hz, 1H), 5.44 (brs, 1H), 5.12 (s, 2H), 4.17 (t, *J* = 5.7 Hz, 2H), 3.49 (q, *J* = 6.0 Hz, 2H), 2.41 (s, 3H), 2.13-2.08 (m, 2H); ^{13}C NMR (75MHz, $CDCl_3$) δ 167.63, 165.83, 157.10, 156.56, 136.77, 133.16, 131.73, 129.35, 128.49,

128.03, 127.95, 127.65, 67.76, 66.66, 38.90, 29.20, 15.59. MS (ESI) *m/z* 527 [M + Na + CH_3OH]$^+$ (95), 529(100).

3-[4-(3-Benzyloxycarbonylamino-propoxy)-3-bromo-phenyl]-2-(4-methoxy-benzyloxy imino)-propionic acid methyl ester (1.68)

Using the general procedure of **D**, 752 mg the title compound was prepared in 31.5% yield as a white solid: mp: 80-82 °C; IR (KBr, cm^{-1}) 3321, 2940, 1701, 1681, 1533, 1514, 1456, 1254; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, *J* = 2.0 Hz, 1H), 7.36-7.30 (m, 5H), 7.29 (d, *J* = 8.6 Hz, 2H), 7.13 (d, *J* = 8.3 Hz, 1H), 6.92 (d, *J* = 8.6 Hz, 2H), 6.73 (d, *J* = 8.3 Hz, 1H), 5.56 (brs, 1H), 5.24 (s, 2H), 5.12 (s, 2H), 4.03 (t, *J* = 5.7, 2H), 3.82 (s, 2H), 3.80 (s, 2H), 3.47 (q, *J* = 5.7, 2H), 2.06-2.02 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.19, 159.97, 156.64, 153.87, 136.67, 133.94, 130.23, 129.33, 129.17, 128.43, 127.95, 127.87, 127.79, 78.20, 67.79, 66.57, 55.27, 39.06, 29.24, 29.20. MS (ESI) *m/z* [M+ Na]$^+$ 607 (40), 609 (40); HRMS (ESI) *m/z* [M+ Na]$^+$ calcd for $C_{28}H_{29}BrN_2O_7Na$ 607.1056, found 607.1078.

[3-(2,4-Dibromo-6-formylphenoxy)propyl]carbamiacid benzyl ester (1.71)

Using the general procedure of **B**, 9.5 g the title compound was prepared in 80.4% yield as a white solid: mp 56 °C; IR (KBr, cm^{-1}) 3319, 3066, 1687, 1678, 1534; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.22 (s, 1H), 7.69 (d, *J* = 2.7 Hz, 1H), 7.61 (d, *J* = 2.7 Hz, 1H), 7.35-7.32 (m, 5H), 5.27 (brs, 1H), 5.10 (s, 2H), 4.09 (t, *J* = 6.0 Hz, 2H), 3.49 (q, *J* = 6.0 Hz, 2H), 2.07 (quin, *J* = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.59, 156.41, 156.15, 136.38, 135.62, 131.20, 130.48, 129.86, 128.41, 128.02, 127.24, 126.84, 74.11, 66.21, 38.07, 30.06; MS (EI) *m/z* [M+ H]$^+$ 382

(20), 338 (14), 192 (28), 91 (100); HRMS (EI) *m/z* $[M+ H]^+$ for $C_{18}H_{18}Cl_2NO_4$ 382.0613, found 382.0619.

[3-(2,4-Dichloro-6-formyl-phenoxy)-propyl]-carbamic acid benzyl ester (1.72)

Using the general procedure of **B**, 4.03 g the title compound was prepared in 78.3% yield as a white solid: mp 56 °C; IR (KBr, cm^{-1}) 3319, 3066, 1687, 1678, 1534; ^1H NMR (300 MHz, $CDCl_3$) δ 10.22 (s, 1H), 7.69 (d, *J* = 2.7 Hz, 1H), 7.61 (d, *J* = 2.7 Hz, 1H), 7.35-7.32 (m, 5H), 5.27 (brs, 1H), 5.10 (s, 2H), 4.09 (t, *J* = 6.0 Hz, 2H), 3.49 (q, *J* = 6.0 Hz, 2H), 2.07 (quin, *J* = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.59, 156.41, 156.15, 136.38, 135.62, 131.20, 130.48, 129.86, 128.41, 128.02, 127.24, 126.84, 74.11, 66.21, 38.07, 30.06; MS (EI) *m/z* $[M+ H]^+$ 382 (20), 338 (14), 192 (28), 91 (100); HRMS (EI) *m/z* $[M+ H]^+$ for $C_{18}H_{18}Cl_2NO_4$ 382.0613, found 382.0619.

{3-[2,4-Dibromo-6-(2-methyl-5-oxo-oxazol-4-ylidenemethyl)phenoxy]propyl}carbamic acid benzyl ester (1.73)

Using the general procedure of **C**, 6.98 g the title compound was prepared in 84.7% yield as an yellow solid: mp 167 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.74 (d, *J* = 2.4 Hz, 1H), 7.74 (d, *J* = 2.4 Hz, 1H), 7.36-7.26 (m, 6H), 5.27 (brs, 1H), 5.11 (s, 2H), 3.97 (t, *J* = 5.8 Hz, 2H), 3.53 (q, *J* = 6.0 Hz, 2H), 2.43 (s, 3H), 2.10 (quin, *J* = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.85, 167.08, 156.51, 155.17, 137.84, 136.53, 134.65, 134.08, 129.92, 128.46, 128.02, 122.18, 118.46, 117.85, 73.28, 66.61, 38.22, 29.94, 15.74. MS (ESI) *m/z* $[M + Na + CH_3OH]^+$ 605 (50), 607(100), 609 (55).

{3-[2,4-Dichloro-6-(2-methyl-5-oxo-oxazol-4-ylidenemethyl)phenoxy]propyl}carbamic acid benzyl ester (1.74)

Using the general procedure of **C**, 4.23 g the title compound was prepared in 91.5 % yield as an yellow solid: mp 159 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (d, *J* = 2.5, 1H), 7.44 (d, *J* = 2.5 Hz, 1H), 7.36-7.32 (m, 6H), 5.24 (brs, 1H), 5.11 (s, 2H), 4.0 (t, *J* = 6.0 Hz, 2H), 3.53 (q, *J* = 6.3 Hz, 2H), 2.45 (s, 3H), 2.10 (quin, *J* = 6.0 Hz, 2H); ^{13}C NMR (75MHz, $CDCl_3$) δ 167.78, 167.12, 156.48, 153.66, 136.50, 134.61, 132.27, 130.42, 130.10, 129.48, 129.02, 128.45, 128.02, 122.16, 73.20, 66.61, 38.21, 29.98, 15.74. MS (ESI) *m/z* $[M + Na + CH_3OH]^+$ 517 (100), 519(55).

3-[2-(3-Benzyloxycarbonylaminopropoxy)-3,5-dibromophenyl]-2-(4-methoxybenzyloxy imino)propionic acid methyl ester (1.75)

Using the general procedure of **D**, 752 mg the title compound was prepared in 31.5% yield as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, *J* = 2.4 Hz, 1H), 7.36-7.32 (m, 5H), 7.18 (d, *J* = 8.7 Hz, 2H), 7.07 (d, *J* = 2.4 Hz, 1H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.26 (brs, 1H), 5.20 (s, 2H), 5.10 (s, 2H), 3.93 (t, *J* = 6.0 Hz, 2H), 3.89 (s, 2H), 3.82 (s, 3H), 3.80 (s, 3H), 3.43 (q, *J* = 6.0 Hz, 2H), 1.99-1.95 (m, 2H).

3-[2-(3-Benzyloxycarbonylaminopropoxy)-3,5-dichlorophenyl]-2-(4-methoxybenzyloxy imino)propionic acid methyl ester (1.76)

Using the general procedure of **D**, 770 mg the title compound was prepared in 32.5% yield as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.32 (m, 5H), 7.22 (d, *J* = 2.0, 1H), 7.17 (d, *J* = 8.3 Hz, 2H), 6.90 (d, *J* = 2.0, 1H), 6.86 (d, *J* = 8.3 Hz, 2H), 5.26 (brs, 1H), 5.21 (s,

2H), 5.11 (s, 2H), 3.95 (t, *J* = 5.9 Hz, 2H), 3.90 (s, 2H), 3.84 (s, 2H), 3.81 (s, 3H), 3.43 (q, *J* = 6.0 Hz, 2H) 1.97 (quin, *J* = 6.0 Hz, 2H); MS (ESI) *m/z* $[M + Na]^+$ 611 (100), $[M + H]^+$ 589 (6).

General procedure **E**

(*Z*)-3-(4-(3-Aminopropoxy)-3,5-dibromophenyl)-2-(hydroxyimino)-N-phenethyl propanamide (1.79 (1.50a, 1.77a)

A mixture of amide **1.78** {**1.50a, 1.77a**} (71 mg, 0.095 mmol)**,** $AlCl_3$ (134 mg, 1 mmol) and anisole (108 mg, 1 mmol) in CH_3NO_2 (10 mL) and CH_2Cl_2 (10 mL) was stirred for 4 h at room temperature. The mixture was stirred after water was added. The solvents were removed under reduced pressure and the crude product was subjected to flash chromatography (ethyl acetate: acetone: formic acid: water = 5: 3: 0.5: 0.5) to afford an oil, which was acidified with 5% HCl to give **1.79** {**1.50a, 1.77a**} hydrochloride salt (50 mg, 95%).^{1}H NMR (300 MHz, CD_3OD) δ 7.50 (s, 2H), 7.27-7.16 (m, 5H), 4.11 (t, *J* = 5.7 Hz, 2H), 3.84 (s, 2H), 3.46 (t, *J* = 7.2 Hz, 2H), 3.31 (t, *J* = 7.2 Hz, 2H), 2.80 (t, *J* = 7.2 Hz, 2H), 2.21 (quin, *J* = 6.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 152.2, 152.0, 140.3, 137.9, 134.6, 129.8, 129.5, 127.4, 118.6, 71.6, 42.0, 38.9, 36.5, 29.0, 28.8. MS (ESI) *m/z* $[M+H]^+$ 512 (53), 514 (100), 516 (50). HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{24}Br_2N_3O_3$ 512.0814, found 512.0815. HPLC: C_{18}, 99%, 7:13 CH_3CN(0.1% TFA)/H_2O (0.1%TFA), t_R = 4.0 min.

(*Z*)-3-(4-(3-Aminopropoxy)-3,5-dibromophenyl)-2-(hydroxyimino)-N-(4-methoxyphen ethyl)propanamide (1.79 (1.50a, 1.77b)

Using general procedure **E,** 39 mg of the title compound was obtained in 85% yield as pale solid. ^{1}H NMR (300 MHz, CD_3OD) δ 7.51 (s, 2H), 7.08 (d, *J* = 5.0 Hz, 2H), 6.80 (d, *J* = 5.0

Hz, 2H), 4.12 (t, *J* = 5.7 Hz, 2H), 3.84 (s, 2H), 3.75 (s, 3H), 3.43 (t, *J* = 7.5 Hz, 2H), 3.31 (t, *J* = 7.5 Hz, 2H), 2.73 (t, *J* = 7.5 Hz, 2H), 2.13 (quin, *J* = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 159.8, 152.3, 152.2, 137.9, 134.6, 132.4, 130.7, 118.6, 115.0, 71.7, 55.7, 42.1, 39.0, 35.6, 29.0, 28.8. MS (ESI) *m/z* $[M+H]^+$ 542 (60), 544 (100), 546 (50). HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{26}Br_2N_3O_4$ 542.0290, found 542.0290. HPLC: C_{18}, 98%, 7:13 CH_3CN(0.1% TFA)/H_2O(0.1%TFA), t_R = 3.5 min.

(*Z*)-3-(4-(3-Aminopropoxy)-3,5-dibromophenyl)-N-(4-chlorophenethyl)-2-(hydroxyimino) propanamide {1.79 (1.50a, 1.77c)}

Using general procedure **E**, 44 mg of the title product was obtained in 89% yield as a pale yellow solid: ^{1}H NMR (300 MHz, CD_3OD) δ 7.48 (s, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 4.08 (t, *J* = 5.7 Hz, 2H), 3.82 (s, 2H), 3.46 (t, *J* = 6.9 Hz, 2H), 3.17 (t, *J* = 4.8 Hz, 2H), 2.79 (t, *J* = 7.0 Hz, 2H), 2.13 (quin, *J* = 6.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 152.3, 152.1, 139.2, 137.9, 134.6, 133.2, 133.4, 129.5, 118.6, 71.7, 41.6, 39.0, 35.7, 29.0, 28.8. MS (ESI) *m/z* $[M+H]^+$ 546 (43), 548 (100), 550 (70). HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{23}Br_2N_3O_3Cl$ 545.9795, found 545.9802. HPLC: C_{18}, 100%, 7:13 CH_3CN(0.1% TFA)/H_2O (0.1%TFA), t_R = 3.6 min.

(*Z*)-N-(2-(1H-Indol-3-yl)ethyl)-3-(4-(3-aminopropoxy)-3,5-dibromophenyl)-2-(hydroxy imino)propanamide {1.79 (1.50a, 1.77d)}

Using general procedure **E,** 26 mg of the title compound was obtained in 50% yield as pale solid ^{1}H NMR (300 MHz, CD_3OD) δ 7.54 (d, *J* = 8.1 Hz, 1H), 7.53 (s, 2H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.07 (t, *J* = 8.1 Hz, 1H), 7.06 (s, 1H), 6.98 (t, *J* = 8.1 Hz, 1H), 4.10 (t, *J* = 5.7 Hz, 2H),

3.85 (s, 2H), 3.29 (t, *J* = 7.4 Hz, 2H), 2.96 (t, *J* = 7.5 Hz, 2H), 2.10 (quin, *J* = 6.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 152.3, 152.1, 138.2, 138.0, 134.6, 128.8, 123.5, 122.6, 119.7, 119.3, 118.6, 117.3, 113.2, 112.2, 71.7, 41.4, 39.0, 29.0, 28.9, 16.3. MS (ESI) *m/z* $[M+H]^+$ 551 (68), 553(100), 555 (80). HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{25}Br_2N_4O_3$ 551.0293, found 551.0289. HPLC: C_{18}, 92%, 7:13 CH_3CN(0.1% TFA)/H_2O(0.1%TFA), t_R = 3.6 min.

(*Z*)-3-(4-(3-Aminopropoxy)-3-bromophenyl)-2-(hydroxyimino)-N-phenethylpropanemide {1.79 (1.50b, 1.77a)}

Using general procedure **E,** 45 mg of the title compound was obtained in 89% yield as pale solid: ^{1}H NMR (300 MHz, CD_3OD) δ 7.46 (d, *J* = 1.8 Hz, 1H), 7.46-7.15 (m, 6H), 6.94 (d, *J* = 8.4 Hz, 2H), 4.15 (t, *J* = 5.5 Hz, 2H), 3.82 (s, 2H), 3.44 (t, *J* = 7.0 Hz, 2H), 3.21 (t, *J* = 7.0 Hz, 2H), 2.78 (t, *J* = 7.2 Hz, 2H), 2.18 (quin, *J* = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 154.7, 153.0, 140.4, 134.7, 132.8, 130.6, 129.8, 127.3, 114.7, 112.7, 67.9, 41.9, 39.0, 36.5, 28.8, 28.3. MS (ESI) *m/z* $[M+H]^+$ 434 (90), 436(100). HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{25}BrN_3O_3$ 434.1079, found 434.1079. HPLC: C_{18}, 99%, 7:13 CH_3CN(0.1% TFA)/H_2O (0.1%TFA), t_R = 2.6 min.

(*Z*)-3-(4-(3-Aminopropoxy)-3-bromophenyl)-2-(hydroxyimino)-N-(4-methoxyphenethyl) propanamide {1.79 (1.50b, 1.77b)}

Using general procedure **E,** 49 mg of the title compound was obtained in 95% yield as pale solid ^{1}H NMR (300 MHz, CD_3OD) δ 7.47 (d, *J* = 2.0 Hz, 1H), 7.20 (dd, *J* = 8.4 Hz, 2.0 Hz, 1H), 7.07 (d, *J* = 8.5 Hz, 2H), 6.94 (d, *J* = 8.5 Hz, 1H), 6.80 (d, *J* = 8.6 Hz, 2H), 4.16 (t, *J* = 6.6 Hz, 2H), 3.82 (s, 2H), 3.75 (s, 3H), 3.41 (t, *J* = 6.9 Hz, 2H), 3.22 (t, *J* = 7.2 Hz, 2H), 2.72 (t, *J* =

7.2 Hz, 2H), 2.18 (quin, *J* = 6.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 159.7, 154.6, 152.9, 134.7, 132.6, 132.3, 130.8, 130.6, 114.9, 114.4, 112.5, 67.6, 55.6, 42.1, 38.9, 35.6, 28.7, 28.2. MS (ESI) *m/z* $[M+H]^+$ 464 (55), 466 (50). HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{27}BrN_3O_4$ 464.1185, found 464.1187. HPLC: C_{18}, 99%, 7:13 CH_3CN(0.1% TFA)/H_2O (0.1%TFA), t_R = 2.6 min.

(*Z*)-3-(4-(3-Aminopropoxy)-3-bromophenyl)-N-(4-chlorophenethyl)-2-(hydroxyimino) propanamide {1.79 (1.50b, 1.77c)}

Usinggeneral procedure **E**, 45 mg of the title product was obtained in 96% yield a pale yellow solid: ^{1}H NMR (300 MHz, CD_3OD) δ 7.43 (s, 1H), 7.23-7.12 (m, 6H), 6.95 (d, *J* = 8.2 Hz, 1H), 4.16 (t, *J* = 6.9 Hz, 2H), 3.81 (s, 2H), 3.44 (t, *J* = 6.9 Hz, 2H), 3.22 (t, *J* = 6.9 Hz, 2H), 2.77 (t, *J* = 6.9 Hz, 2H), 2.18 (brs, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 154.6, 152.8, 139.2, 134.7, 133.0, 132.4, 131.5, 130.5, 129.4, 114.4, 112.5, 106.5, 67.6, 41.6, 38.8, 35.7, 28.7, 28.2; MS (ESI) *m/z* $[M+H]^+$ 468 (70), 470 (100). HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{24}BrN_3O_3Cl$ 468.0690, found 468.0692. HPLC: C_{18}, 97%, 7:13 CH_3CN(0.1% TFA)/H_2O (0.1%TFA), t_R = 4.30 min.

(*Z*)-N-(2-(1H-Indol-3-yl)ethyl)-3-(4-(3-aminopropoxy)-3,5-dibromophenyl)-2-(hydroxyl imino)propanamide {1.79 (1.50b, 1.77d)}

Using general procedure **E,** 40 mg of the title compound was obtained in 87% yield as pale solid: ^{1}H NMR (300 MHz, CD_3OD) δ 7.54 (d, *J* = 7.9 Hz, 1H), 7.48 (d, *J* = 1.9 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.21 (dd, *J* = 8.1 Hz, 1.8 Hz, 1H), 7.07 (t, *J* = 7.2 Hz, 1H), 7.04 (s, 1H), 6.97 (t, *J* = 7.2 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 4.14 (t, *J* = 5.6 Hz, 2H), 3.83 (s, 2H), 3.53 (t, *J*

= 7.3 Hz, 2H), 3.20 (t, *J* = 7.1 Hz, 2H), 2.94 (t, *J* = 7.2 Hz, 2H), 2.16 (quin, *J* = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 154.6, 152.9, 138.1, 134.7, 132.6, 130.6, 128.7, 123.4, 122.3, 119.6, 119.3, 114.4, 113.1, 112.5, 112.2, 67.6, 41.4, 38.9, 28.2, 26.3. MS (ESI) *m/z* $[M+H]^+$ 473 (92), 475 (100). HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{26}BrN_3O_3$ 473.1188, found 473.1194. HPLC: C_{18}, 98%, 7:13 CH_3CN(0.1% TFA)/H_2O(0.1%TFA), t_R = 2.4 min.

(*Z*)-3-(2-(3-Aminopropoxy)-3,5-dibromophenyl)-2-(hydroxyimino)-N-phenethyl propanamide{1.79 (1.50c, 1.77a)}

Using general procedure **E**, 44 mg of the title compound was obtained in 89% yield as a pale yellow solid: ^{1}H NMR (300 MHz, CD_3OD) δ 7.62 (d, *J* = 2.3 Hz, 1H), 7.24-7.14 (m, 6H), 4.09 (t, *J* = 6.0 Hz, 2H), 3.95 (s, 2H), 3.47 (t, *J* = 6.9 Hz, 2H), 3.10 (t, *J* = 7.0 Hz, 2H), 2.80 (t, *J* = 7.2 Hz, 2H), 2.10 (quin, *J* = 6.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 154.3, 152.3, 140.4, 135.6, 135.1, 133.5, 129.8, 129.5, 127.4, 119.2, 118.4, 72.1, 42.0, 39.1, 36.5, 29.0, 24.7. MS (ESI) *m/z* $[M+H]^+$ 512 (50), 514(100), 516(50). HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{20}H_{23}Br_2N_3O_3Na$ 534.0004, found 534.0012. HPLC: C_{18}, 91%, 7:13 CH_3CN(0.1% TFA)/H_2O(0.1%TFA), t_R = 9.0 min.

(*Z*)-3-(2-(3-Aminopropoxy)-3,5-dibromophenyl)-2-(hydroxyimino)-N-(4-methoxy phenethyl)propanamide {1.79 (1.50c, 1.77b)}

Using general procedure **E,** 45 mg of the title compound was obtained in 90% yield as pale solid: ^{1}H NMR (300 MHz, CD_3OD) δ 7.62 (d, *J* = 2.3 Hz, 1H), 7.25 (d, *J* = 2.3 Hz, 1H), 7.07 (d, *J* = 8.6 Hz, 2H), 6.78 (d, *J* = 8.6 Hz, 2H), 4.11 (t, *J* = 5.9 Hz, 2H), 3.96 (s, 2H), 3.74 (s, 3H), 3.44 (t, *J* = 7.0 Hz, 2H), 3.28 (t, *J* = 7.1 Hz, 2H), 2.73 (t, *J* = 7.2 Hz, 2H), 2.21 (quin, *J* = 6.3

Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 159.7, 154.3, 152.3, 135.6, 135.0, 133.4, 132.3, 130.8, 119.2, 118.4, 114.9, 71.9, 55.7, 42.2, 38.9, 35.6, 29.0, 24.6. MS (ESI) *m/z* $[M+H]^+$ 542 (50), 544(100), 546(50). HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{26}Br_2N_3O_4$ 542.0290, found 542.0291. HPLC: C_{18}, 100%, 7:13 CH_3CN(0.1% TFA)/H_2O(0.1%TFA), t_R = 7.7 min.

(*Z*)-3-(2-(3-Aminopropoxy)-3,5-dibromophenyl)-N-(4-chlorophenethyl)-2-(hydroxyimino) propanamide {1.79 (1.50c, 1.77c)}

Using general procedure **E,** 46 mg of the title compound was obtained in 90% yield as pale solid: ^{1}H NMR (300 MHz, CD_3OD) δ 7.63 (d, *J* = 2.2 Hz, 1H), 7.22 (d, *J* = 2.2 Hz, 1H), 7.20 (d, *J* = 8.7 Hz, 2H), 7.13 (d, *J* = 8.6 Hz, 2H), 4.11 (t, *J* = 5.7 Hz, 2H), 3.95 (s, 2H), 3.47 (t, *J* = 7.1 Hz, 2H), 3.28 (t, *J* = 7.2 Hz, 2H), 2.78 (t, *J* = 7.0 Hz, 2H), 2.21 (quin, *J* = 6.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 154.3, 152.3, 139.2, 135.5, 135.1, 133.4, 131.4, 129.5, 129.4, 119.2, 118.4, 72.0, 41.6, 39.0, 35.8, 29.0, 24.7. MS (ESI) *m/z* $[M+H]^+$ 546 (50), 548 (100), 550 (70). HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{23}Br_2N_3O_3Cl$ 545.9795, found 545.9774. HPLC: C_{18}, 98%, 7:13 CH_3CN(0.1% TFA)/H_2O(0.1%TFA), t_R = 15.7 min.

(*Z*)-N-(2-(1H-Indol-3-yl)ethyl)-3-(2-(3-aminopropoxy)-3,5-dibromophenyl)-2-(hydroxyl imino)propanamide {1.79 (1.50c, 1.77d)}

Using general procedure **E**, 26 mg of the title compound was obtained in 87% yield as a pale yellow solid: ^{1}H NMR (300 MHz, CD_3OD) δ 7.62 (d, *J* = 2.3 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 2.3 Hz, 1H), 7.09-7.07 (m, 1H), 7.04 (s, 1H), 7.00-6.95 (m, 1H), 4.08 (t, *J* = 5.7 Hz, 2H), 3.96 (s, 2H), 3.56 (t, *J* = 7.2 Hz, 2H), 3.25 (t, *J* = 7.1 Hz, 2H), 2.96 (t, *J* = 7.2 Hz, 2H), 2.19 (quin, *J* = 6.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3,

154.2, 152.1, 138.0, 135.6, 134.9, 133.5, 128.6, 123.5, 122.3, 119.5, 119.3, 119.2, 118.3, 113.0, 112.2, 71.9, 46.0, 38.9, 29.0, 26.2, 24.8. MS (ESI) *m/z* $[M+H]^+$ 551 (54), 553 (100), 555 (42). HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{25}Br_2N_4O_3$ 551.0293, found 551.0283. HPLC: C_{18}, 98%, 7:13 CH_3CN(0.1% TFA)/H_2O(0.1%TFA), t_R = 7.6 min.

(*Z*)-3-(2-(3-Aminopropoxy)-3,5-dichlorophenyl)-2-(hydroxyimino)-N-phenethyl propanamide {1.79 (1.50d, 1.77a)}

Using general procedure **E,** 38 mg of the title compound was obtained in 91 % yield as pale solid: ^{1}H NMR (300 MHz, CD_3OD) δ 7.34 (d, *J* = 2.5 Hz, 1H), 7.26-7.15 (m, 5H), 7.07 (d, *J* = 2.5 Hz, 1H), 4.12 (t, *J* = 5.7 Hz, 2H), 3.96 (s, 2H), 3.48 (t, *J* = 6.9 Hz, 2H), 3.27 (t, *J* = 7.1 Hz, 2H), 2.80 (t, *J* = 7.2 Hz, 2H), 2.04 (quin, *J* = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 152.8, 152.3, 140.4, 135.2, 130.8, 129.8, 129.7, 129.5, 129.3, 127.4, 72.0, 41.9, 39.0, 36.5, 29.1, 24.6. MS (ESI) *m/z* $[M+H]^+$ 424 (100), 426 (65). HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{20}H_{24}Cl_2N_3O_3$ 424.1195, found 424.1198. HPLC: C_{18}, 99%, 7:13 CH_3CN(0.1% TFA)/H_2O (0.1%TFA), t_R = 7.0 min.

(*Z*)-3-(2-(3-Aminopropoxy)-3,5-dichlorophenyl)-2-(hydroxyimino)-N-(4-methoxyphene thyl)propanamide {1.79 (1.50d, 1.77b)}

Using general procedure **E,** 37 mg of the title compound was obtained in 88 % yield as pale solid: ^{1}H NMR (300 MHz, CD_3OD) δ 7.34 (d, *J* = 2.3 Hz, 1H), 7.09 (d, *J* = 2.3 Hz, 1H), 7.07 (d, *J* = 8.6 Hz, 2H), 6.78 (d, *J* = 8.5 Hz, 2H), 4.12 (t, *J* = 5.7 Hz, 2H), 3.95 (s, 2H), 3.74 (s, 3H), 3.44 (t, *J* = 7.0 Hz, 2H), 3.27 (t, *J* = 7.1 Hz, 2H), 2.73 (t, *J* = 7.2 Hz, 2H), 2.20 (quin, *J* = 6.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 159.8, 152.8, 152.3, 135.2, 132.3, 130.7, 129.8,

129.7, 129.3, 115.0, 72.0, 55.7, 42.1, 39.0, 35.6, 29.0, 24.6. MS (ESI) *m/z* $[M+H]^+$ 454 (100), 456 (70). HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{26}Cl_2N_3O_4$ 454.1300, found 454.1313. HPLC: C_{18}, 99%, 7:13 CH_3CN(0.1% TFA)/H_2O(0.1%TFA), t_R = 6.1 min.

(*Z*)-3-(2-(3-Aminopropoxy)-3,5-dichlorophenyl)-N-(4-chlorophenethyl)-2-(hydroxyimino) propanamide {1.79 (1.50d, 1.77c)}

Using general procedure **E,** 38 mg of the title compound was obtained in 87% yield as pale solid: ^{1}H NMR (300 MHz, CD_3OD) δ 7.34 (d, *J* = 2.4 Hz, 1H), 7.20 (d, *J* = 8.7 Hz, 2H), 7.14 (d, *J* = 8.7 Hz, 2H), 7.05 (d, *J* = 2.4 Hz, 1H), 4.11 (t, *J* = 5.7 Hz, 2H), 3.94 (s, 2H), 3.47 (t, *J* = 7.2 Hz, 2H), 3.27 (t, *J* = 7.1 Hz, 2H), 2.79 (t, *J* = 7.0 Hz, 2H), 2.20 (quin, *J* = 6.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 152.8, 152.4, 139.2, 135.1, 133.1, 131.5, 130.7, 129.8, 129.7, 129.4, 71.9, 41.6, 38.9, 35.8, 29.0, 24.5. MS (ESI) *m/z* $[M+H]^+$ 458 (100), 460 (100). HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{20}H_{22}Cl_3N_3O_3Na$ 480.0624, found 480.0627. HPLC: C_{18}, 99%, 7:13 CH_3CN(0.1% TFA)/H_2O(0.1%TFA), t_R = 13.0 min.

(*Z*)-N-(2-(1H-Indol-3-yl)ethyl)-3-(2-(3-aminopropoxy)-3,5-dichlorophenyl)-2-(hydroxyl imino)propanamide {1.79 (1.50d, 1.77d)}

Using general procedure **E,** 32 mg of the title compound was obtained in 64% yield as pale solid : ^{1}HNMR (300 MHz, CD_3OD) δ 7.54 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 2.5 Hz, 1H), 7.31(d, *J* = 7.8 Hz, 1H), 7.11 (d, *J* = 2.5 Hz, 1H), 7.07 (t, *J* = 7.8 Hz, 1H), 7.04 (s, 1H), 6.97 (t, *J* = 7.8 Hz, 1H), 4.08 (t, *J* = 5.7 Hz, 2H), 3.96 (s, 2H), 3.56 (t, *J* = 7.1 Hz, 2H), 3.23 (t, *J* = 7.1 Hz, 2H), 2.96 (t, *J* = 7.2 Hz, 2H), 2.17 (quin, *J* = 6.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 153.0, 152.5, 138.4, 135.4, 130.9, 130.1, 129.5, 123.7, 122.5, 119.8, 119.5, 113.3, 112.4, 72.2,

41.5, 39.1, 29.2, 26.4, 24.8. MS (ESI) *m/z* $[M+H]^+$ 463 (100), 465 (75). HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{25}Cl_2N_4O_3$ 463.1304, found 463.1310. HPLC: C_{18}, 99%, 7:13 CH_3CN(0.1% TFA)/H_2O(0.1%TFA), t_R = 6.1 min.

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2.0 MIXTURE SYNTHESIS APPROACH TO NATURAL PRODCUT SETEROISOMER: SYNTHESIS OF FOUR ISOMERS OF LANGUNAPYRONE

2.1 INTRODUCTION:

2.1.1 FLUOROUS MIXTURE SYNTHESIS (FMS)

Organic and natural products synthesis has been an exciting field for more than a century since the synthesis of (+)-glucose by Emil Fischer in 1890.[1] Synthetic chemists now not only can synthesize genes and proteins in the laboratory, but also assemble complex and fascinating molecular structures from the realm of natural products by rational methods from simple starting materials. Furthermore, a myriad of designed and random molecular frameworks can be synthesized on demand and tested for various applications. Such useful compounds range from biological tools and medicines to high-value materials for cosmetics, computers, sophisticated machines, etc.

Traditionally, the goal of total synthesis of a natural product with stereogenic centers was to obtain the target molecule in enantiomerically pure form. The synthesis of its stereoisomers is sometimes necessary when its diastereomers are also natural products (such as epoxyquinol A

and B[2]) or when the structure has not fully assigned (such as aurilol[3]) or the original structure assignment is not correct (for example homononactinic acid[4a] and azaspiracid-1[4b]). As the complexity of the natural products increase, the structure assignment, especially the stereochemistry assignment, is no longer trivial. Total synthesis can prove or disprove a proposed structure with spectroscopic and optical data as the commonly used tools for comparison of natural and synthetic product.

One significant challenge of the traditional solution phase synthesis in synthesizing multiple stereoisomers of natural products is a huge amount of work involved. Parallel solution phase synthesis techniques are thus applied to increase the efficacy of the synthesis. However, the purification and characterization of the compounds is a common problem.

The split-mix approach using polymer-bound substrates is sometimes applied to synthesize stereoisomers of natural products.[5] However, deconvolution of libraries can be cumbersome and the time saved during the synthesis is, at least in part, spent during the analysis and identification of the hit structure. The newly emerging technique of Fluorous Mixture Synthesis (FMS)[6] allows solution phase organic synthesis to be carried out on mixtures of compounds with predictable separation and hence provides unique advantage for library generation.

Fluorous mixture synthesis (FMS) has three stages: premix, mixture synthesis and post mix. The representative illustration of various stages is shown in Figure 2.1.

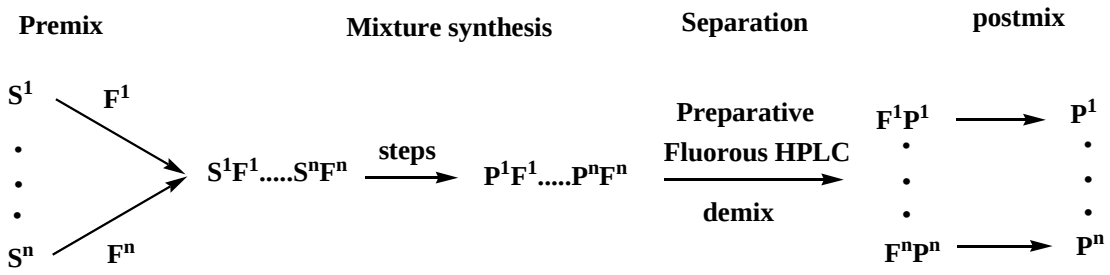


Figure 2.1. A Representative Scheme of Fluorous Mixture Synthesis

During the premix, each different precursor is prepared individually with traditional organic synthetic methods and is attached to a protecting group bearing a different unique perfluoroalkyl chain. The fluorous-tagged precursors are mixed and taken through a series of synthetic steps. At the end of the synthesis, the mixture is separated by preparative fluorous HPLC based on the difference of the fluorine content. Compounds with higher fluorine content have longer retention time on fluorous HPLC column. In the final stage, the fluorous protecting group was removed to generate a library of different compounds.

FMS can be classified into three categories by the nature of the target library. If two different enantiomers are tagged with two different fluorous tags and mixed, a quasiracemic mixture is obtained. When the quasiracemic mixture is conducted to the whole synthesis, two enantiomers can be obtained in the final stage. Both the enantiomers of pyridovercin and mappicine[7] have been synthesized with this approach. The next level is the synthesis of diastereomers with FMS. Different diastereomers are attached to the fluorous tags and mixed and conducted to the whole synthesis. Syntheses of 16 isomers of Pine sawfly sex pheromone,[8] 16 isomers of passifloricin A[9] and 28 isomers of murisolin[10] have been achieved with this way. The third level is the synthesis of a library of structurally diverse analogs of natural product. 560 analogs of the natural product mappicine have been synthesized with FMS recently.[11]

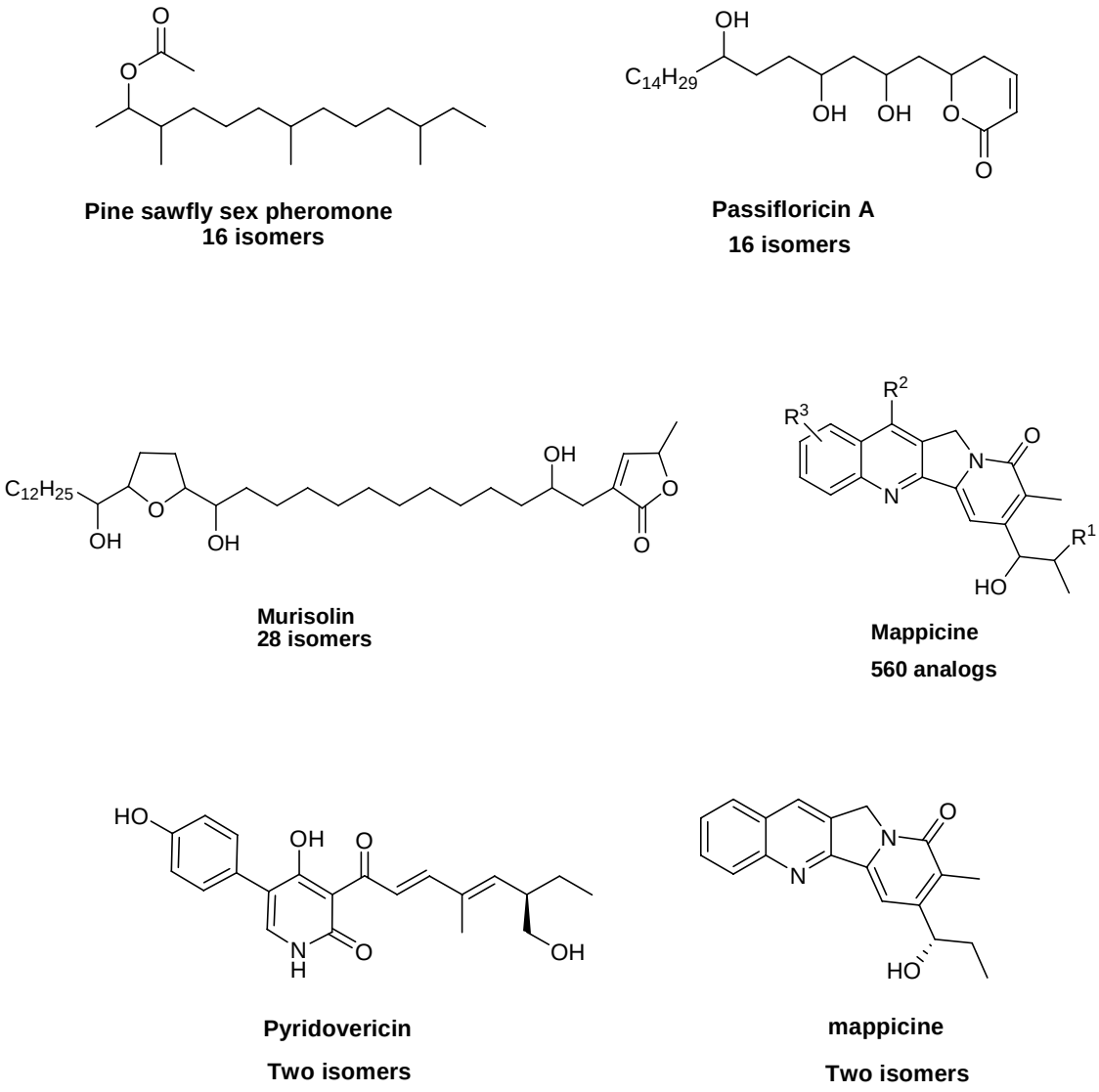


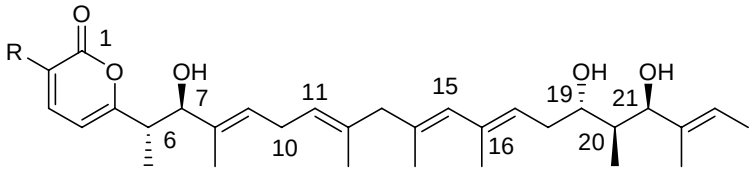
Figure 2.2. Synthesized natural products and their stereoisomers with FMS

2.1.2 LAGUNAPYRONES A-C

Lagunapyrones A-C (Figure 2.3) are marine natural products which were produced in a seawater-based medium by an unidentified marine actinomycete (culture CNB-984) isolated from sediment collected in the Agua Hedionda Lagoon in Carlsbad, California in 1996.[12]

Lagunapyrone B shows modest modest cytotoxicity, ED_{50} = 3.5 μg/mL, against the human colon cancer cell.[12]

Based on the study of their IR, NMR and UV spectra, the lagunapyrones consist of an α-pyrone and a long carbon chain bearing one conjugate diene and two skipped dienes. The pyrone moiety is adjacent to a stereogenic center. The five stereogenic centers in the molecule are separated into two groups by the long carbon chain. Two stereogenic centers are located on the left side of the molecule and the other three are located on the right side. Lagunapyrone B possesses a propyl substituent at the 2-position of the pyrone ring; lagunapyrone A and C possess a methyl and a butyl instead.



Lagunapyrone A R = CH_3
B R = $CH_2CH_2CH_3$
C R = $CH_2CH_2CH_2CH_3$

Figure 2.3. A general structure for lagunapyrones

Assignment of the relative stereochemistry at C-6 and C-7 was accomplished by computer analysis of the vicinal proton coupling constants, and by comparison of these values with two isomeric synthetic analogs in which phenyl is substituted for the α-pyrone.[13] The relative stereochemistry of C-19 through C-21 was assigned by converting langunapyrone B to an acetonide. ^{13}C NMR and NOE analysis showed that C-19 through C-21 is anti/syn configuration. Since the stereochemistry of C-6, C-7 could not be related to the stereochemistry of C-19 through C-21, there are four possible configurations for the natural product.

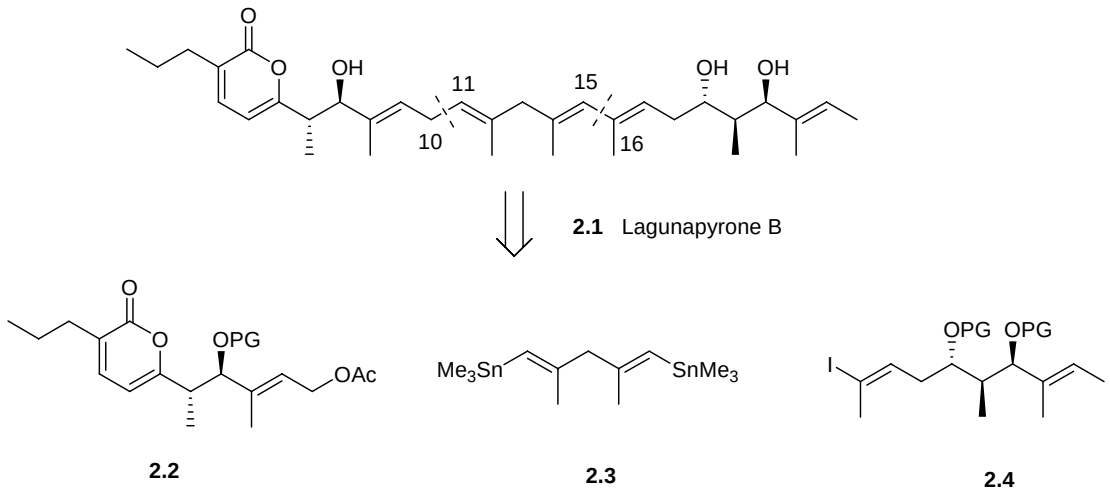
The absolute stereochemistry of lagunapyrones has not been assigned and no total synthesis of langunapyrones has been reported. Our goal of this project was to apply FMS (fluorous mixture synthesis) for the synthesis of four stereoisomers of lagunapyrone B and assign the absolute configuration of these natural products.

Three free hydroxyl groups in lagunapyrone B provide desirable locations for the fluorous tags. Our tagging strategy for this mixture synthesis is that one fluorous tag is attached to C19 hydroxyl group and the other one attached to C7 hydroxyl group. The double tagging strategy has only been used once for the synthesis of passifloricin A[9] in our group. In this synthesis, triisopropylsilyl (TIPS) protecting group is used as the fluorous tag. The fluorous TIPS group is advantageous because it is stable under most reaction conditions and easy to be deprotected. However, the bulkiness of this big protecting group could cause some problems to the reactivities of the substrate.

2.1.3 RETROSYNTHESIS OF LAGUNAPYRONE

The retrosynthesis to assemble the backbone of the target structure **2.1** is shown in Scheme 2.1. Since all the seven double bonds in lagunapyrone B are trisubstituted, the formation of these double bonds is not suitable by Wittg reaction[14] or Julia olefination reaction.[15] Especially the skipped dienes in the molecule might undergo isomerization under these harsh conditions. Palladium catalyzed coupling reactions (Stille coupling,[16] Negishi coupling,[17] Suzuki coupling[18]) are widely used for carbon-carbon bonds formation in the synthesis of complex molecules since they are usually performed under mild conditions and provide excellent selectivities. We thus designed our retrosynthesis based on palladium catalyzed coupling reactions.

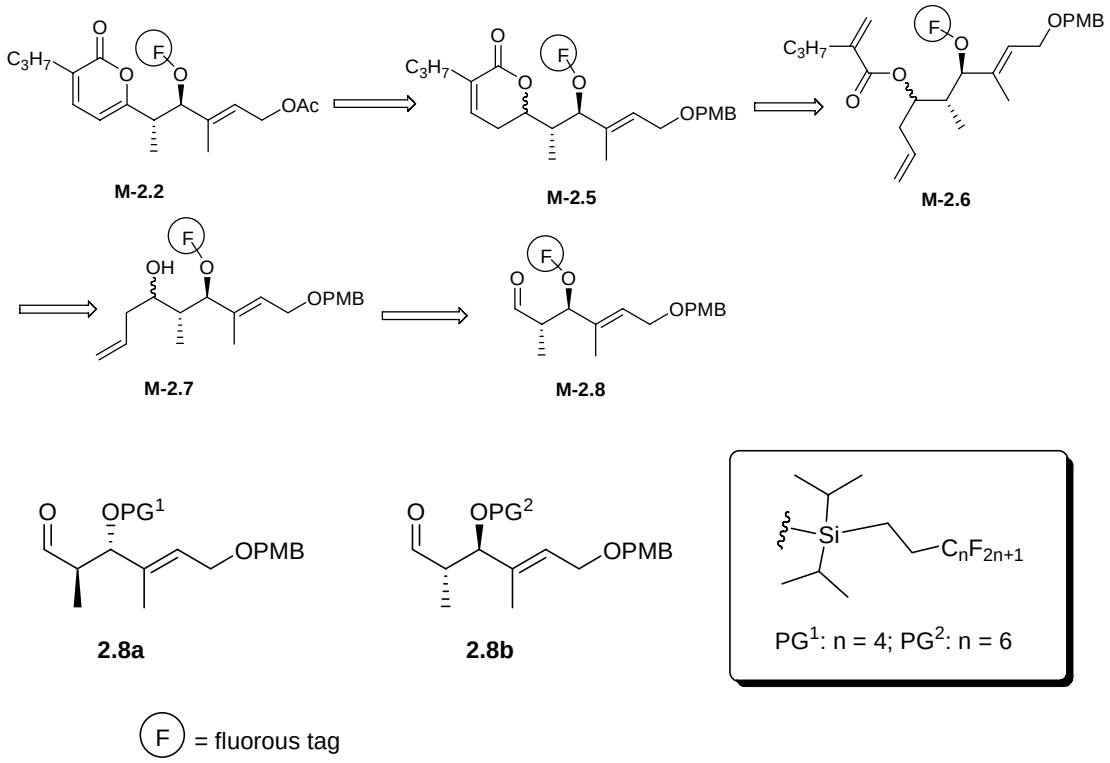
Cleavage of bond between C-10 and C11 and bond between C-15 and C-16 provides three fragments. Fragment **2.2** is an allylic acetate bearing a pyrone and two stereogenic centers; Fragment **2.3** is a symmetric divinylstannane; Fragment **2.4** is a vinyliodide bearing three stereogenic centers. Fragments **2.2** and **2.3** can be assembled by Stille coupling and the same as fragment **2.3** and **2.4.**



Scheme 2.1 Retrosynthetic analysis of lagunapyrone B

2.1.4 RETROSYNTHESIS OF FRAGMENT 2.2

The original plan for synthesizing pyrone **M-2.2** is from α,β-unsaturated lactone **M-2.5**, which can be constructed by triene **M-2.6** with metathesis approach. Further retrosynthetic analysis leads to alcohol **M-2.7**, which can be synthesized from aldehyde **M-2.8**. Aldehyde **M-2.8** can be constructed by Paterson's anti aldol reaction approach.[19] In the numbering this document, "M" denotes a quasiracemic mixture, although it is drawn as a single isomer in this whole document in order to simplify the structure.



Scheme 2.2 Retrosynthetic analysis of fragment 2.2 of lagunapyrone B

2.2 RESULTS AND DISCUSSION

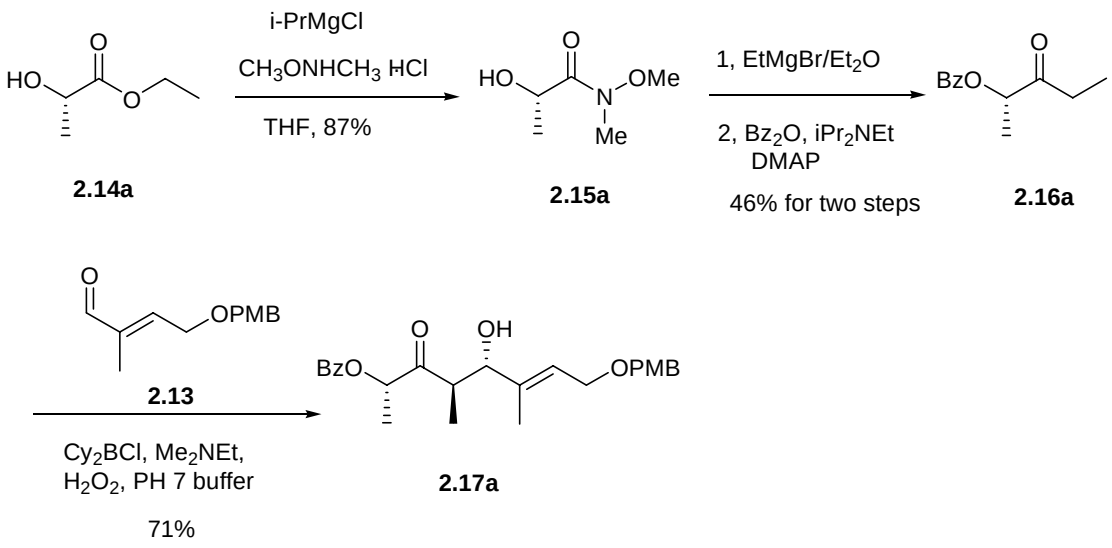
2.2.1 MIXTURE SYNTHESIS OF FRAGMENT M-2.2 OF LAGUNAPYRONE B BY TAGGING C7 HYDROXYL GROUP WITH FLUOROUS TIPS GROUP

The synthesis of aldehyde **2.13** started from the commercially available 2-butene-1,4-diol **2.9**, which was treated with sodium hydride and PMBCl in DMF to provide the bis-PMB ether **2.10** in 71% yield. Cleavage of the double bond in compound **2.10** by ozonolysis afforded the

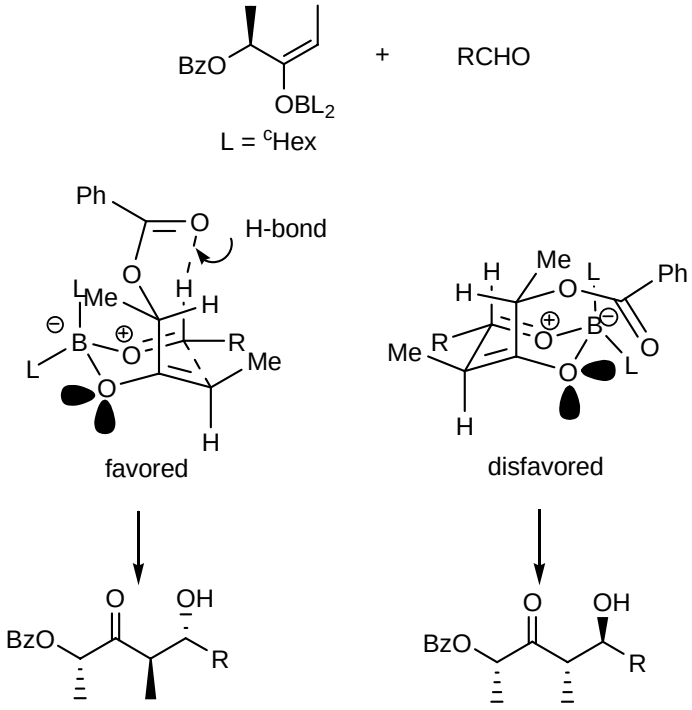
aldehyde **2.11** in 85% yield. Aldehyde **2.11** was reacted with commercially available Wittg reagent **2.12** to give α,β-unsaturated aldehyde **2.13** in 90% yield as a single compound.

Scheme 2.3 Synthesis of α,β-unsaturated aldehyde 2.13

The synthesis of anti-aldol compound **2.17a** was achieved by Paterson's approach.[19] Commercially available ethyl (*S*)-(–)-lactate **2.14a** was reacted with *N*,*O*-dimethylhydroxylamine hydrochloride, in the presence of *i*-PrMgCl, to give the Weinreb amide (*S*)-**2.15a** in 87% yield. Addition of EtMgBr to (*S*)-**2.15a**, followed by benzoylation of the resulting α-hydroxy ketone with benzoic anhydride (Bz_2O), then provided (*S*)-**2.16a** in 46% overall yield. The low yield was probably caused by the volatility of the intermediate α-hydroxy ketone (structure not shown). (S)-**2.16a** was treated with *c*-Hex_2BCl then followed by addition of aldehyde **2.13** to generate the anti-aldol product **2.17a** in 71% yield as a single diastereomer. The outcome of stereochemistry of compound **2.17a** could be explained based on the model (Scheme 2.5) which was cited from Paterson's paper.[19]

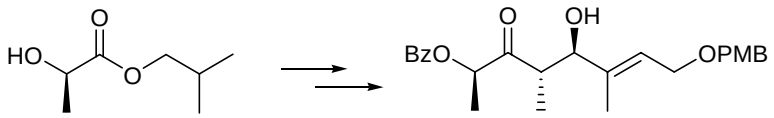


Scheme 2.4 Synthesis of antialdol compound 2.17a



Scheme 2.5 Model for the outcome of Paterson's anti-aldol reaction

Similarly, antialdol product **2.17b**, the enantiomer of compound **2.17a**, was synthesized from commercially available isobutyl (*R*)-(+)-lactate **2.14b.**

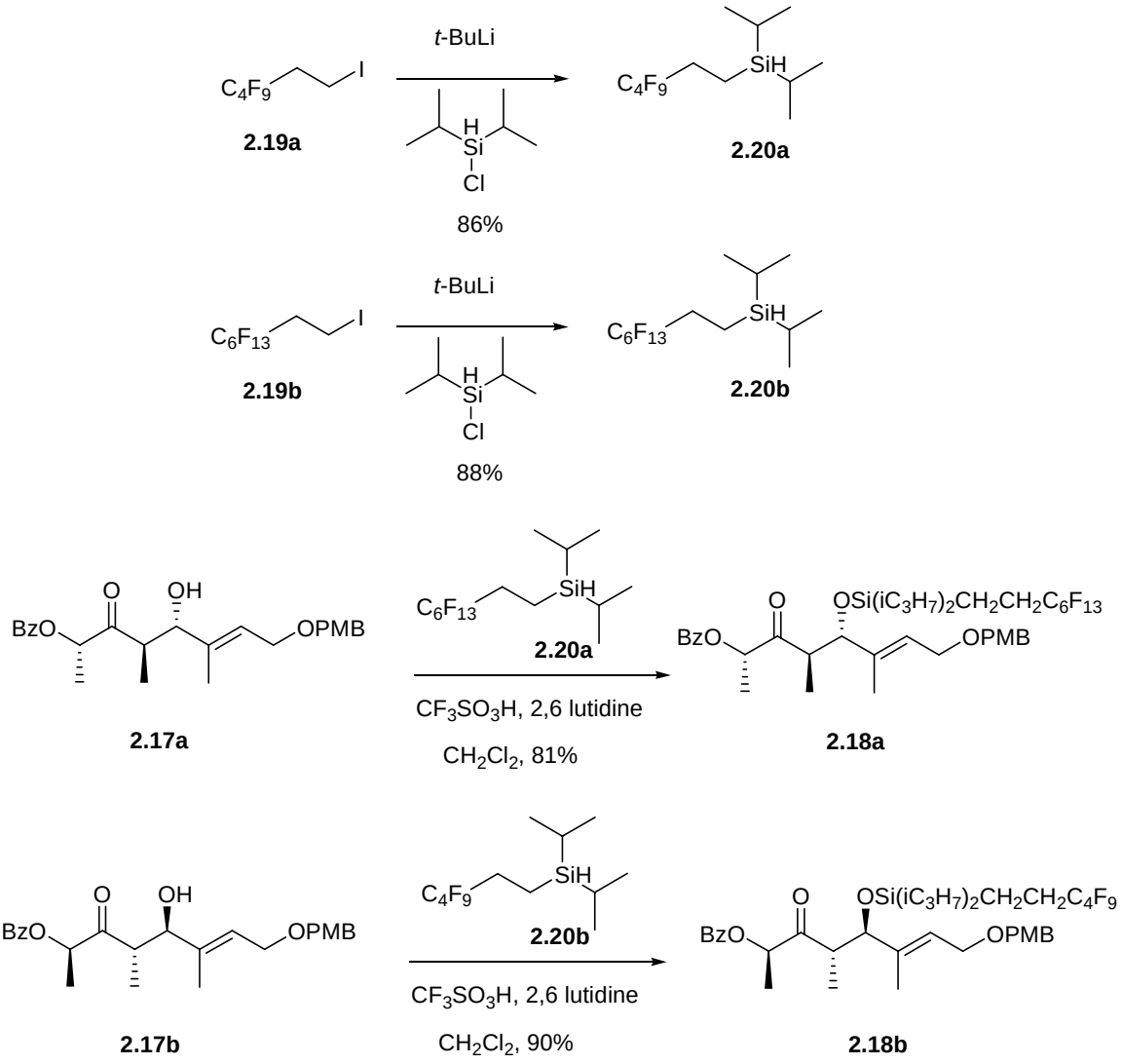


2.14b **2.17b**

Scheme 2.6 Synthesis of anti-aldol compound 2.17b

These two stereoisomeric alcohols **2.17a** and **2.17b** were then individually tagged with two different fluorous tags (**2.20a** and **2.20b**), which were synthesized from corresponding perfluoroalkyl iodide and chlorodiisopropylsilane.[7] The perfluoro carbon units in the two fluorous tags are C_4F_9 and C_6F_{13}. It was reported that the tagged components with one CF_2 difference in the fluorous tags are easy to be separated by fluorous HPLC.[20] We chose the C_2F_4 difference in the tags to make sure the tagged enantiomers can be isolated at the demixing stage.

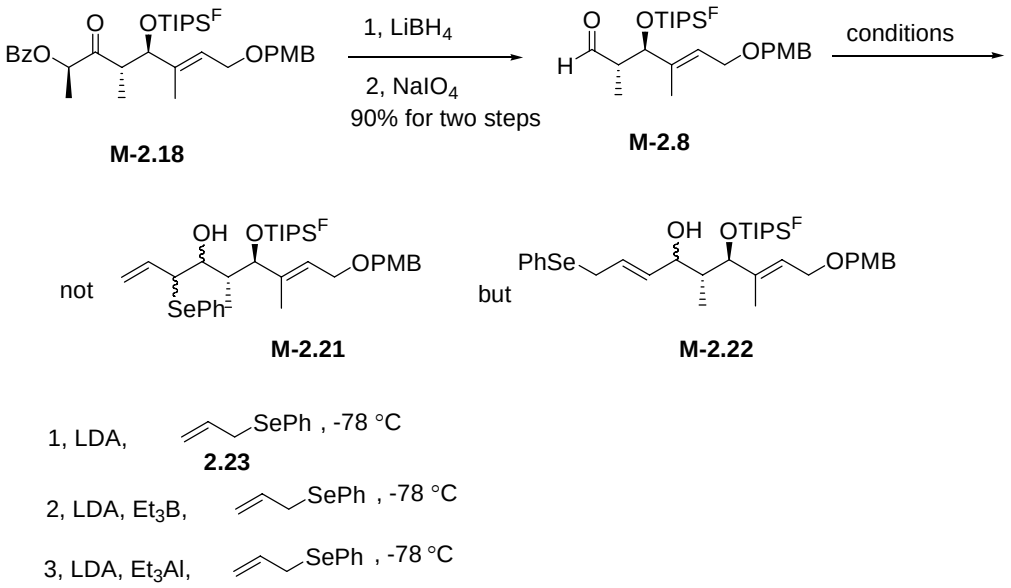
Fluorosilane **2.20a** was treated with trifluoromethansulfonic acid at –78 °C to generate TIPSOTf in situ, which then reacted with alcohol **2.17a** to afford TIPS ether **2.18a**. When only 1 equiv of fluorosilane **2.20a** was applied for the protection reaction, the yield of **2.18a** was around 40%. However, when two equiv of fluorosilane was applied, the desired product **2.18a** was obtained in 81% yield. Similarly, alcohol **2.17b** was protected with TIPSOTf derived from fluorous **2.20b** to afford **2.18b** in 90% yield.



Scheme 2.7 Synthesis of fluorous-tagged TIPS ether

These two fluorous-tagged quasienantiomers **2.18a** (5.91 g, 7.5 mmol) and **2.18b** (6.66 g, 7.5 mmol) were weighed and mixed in a 1:1 molar ratio to generate the starting quasiracemic mixture **M-2.18**. $LiBH_4$ reduction of the ketobenzoic ester **M-2.18** afforded the diol intermediate, which was cleaved by $NaIO_4$ to provide aldehyde **M-2.8** in 90% yield in a two-step sequence. The next goal is to convert aldehyde **M-2.8** to alcohol **M-2.21**. The purpose of the introduction of a phenylselanyl group in compound **M-2.21** is for the elimination to synthesize pyrone from a

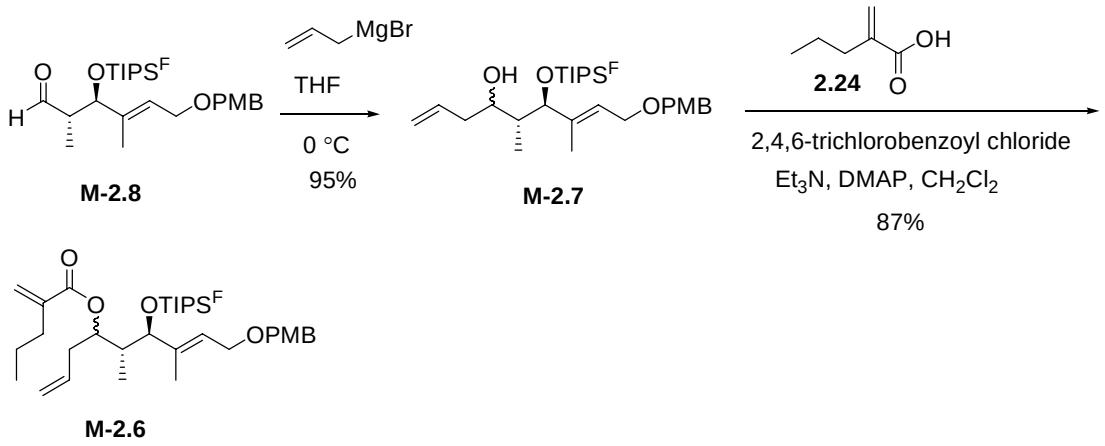
α,β-unsaturated lactone in the final stage. However, treatment of allylphenylselenide **2.23** with LDA[21] followed by addition of the aldehyde **M-2.8** only afforded the undesired compound **M-2.22**, the regioisomer of desired compound **M-2.21**, in moderate yield. Addition of Et_3B or Me_3Al as the additives[22] in this reaction also gave similar results. However, when a simple aldehyde, such as hexanal, was tested for a model reaction under the same condition, the desired product could be obtained in moderate yield (not shown). We suspected that the bulky fluorous TIPS group in aldehyde **M-2.8** changed the regioselectivities of this reaction.



Scheme 2.8 Attempt to synthesize phenylselenyl alcohol M-2.21

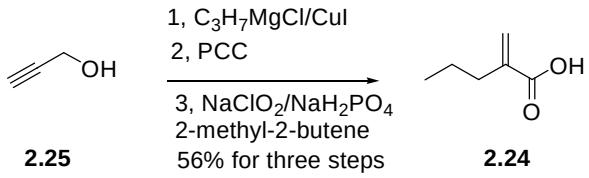
Since conversion of aldehyde **M-2.8** to alcohol **M-2.21** was not successful, aldehyde **M-2.8** was simply treated with allyl magnesium bromide to generate alcohol **M-2.7** in 95% yield. However, the coupling reaction of alcohol **M-2.7** and acid **2.24** with DCC and other coupling reagents recovered only starting materials. Converting the acid **2.24** to acid chloride followed by

reacting with alcohol **M-2.7** also failed to afford the desired ester **M-2.6**. The preparation of ester **M-2.6** was finally achieved by Yamaguchi conditions[23] in 87% yield.



Scheme 2.9 Synthesis of the RCM reaction precursor M-2.6

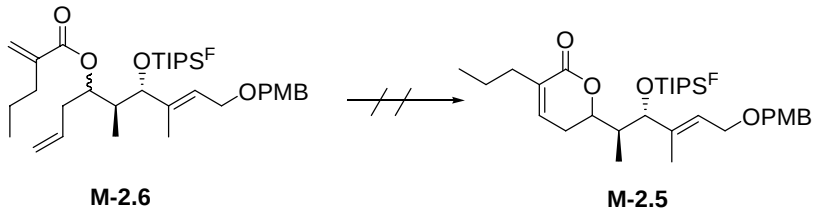
Acid **2.24** was prepared in a three-step procedure based on the literature.[24] Propargyl alcohol **2.25** was treated with propylmagnesium chloride in the presence of copper (I) iodide followed by PCC oxidation to afford the aldehyde as the intermediate, which was then oxidized with $NaClO_2$ to give the α,β-unsaturated acid **2.24** in 56% yield for total three steps.



Scheme 2.10 Synthesis of α,β-unsaturated acid 2.24

Synthesis of α,β-unsaturated lactone **M-2.5** was then attempted by metathesis of enone[25] **M-2.6** (Scheme 2.11). When substrate **M-2.6** was first treated with 1st generation Grubbs catalysts in a refluxing CH_2Cl_2 (0.01 M) to effect an intramolecular metathesis reaction, a TLC analysis showed predominately the starting ester. No desired lactone was detected either by TLC

or ^{1}H NMR spectroscopy. When 2st generation Grubbs catalyst was employed in this transformation, decomposition happened even when the reaction was conducted at low temperature. TLC showed multiple spots and ^{1}H NMR analysis did not detect any desired product **M-2.5**. A number of reaction conditions, by varying the concentration and the temperature, were tested with the substrate to effect this transformation. However, either starting material recovered or decomposition happened under all conditions. We hypothesized that the other double bond in the substrate interrupted the desired reaction, because it also could generate 6-member ring. However, we could not isolate any pure products derived from the competing pathway either.

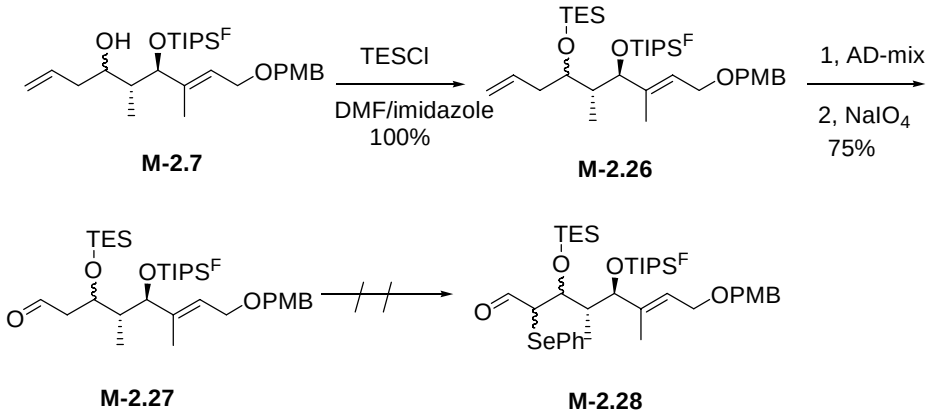


M-2.6 **M-2.5**

Scheme 2.11 Attempt to synthesize α,β-unsaturated lactone M-2.5 with RCM reaction

After these unsuccessful attempts to install the lactone **M-2.5** by employing metathesis approach, we decided to abandon this strategy and investigate alternative approaches for preparation of the desired lactone **M-2.5** (Scheme 2.12). TESCl protection of alcohol **M-2.7** afforded **M-2.26** in 95% yield. Treatment of **M-2.26** with AD-mix[26] and followed by $NaIO_4$ cleavage gave aldehyde **M-2.27** in 75% overall yield. Because lactone **M-2.5** had to be converted to α-pyrone in the final stage, we planned to introduce a phenylselanyl group in the α position of carbonyl group of aldehyde **M-2.27**. We first conducted a model reaction to verify the feasibility of that transformation. 3-Phenylpropanal was treated with phenylselenyl chloride

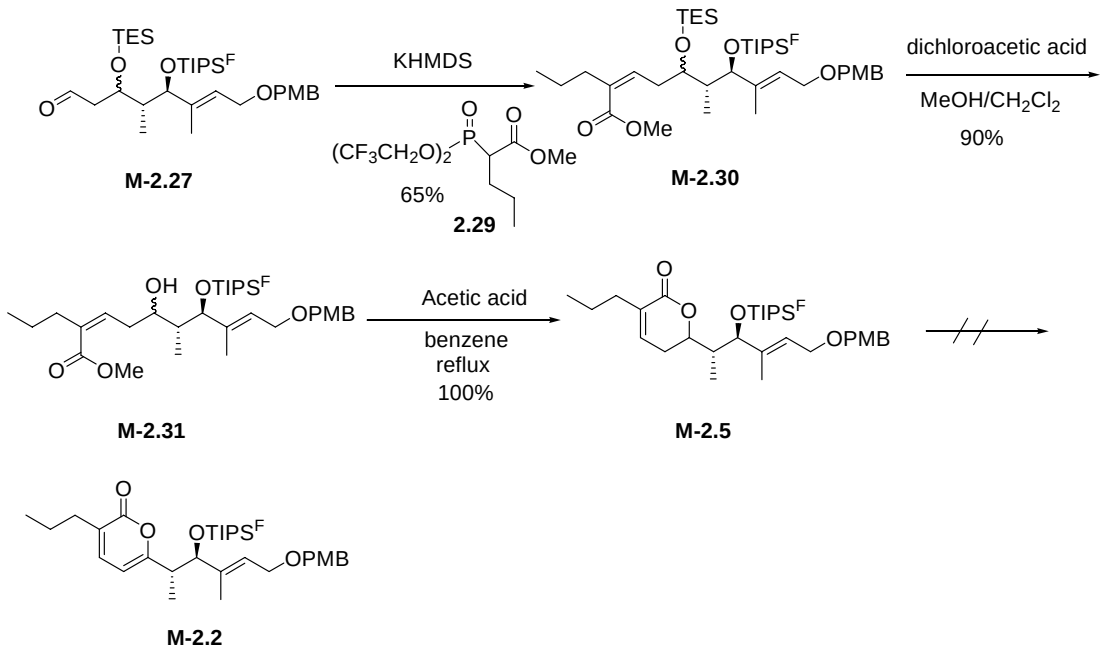
in EtOAc to give the desired α-substituted phenylselenyl aldehyde in 80% yield (not shown). However, when aldehyde **M-2.27** was treated with phenylselenyl chloride under the same conditions, decomposition happened. A variety of conditions were tested for that transformation, unfortunately, no α-substituted phenylselenyl aldehyde **M-2.28** was detected either by TLC or ^{1}H NMR spectroscopy.



Scheme 2.12 Attempt to synthesize α-substituted phenylselenyl aldehyde M-2.28

Aldehyde **M-2.27** was submitted to Still (Z)-variant of the Wittg reaction condition[27] to give (Z) unsaturated ester **M-2.30** in 65% yield (Scheme 2.13). The TES protecting group was removed with dichloroacetic acid in MeOH/CH_2Cl_2 (1:1) to provide alcohol **M-2.31** in 90% yield. When **M-2.31** was refluxing with acetic acid in benzene, α,β-unsaturated lactone **M-2.5** was obtained in quantitative yield. However, the conversion of lactone **M-2.5** to α-pyrone **M-2.2** was problematic. When **M-2.5** was treated with LDA followed by quenching with PhSeCl, however, the lactone ring was opened to give the dienoic acid (structure not shown). Bromination of **M-2.5** with NBS provided multiple spots from TLC analysis. The direct

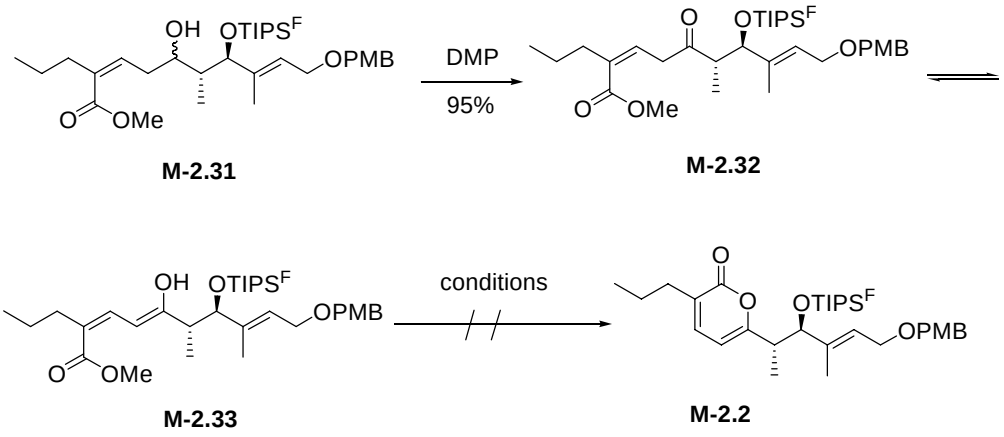
oxidation of **M-2.5** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[28] only provided the recovered starting material.



Scheme 2.13 Attempt to synthesize α-pyrone M-2.2

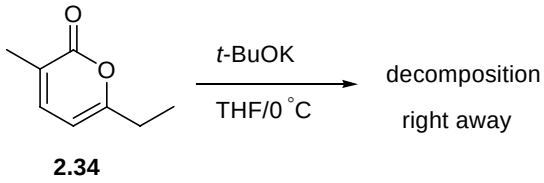
Since **M-2.31** was successfully cyclized under acidic conditions, we hypothesized that ketone **M-2.32** could undergo enolization to yield the intermediate **M-2.33**, which was easy to cyclize to α-pyrone **M-2.2** (Scheme 2.14). Thus, ketone **M-2.32** was synthesized by oxidizing the alcohol **M-2.31** with Dess-Martin periodinane to test the hypothesis. From ^{1}H NMR and ^{13}C NMR spectra, ketone **M-2.32** was only observed as a single compound and no enol form **M-2.33** was observed. *t*-BuOK was first explored as the base for that cyclization reaction. When the reaction was conducted at room temperature, an unidentifiable product was obtained, along with a tiny amount of desired pyrone **M-2.2**, which could be detected by mass spectroscopy (ESI). When the reaction was conducted at –78 °C, only starting material was recovered. When the

reaction was conducted at –78 °C then warmed to room temperature, decomposition also resulted.



Scheme 2.14 Attempt to synthesize α-pyrone M-2.2 from ketone M-2.32

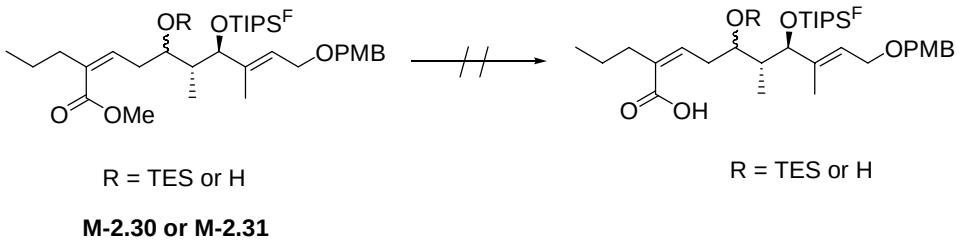
Suspecting the α-pyrone **M-2.2** was unstable under strong basic conditions like *t*-BuOK, we conducted a model reaction to test the stability of α-pyrone under basic conditions. When a simple α-pyrone **2.34** was treated with *t*-BuOK at 0 °C, it decomposed right away (Scheme 2.15). However, α-pyrone **2.34** was stable when treated with NaH in THF at room temperature. Based on this test, we hypothesized that ketone **M-2.32** did cyclize to afford α-pyrone **M-2.2** with *t*-BuOK; however, the formed product rapidly decomposed.



Scheme 2.15 Test reaction of α-pyrone 2.34 with t-BuOK

A variety of other conditions were tested for the cyclization reaction of ketoester **M-2.32**. Since sodium hydride did not destroy pyrone **2.34** at room temperature, it was employed for the cyclization reaction of **M-2.33**. However, we only observed decomposition of the starting material. When acids (acetic acid and trichloroacetic acid) were employed to catalyze this reaction, an unidentifiable compound was obtained. At this point, we thought the difficulty of the cyclization reaction was probably caused by methoxyl group, which is a poor leaving group. If a better leaving group, like carboxylate group, was employed in this reaction, the cyclization probably could proceed easily.

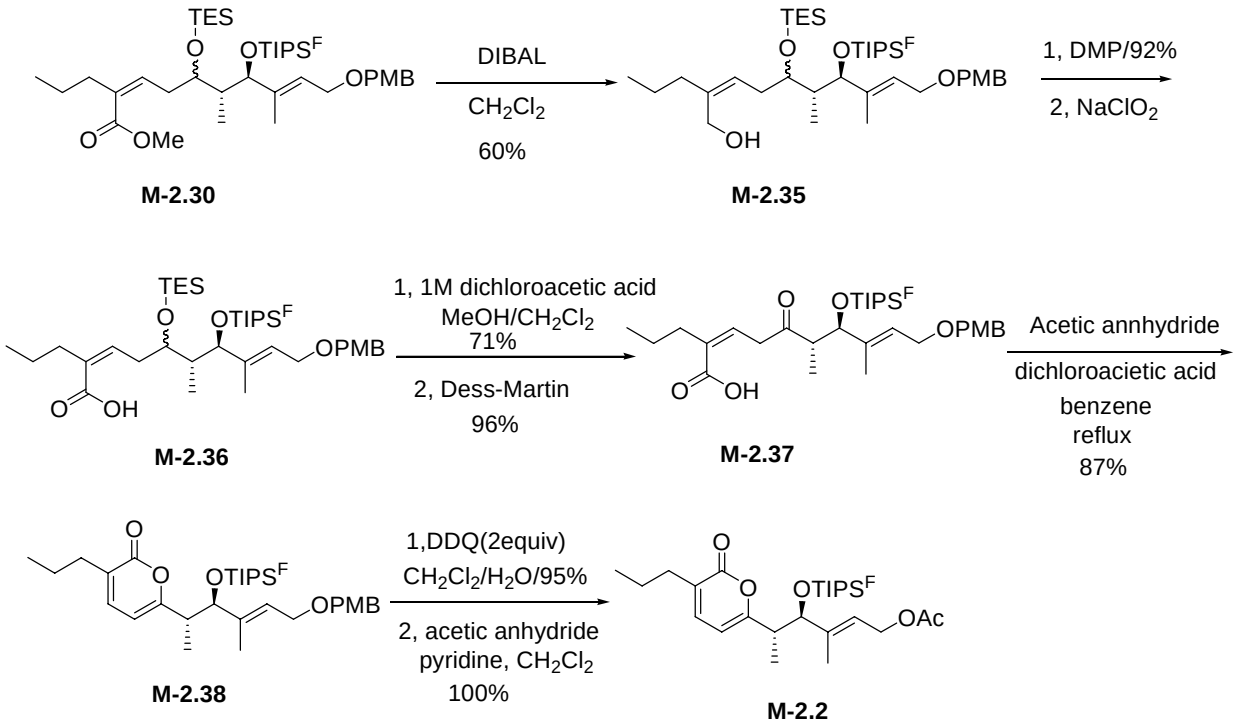
We next decided to synthesize the carboxylic acid for the cyclization reaction. Usually a methyl ester is easily hydrolyzed to the corresponding acid under mild basic conditions.[29] Unfortunately, hydrolysis of methyl ester **M-2.30** or **M-2.31** to the corresponding acids failed under various conditions, even refluxing in KOH solution (Scheme 2.16). In most conditions, only starting material was recovered.



Scheme 2.16 Attempt to hydrolyze methyl ester to corresponding carboxylic acid

An alternative approach to synthesize acid **M-2.36** is shown below (Scheme 2.17). Reduction of α,β-unsaturated ester **M-2.30** formed alcohol **M-2.35** in 60% yield, which was then oxidized to corresponding acid **M-2.36** as a two-step sequence in 87% yield. Deprotection of TES group with dichloroacetic acid followed by Dess-Martin oxidation afforded ketoacid **M-**

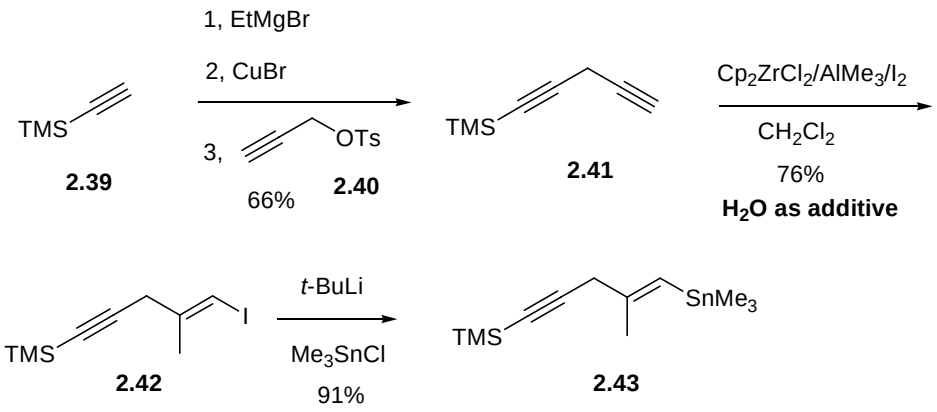
2.37 in 68% overall yield. As we expected, when ketoacid **M-2.37** was refluxed in the presence of acetic anhydride and trichloroacetic acid in benzene, the desired α-pyrone **M-2.38** was generated smoothly in 87% yield. The leaving group in this reaction is a carboxylate group, which is a much better leaving group than methoxyl group. **M-2.38** was then converted to allylic acetate **M-2.2** with DDQ deprotection followed by treatment with acetic anhydride in an overall 95% yield for two steps.



Scheme 2.17 Synthesis of α-pyrone M-2.2

2.2.2 SYNTHESIS OF THE MIDDLE FRAGMENT VINYLSTANNANE 2.43

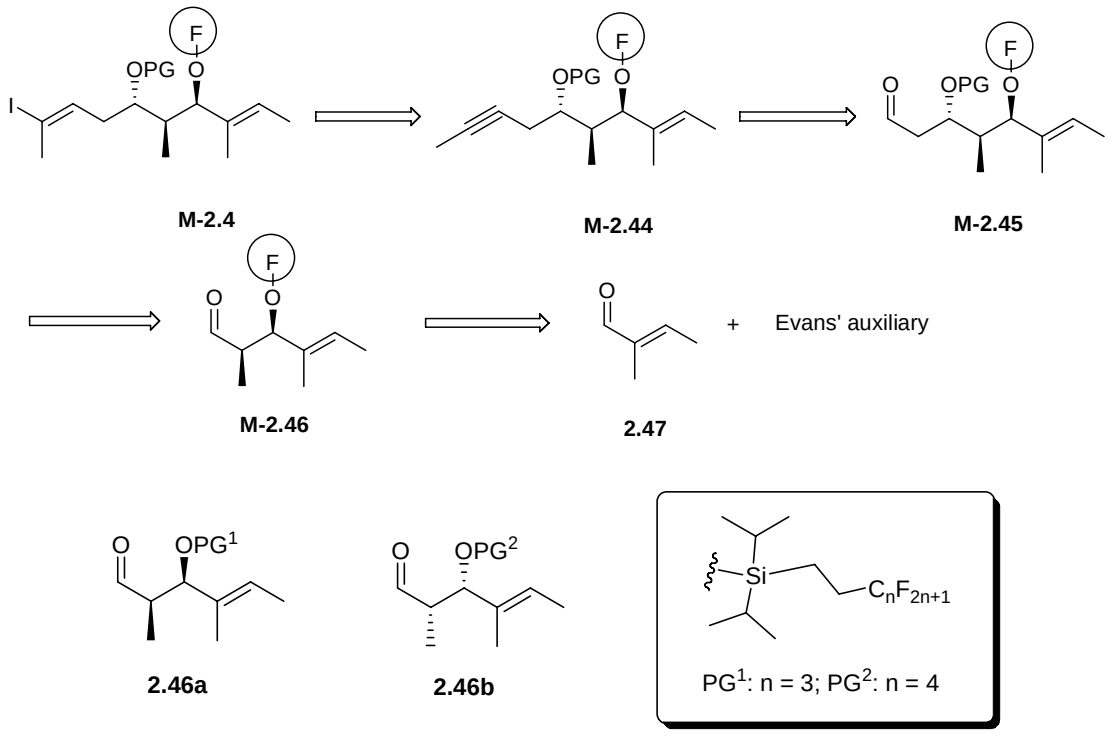
The middle fragment **2.2** can be easily accessible from vinylstannane **2.43**. Instead of synthesizing compound **2.2**, we started to synthesize compound **2.43**. Since vinyl iodide **2.42** was already reported, our synthesis was just closely following Shair's procedure[30] with modifications of experimental conditions to improve the yields (Scheme 2.18). Trimethylsilylacetylene **2.39** was treated with ethylmagnesium bromide then coupled with **2.40** in the presence of copper (I) bromide to afford diyne **2.41** in 66% yield. When we employed Shair's condition (without water as additive) to convert **2.41** to vinyl iodide **2.42**, only 50% yield was obtained and the reaction took overnight to complete. When we employed Wipf's procedure[31] (1.5 eq water as additive), the reaction is in higher yield (76%) and shorter time (30 min). Finally, transmetallation of vinyl iodide **2.42** with *t*-BuLi followed by addition of trimethyltin chloride provided the vinylstannane **2.43** in 91% yield (crude).



Scheme 2.18 Synthesis of vinylstannane 2.43

2.2.3 SYNTHESIS OF THE RIGHT FRAGMENT OF LAGUNAPYRONE B

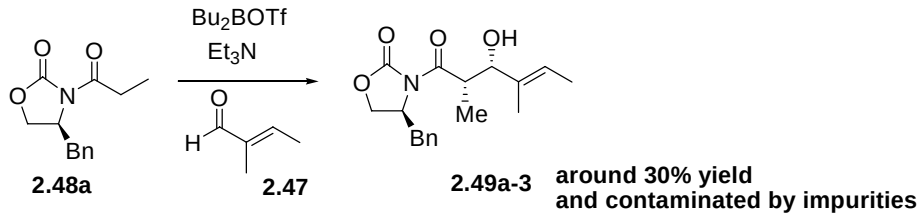
After successful synthesis of the left fragment and the middle fragment of lagunapyrone B, our next goal was to achieve the synthesis of the right fragment. The retrosynthetic analysis of compound **M-2.4** is shown in Scheme 19. Vinyl iodide **M-2.4** can be constructed from alkyne **M-2.44**. Further retrosynthetic analysis leads to aldehyde **M-2.45**, which can be constructed from aldehyde **M-2.46**. Aldehyde **M-2.46** can be synthesized with Evans' aldol reaction from aldehyde **2.47.**



Scheme 2.19 Retrosynthetic analysis of vinyl iodide M-2.4

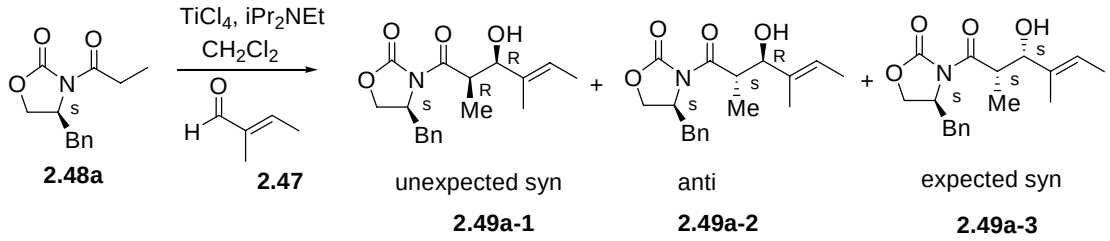
The standard Evans' aldol reaction[32] was first tried to synthesize the alcohol **2.49a-3** (Scheme 2.20). When Bu_2BOTf was used as the Lewis acid and Et_3N as the base for this

reaction, the desired alcohol **2.49a-3** was only obtained in low yield (around 30%) and contaminated by other inseparable isomers. Because of the inseparable impurities, we decided to explore other Lewis acids to catalyze this reaction.



Scheme 2.20 Aldol reaction of aldehyde 2.49a-3 with Bu2BOTf

Table 1 summarized the results of the aldol reaction with titanium tetrachloride as the Lewis acid and diisopropylethylamine as the base.[33] When a slight excess of titanium tetrachloride and diisopropylethylamine were used, the unexpected syn product **2.49a-1** was obtained in 47% yield, anti product **2.49a-2** was obtained in 11% yield and the expected syn product **2.49a-3** was obtained in tiny amount (< 2%). Compound **2.49a-1** and **2.49a-2** could be easily separated by column flash chromatography. When a large excess of diisopropylethylamine, titanium tetrachloride, and tiglic aldehyde **2.47** were present, the yield of **2.49a-1** could be improved to 67%. But in all cases, only tiny amounts of **2.49a-3** were obtained. The ^{1}H NMR data (Figure 2.4) of compound **2.49a-1** is slightly different from compound **2.49a-3**, which was kindly donated by professor Hamada in Japan. The absolute configuration of **2.49a-1** was determined by X-ray analysis (Figure 2.5).



Scheme 2.21 Synthesis of compound 2.49a with Evans' auxiliary

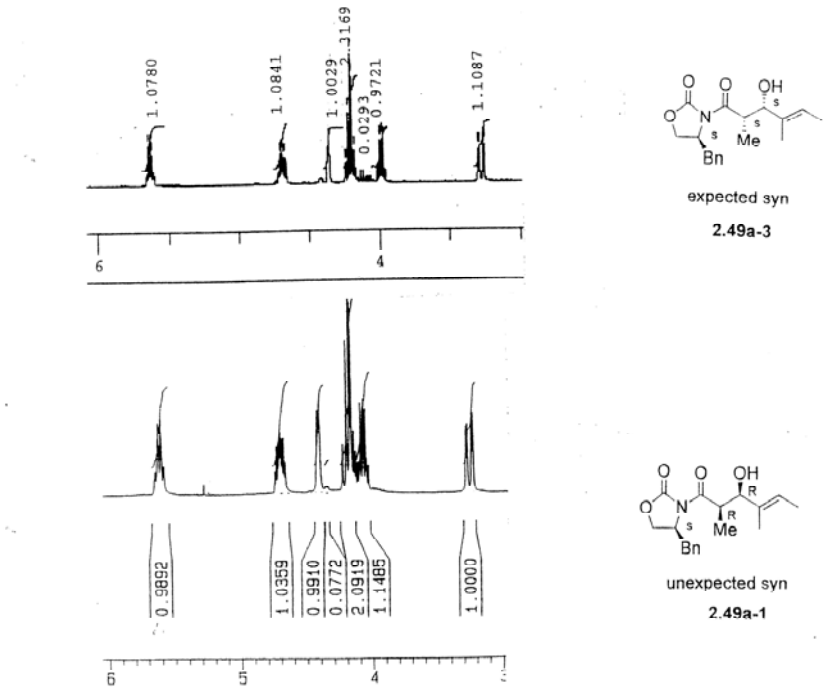


Figure 2.4. Comparison of ^{1}H NMR of **2.49-1** and **2.49-2**

Table 2.1. $TiCl_4$ assisted aldol reaction of aldehyde **2.47** conditions

Auxiliary	$TiCl_4$	Base	Tiglic aldehyde **2.47**	Recovered **2.48a**	Unexpected Syn product **2.49a-1**	Anti product **2.49a-2**	Expected Syn **2.49a-3**
1eq	1.2eq	1.3eq	2eq	15%	47%	11%	< 2%
1eq	1.5eq	1.6eq	2eq	19%	48%	11%	< 2%
1eq	1.5eq	1.6eq	2eq	13%	45%	9%	< 2%
1eq	1.5eq	2.6eq	2.5eq	-	62%	11%	< 2%
1eq	1.5eq	2.6eq	2.5eq	5%	67%	9%	< 2%

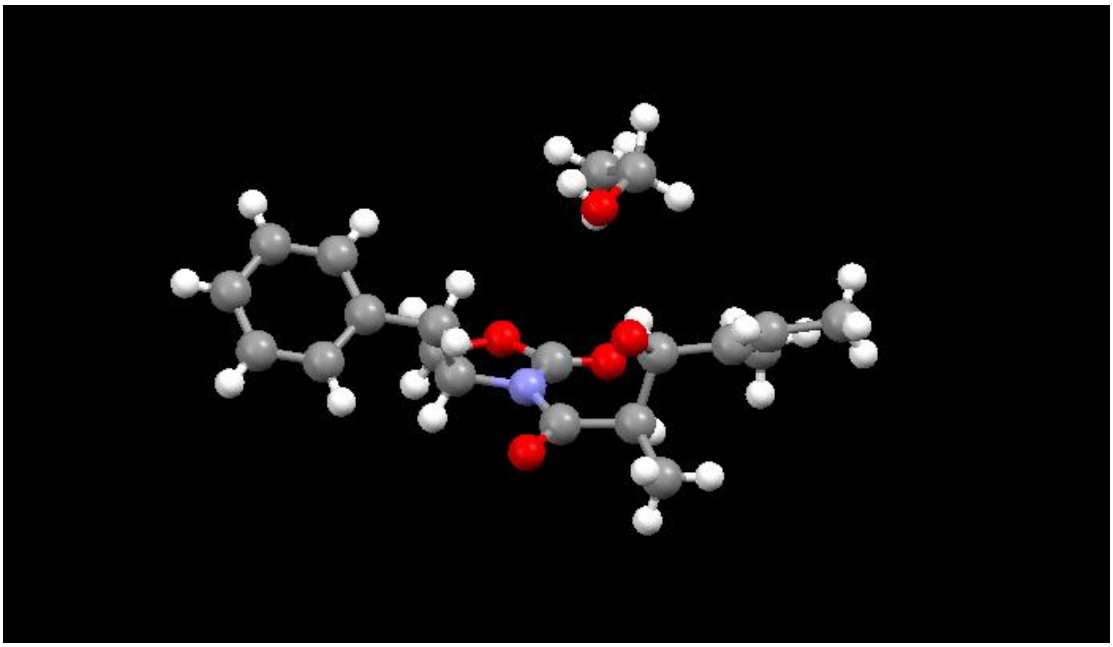
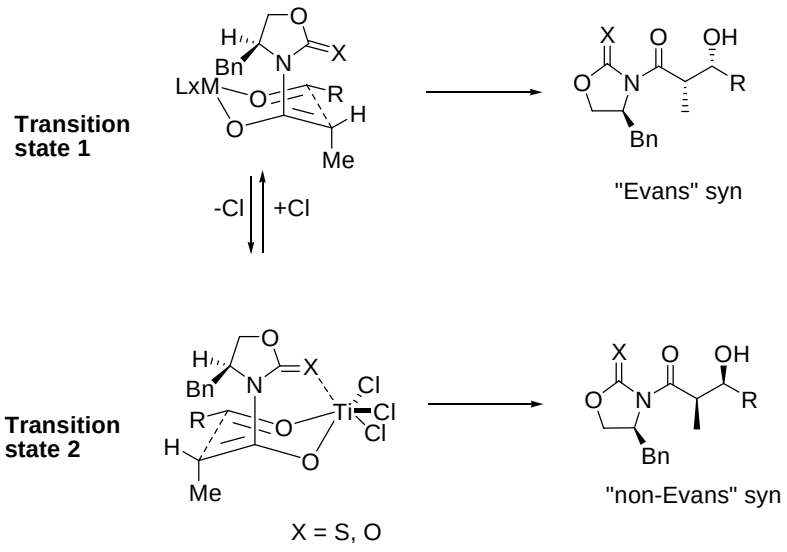


Figure 2.5. The X-ray structure of compound **2.49a-1**

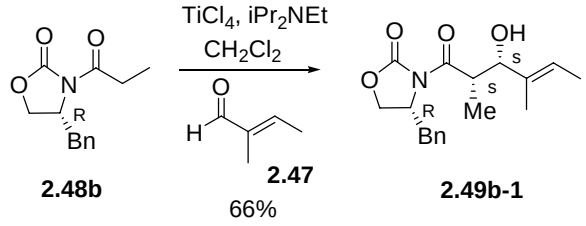
The unexpected stereoselectivities of aldol reaction can be explained according to the model[34] in Scheme 2.22. Transition state 1, where the X atom (such as S, O) in the oxazolidinones does not coordinate with the metal M (such as boron, titanium), leads to Evans's syn product. If a chloride ion is lost, the transition state 1 becomes transition 2, where the X atom

(S, O) in the oxazolidinones does not coordinate with the metal M (B, Ti etc). Transition 2 leads to non-Evans syn product.



Scheme 2.22 Possible transition state for non-Evans' syn aldol reaction

Similarly, syn-aldol product **2.49b-1**, the enantiomer of compound **2.49a-1**, was synthesized from (R) auxiliary **2.48b** in 66% yield (Scheme 2.23).

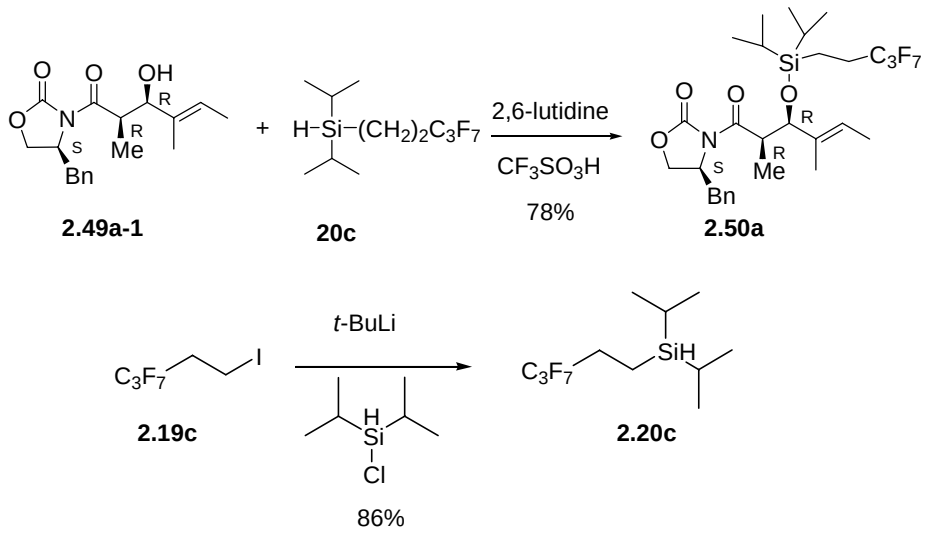


Scheme 2.23 Synthesis of compound 2.49b-1 with Evans' auxiliary

These two enantiomeric alcohols **2.49a-1** and **2.49b-1** were then individually tagged with two different fluorous tags (**2.20c** and **2.20b**), which were synthesized from corresponding perfluoroalkyliodide and chlorodiisopropylsilane. The perfluorocarbon units in the two fluorous

tags are C_3F_7 and C_4F_9. Since we already used C_4F_9 and C_6F_{13} fluorous tags in the synthesis of fragment **M-2.2**, we will have four combinations for the tagged components after the coupling reaction of fragment **M-2.2** and fragment **M-2.2**. These four combinations are C_3F_7 + C_4F_9, C_3F_7 + C_6F_{13}, C_4F_9 + C_4F_9 and C_4F_9 + C_6F_{13}. The sum of two tags in the four final components is C_7F_{16}, C_8F_{18}, C_9F_{20}, and $C_{10}F_{22}$. One CF_2 difference in the fluorous tags should be enough to separate these four compounds with fluorous HPLC.

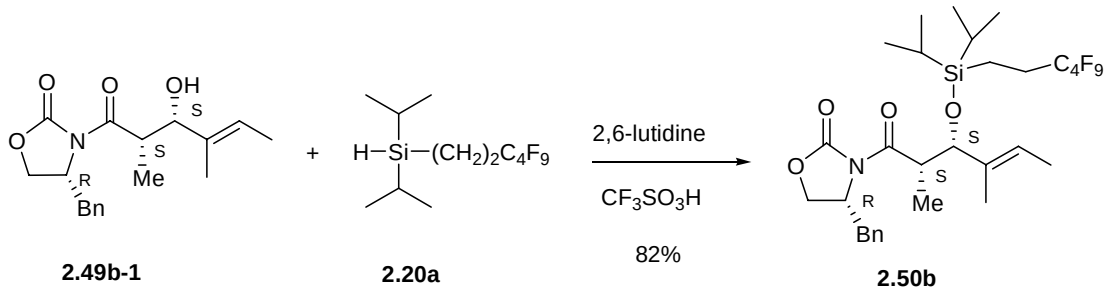
Fluorosilane **2.20c** was treated with trifluoromethansulfonic acid at –78 °C to generate TIPSOTf in situ, which then reacted with alcohol **2.49a-1** to afford TIPS ether **2.50a** in 78% yield and 20% recovered alcohol **2.49a-1** (Scheme 2.24). Similarly, alcohol **2.49b-1** was protected with TIPSOTf derived from fluorous silane **2.20a** to afford **2.50b** in 82% yield and 7% recovered alcohol **2.49b-1** (Scheme 2.25). The fluorous silane **2.20c** was synthesized from the corresponding iodide **2.19c**, which is commercially available from Fluorous Technologies, Inc.



2.49a-1 + 20c → 2.50a

2.19c → 2.20c

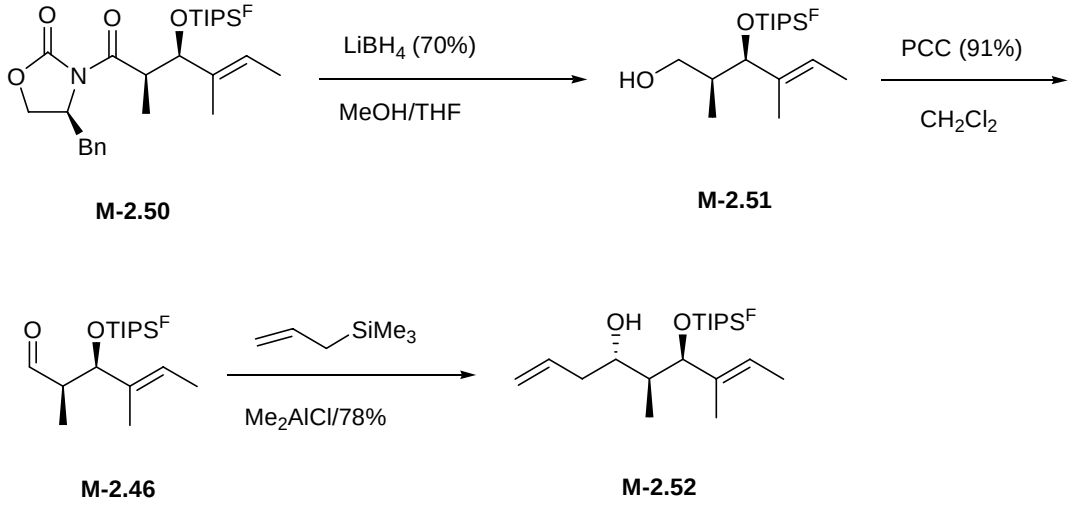
Scheme 2.24 Synthesis of fluorous-tagged TIPS ether 2.50a



2.49b-1 **2.20a** **2.50b**

Scheme 2.25 Synthesis of fluorous-tagged TIPS ether 2.50b

The two fluorous-tagged quasienantiomers **2.50a** (6.0 g, 9.6 mmol) and **2.50b** (6.5 g, 9.6 mmol) were weighed and mixed with 1:1 molar ratio to generate the starting mixture **M-2.50**. **M-2.50** was reduced by $LiBH_4$ followed by PCC oxidation to afford the aldehyde **M-2.46** in 91% yield which was then converted to homoallylic alcohol **M-2.52** with trimethylallylsilane in the presence of Me_2AlCl at –78°C in 78% yield as a single isomer [35] (Scheme 2.26).



M-2.50 **M-2.51**

M-2.46 **M-2.52**

Scheme 2.26 Synthesis of homoallylic alcohol M-2.52

It is known that the carbons in methyl groups in the acetonide in a 1,3-diol will exhibit different chemical shifts depending on their stereochemistry.[36] For example, in the case of *syn*-1,3-diol acetonide, the two methyl groups adopt different orientations (one is axial and the other is equatorial) so they have different chemical shifts, and also the tertiary carbon appears at 98.5 ppm. In the case of *anti*-1,3-diol, however, the acetonide will adopt the twist-boat form and the two methyl groups become more equivalent (Figure 2.6). They therefore have a similar chemical shift, and the tertiary carbon usually appears around 100 ppm.

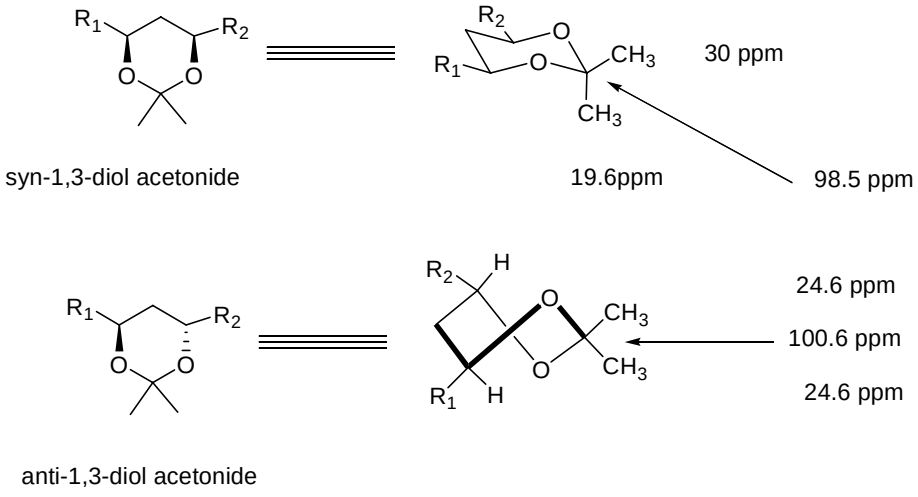
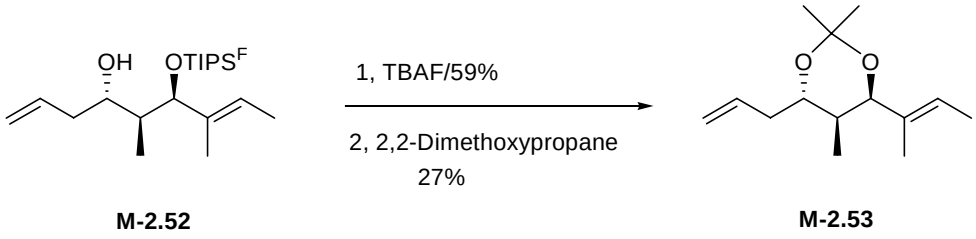


Figure 2.6. Rychnovsky ^{13}C acetonide method for 1,3-diol stereo assignment

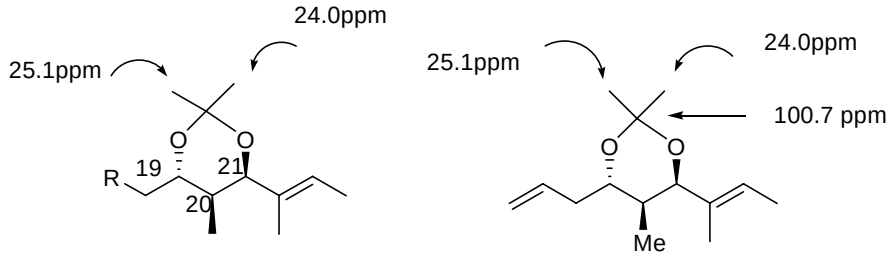
To determine the absolute configuration of the newly generated stereocenter, the homoallylic alcohol **M-2.52** was deprotected by TBAF followed by protection with 2,2-dimethoxypropane to provide acetonide **M-2.53** (Scheme 2.27). In the original paper,[12] the 1,3-diol on the carbons C-19 and C-21of langunapyrone B was converted to acetonide **2.54**. The similar chemical shifts on these two methyl groups in acetonide **2.54** mean that the 1,3-diol in the natural product is anti configuration. The chemical shifts of the two methyl groups in the

acetonide **M-2.53** derived from diol **M-2.52** were the same as the chemical shifts in the acetonide **17** which was derived from the natural product (Figure 2.7). From the comparison of the ^{13}C NMR data, we can conclude that 1,3-diol in compound **M-2.52** is anti configuration and has the same configuration as 1,3-diol on carbon C-19 and C21 in natural product.



M-2.52 **M-2.53**

Scheme 2.27 Synthesis of acetonide M-2.53

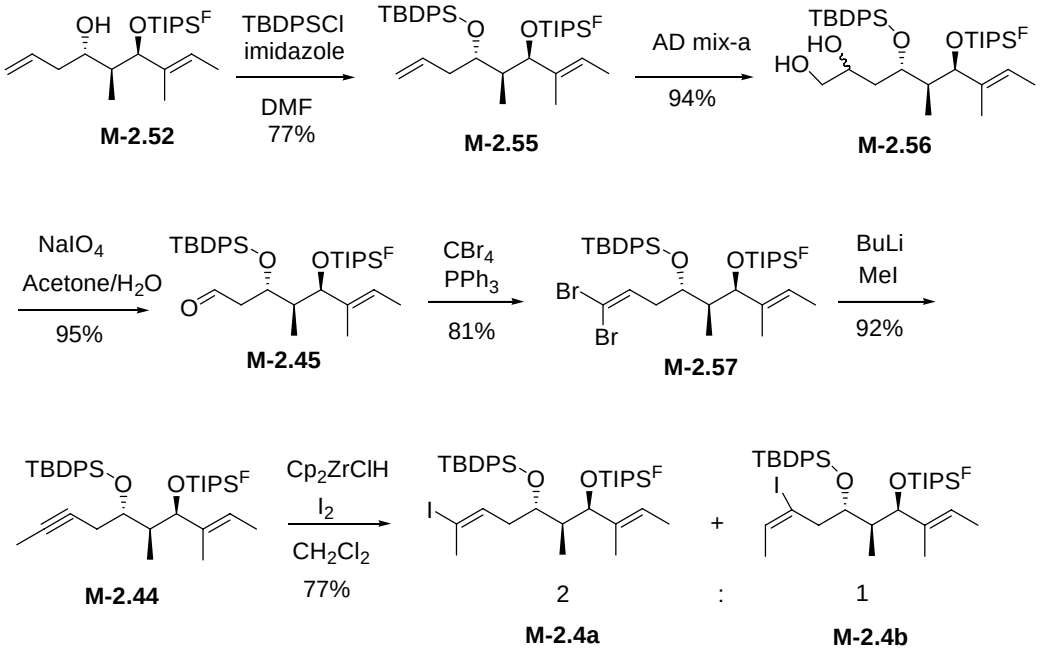


2.54 from Langunapyrone **M-2.53**

Figure 2.7. Comparison of ^{13}C NMR of acetonide **2.53** and acetonide **M-2.54**

Protection of the alcohol **M-2.52** with TBDPS gave the silylether **M-2.55** in 77% yield with 17% recovered starting alcohol **M-2.52** even after 70 hours (Scheme 2.28). The slow reaction and incomplete conversion was probably caused by the hinderance of the bulky fluorous TIPS group. The big diisopropyl group and the long fluorous chain make the fluorous TIPS group even bulkier than regular TIPS group. Treatment of **M-2.55** with AD-mix selectively dihydroxylated the terminal alkene in the presence of internal alkene to afford diol **M-2.56** in

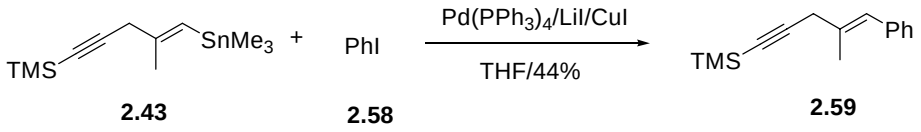
94% yield. Cleavage of diol **M-2.56** with $NaIO_4$ in methanol and water as the solvent resulted in recovery of the starting material, which was caused by the insolubility of the diol in the solvent system of methanol and water. The problem was solved by changing the solvent system to acetone and water, which gave the desired aldehyde **M-2.45** in 95% yield. Aldehyde **M-2.45** was converted to the corresponding alkyne **M-2.44** under Corey-Fuchs conditions[37] in 75% yield. Treatment of alkyne **M-2.44** with Schwartz's reagent[38] in CH_2Cl_2 provided vinyl iodide **M-2.4a** and **M-2.4b** in 77% yield with 2:1 ratio and the major product **M-2.4a** was the desired one. These two regioisomers were separated by careful column flash chromatorgraphy.



Scheme 2.28 Synthesis of vinyl iodide M-2.4a

2.2.4 COUPLING REACTION OF RIGHT FRAGMENT WITH MIDDLE FRAGMENT

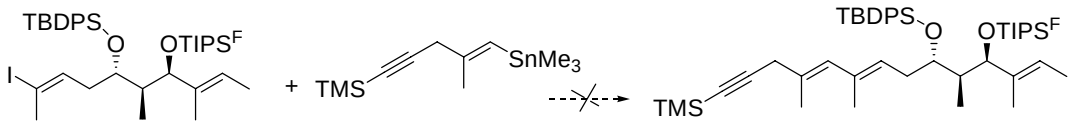
After completing the synthesis of **M-2.4a**, we initiated our task for the coupling reaction of vinyl iodide **M-2.4a** and vinylstannane **2.43**. Before the real substrate was performed in the coupling reaction, a model coupling reaction of vinylstannane **2.43** and phenyl iodide **2.58** was conducted (Scheme 2.29). The desired product **2.59** was obtained in moderate yield (44%) under standard Stille coupling condition.[39]



2.43 **2.58** **2.59**

Scheme 2.29 Model coupling reaction of vinylstanne 2.43 with phenyl iodide 2.58

The coupling reaction of the real vinyl iodide **M-2.4a** and vinylstannane **2.43** failed under a variety of conditions (Scheme 2.30). We first tried $Pd(CH_3CN)_2Cl_2$ as the catalyst[40] at room temperature, but starting material was recovered. When the reaction was conducted refluxing in $CHCl_3$, no desired product was detected by TLC analysis and just starting material was obtained. Some other conditions were tested for this reaction including changing catalyst and solvent systems at different temperatures. In most cases, only starting material was recovered. We suspected substrate **M-2.4a** was extremely hindered because of the bulky TBDPS group and fluorous TIPS group. We decided to switch to Negishi coupling to assemble these two fragments.



M-2.4a **2.43** **M-2.60**

1, $Pd(CH_3CN)_2Cl_2$, PPh_3, $CHCl_3$, reflux, recovered starting material

2, $Pd(CH_3CN)_2Cl_2$, DMF, rt, recovered starting material

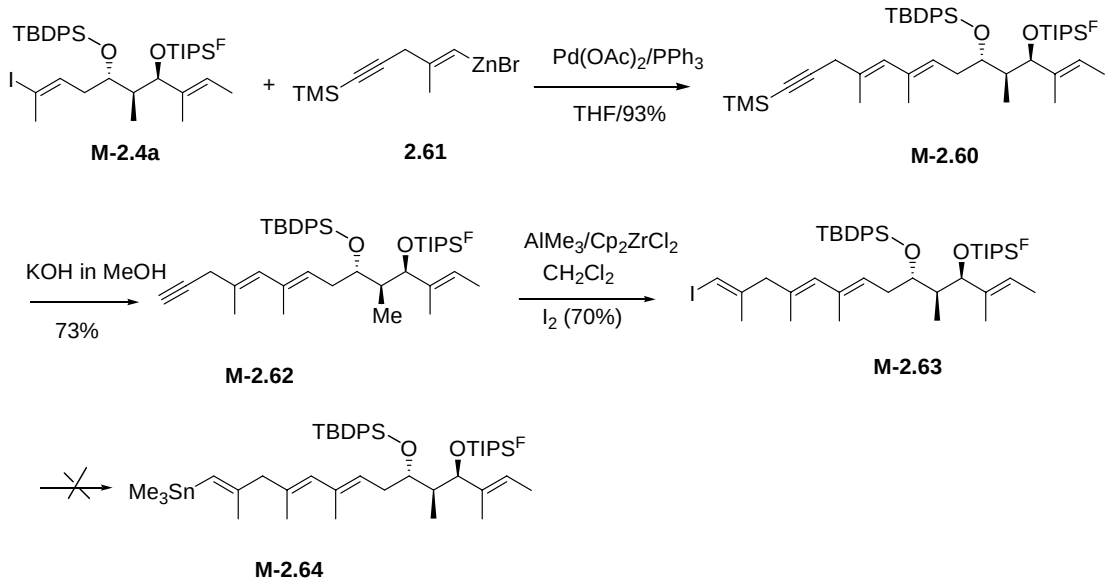
3, $Pd(CH_3CN)_2Cl_2$, DMF, 90^0C, recovered starting material

4, $Pd(PPh_3)_2Cl_2$, DMF, LiCl, reflux, messy

5, $Pd(PPh_3)_4$, Bezene reflux, recovered starting material

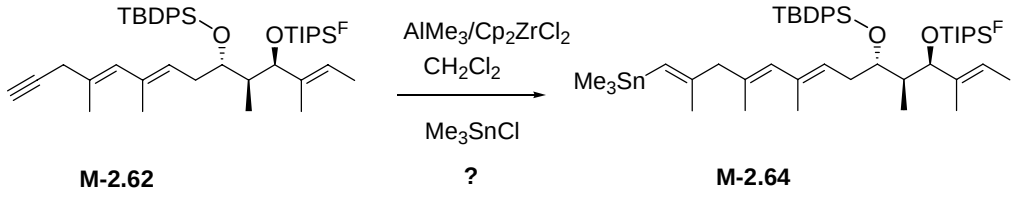
Scheme 2.30 Unsuccessful Stille coupling reactions M-2.4a and 2.43

The Negishi coupling between **M-2.4a** and vinylzinc **2.61**[28] proceeded smoothly to provide yne-diene **M-2.60** in 93% yield (Scheme 2.31). The TMS group of alkyne **M-2.60** was then removed with KOH in methanol to form terminal alkyne **M-2.62** in 73% yield, which was converted to vinyl iodide **M-2.63** with $Cp_2ZrCl_2/AlMe_3$. However, the transformation of the vinyl iodide **M-2.63** to vinylstannane **M-2.64** proved problematic. When *t*-BuLi was used for the transmetallation in ether at –78 ºC, isomerization happened because the 1,4-diene was too acidic. Even when *n*-BuLi was used for the transmetallation in THF at –78 ºC, the major product was still the isomerized one.



Scheme 2.31 Synthesis of vinyl iodide M-2.63

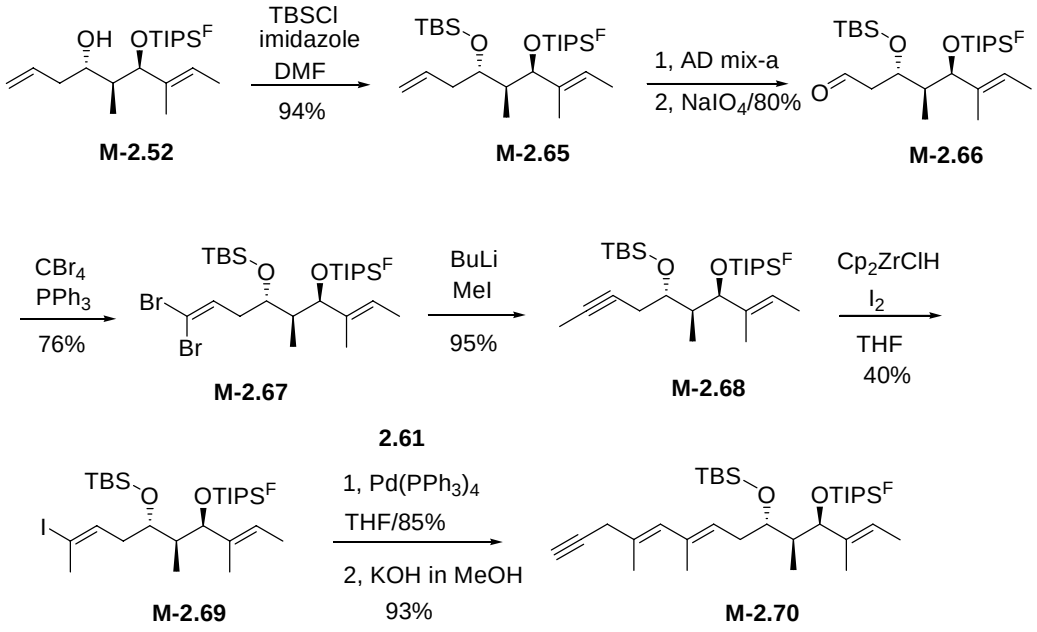
Faced with difficulty of converting vinyl iodide **M-2.63** to vinylstannane **M-2.64**, we planned to convert the alkyne **M-2.62** to the vinylstannane **M-2.64** directly through quenching the aluminum intermediate with trimethyltin chloride rather than iodine (Scheme 2.32).



Scheme 2.32 Possible direct transformation of alkyne M-2.62 to vinylstannane M-2.64

At this point, we were running out of **M-2.62**. We chose to synthesize alkyne **M-2.70** instead (Scheme 2.33). The difference between alkyne **M-2.62** and alkyne **M-2.70** was the TBDPS protecting group in **M-2.62** was replaced by TBS group in **M-2.70**, which is easier to be deprotected in the final stage. The synthesis of alkyne **M-2.70** was almost exactly the same as that of alkyne **M-2.62**. Protection of alcohol **M-2.52** with TBSCl gave the silylether **M-2.65** in

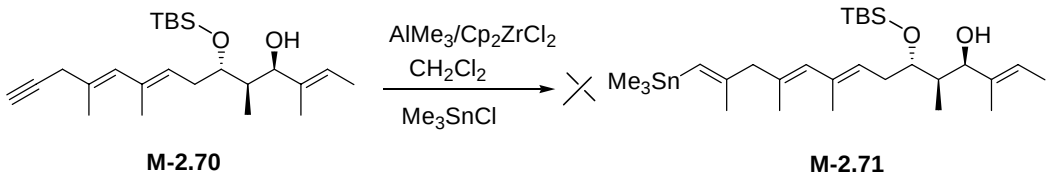
94% yield. Treatment of **M-2.65** with AD-mix followed by $NaIO_4$ afforded aldehyde **M-2.66** in an overall 80% yield. Aldehyde **M-2.66** was converted to alkyne **M-2.67** under Corey-Fuchs conditions in 72% yield in a two-step sequence. Treatment of the alkyne **M-2.68** with Schwartz's reagent in THF provided vinyl iodide **M-2.69** as a single isomer in 40% yield. The regioselectivities of this reaction in THF was much better than in CH_2Cl_2. We did not see any other regioisomers. We suspected that the low yield of this reaction was caused by the TBS group, which is not stable with Schwartz's reagent. The coupling reaction between vinyl iodide **M-2.69** and zinc reagent **2.61** with $Pd(PPh_3)_4$ in THF followed by deprotection with potassium hydroxide in methanol formed the desired **M-2.70** in 79% yield.



Scheme 2.33 Synthesis of TBS protected alkyne M-2.70

Alkyne **M-2.70** was treated with $AlMe_3$ and Cp_2ZrCl_2 to generate the vinylzirconocene intermediate, which was then quenched with Me_3SnCl (Scheme 2.34). However, no desired

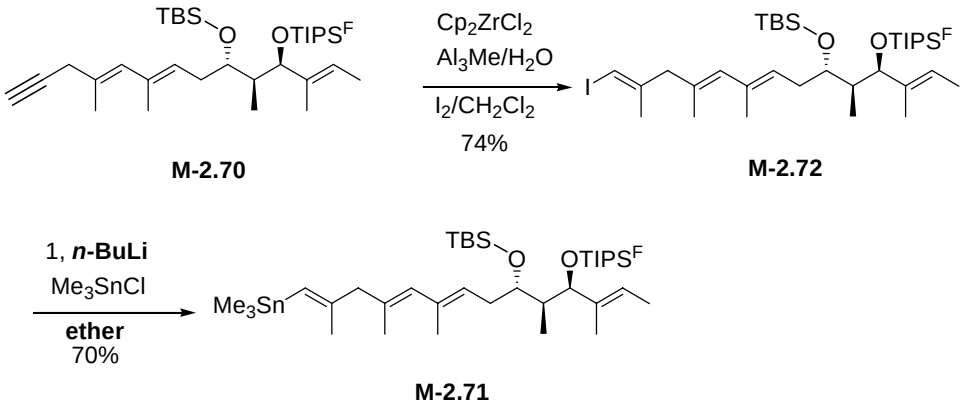
vinylstannane **M-2.71** was obtained based on ^{1}H NMR analysis. The only product obtained was the alkene derived from the alkyne reduced.



M-2.70 **M-2.71**

Scheme 2.34 Unsuccessful synthesis of M-2.71 directly from M-2.70

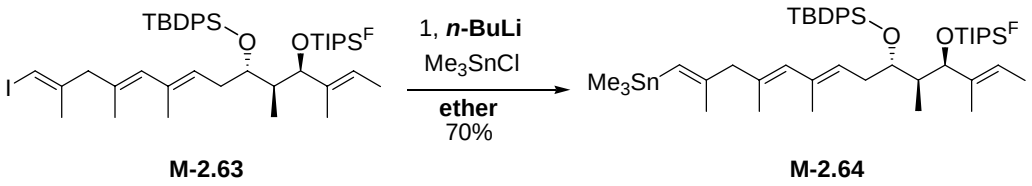
Alkyne **M-2.70** was converted to vinyl iodide **M-2.72** with $Cp_2ZrCl_2/AlMe_3$ in 74% yield (Scheme 2.35). We found out when the vinyl iodide **M-2.72** was treated with *n*-BuLi in ether and quenched with Me_3SnCl, the desired vinylstannane **M-2.71** can be obtained in 70% yield always with small amount of reduced alkene. Vinylstannane **M-2.71** was not purified for the next coupling reaction since it is not stable to silica gel. Following the same procedure, vinylstannane **M-2.64** was synthesized from vinyl iodide **M-2.63** (Scheme 2.36).



M-2.70 **M-2.72**

M-2.71

Scheme 2.35 Synthesis of vinylstannane M-2.71

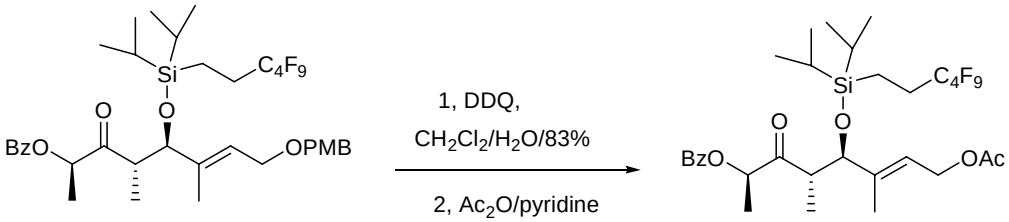


M-2.63 **M-2.64**

Scheme 2.36 Synthesis of vinylstannane M-2.64

2.2.5 COUPLING REACTION OF THE FINAL TWO FRAGMENTS OF LAGUNAPYRONE B

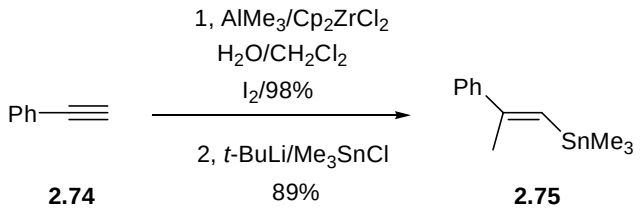
With the two coupling partners allylic acetate **M-2.2** and vinylstannane **M-2.64** and **M-2.71** in hand, we were ready to carry out the crucial Stille coupling reaction. Since allylic acetate **M-2.2** is very hindered because of the bulky fluorous TIPS group, we suspected that we might have problem with the coupling reaction. A model reaction was first conducted with the allylic acetate **2.73**, which was prepared in two steps (Scheme 2.37). PMB deprotection of compound **2.18b** followed by treatment with acetic anhydride gave compound **2.73** in a total 82% yield.



2.18b **2.73**

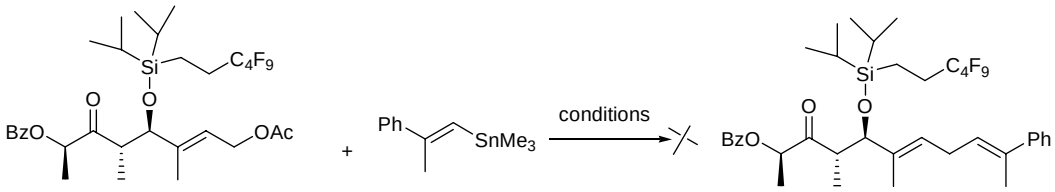
Scheme 2.37 Synthesis of allylic acetate 2.73 for model coupling reaction

Vinylstannane **2.75** for the model coupling reaction was synthesized from phenylacetylene **2.74** in two steps (Scheme 2.38). Phenylacetylene was treated with Cp_2ZrCl_2 and $AlMe_3$ to yield the vinyl iodide, which was converted to vinylstannane **2.75** in 99% yield.



Scheme 2.38 Synthesis of vinylstannane 2.75 for model coupling reaction

The coupling reaction between allylic acetate **2.73** and vinylstannane **2.75** was conducted under a variety of conditions (Scheme 2.39). We first attempted the coupling reaction with $Pd_2(dba)_3$ and LiCl in DMF at room temperature.[41] That condition resulted in only the recovery of the starting material. Elevated temperature with the same catalyst still recovered the starting materials. Conducting the reaction with microwave also resulted in recovery of the starting material. Some other conditions including different catalyst and different solvent all gave the same results.



2.73 **2.75** **2.76**

1, $Pd_2(dba)_3$, LiCl, DMF, room temperature recovered starting material

2, $Pd_2(dba)_3$, LiCl, DMF, 100 °C recovered starting material

3, $Pd_2(dba)_3$, LiCl, DMF, Microwave 100 °C recovered starting material

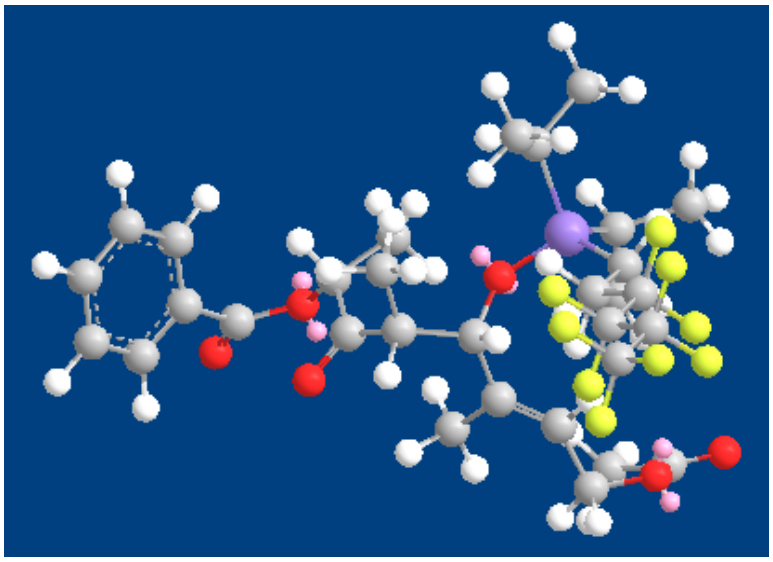
4, $Pd_2(dba)_3$, LiCl, DMF, $AsPh_3$, 100 °C recovered starting material

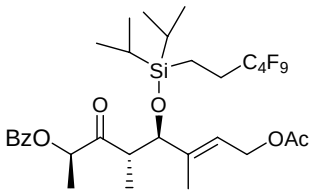
5, $Pd(PPh_3)_4$, LiCl, THF, reflux recovered starting material

6, $Pd(PPh_3)_4$, LiCl, DMF, 100 °C recovered starting material

Scheme 2.39 Model coupling reaction between compound 2.73 and 2.75

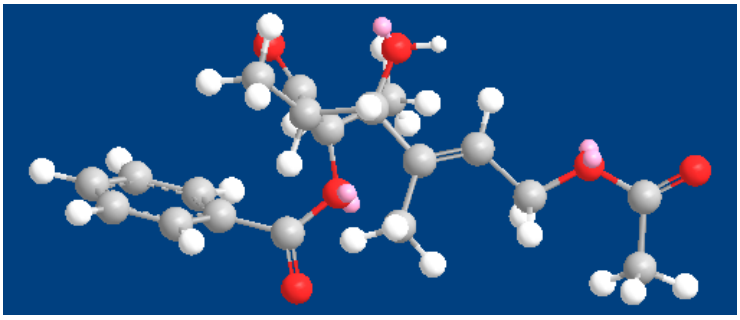
To construct the model of the compound **2.73**, a conformation search using MMD calculation was carried out. The image of the lowest energy conformer was shown in figure 2.8. The image shows that two isopropyl groups and the fluorous chain from the TIPS group completely cover the allylic acetate part and block the approach of the palladium catalyst. However, the allylic acetate part in compound **2.77** (Figure 2.9), which was derived from **2.73** after removing of the bulky fluorous TIPS group, is completely exposed to the palladium catalyst.

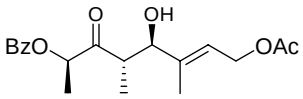




2.73

Figure 2.8. MMD image of the predicted lowest energy conformer of **2.73**

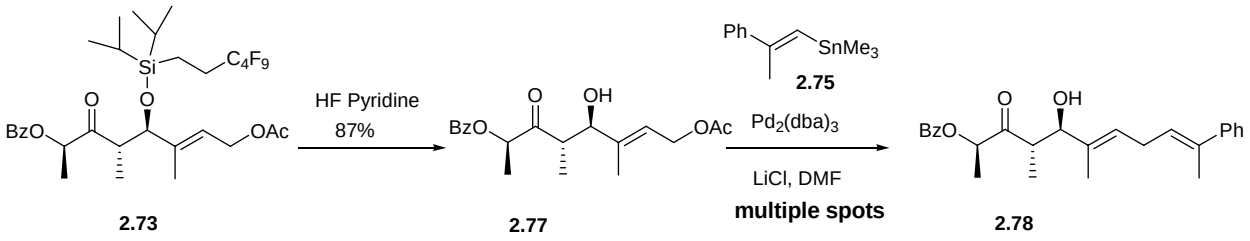




2.77

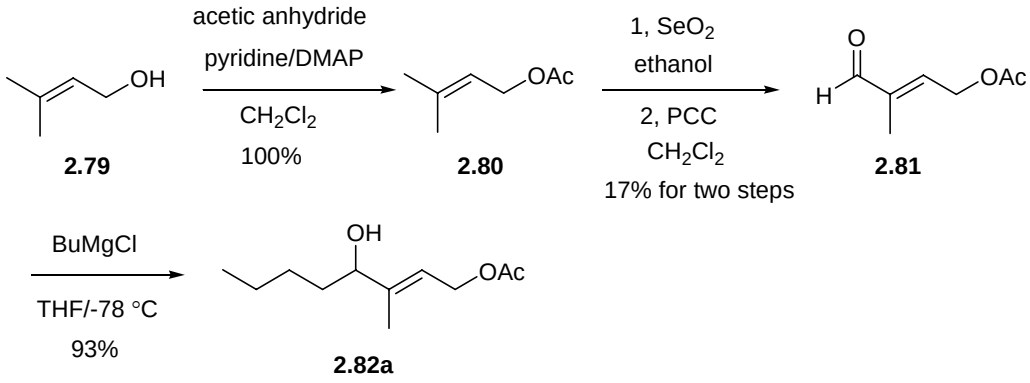
Figure 2.9. MMD image of the predicted lowest energy conformer of **2.77**

Deprotection of the compound **2.73** with HF pyridine afforded alcohol **2.77** in 87% yield. The coupling reaction between **2.77** and the vinylstannane **2.75** was conducted under a variety of conditions (Scheme 2.40). In most conditions, we observed multiple spots on TLC.



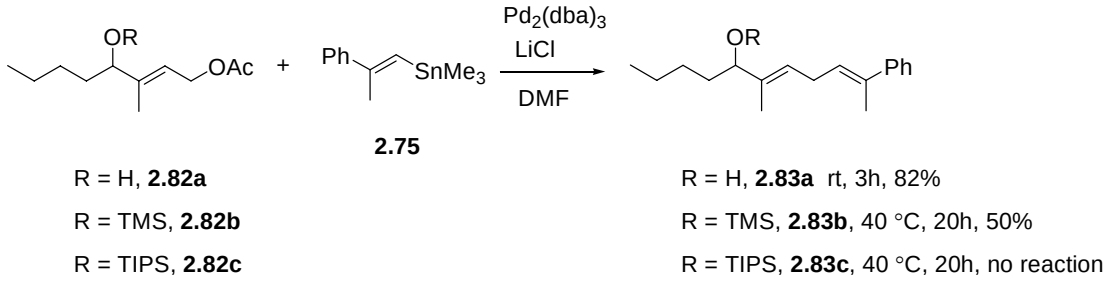
Scheme 2.40 Coupling reaction of 2.77 with 2.75

In order to know that if the free hydroxyl group in substrate **2.77** affected the coupling reaction, another model substrate **2.82** was prepared (Scheme 2.41). The synthesis commences with the allylic alcohol **2.79** upon treatment with acetic anhydride in the presence of pyridine and DMAP to afford the corresponding acetate **2.80** in quantitative yield. The E-methyl group of acetate **2.80** was selectively oxidized with SeO_2 to give the allylic alcohol,[42] which was further oxidized to corresponding aldehyde **2.81** with PCC in an overall 17% yield. Butyl magnesium chloride addition to the aldehyde at –78 °C generated the model substrate **2.82** in 93% yield.



Scheme 2.41 Synthesis of model substrate 2.82a with free hydroxyl group

The coupling reaction between allylic acetate with free hydroxyl group **2.82a** and vinylstannane **2.75** proceeded smoothly under standard Stille coupling reaction condition (Scheme 2.42). The desired coupling product **2.83a** was obtained in 82% yield after the reaction mixture was stirred for 3 h at room temperature. When the free hydroxyl group was protected with a TMS group, the coupling reaction only gave the desired product **2.83b** in 50% yield at 40 °C for 20 h. If the free hydroxyl group was protected with TIPS group, the coupling reaction did not proceed at all under the same conditions. These results implied that the protecting group next to the allylic acetate slowed down the coupling reaction. The bulkier of the protecting group, the poorer of the yield of the coupling reaction. However, the free hydroxyl group does not affect the coupling reaction.

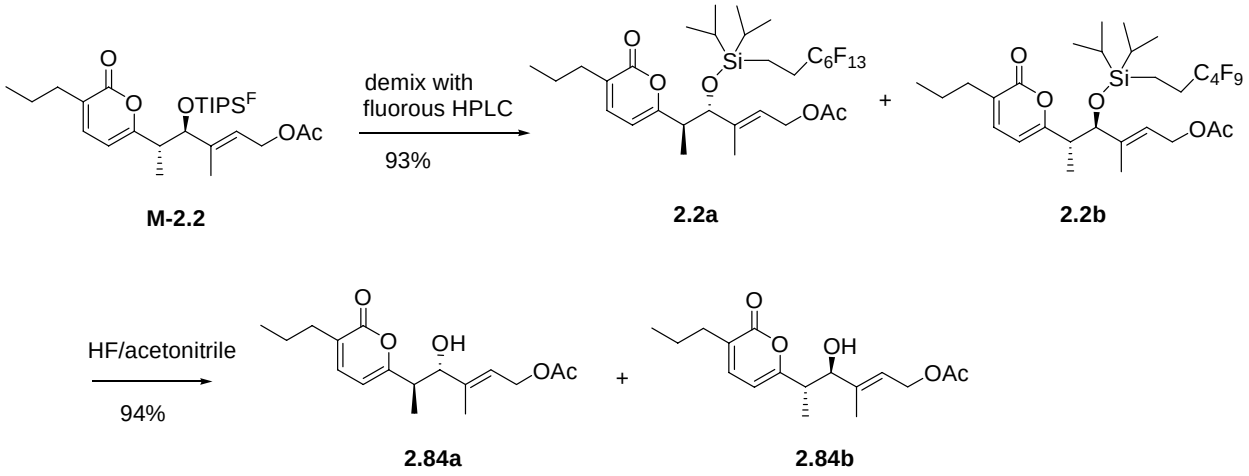


Scheme 2.42 Stille coupling reactions of different model substrates

Pyrone **M-2.2** was demixed by preparative fluorous HPLC (10 × 250 mm) (Scheme 2.43). The gradient fluent started at 80% CH_3CN-20% H_2O. After staying that condition for 10 min, the eluent changed from 80% CH_3CN-20% H_2O to 90% CH_3CN-10% H_2O in 10 min and to 100% CH_3CN in 10 min. The elution lasted for another 10 min with 100% CH_3CN. The flow rate is 10 mL/min. Under above conditions, two fractions were collected with the retention times of 10 min and 15 min individually. The first fraction contains compound **2.2b** while the second

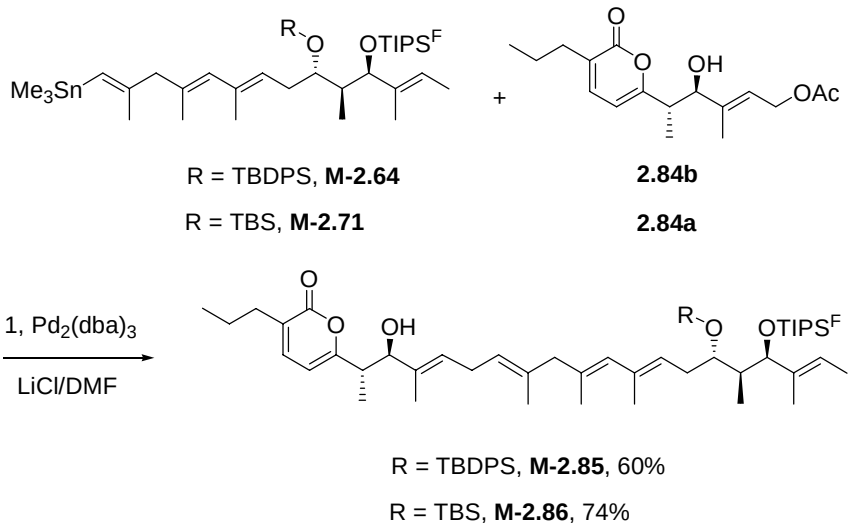
fraction contains compound **2.2a**. 102 mg **M-2.2** was injected totally, and 51 mg **2.2a** and 44 mg **2.2b** were obtained after the separation. The total recovery was 93%. The molar ratio for **2.2a** and **2.2b** is 1:1, which is the same as the ratio of the starting mixture **2.18a** and **2.18b**. Thus, during the whole synthesis, these two fluorous protected quasienantiomers behaved exactly the same. The optical rotation $[\alpha]_D^{25}$ of **2.2a** is +27.9 (0.3, $CHCl_3$) and that of **2.2b** is –28.5 (0.3, $CHCl_3$). These values are roughly the same magnitude but in opposite direction.

Compounds **2.2a** and **2.2b** were then deprotected with HF in acetonitrile to afford **2.84a** and **2.84b** both in 94% and 95% yields, respectively. Other approaches such as TBAF and HF pyridine could not afford the desired products in good yield.



Scheme 2.43 Synthesis of hydroxyl pyrone 2.84a and 2.84b

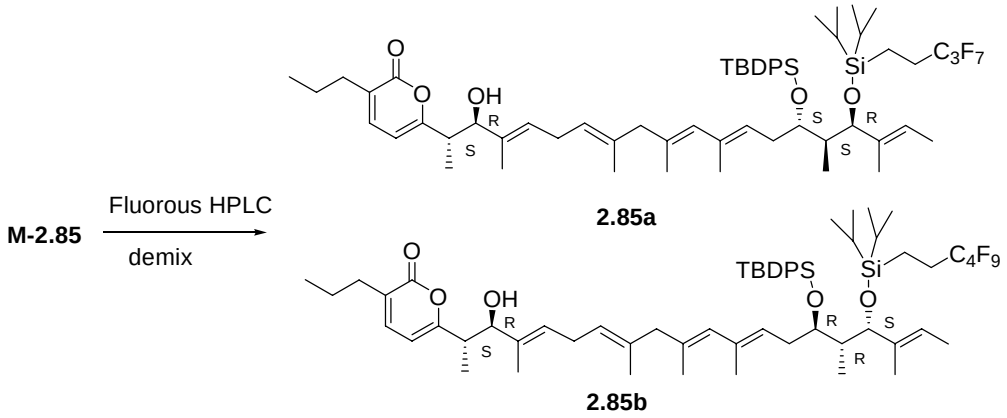
The coupling reaction between vinylstannane **M-2.64** and allylic acetate **2.84b** with $Pd_2(dba)_3$ as the catalyst afforded desired product **M-2.85** in 60% yield at room temperature (Scheme 2.44). Under the same condition, the coupling reaction between **M-2.71** and **2.84a** afforded the desired products **M-2.86** in 74% yield. Compounds **M-2.85** and **M-2.86** are both a mixture of two compounds, now ready for preparative HPLC demixing in the next step.



Scheme 2.44 Synthesis of compounds M-2.85 and M-2.86 with Stille coupling reaction

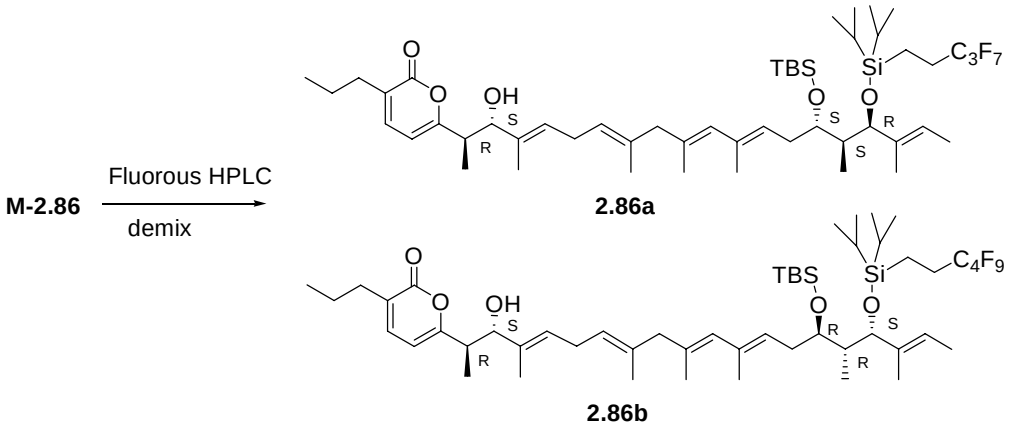
2.2.6 FINISHING THE SYNTHESIS OF FOUR ISOMERS OF LAGUNAPYRONE B

Pyrone **M-2.85** was demixed by preparative fluorous HPLC (10 × 250 mm) (Scheme 2.45). The gradient fluent started at 70% CH_3CN-30% H_2O. After staying that condition for 10 min, the fluent changed from 70% CH_3CN-30% H_2O to 80% CH_3CN-20% H_2O in 5 min and t to 80% CH_3CN-20% H_2O in 5 min then to 100% CH_3CN in 5min. The elution was lasted for another 20 min with 100% CH_3CN. The flow rate is 10 mL/min. Under these conditions, the two fractions were collected with the retention times of 32 min and 37 min. The first fraction contains compound **2.85a** while the second fraction contains compound **2.85b**. 27 mg **M-2.85** was injected to semi-preparative HPLC, 14 mg **2.85a** and 10 mg **2.85b** were obtained after the separation. The total recovery was 89%.



Scheme 2.45 Demixing M-2.85 with fluorous HPLC

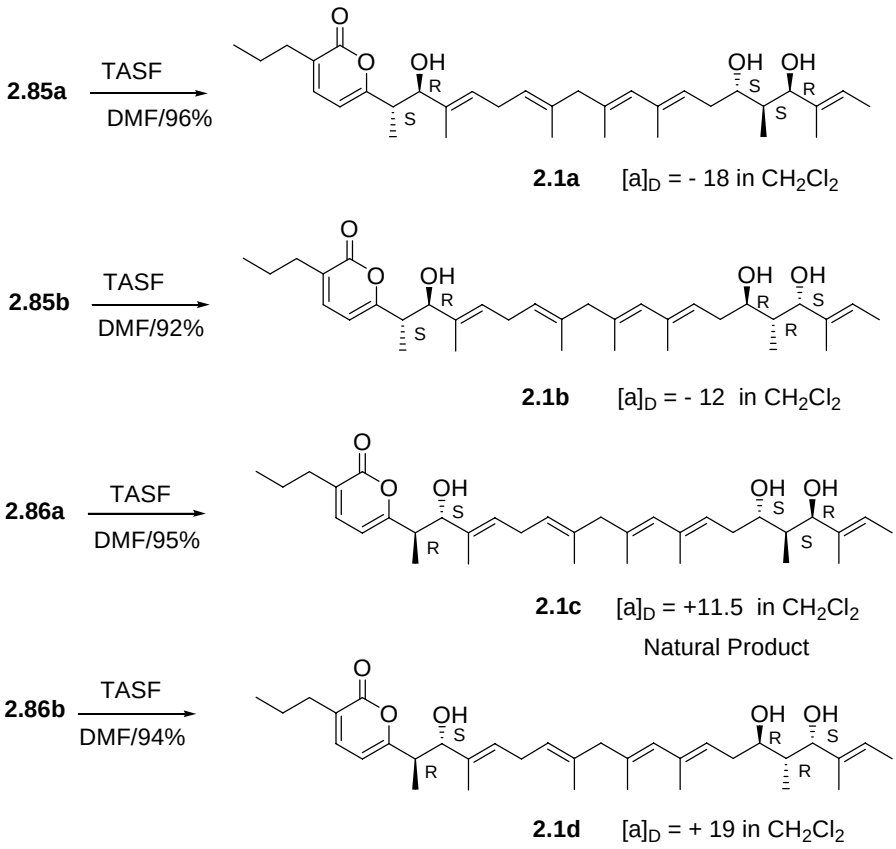
Pyrone **M-2.86** was also demixed by preparative fluorous HPLC (10 × 250 mm) with the same conditions as above (Scheme 2.46). Under these conditions, the two fractions were collected with the retention times of 30 min and 32 min. The first fraction contains compound **2.86a** while the second fraction contains compound **2.86b**. 32 mg **M-2.86** was injected to semi-preparative HPLC, 18 mg **2.86a** and 11 mg **2.86b** were obtained after the separation. The total recovery was 91%. The molar ratio for **2.86a** and **2.86b** is 1.6:1. However, at the beginning of the mixture synthesis, compounds **2.50a** and **2.50b** were mixed with 1:1 ratio.



Scheme 2.46 Demixing M-2.86 with preparative fluorous HPLC

Compounds **2.85a**, **2.85b**, **2.86a**, **2.86b** were then individually deprotected by using TASF[43] in DMF to give four final compounds in 95% yields (Scheme 2.47). Other approaches such as TBAF, HF, decomposed the starting material. These four final compounds were first purified by flash chromatography on silica gel then by preparative HPLC with a Symmetry C18 column (20 × 250 mm) under gradient conditions.

Compounds **2.1a** and **2.1d** are enantiomers. The optical rotation $[\alpha]_D^{25}$ of compound **2.1a** is –18.0 and that of **2.1d** is +19.0. Compounds **2.1b** and **2.1c** are enantiomers. The optical rotation $[\alpha]_D^{25}$ of compound **2.1b** is -12 and that of **2.1c** is +11.5. These are roughly the same magnitude but in opposite direction. The reported optical rotation of $[\alpha]_D^{25}$ of the natural lagunapyrone B is +10.9. Based on comparison of the optical rotation of these four compounds, we concluded that compound **2.1c** is the natural lagunapyrone B. The configuration of this natural product is 6R, 7S, 19S, 20S, 21R. Since we can not obtain the authentic lagunapyrone B sample from the group which isolated the natural product (which already decomposed), the only way to determine the structure of lagunapyrone is by comparing the value of optical rotation.



Scheme 2.47 Deprotection of 2.85 and 2.86

All four lagunapyrone B isomers were analyzed by ^{1}H NMR and ^{13}C NMR on Bruker Avance^{TM} 600 NMR spectrometer. **2.1c** was also analyzed by HMQC and HMBC. They are pure as judged by ^{1}H, ^{13}C NMR spectra and HPLC analysis. The ^{1}H NMR and ^{13}C NMR data of the four synthetic isomers were compared with those of lagunapyrone reported in the literature. All the ^{1}H NMR and ^{13}C NMR data of the four compounds are indistinguishable and identical to those of lagunapyrone B. HPLC analysis showed that with Waters Nava-Pak®Silica column (3.9 × 150 mm), these four compounds had a single peak at 24.5 min with 60% CH_3CN and 40% H_2O as the eluent.

2.3 CONCLUSION

Fluorous quasiracemic synthesis was applied to the total synthesis of lagunapyrone B and its isomers. This new technique features the tagging and mixing of each enantiomer of the chiral starting material with a different fluorous TIPS group. The corresponding mixture undergoes a serial of steps to make the fluorous-tagged products, which are separated by fluorous HPLC in the demixing stage to provide the final enantiomeric pure products.

Lagunapyrone B and three its isomers was synthesized by using fluorous quasiracemic synthesis. The ^{1}H and ^{13}C NMR of these four compounds are indistinguishable. By comparing the $[\alpha]_D^{25}$ data of these compounds, compound **2.1c** was determined to be the natural product, whose configuration is 6R, 7S, 19S, 20S, 21R.

2.4 EXPERIMENTAL

General Procedures:

All reactions were performed under an atmosphere of argon unless the reaction solvent contained water. Reaction solvents were freshly dried either by distillation or by passing through an activated alumina column. Benzene was distilled from Na/benzophenone. Methylene chloride, THF, ether, toluene were dried by activated alumina according to Pangborn, A.; Giardello, M. A.; Grubbs, R, H.; Rosen, R. K.; Timmers, F.; *J. Organometallics*, **1996**, *15*, 1518.

Products and reactions are analyzed by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, FT-IR, high and low resolution mass spectroscopy, HPLC and TLC. NMR spectra were taken on a Bruker WH-300, IBM AF-300 or a Bruker Avance^{TM} 600 NMR spectrometer. Spectra were recorded at room temperature in the indicated deuteriated solvents and chemical shifts are reported in parts per million (ppm) downfield relative to TMS using the residual solvent proton resonance of $CDCl_3$ (7.27 ppm) or central $CDCl_3$ carbon peak (77.0 ppm) as the internal standard. In reporting spectral data, the following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintuplet, m = multiplet, dd = doublet doublet, dt = doublet triplet. Infrared spectra were taken on a Mattson Genesis Series FTIR using thin film on NaCl plate or KBr. Peaks are reported in wavenumbers (cm^{-1}). High resolution mass spectra were obtained on a V/G 70/70 double focusing machine and were reported in units of *m/e*. HPLC analysis was performed on a Waters 600 E system with a UV detector using a Fluofix 120E column. LC-MS spectra were obtained on a Hewlett Parkard-1100 LC-MS using APCI mode or ESI mode. For the compounds using APCI mode, they only showed $(M\text{-}OTIPS^{F})^{+}$ peak rather than the molecular weight.

(4R,5S,E)-4-(Diisopropyl(3,3,4,4,5,5,6,6,6-nonafluorohexyl)silyloxy)-3-methyl-5-(6-oxo-5-propyl-6H-pyran-2-yl)hex-2-enyl acetate (2.2b)

DDQ (30 mg, 0.13 mmol) was added to a solution of compound "**M-"2.38** (52 mg, 0.065 mmol) in CH_2Cl_2 (2 mL) and water (0.1 mL). After 3 h at room temperature, the reaction mixture was diluted with ether (40 mL), washed with brine, and dried over $MgSO_4$. The crude product was purified by column chromatography (hexane/EtOAc = 4:1) afford the corresponding alcohol (42 mg, 95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (d, *J* = 6.6 Hz, 1H), 5.96 (d, *J* = 6.6 Hz, 1H), 5.64 (t, *J* = 6.3 Hz, 1H), 4.60 (d, *J* = 6.9 Hz, 2H), 4.30 (d, *J* = 9.0 Hz, 1H), 2.68-2.61 (m, 1H), 2.46-2.34 (m, 2H), 2.05 (s, 3H), 2.07-1.92 (m, 2H), 1.68 (s, 3H), 1.64-1.53 (m, 3H), 1.03 (d, *J* = 7.1 Hz, 3H), 0.97-0.83 (m, 17H), 0.75-0.66 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.47, 163.46, 138.81, 137.64, 128.78, 127.07, 104.16, 80.49, 58.86, 43.63, 32.40, 25.28, 21.10, 17.50, 17.39, 15.13, 13.57, 12.63, 12.55, 10.90; IR (neat) 3392, 2966, 2871, 1701, 1638, 1578, 1461, 1237, 1133, 885 cm^{-1}; MS (ESI) for a: *m/z* 649 (M^+ + Na); b: *m/z* 749 (M^+ + Na); HRMS (ESI) for a: *m/z* (M^+ + Na) calcd for $C_{27}H_{39}NaF_9SiO_4$ 649.2372, found 649.2377; b: *m/z* (M^+ + Na) calcd for $C_{29}H_{39}NaF_{13}SiO_4$ 749.2308, found 749.2296.

Acetic anhydride (43 mg, 0.426 mmol) was added to a mixture of the above alcohol (96 mg, 0.142 mmol), pyridine (45 mg, 0.568 mmol), DMAP (17 mg, 0.142 mmol) in CH_2Cl_2 (5 mL) at room temperature. The reaction mixture was stirred for 2 h at room temperature and diluted with ether (40 mL). The resulting solution was washed successively with water and $CuSO_4$ solution, and dried over $MgSO_4$. The organic solvent was removed under reduced pressure to afford compound "**M-"2.2**. Compound "**M-"2.2b** (102 mg, 0.142 mmol) was demixed by preparative fluorous HPLC to afford the title compound **2.2b** (44 mg, 93%), $[\alpha]_D^{25}$ = - 28.5 (c = 0.30, $CHCl_3$) and **2.2a** (51 mg, 93%). $[\alpha]_D^{25}$ = + 27.9 (c = 0.30, $CHCl_3$). ^{1}H NMR

(300 MHz, $CDCl_3$) δ 7.00 (d, *J* = 6.6 Hz, 1H), 5.95 (d, *J* = 6.6 Hz, 1H), 5.58 (t, *J* = 6.5 Hz, 1H), 4.60 (d, *J* = 6.9 Hz, 2H), 4.30 (d, *J* = 9.2 Hz, 1H), 2.67-2.61 (m, 1H), 2.44-2.36 (m, 2H), 2.04 (s, 3H), 2.03-1.93 (m, 2H), 1.68 (s, 3H), 1.64-1.54 (m, 2H), 1.03 (d, *J* = 7.1 Hz, 3H), 0.95 (t, *J* = 7.3 Hz, 3H), 0.93 (s, 12H), 0.78-0.66 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.76, 164.32, 163.26, 140.25, 138.64, 127.19, 123.76, 122-110 (m, 4C), 104.10, 80.34, 60.39, 43.72, 32.46, 25.31 (t, *J* = 24 Hz, 1C), 21.13, 20.64, 17.48, 17.39, 15.04, 13.60, 12.64, 12.54, 11.04. IR (neat) 2959, 2925, 2854, 1715, 1639, 1577, 1462, 1233 cm^{-1}; MS (ESI) *m/z* 691 (M^+ + Na); HRMS (ESI) calcd for $C_{29}H_{41}NaF_9SiO_5$ 691.2477, found 691.2488.

7-((*E*)-But-2-en-2-yl)-perfluoro-5-((*E*)-3-iodobut-2-enyl)-9,9-diisopropyl-2,2,6-trimethyl-3,3-diphenyl-4,8-dioxa-3,9-disilatetradecane (“M-”2.4a)

Cp_2ZrClH (2.3 g, 8.94 mmol) was added to a solution of alkyne “**M-”2.44** (2.30 g, 2.98 mmol) in CH_2Cl_2 (30 mL) at 0 °C, and the resulting suspension was then stirred for 1 h at room temperature in the dark. I_2 (2.54 g, 10 mmol) in THF (10 mL) was added at 0 °C and the reaction mixture was stirred for another 30 min. Water was added and the solution was extracted with ether (3 × 40 mL). The combined organic extracts were washed with sodium thiosulfate solution and brine, and dried over $MgSO_4$. The crude product was purified by careful column chromatography (hexane/EtOAc = 100:1) to afford the title compound “**M-”2.4a** (1.51 g, 56%) and the regioisomer “**M-”2.4b** (552 mg, 21%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.66-7.62 (m, 4H), 7.45-7.26 (m, 6H), 5.91 (t, *J* = 7.5 Hz, 1H), 5.14 (q, *J* = 6.3 Hz, 1H), 3.62 (d, *J* = 9.8 Hz, 1H), 3.46 (ddd, *J* = 11.4, 9.6, 3.3 Hz, 1H), 2.19 (s, 3H), 2.16-2.08 (m, 1H), 2.00-1.82 (m, 4H), 1.34 (d, *J* = 6.6 Hz, 3H), 1.20-1.08 (m, 15H), 1.00-0.94 (m, 14H), 0.76-0.70 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.07, 136.99, 136.14, 133.94, 133.83, 129.52, 127.47, 122.61, 94.93, 81.76, 72.46,

43.31, 32.88, 29.71, 27.43, 27.02, 25.72-25.09 (m, 1C), 19.30, 17.74, 17.61, 17.52, 12.77, 12.55, 10.62, 10.17; IR (neat) 2943, 2866, 1463, 1428, 1230, 1110, 1045, 702 cm^{-1}; MS (APCI): *m/z* (M^+ - $OTIPS^F$) 546.

(*E*)-6-(3-(Diisopropyl(perfluorobutyl)silyloxy)-6-(4-methoxybenzyloxy)-4-methylhex-4-en-2-yl)-3-propyl-2H-pyran-2-one ("M-"2.5)

A mixture of compound "**M-"2.31** (8.2 mg, 0.01 mmol) and acetic acid (10 μL) in benzene (2 mL) was refluxed for 14 h. After the reaction mixture was cooled to room temperature, ether (20 mL) was added and the resulting solution was washed with aqueous Na_2CO_3 and water, and dried over $MgSO_4$. The crude product was purified by column flash chromatography to afford the title compound "**M-"2.5** (8.1 mg, 100%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.60 (d, *J* = 5.9 Hz, 1H), 5.64 (t, *J* = 6.2 Hz, 1H), 4.87-4.82 (m, 1H), 4.43 (s, 2H), 4.22 (d, *J* = 9.8 Hz, 1H), 4.07-4.03 (m, 2H), 3.82 (s, 3H), 2.59-2.37 (m, 2H), 2.15-2.01 (m, 3H), 1.69-1.60(m, 2H), 1.61 (s, 3H), 1.58-1.45 (m, 2H), 1.08-1.01 (m, 14H), 0.92 (d, *J* = 7.3 Hz, 3H), 0.86-0.81 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.38, 159.26, 138.76, 138.72, 132.81, 130.51, 129.21, 126.77, 113.83, 80.27, 75.73, 71.88, 65.83, 55.27, 40.79, 32.94, 28.10, 25.38, 21.48, 17.70, 17.64, 17.58, 13.50, 12.73, 10.80, 9.99; IR (neat) 2928, 2868, 1723, 1613, 1514, 1239, 1040, 885 cm^{-1}; MS (ESI) for **2.5-C_4F_9**: *m/z* 771 (M^+ + Na); **2.5-C_6F_{13}**: *m/z* 871 (M^+ + Na); HRMS (ESI) for **2.5-C_4F_9**: *m/z* (M^+ + Na) calcd for $C_{35}H_{49}NaF_9SiO_5$ 771.3103, found 771.3127; **2.5-C_6F_{13}**: *m/z* (M^+ + Na) calcd for $C_{37}H_{49}NaF_{13}SiO_5$ 871.3039, found 871.3039.

(*E*)-6-(Diisopropyl(perfluorobutyl)silyloxy)-9-(4-methoxybenzyloxy)-5,7-dimethylnona-1,7-dien-4-yl 2-methylenepentanoate (“M-”2.6)

A mixture of *i*-Pr_2NEt (600 mg, 4.6 mmol), trichlorobenzoyl chloride (1.07 g, 4.4 mmol), DMAP (1.22 g, 10 mmol) and acid **2.24** (228 mg, 2 mmol) in benzene (25 mL) was stirred for 5 min. Alcohol “**M-”2.7** (736 mg, 1 mmol) in benzene (20 mL) was then added. After stirring for 20 h at room temperature, the reaction mixture was diluted with ether (150 mL), washed with water, and dried over $MgSO_4$. The crude product was purified by column chromatography (hexane/EtOAc = 10:1) to afford the title compound “**M-”2.6** (725 mg, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.2 Hz, 2H), 6.87 (d, *J* = 8.2 Hz, 2H), 6.10 (s, 1H), 5.78-5.69 (m, 1H), 5.53-5.51 (m, 1H), 5.48 (s, 1H), 5.30-5.20 (m, 1H), 5.08 (d, *J* = 15.6 Hz, 1H), 5.05 (d, *J* = 8.9 Hz, 1H), 2.37-2.03 (m, 6H), 1.84-1.70 (m, 1H), 1.58 (d, *J* = 9.6 Hz, 3H), 1.55-1.21 (m, 6H), 1.03 (d, *J* = 7.0 Hz, 12H), 1.05-0.98 (m, 2H), 0.95-0.90 (m, 2H), 0.92 (t, *J* = 6.8 Hz, 3H), 0.81 (t, *J* = 6.8 Hz, 3H); MS (ESI) for **2.6-C_4F_9**: *m/z* 799 (M^+ + Na); **2.6-C_6F_{13}**: *m/z* 899 (M^+ + Na); HRMS (ESI) for **2.6-C_4F_9**: *m/z* (M^+ + Na) calcd for $C_{37}H_{53}NaF_9SiO_5$ 799.3416, found 799.3456; **2.6-C_6F_{13}**: *m/z* (M^+ + Na) calcd for $C_{39}H_{53}NaF_{13}SiO_5$ 899.3352, found 899.3322.

(*E*)-6-(Diisopropylperfluorononyl)silyloxy)-9-(4-methoxybenzyloxy)-5,7-dimethylnona-1,7-dien-4-ol (“M-”2.7)

Allyl magnesium bromide (9 mL, 18 mmol) was added to a solution of aldehdyde “**M-” 2.8** (8.28 g, 12 mmol) in THF (100 mL) at –78 °C. The reaction mixture was warmed to room temperature and quenched with aqueous NH_4Cl solution. The resulting mixture was extracted with ether (4 × 100 mL). The combined organic extracts were washed with brine, and dried over $MgSO_4$. The crude product was purified by column chromatography (hexane/EtOAc = 5:1) to

afford the title compound "**M-"2.7** as a colorless oil (8.34 g, 95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 5.91-5.66 (m, 2H), 5.16-5.07 (m, 2H), 4.43 (s, 2H), 4.12 and 4.04 (t, *J* = 7.6 Hz, 3H), 3.81 (s, 3H), 3.80-3.65 (m, 1H), 2.33-2.05 (m, 4H), 1.61, 1.57 (s, 3H), 1.84-1.76, 1.67-1.59 (m, 1H), 1.05 (d, *J* = 7.8 Hz, 12H), 1.07-1.03 (m, 2H), 0.90-0.84 (m, 2H), 0.85 and 0.73 (d, *J* = 7.0 Hz, 3H); MS (ESI) for **2.7-C_4F_9**: *m/z* 703 (M^+ + Na); **2.7-C_6F_{13}**: *m/z* 803 (M^+ + Na); IR (neat) 3498, 2927, 2868, 1613, 1514, 1464, 1240 cm^{-1}; HRMS (ESI) for **2.7-C_4F_9**: *m/z* (M^+ + Na) calcd for $C_{31}H_{45}NaF_9SiO_4$ 703.2841, found 703.2839; **2.7-C_6F_{13}**: *m/z* (M^+ + Na) calcd for $C_{33}H_{45}NaF_{13}SiO_4$ 803.2777, found 803.2787.

(*E*)-3-(Diisopropylperfluorononyl)silyloxy)-6-(4-methoxybenzyloxy)-2,4-dimethylhex-4-enal ("M-"2.8)

$LiBH_4$ (75 mL in THF, 150 mmol) was added to a solution of compound **2.18a** (5.91 g, 7.5 mmol) and compound **2.18b** (6.66 g, 7.5 mmol) in THF (400 mL) at –78 °C. The reaction mixture was warmed to room temperature and stirred for 20 h. Water was added (very carefully), then most of the organic solvent was removed under vacuum and the residue was extracted with ether (4 × 100 mL). The combined organic extracts were washed with brine, and dried over $MgSO_4$. The crude diol was used for the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) 7.25 (d, *J* = 8.3 Hz, 2H), 6.87 (d, *J* = 8.3 Hz, 2H), 5.61 (t, *J* = 6.0 Hz, 1H), 4.68 (s, 1H), 4.42 (s, 2H), 4.21 (d, *J* = 7.7 Hz, 1H), 4.02 (d, *J* = 6.1 Hz, 2H), 3.80 (s, 3H), 3.77 (d, *J* = 7.5 Hz, 1H), 3.62 (dd, *J* = 9.0 Hz, 3.0 Hz, 1H), 2.40 (brs, 1H), 2.19-2.20 (m, 2H), 1.92 (brs, 1H), 1.72-1.58 (m, 1H), 1.62 (s, 3H), 1.14 (d, *J* = 6.3 Hz, 3H), 1.09-1.04 (m, 14H), 0.92-0.82 (m, 2H), 0.71 (d, *J* = 6.9 Hz, 3H); IR (neat) 3417, 2944, 1868, 1611, 1376, 1350, 1133, 1039, 886 cm^{-1}; MS (ESI) for a: *m/z* 707 (M^+ + Na); b: *m/z* 807 (M^+ + Na); HRMS (ESI) for a: *m/z* (M^+ + Na)

calcd for $C_{30}H_{45}NaF_9SiO_5$ 707.2790, found 707.2793; b: *m/z* (M^+ + Na) calcd for $C_{32}H_{45}NaF_{13}SiO_5$ 807.2726, found 807.2750.

$NaIO_4$ (14.9 g, 75 mmol) was added to a solution of the crude diol in acetone (400 mL) and water (100 mL). The reaction mixture was stirred for 24 h at room temperature. Most of the organic solvent was removed under reduced pressure. The resulting suspension was then extracted with ether (4 × 100 mL). The combined organic extracts were washed with brine and dried over $MgSO_4$. The crude product was purified by column chromatography (hexane/EtOAc = 5:1) to afford the title compound "**M-"2.8** (9.37 g, 90% for two steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (d, *J* = 2.9 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.64 (t, *J* = 5.9 Hz, 1H), 4.43 (s, 2H), 4.27 (d, *J* = 8.5 Hz, 1H), 4.04 (d, *J* = 6.0 Hz, 2H), 3.80 (s, 3H), 2.66-2.56 (m, 1H), 2.15-1.97 (m, 2H), 1.61 (s, 3H), 1.01 (d, *J* = 4.1 Hz, 12H), 1.10-1.01 (m, 2H), 0.91 (d, *J* = 7.1 Hz, 3H), 0.87-0.81 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.04, 159.21, 137.37, 130.18, 129.25, 126.61, 113.76, 80.07, 72.02, 65.81, 55.21, 50.38, 25.15 (t, 1C), 17.59, 17.48, 12.59, 11.38, 11.04; IR (neat) 2942, 2869, 1728, 1613, 1514, 1239 cm^{-1}; MS (ESI) for **2.8-C_4F_9**: *m/z* 661 (M^+ + Na); **2.8-C_6F_{13}**: *m/z* 761 (M^+ + Na); HRMS (ESI) for a: *m/z* (M^+ + Na) calcd for **2.8-C_4F_9**: $C_{28}H_{39}NaF_9SiO_4$ 661.2372, found 661.2345; **2.8-C_6F_{13}**: *m/z* (M^+ + Na) calcd for $C_{30}H_{39}NaF_{13}SiO_4$ 761.2308, found 761.2309.

1,4-Bis(4-methoxybenzyloxy)but-2-ene (2.10)

2-Butene-1,4-diol **2.9** (7.92 g, 90 mmol) in DMF (50 mL) was added a suspension of NaH (8.0 g, 200 mmol from 60% in mineral oil after washed with hexane) in DMF (150 mL). The reaction was then heated to 60 °C and stirred for another 2 h. After cooling to room temperature, water was added and extracted with ether (4 × 100 mL). The resulting mixture was

dried over $MgSO_4$. The crude product was purified by column chromatography (hexane/EtOAc = 5:1) to afford **2.10** (21.6 g, 71%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.4 Hz, 4H), 6.87 (d, *J* = 8.4 Hz, 4H), 5.76 (t, *J* = 4.5 Hz, 2H), 4.41 (s, 4H), 4.02 (d, *J* = 4.5 Hz, 4H), 3.78 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.10, 130.16, 129.36, 129.17, 113.65, 71.70, 65.33, 55.04.

2-(4-Methoxybenzyloxy)acetaldehyde (2.11)

Ozone was bubbled through a solution of the alkene **2.10** (18.2 g, 54 mmol) in CH_2Cl_2 (600 mL) and MeOH (20 mL) at –78 °C. After the solution turned blue (about 40 min), Me_2S (16.7 g, 270 mmol) was added. The reaction mixture was stirred for 10 min at the same temperature, before being warmed to room temperature and stirred for another 4 h. Water (100 mL) was added, and most of the organic solvent was removed under reduced pressure. The residue was extracted with ether (4 × 100 mL), and dried over $MgSO_4$. The crude product was purified by column chromatography (hexane/EtOAc = 1:1) to afford the title compound **2.11** (17.1 g, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.71 (s, 1H), 7.29 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 4.57 (s, 2H), 4.07 (s, 2H), 3.81 (s, 3H).

(*E*)-4-(4-Methoxybenzyloxy)-2-methylbut-2-enal (2.13)

2-(Triphenylphosphoranylidene)propionaldehyde **2.12** (15.3 g, 48 mmol) was added to a solution of aldehyde **2.11** (7.36 g, 40 mmol) in toluene (300 mL). After 72 h at room temperature, water (100 mL) was added. Most of toluene was removed under reduced pressure and the residue was extracted with ether (5 × 100 mL). The combined organic extracts were washed with brine, and dried over $MgSO_4$. The crude product was purified by column

chromatography (hexane/EtOAc = 3:1) to afford the title compound **2.13** (7.98 g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.43 (s, 1H), 7.28 (d, *J* = 8.5 Hz, 2H), 6.90 (d, *J* = 8.5 Hz, 2H), 6.59 (t, *J* = 5.4 Hz, 1H), 4.51 (s, 2H), 4.32 (d, *J* = 5.4 Hz, 2H), 3.81 (s, 3H), 1.72 (s, 3H);

(S)-3-Oxopentan-2-yl benzoate (2.16a)

(R)-3-Oxopentan-2-yl benzoate (2.16b)

EtMgBr (60 mL, 180 mmol) was added to a solution of amide **2.15a** (8.0 g, 60 mmol) in ether (300 mL) at 0 °C in 30 min. After the reaction mixture was stirred for 2 h at room temperature, aqueous NH_4Cl solution (200 mL) was added. The resulting suspension was extracted with CH_2Cl_2 (5 × 150 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under vacuum to afford the crude product. Since the product is volatile, it was used for the next step without purification.

Bz_2O (20.3 g, 90 mmol), DMAP (1.46 g, 12 mmol) and *i*-Pr_2NEt (15.5 g, 120 mmol) were added successively to a solution of the above alcohol in CH_2Cl_2 (250 mL). After stirring 15 h, excess of Bz_2O was removed by addition of ethylenediamine (3 g, 50 mmol). Aqueous NH_4Cl solution (200 mL) was added, the mixture was extracted ether (5 × 150 mL), then the organic extracts were dried over $MgSO_4$. The crude product was purified by column chromatography (hexane/EtOAc = 4:1) to afford the title compound **2.16a** (5.62 g, 46% for two steps) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.3 Hz, 2H), 7.58 (t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 2H), 5.36 (q, *J* = 7.0 Hz, 1H), 2.73-2.46 (m, 2H), 1.53 (d, *J* = 7.0 Hz, 3H), 1.10 (t, *J* = 7.2 Hz, 3H);

(2S,4R,5S,*E*)-5-Hydroxy-8-(4-methoxybenzyloxy)-4,6-dimethyl-3-oxooct-6-en-2-ylbenzoate (2.17a)

Me_2NEt (neat, 3.5 g, 48 mmol) and ketone **2.16a** (4.94 g, 24 mmol in 50 mL ether) were successively added to a solution of $(c\text{-hex})_2BCl$ (7.65 g, 36 mmol) in ether (60 mL) at –78 °C. The reaction mixture was warmed to 0 °C and stirred for 2 h before recooling to –78 °C. Aldehyde **2.13** (4.48 g, 20 mmol) in ether (10 mL) was added and the stirring continued for further 2 h, before being transferred to a freezer (-26 °C) for fourteen hours. The reaction was quenched by addition of MeOH (60 mL) and pH 7 buffer (60 mL) at 0 °C. H_2O_2 (60 mL, 30%) was added and the stirring continued for 1 h. Most of the organic solvent was removed under reduced pressure and the residue was extracted with ether (4 × 100 mL). The combined organic extracts were washed with brine, and dried over $MgSO_4$. The crude product was purified by column chromatography (hexane/EtOAc = 23:1) to afford the title compound **2.17a** (6.08 g, 71%). $[\alpha]_D^{25}$ = + 26.0 (c = 0.50, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, J = 8.1 Hz, 2H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.62 (t, *J* = 6.3 Hz, 1H), 5.44 (q, *J* = 7.0 Hz, 1H), 4.43 (s, 2H), 4.22 (d, *J* = 9.3 Hz, 1H), 4.02 (t, *J* = 6.0 Hz, 2H), 3.78 (s, 3H), 3.03 (quintet, *J* = 7.1 Hz, 1H), 2.33 (brs, 1H), 1.62 (s, 3H), 1.56 (d, *J* = 7.0 Hz, 3H), 1.05 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.65, 165.77, 159.10, 138.23, 133.17, 130.11, 129.68, 129.44, 129.31, 128.32, 125.89, 113.67, 79.40, 75.06, 71.90, 65.68, 55.14, 45.33, 15.36, 14.41, 10.98; IR (neat) 3500, 2944, 2868, 1723, 1613, 1514, 1464, 1236, 1133, 885 cm^{-1}; MS (ESI) *m/z* 449 (M^+ + Na); HRMS (ESI) *m/z* (M^+ + Na) calcd for $C_{25}H_{30}NaO_6$ 449.1940, found 449.1945.

(2R,4S,5R,*E*)-5-Hydroxy-8-(4-methoxybenzyloxy)-4,6-dimethyl-3-oxooct-6-en-2-ylbenzoate (2.17b)

Following the same procedure as above, the title compound **2.17b** was prepared as colorless oil (5.4 g, 63%). $[\alpha]_D^{25}$ = - 25.4 (c = 0.50, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) 8.08 (d, *J* = 7.3 Hz, 2H), 7.57 (t, *J* = 7.3 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.26 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.63 (t, *J* = 6.1 Hz, 1H), 5.45 (q, *J* = 7.0 Hz, 1H), 4.44 (s, 2H), 4.25 (d, *J* = 9.2 Hz, 1H), 4.04 (t, *J* = 6.0 Hz, 2H), 3.80 (s, 3H), 3.04 (dq, *J* = 9.8 Hz, 7.0 Hz, 1H), 1.63 (s, 3H), 1.57 (d, *J* = 6.9 Hz, 3H), 1.07 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.55, 165.71, 159.07, 138.33, 133.07, 130.08, 129.61, 129.48, 129.21, 128.25, 125.70, 113.65, 79.35, 75.07, 71.80, 65.61, 55.06, 45.32, 15.28, 14.30, 10.91; IR (neat) 3500, 2944, 2868, 1723, 1613, 1514, 1464, 1236, 1133, 885 cm^{-1}; MS (ESI) *m/z* 449 (M^+ + Na); HRMS (ESI) *m/z* (M^+ + Na) calcd for $C_{25}H_{30}NaO_6$ 449.1940, found 449.1944.

(2R,4S,5R,*E*)-5-(Diisopropyl(3,3,4,4,5,5,6,6,6-nonafluorohexyl)silyloxy)-8(4methoxybenzyl oxy)-4,6-dimethyl-3-oxooct-6-en-2-yl benzoate (2.18b)

Trifluoromethanesulfonic acid (neat, 3.4 g, 22.5 mmol) was added to silane **2.20b** (neat, 8.15 g, 22.5 mmol) at 0 °C in 40 min by syringe pump. The reaction mixture was stirred for 15 h at room temperature. Alcohol **2.17b** (3.21 g, 7.5 mmol) and 2,6-lutidine (3.45 mL) in CH_2Cl_2 (20 mL) was added at 0 °C in 40 min with syringe pump. The solution was stirred for another 30 min at 0 °C, then quenched with aqueous NH_4Cl solution. The reaction mixture was extracted with ether (4 × 50 mL) and the combined organic extracts were washed with brine, and dried over $MgSO_4$. The crude product was purified by column chromgatography (hexane/EtOAc = 5:1) to afford the title compound **2.18b** (5.33 g, 90%). $[\alpha]_D^{25}$ = - 10.1 (c = 0.50, $CHCl_3$). ^{1}H NMR (300

MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.3 Hz, 2H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.63 (t, *J* = 5.9 Hz, 1H), 5.45 (q, *J* = 6.9 Hz, 1H), 4.42 (s, 2H), 4.39 (d, *J* = 9.7 Hz, 1H), 4.03 (d, *J* = 6.0 Hz, 2H), 3.80 (s, 3H), 3.06-2.96 (m, 1H), 2.14-1.99 (m, 2H), 1.59 (s, 3H), 1.54 (d, *J* = 6.9 Hz, 3H), 0.99 (brs, 17H), 0.84-0.79 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.91, 165.69, 159.25, 137.50, 133.23, 130.31, 129.78, 129.67, 129.22, 128.40, 127.20, 121.3-108.52 (m, 4C), 113.80, 80.82, 75.08, 72.03, 65.86, 55.22, 46.21, 25.18 (t, 1C), 17.53, 15.25, 14.63, 12.66, 11.00; IR (neat) 3512, 2944, 2868, 1723, 1613, 1463, 1236, 1180, 1132, 885 cm^{-1}; MS (ESI) *m/z* 809 (M^+ + Na); HRMS (ESI) calcd for $C_{37}H_{47}KF_9SiO_5$ 809.2686, found 809.2655.

(2S,4R,5S,*E*)-5-(Diisopropyl(3,3,4,4,5,5,6,6,7,7,8,8,9,9,9-pentadecafluorononyl)silyloxy)-8-(4-methoxybenzyloxy)-4,6-dimethyl-3-oxooct-6-en-2-yl benzoate (2.18a)

Following the same procedure as above, the title compound **2.18a** was prepared as colorless oil (5.03 g, 81%). $[\alpha]_D^{25}$ = + 9.6 (c = 0.50, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) 8.07 (d, *J* = 7.3 Hz, 2H), 7.58 (t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.25 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.64 (t, *J* = 5.9 Hz, 1H), 5.45 (q, *J* = 7.0 Hz, 1H), 4.42 (s, 2H), 4.39 (d, *J* = 9.8 Hz, 1H), 4.03 (d, *J* = 6.0 Hz, 2H), 3.80 (s, 3H), 3.01 (dq, *J* = 9.8 Hz, 7.0 Hz, 1H), 2.14-1.99 (m, 2H), 1.59 (s, 3H), 1.54 (d, *J* = 7.3 Hz, 3H), 1.00-0.97 (m, 17H), 0.88-0.77 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.93, 165.70, 159.19, 137.44, 133.25, 130.22, 129.77, 129.58, 129.25, 128.39, 127.18, 113.75, 80.73, 75.04, 72.00, 65.84, 55.21, 46.20, 17.53, 15.20, 14.66, 12.64, 10.97; IR (neat) 3512, 2944, 2868, 1723, 1613, 1463, 1236, 1180, 1132, 885 cm^{-1}; MS (ESI) *m/z* 909 (M^+ + Na); HRMS (ESI) *m/z* (M^+ + Na) calcd for $C_{39}H_{47}KF_{13}SiO_5$ 909.2622, found 909.2574.

Diisopropyl(3,3,4,4,5,5,6,6,6-nonafluorohexyl)silane (2.20a)

t-BuLi (32.6 mL in pentane, 55.4 mmol) was added to a solution of iodide **2.19a** (9.87 g, 26.4 mmol) in Et_2O (70 mL) at –78 °C in 30 min. After stirring 10 min at the same temperature, the reaction mixture was warmed to –15 °C and stirred for another 10 min, before recooling to –78 °C. Diisopropyl chloride (3.41 g, 15.5 mmol) was then added in 15 min. After stirring for 10 min at –78 °C, the reaction mixture was stirred 15 h at room temperature. Dilute hydrochloride (70 mL, 1M) was added at 0 °C and the resulting mixture was extracted with ether (4 × 50 mL), dried over $MgSO_4$. The crude product was purified by column chromatography (100% hexane) to afford the title compound **2.20a** (6.82 g, 86%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.49 (s, 1H), 2.20-2.05 (m, 2H), 1.12-1.01 (m, 2H), 1.05 (s, 12H), 0.88-0.82 (m, 2H).

Diisopropyl(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)silane (2.20b)

Following the same procedure as above, the title compound **2.20b** was prepared (8.84 g, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.49 (s, 1H), 2.20-2.05 (m, 2H), 1.12-1.01 (m, 2H), 1.05 (s, 12H), 0.88-0.82 (m, 2H).

(3,3,4,4,5,5,5-Heptafluoropentyl)diisopropylsilane (2.20c)

Following the same procedure as above, the title compound **2.20c** was prepared (18.2 g, 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.49 (s, 1H), 2.20-2.05 (m, 2H), 1.12-1.01 (m, 2H), 1.05 (s, 12H), 0.88-0.82 (m, 2H).

2-Methylenepentanoic acid (2.24)

Propylmagesium chloride (50 mL, 100 mmol) was added to a suspension of propargyl alcohol **2.25** (2.24 g, 40 mmol) and CuI (784 mg, 4 mmol) in ether (80 mL) at –10 °C in 25 min. After stirring 12 h at room temperature, the reaction mixture was quenched with aqueous NH_4Cl solution at 0 °C. The resulting mixture was extracted with ether (3 × 80 mL) and the combined organic extracts were washed with brine, dried over $MgSO_4$. The crude product was purified by column chromatography (hexane/EtOAc = 5:1) to afford the alcohol (2.63 g, 66%)

PCC (4.85 g, 22.5 mmol) was added to a solution of the above alcohol (1.5 g, 15 mmol) in CH_2Cl_2 at 0 °C. After stirring for 2.5 h at room temperature, the reaction mixture was filtered through a pad of silica gel. The filtrate (volatile, very carefully) was concentrated under reduced pressure to afford the crude aldehyde.

To the above aldehyde, THF (65 mL), water (32 mL), 2-methyl-2-butene (30 mL in THF, 60 mmol), NaH_2PO_4 (6.21 g, 45 mmol) and $NaClO_2$ (5.09 g, 45 mmol) were added 0 °C. The reaction mixture was stirred for another 2 h at room temperature. Most of the organic solvent was removed under reduced pressure and the resulting residue was extracted with EtOAc (3 × 50 mL), and dried over $MgSO_4$. The crude product was purified by column chromatography (hexane/EtOAc = 2:1) to afford the title compound **2.24** (1.45 g, 85% for two steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.31 (s, 1H), 5.65 (s, 1H), 2.29 (t, J = 7.3 Hz, 2H), 1.54 (q, J = 7.3 Hz, 2H), 0.95 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.79, 139.96, 127.05, 33.48, 21.50, 13.62.

(*E*)-5-Allyl-3,3-Diethyl-perfluoro-9,9-diisopropyl-7-(4-(4-methoxybenzyloxy)but-2-en-2-yl)-6-methyl-4,8-dioxa-3,9-disilaoctadecane (“M-”2.26)

TESCl (2.25 g, 15 mmol) was added to a solution of alcohol “**M-”2.7** (3.68 g, 5 mmol) and imidazole (1.36 g, 20 mmol) in DMF (20 mL). The reaction mixture was stirred for 2 h at 0 °C. Water (50 mL) was added to quench the reaction. The resulting suspension was extracted with ether (4 × 50 mL), washed with water and dried over $MgSO_4$. The crude product was purified by column chromatography (hexane/EtOAc = 15:1) to afford the title compound “**M-” 2.26** (4.05 g, 100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 5.91-5.80 (m, 1H), 5.53 (t, *J* = 7.3 Hz, 1H), 5.03 (d, *J* = 17.1 Hz, 1H), 5.01 (d, *J* = 9.9 Hz, 1H), 4.42 (s, 2H), 4.10-4.05 (m, 1H), 4.02 (d, *J* = 9.3 Hz, 2H), 3.80 (s, 3H), 2.40-2.25 (m, 2H), 2.15-1.99 (m, 2H), 1.64-1.56 (m, 1H), 1.57 and 1.54 (s, 3H), 1.03 (d, *J* = 7.8 Hz, 12H), 1.01-0.80 (m, 13H), 0.70-0.53 (m, 9H); IR (neat) 2930, 2858, 1514, 1464, 1240, 1045 cm^{-1}; MS (ESI) for **2.26-C_4F_9**: *m/z* 817 (M^+ + Na); **2.26-C_6F_{13}**: *m/z* 917 (M^+ + Na); HRMS (ESI) for a: *m/z* (M^+ + Na) calcd for **2.26-C_4F_9**: $C_{37}H_{59}NaF_9Si_2O_4$ 817.3706, found 817.3729; **2.26-C_6F_{13}**: *m/z* (M^+ + Na) calcd for $C_{39}H_{59}NaF_{13}Si_2O_4$ 917.3642, found 917.3691.

(*E*)-5-(Diisopropylperfluorononyl)silyloxy)-8-(4-methoxybenzyloxy-4,6-dimethyl-3-(triethylsilyloxy)oct-6-enal (“M-”2.27)

A mixture of alkene “**M-”2.26** (4.02 g, 5 mmol), AD-mix α (17.5 g, 12.5 mmol) in *t*-BuOH (25 mL) and water (25 mL) was stirred for 40 h at room temperature. Most of the organic solvent was removed under reduced pressure. The residue was extracted with EtOAc (4 × 50 mL). The organic extracts were washed with brine, and dried over $MgSO_4$ and concentrated

under vacuum to give the crude diol as pale yellow oil which was used for the next step without further purification.

$NaIO_4$ (5.09 g, 23.8 mmol) was added to a solution of the above diol in acetone (150 mL) and water (30 mL). The reaction mixture was stirred for 12 h at room temperature. Most of the organic solvent was removed under reduced pressure. The resulting suspension was then extracted with ether (4 × 50 mL). The combined organic extracts were washed with brine and dried over $MgSO_4$. The crude product was purified by column chromatography (hexane/EtOAc = 5:1) to afford the title compound "**M-"2.27** (3.02 g, 75% for two steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.81 (dd, *J* = 3.0, 1.5 Hz, 0.5H), 9.75 (t, *J* = 2.4 Hz, 0.5H), 7.25 (d, *J* = 8.3 Hz, 2H), 6.88 (d, *J* = 8.3 Hz, 2H), 5.54 (t, *J* = 6.0 Hz, 1H), 4.62-4.58 (m, 1H), 4.43 (s, 2H), 4.06 (d, *J* = 8.4 Hz, 1H), 4.02 (d, *J* = 6.0 Hz, 2H), 3.80 (s, 3H), 2.68-2.37 (m, 2H), 2.18-2.00 (m, 2H), 1.63-1.56 (m, 2H), 1.04 (d, *J* = 5.3 Hz, 12 H), 0.97 (t, *J* = 8.0 Hz, 9H), 0.96-0.82 (m, 4H), 0.72 (d, *J* = 6.9 Hz, 3H), 0.61 (t, *J* = 8.0 Hz, 6H); MS (ESI) for a: *m/z* 819 (M^+ + Na); b: *m/z* 919 (M^+ + Na); IR (neat) 2932, 2868, 1717, 1686, 1607, 1514, 1240, 844 cm^{-1}; HRMS (ESI) for **2.27-C_4F_9**: *m/z* (M^+ + Na) calcd for $C_{36}H_{57}NaF_9Si_2O_5$ 819.3499, found 819.3471; **2.27-C_6F_{13}**: *m/z* (M^+ + Na) calcd for $C_{38}H_{57}NaF_{13}Si_2O_5$ 919.3435, found 919.3442.

Bis(2,2,2-trifluoroethyl) 3-oxoheptan-4-ylphosphonate (2.29)

KO^tBu (1.34 g, 12 mmol) was added to a solution of methyl P,P-bis (2, 2, 2-trifluoroethyl) phosphonoacetate (3.18 g, 10 mmol) in THF (60 mL) at room temperature. After 1.5 h at the same temperature, iodopropane (neat, 6.8 g, 40 mmol) was added. The reaction mixture was refluxing for 4 h before recooling to 0 °C. Aqueous NH_4Cl solution was added and the resulting mixture was extracted with EtOAc (4 × 40 mL). The combined organic extracts

were washed with brine, and dried over $MgSO_4$. The crude product was purified by column chromatography (hexane/EtOAc = 2:1) to afford the title compound **2.29** (1.85 g, 50%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.49-4.37 (m, 4H), 3.78 (s, 3H), 3.13 (ddd, *J* = 22, 10.1, 4.3 Hz, 1H), 2.00-1.81 (m, 2H), 1.47-1.34 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H); IR (neat) 2969, 2880, 1742, 1438, 1420, 1298, 1262, 1174, 964 cm^{-1}.

(2*Z*,8*E*)-Methyl-7-(diisopropylperfluorobutyl)silyl)-10-(4-methoxybenzyloxy)-6,8-dimethyl-2-propyl-5-(triethylsilyloxy)deca-2,8-dienoate ("M-"2.30)

KHMDS (5.5 mL in toluene, 2.75 mmol) was added to a solution of compound **2.29** (1.0 g, 2.78 mmol) and 18-crown-6 (0.79 g, 3 mmol) in THF at –78 °C. After 5 min, aldehyde "**M-"2.27** (1.62 g, 2 mmol) in THF (5 mL) was added and the reaction mixture was stirred for 40 min at the same temperature. Aqueous NH_4Cl solution was added to quench the reaction. The organic mixture was extracted with ether (3 × 40 mL) and the combined organic extracts were washed with water, and dried over $MgSO_4$. The crude product was purified by column chromatography. Elution with (hexane/EtOAc = 10:1) provided the title compound "**M-"2.30** (1.17 g, 65%). Elution with (hexane/EtOAc = 5:1) provided recovered starting material (280 mg, 17.3%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.77 (t, *J* = 7.2 Hz, 1H), 5.52 (t, *J* = 6.0 Hz, 1H), 4.42 (s, 2H), 4.18-4.10 (m, 1H), 4.06-4.01 (m, 3H), 2.76-2.66 (m, 2H), 2.25-2.19 (m, 2H), 2.16-1.99 (m, 2H), 1.57-1.52 (m, 1H), 1.53 (s, 3H), 1.43 (q, *J* = 7.4 Hz, 2H), 1.03-0.80 (m, 29H), 0.70-0.48 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.42, 159.16, 139.55, 137.06, 133.34, 130.46, 129.22, 125.66, 113.74, 80.19, 71.80, 71.08, 65.98, 55.20, 51.19, 41.65, 36.72, 35.86, 22.08, 17.88, 17.82, 17.69, 17.66, 13.47, 12.93, 12.78, 11.37, 9.37, 7.02, 5.82. IR 2957, 1719, 1613, 1513; IR (neat) 2928, 2878, 1719, 1608, 1514, 1463, 1239, 886 cm^{-1};

MS (ESI) for **2.30-C_4F_9**: *m/z* 917 (M^+ + Na); **2.30-C_6F_{13}**: *m/z* 1017 (M^+ + Na); HRMS (ESI) for **2.30-C_4F_9**: *m/z* (M^+ + Na) calcd for $C_{42}H_{67}NaF_9Si_2O_6$ 917.4230, found 917.4273; **2.30-C_6F_{13}**: *m/z* (M^+ + Na) calcd for $C_{44}H_{67}NaF_{13}Si_2O_6$ 1017.4166, found 1017.4182.

(2*Z*,8*E*)-Methyl7-(diisopropyl(perfluorobutyl)silyloxy)-5-hydroxy-10-(4-methoxybenzyloxy) -6,8-dimethyl-2-propyldeca-2,8-dienoate ("M-"2.31)

A mixture of compound "**M-"2.30** (220 mg, 0.223 mmol) and dichloroacetic acid (387 mg, 3 mmol) in MeOH (5 mL) and CH_2Cl_2 (5 mL) was stirred at 0 °C for 4 h. Aqueous $NaHCO_3$ solution was added and most of organic solvent was removed under reduced pressure. The resulting residue was extracted with ether (3 × 20 mL) and the combined organic extracts were dried over $MgSO_4$. The crude product was purified by column chromatography (hexane/EtOAc = 5:1) to afford the title compound "**M-"2.31** (167 mg, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.94 (t, *J* = 7.6 Hz, 1H), 5.65 (t, *J* = 6.0 Hz, 1H), 4.43 (s, 2H), 4.13 (d, *J* = 7.2 Hz, 1H), 4.06 (d, *J* = 6.2 Hz, 3H), 3.80 (s, 3H), 3.73 (s, 3H), 2.72-2.61 (m, 2H), 2.45-2.37 (m, 1H), 2.23 (q, *J* = 7.2 Hz, 2H), 2.16-2.05 (m, 2H), 1.64-1.57 (m, 1H), 1.58 (s, 3H), 1.44 (sextet, *J* = 7.4 Hz, 2H), 1.05 (d, *J* = 6.3 Hz, 12H), 1.06-1.04 (m, 2H), 0.97-0.85 (m, 2H), 0.88 (t, *J* = 7.2 Hz, 3H), 0.84 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.84, 159.13, 139.13, 138.26, 133.83, 130.42, 129.17, 124.91, 113.70, 81.42, 71.71, 69.53, 65.84, 55.16, 51.32, 40.87, 36.46, 35.44, 22.04, 17.65, 17.58, 13.38, 12.72, 12.10, 9.86; IR (neat) 3491, 2929, 2868, 1719, 1646, 1613, 1514, 1462, 1240, 921, 743 cm^{-1}; MS (ESI) for **2.31-C_4F_9**: *m/z* 803 (M^+ + Na); **2.31-C_6F_{13}**: *m/z* 903 (M^+ + Na); HRMS (ESI) for **2.31-C_4F_9**: *m/z* (M^+ + Na) calcd for $C_{36}H_{53}NaF_9SiO_6$ 803.3365, found 803.3401; **2.31-C_6F_{13}**: *m/z* (M^+ + Na) calcd for $C_{38}H_{53}NaF_{13}SiO_6$ 903.3302, found 903.3328.

(2*Z*,8*E*)-Methyl7-(diisopropyl(perfluorobutyl)silyloxy)-10-(4-methoxybenzyloxy)-6,8-dimethyl-5-oxo-2-propyldeca-2,8-dienoate (“M-”2.32)

Dess-Martin periodinane (164 mg, 0.386 mmol) was added to a solution of alcohol “**M-” 2.31** (160 mg, 0.193 mmol) in CH_2Cl_2 (10 mL). The solution was stirred for 1 h at 0 °C. The reaction mixture was diluted with ether (50 mL), washed with water, and dried over $MgSO_4$. The crude product was purified by column chromatography (hexane/EtOAc = 5:1) to afford the title compound “**M-”2.32** (152 mg, 95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 6.31 (t, *J* = 6.5 Hz, 1H), 5.62 (t, *J* = 5.7 Hz, 1H), 4.42 (s, 2H), 4.27 (d, *J* = 9.6 Hz, 1H), 4.03 (d, *J* = 6.0 Hz, 2H), 3.90 (dd, *J* = 21, 6.6 Hz, 1H), 3.80 (s, 3H), 3.73 (s, 3H), 3.70 (dd, *J* = 21, 6.6 Hz, 1H), 2.89-2.79 (m, 1H), 2.28 (t, *J* = 7.4 Hz, 2H), 2.12-2.01 (m, 2H), 1.60 (s, 3H), 1.46 (sextet, *J* = 7.5 Hz, 2H), 1.02-0.96 (m, 2H), 0.97 (d, *J* = 6.3 Hz, 12H), 0.91 (t, *J* = 7.4 Hz, 3H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.85-0.76 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.73, 167.92, 159.19, 137.67, 133.78, 133.39, 130.26, 129.21, 126.86, 113.74, 81.66, 71.92, 65.80, 55.16, 51.22, 49.32, 44.81, 36.19, 22.13, 17.52, 17.48, 17.45, 13.90, 13.47, 12.57, 12.54, 10.88.

(2*Z*,8*E*)-7-(Diisopropyl(perfluorobutyl)silyl)-10-(4-methoxybenzyloxy)-6,8-dimethyl-2-propyl-5-(triethylsilyloxy)deca-2,8-dien-1-ol (“M-”2.35)

Dibal (3 mL, 3 mmol) was added to a solution of compound “**M-”2.30** (1.15 g, 1.27 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The solution was stirred for 1 h at the same temperature and quenched with aqueous NH_4Cl solution. The resulting mixture was extracted with ether (3 × 30 mL) and the combined organic extracts were washed with brine, and dried over $MgSO_4$. The crude product was purified by column chromatography (hexane/EtOAc = 4:1) to afford the title

compound "**M-"2.35** (710 mg, 60%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.52 (t, *J* = 6.1 Hz, 2H), 5.22 (t, *J* = 7.4 Hz, 1H), 4.22 (s, 2H), 4.15-4.10 (m, 3H), 4.04 (d, *J* = 8.5 Hz, 1H), 4.02 (d, *J* = 5.1 Hz, 2H), 3.80 (s, 3H), 2.35 (t, *J* = 7.6 Hz, 2H), 2.10-2.02 (m, 4H), 1.61-1.56 (m, 1H), 1.53 (s, 3H), 1.46 (q, *J* = 7.4 Hz, 2H), 1.03 (d, *J* = 5.0 Hz, 12H), 1.06-0.1.01 (m, 2H), 0.96 (t, *J* = 7.7 Hz, 9H), 0.86 (t, *J* = 7.3 Hz, 3H), 0.86-0.81 (m, 2H), 0.65 (d, *J* = 6.6 Hz, 3H), 0.62 (t, *J* = 7.5 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.17, 142.32, 138.90, 130.41, 129.20, 124.76, 124.42, 113.76, 82.13, 71.85, 68.98, 65.81, 59.87, 55.24, 40.36, 38.53, 33.72, 21.31, 17.67, 17.63, 17.59, 17.55, 13.75, 13.09, 12.71, 12.64, 10.69, 6.57, 5.79; IR 3450, 2957, 1614, 1514, 1463; IR (neat) 3451, 2957, 1614, 1514, 1464, 1236, 886 cm^{-1}; MS (ESI) for **2.35-C_4F_9**: *m/z* 889 (M^+ + Na); **2.35-C_6F_{13}**: *m/z* 989 (M^+ + Na); HRMS (ESI) for **2.35-C_4F_9**: *m/z* (M^+ + Na) calcd for $C_{41}H_{67}NaF_9Si_2O_5$ 889.4281, found 889.4280; **2.35-C_6F_{13}**: *m/z* (M^+ + Na) calcd for $C_{43}H_{67}NaF_{13}Si_2O_5$ 989.4217, found 989.4244.

(2*Z*,8*E*)-7-(Diisopropyl(perfluorobutyl)silyl)-10-(4-methoxybenzyloxy)-6,-dimethyl-2-propyl-5-(triethylsilyloxy)deca-2,8-dienoic acid (M-2.36)

Dess-Martin periodinane (636 mg, 1.5 mmol) was added to a solution of alcohol "**M-" 2.35** (440 mg, 0.5 mmol) and pyridine (158 mg, 2 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred for 1 h at room temperature, then diluted with ether (50 mL) and washed successively with water and $CuSO_4$ solution. The crude product was purified by column chromatography (hexane/EtOAc = 10:1) to afford the corresponding aldehyde (405 mg, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.10 (s, 1H), 7.25 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.37 (t, *J* = 8.1 Hz, 1H), 5.52 (t, *J* = 6.0 Hz, 1H), 4.42 (s, 2H), 4.26-4.21 (m, 1H), 4.04 (d, *J* = 8.6 Hz, 1H), 4.01 (d, *J* = 5.2 Hz, 2H), 3.80 (s, 3H), 2.90-2.75 (m, 2H), 2.25-1.98 (m, 4H), 1.61-1.56

(m, 1H), 1.51 (s, 3H), 1.40 (q, *J* = 7.3 Hz, 2H), 1.02 (d, *J* = 7.6 Hz, 12H), 1.03-0.99 (m, 2H), 0.97 (t, *J* = 7.7 Hz, 9H), 0.86 (t, *J* = 7.3 Hz, 3H), 0.86-0.81 (m, 2H), 0.67 (d, *J* = 6.9 Hz, 3H), 0.62 (t, *J* = 8.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.70, 159.27, 144.55, 141.55, 139.17, 130.45, 129.17, 126.13, 113.79, 80.52, 71.98, 71.17, 65.95, 55.17, 41.66, 33.37, 32.38, 25.19, 21.90, 13.61, 12.99, 12.85, 11.36, 9.54, 6.93, 6.76, 5.82, 5.09; IR (neat) 2959, 2873, 2246, 1678, 1613, 1514, 1463, 1240, 910, 735 cm^{-1}.

A mixture of $NaH_2PO_4 \bullet H_2O$ (189 mg, 1.37 mmol), $NaClO_2$ (155 mg, 1.37 mmol), 2-methyl-2-butene (1.38 mmol) and the above aldehyde (400 mg, 0.458 mmol) in THF (12 mL) and water (6 mL) was stirred for 2 h at 0 °C. Most of the organic solvent was removed under reduced pressure and the residue was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under vacuum to afford the title compound "**M-"2.36** (380 mg, 95%) without further purification for next step. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, *J* = 7.8 Hz, 2H), 6.87 (d, *J* = 7.8 Hz, 2H), 5.95 (t, *J* = 7.2 Hz, 1H), 5.52 (t, *J* = 6.0 Hz, 1H), 4.42 (s, 2H), 4.18 (t, *J* = 6.7 Hz, 1H), 4.05 (d, *J* = 9.0 Hz, 1H), 4.01 (d, *J* = 7.4 Hz, 2H), 3.80 (s, 3H), 2.79 (t, *J* = 6.9 Hz, 2H), 2.24 (t, *J* = 7.5 Hz, 2H), 2.18-1.98 (m, 2H), 1.53 (s, 3H), 1.60-1.44(m, 3H), 1.03 (d, *J* = 5.9 Hz, 12H), 1.04-0.98 (m, 2H), 0.95 (t, *J* = 8.1 Hz, 9H), 0.88 (d, *J* = 7.5 Hz, 3H), 0.89-0.81 (m, 2H), 0.67 (t, *J* = 6.6 Hz, 3H), 0.59 (t, *J* = 8.1 Hz, 6H); IR (neat) 3435, 2962, 2869, 2248, 1692, 1614, 1514, 1443, 1240, 910, 886 cm^{-1}.

(2*Z*,8*E*)-7-(Diisopropyl(perfluorobutyl)silyl)-10-(4-methoxybenzyloxy)-6,8-dimethyl-5-oxo-2-propyldeca-2,8-dienoic acid ("M-"2.37)

A mixture of compound "**M-"2.36** (380 mg) and dichloroacetic acid (387 mg, 3 mmol) in MeOH (5 mL) and CH_2Cl_2 (5 mL) was stirred at 0 °C for 4 h. Aqueous $NaHCO_3$ solution was

added and most of organic solvent was removed under reduced pressure. The resulting residue was extracted with EtOAc (3 × 20 mL) and the combined organic extracts were dried over $MgSO_4$. The crude product was purified by column chromatography (hexane/EtOAc = 1:1) to afford the hydroxyl acid (230 mg, 71%). ^{1}H NMR (300 MHz, $CDCl_3$) 7.25 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.94 (t, *J* = 7.8 Hz, 1H), 5.70 (t, *J* = 6.1 Hz, 1H), 4.44 (s, 2H), 4.25 (d, *J* = 5.0 Hz, 1H), 4.06 (d, *J* = 6.3 Hz, 3H), 3.80 (s, 3H), 2.38-2.01 (m, 6H), 1.66-1.59 (m, 1H), 1.58 (s, 3H), 1.44 (sextet, *J* = 7.4 Hz, 2H), 1.06 (d, *J* = 7.8 Hz, 12 H), 1.07-0.99 (m, 2H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.93-0.86 (m, 2H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.71, 159.22, 139.02, 137.78, 134.69, 130.38, 129.16, 124.69, 113.78, 81.79, 71.84, 69.69, 65.81, 58.29, 55.17, 40.70, 36.51, 35.39, 25.17, 21.97, 18.21, 17.53, 13.38, 12.69, 12.59, 10.23; IR: 3434 (br), 2962, 2248, 1692, 1613, 1514.

Dess-Martin periodinane (636 mg, 1.5 mmol) was added to a solution of the above hydroxyl acid (60 mg, 0.079 mmol) in CH_2Cl_2 (3 mL). The solution was stirred for one hour at room temperature. The reaction mixture was diluted with ether (30 mL), washed with water, and dried over $MgSO_4$. The crude product was purified by column chromatography (hexane/EtOAc = 2:1) to afford the title compound "**M-"2.37** (58 mg, 96%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.48 (t, *J* = 6.3 Hz, 1H), 5.61 (t, *J* = 6.0 Hz, 1H), 4.42 (s, 2H), 4.27 (d, *J* = 9.5 Hz, 1H), 4.03 (d, *J* = 6.0 Hz, 2H), 4.04-3.70 (m, 2H), 3.80 (s, 3H), 2.89-2.78 (m, 1H), 2.30 (t, *J* = 7.5 Hz, 2H), 2.11-1.96 (m, 2H), 1.60 (s, 3H), 1.51 (q, *J* = 7.4 Hz, 2H), 0.95 (d, *J* = 7.6 Hz, 12H), 0.96-0.90 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H), 0.83 (d, *J* = 7.1 Hz, 3H), 0.81-0.76 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.39, 172.59, 159.32, 137.79, 136.02, 133.33, 130.35, 129.21, 126.89, 113.85, 81.70, 71.98, 65.81, 55.20, 49.59, 44.92, 36.09, 22.19, 20.59, 17.52, 17.49, 13.85, 13.43, 12.66, 10.97.

(*E*)-6-(3-(Diisopropyl(perfluorobutyl)silyl)-6-(4-methoxybenzyloxy)-4-methylhex-4-en-2-yl)-3-propyl-2H-pyran-2-one ("M-"2.38)

A mixture of acetic anhydride (21.6 mg, 0.21 mmol), dichloroacetic acid (234 mg, 1.81 mmol) and compound "**M-"2.37** (48 mg, 0.059 mmol) in benzene (3 mL) was refluxing overnight. After cooling to room temperature, the solution was diluted with ether (30 mL). The resulting mixture was washed with aqueous $NaHCO_3$ solution, and dried over $MgSO_4$. The crude product was purified by column chromatography (hexane/EtOAc = 5:1) to afford the title compound "**M-"2.38** (42 mg, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.6 Hz, 2H), 7.01 (d, *J* = 6.6 Hz, 1H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.96 (d, *J* = 6.6 Hz, 1H), 5.65 (t, *J* = 6.0 Hz, 1H), 4.43 (s, 2H), 4.32 (d, *J* = 9.3 Hz, 1H), 4.04 (d, *J* = 5.7 Hz, 2H), 3.80 (s, 3H), 2.68-2.59 (m, 1H), 2.47-2.34 (m, 2H), 2.08-1.91 (m, 3H), 1.60 (s, 3H), 1.60-1.53 (m, 1H), 1.05 (d, *J* = 7.1 Hz, 3H), 1.02-0.86 (m, 17H), 0.75-0.69 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.63, 163.36, 159.28, 138.72, 138.03, 130.39, 129.18, 127.06, 127.01, 113.83, 104.06, 80.63, 71.91, 65.78, 55.21, 43.71, 32.43, 29.66, 25.94-25.00 (m, 1C), 21.11, 17.51, 17.41, 15.21, 13.57, 12.62, 12.56, 10.97; IR (neat) 2940, 2869, 1720, 1645, 1614, 1514, 1464, 1248, 886; MS (ESI) for **2.38-C_4F_9**: *m/z* 769 (M^+ + Na); **2.38-C_6F_{13}**: *m/z* 869 (M^+ + Na); HRMS (ESI) for **2.38-C_4F_9**: *m/z* (M^+ + Na) calcd for $C_{35}H_{47}NaF_9SiO_5$ 917.4230, found 769.2947; **2.38-C_6F_{13}**: *m/z* (M^+ + Na) calcd for $C_{37}H_{47}NaF_{13}SiO_5$ 869.2883, found 869.2869.

(*E*)-(5-Iodo-4-methylpent-4-en-1-ynyl)trimethylsilane (2.42)

Me_3Al (10 mL in hexane, 20 mmol) was added to a solution of Cp_2ZrCl_2 (730 mg, 2.5 mmol) in CH_2Cl_2 (12 mL) at –23 °C. Water (135 mg, 7.5 mmol) was then added very carefully. After the reaction was stirred for 10 min at the same temperature, alkyne **2.41** (680 mg, 5 mmol)

in CH_2Cl_2 (5 mL) was added. The solution was stirred for another 15 min and I_2 (1.91 g, 7.5 mmol) in THF (10 mL) was added. The reaction mixture was stirred for another 10 min at -23 °C before warmed to room temperature. Water (20 mL) was added and the reaction mixture was extracted with ether (3 × 50 mL). The combined organic extracts were washed with sodium thiosulfate solution and water, and dried over $MgSO_4$. The crude product was purified by column chromatography (100% pentane) to afford the title compound **2.42** (1.06 g, 76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.27 (s, 1H), 3.10 (s, 2H), 1.90 (s, 3H), 0.17 (s, 9H).

(*E*)-Trimethyl(4-methyl-5-(trimethylstannyl)pent-4-en-1-ynyl)silane (2.43)

t-BuLi (15 mL in pentane, 25.5 mmol) was dropwise added to a solution of vinyl iodide **2.42** (1.47 g, 6 mmol) in Et_2O (30 mL) at –78 °C. After 35 min at the same temperature, Me_3SnCl (9 mL in THF, 9 mmol) was added and the reaction was stirred for another 30 min before warmed to temperature. Ether (70 mL) and aqueous $NaHCO_3$ solution was added. The resulting mixture was washed water, and dried over $MgSO_4$ and concentrated under vacuum to afford the title compound **2.43** (1.72 g, 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88 (t, J = 36 Hz, 1H), 3.07 (s, 2H), 1.84 (t, J = 5.3 Hz, 3H), 0.18 (d, J = 3.0 Hz, 9H).

(*E*)-7-(But-2-en-2-yl)-5-(but-2-ynyl)-perfluoro-9,9-diisopropyl-2,2,6-trimethyl-3,3-diphenyl-4,8-dioxa-3,9-disilatetradecane (“M-”2.44)

BuLi (9.24 mL, 14.8 mmol) was added to a solution of dibromide “**M-”2.57** (5.65 g, 6.16 mmol) in THF (80 mL) at –78 °C. After 30 min, the reaction mixture was warmed to –25 °C and stirred for another 1 h. After the resulting mixture was cooled to –78 °C, MeI (1.14 g, 8 mmol) in THF (10 mL) was added in 20 min. The reaction mixture was then warmed to room temperature

and stirred for 1 h. Aqueous NH_4Cl solution was added and resulting suspension was extracted with ether (4 × 60 mL). The combined organic extracts were washed with brine and dried over $MgSO_4$. The crude product was purified by column chromatography (hexane/EtOAc = 50:1) to afford the title compound "**M-"2.44** (4.38 g, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69-7.65 (m, 4H), 7.42-7.25 (m, 6H), 5.22 (q, *J* = 6.3 Hz, 1H), 3.84 (d, *J* = 9.6 Hz, 1H), 3.68-3.63 (m, 1H), 2.28-2.16 (m, 2H), 2.08-1.95 (m, 2H), 1.88-1.80 (m, 1H), 1.54 (t, *J* = 2.4 Hz, 3H), 1.37 (d, *J* = 6.5 Hz, 3H), 1.06 (brs, 15H), 1.05-0.96 (m, 15H), 0.77-0.71 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.96, 136.16, 134.43, 133.88, 129.58, 129.29, 127.47, 127.17, 122.59, 81.10, 77.52, 77.13, 72.73, 43.30, 26.94, 25.78-24.80 (m, 1C), 22.59, 19.35, 17.72, 17.59, 17.50, 12.80, 12.64, 10.53, 10.27, 3.29. ^{19}F NMR (282MHz, $CDCl_3$) δ –79.47 (t, *J* = 9.6 Hz, 3F), 79.86 (t, *J* = 9.6 Hz, 3F), -115.83 (quin, *J* = 1.4 Hz, 2F), -116.44- -116.61 (m, 2F), -123.09--123.17 (m, 2F), -124.89 (t, *J* = 1.4 Hz, 2F), -126.47 (s, 2F); IR (neat) 2943, 2866, 1463, 1230, 1133, 1045 cm^{-1}; MS (APCI): *m/z* (M^+ - $OTIPS^F$) 417.

(*E*)-3-(tert-Butyldiphenylsilyloxy)-5-((perfluoropentyl)diisopropylsilyloxy)4,6-dimethyloct-6-enal ("**M-"2.45)**

$NaIO_4$ (8.15 g, 38.1 mmol) was added to a solution of diol "**M-"2.56** (6.03 g, 7.62 mmol) in acetone (240 mL) and water (60 mL). The reaction mixture was stirred for 16 h at room temperature. Most of the organic solvent was removed under reduced pressure. The resulting suspension was then extracted with ether (4 × 50 mL). The combined organic extracts were washed with brine and dried over $MgSO_4$. The crude product was purified by column chromatography (hexane/EtOAc = 20:1) to afford the title compound "**M-"2.45** (5.51 g, 95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.44 (dd, J = 3.3, 1.6 Hz, 1H), 7.67-7.57 (m, 4H), 7.47-7.33 (m,

6H), 5.11 (q, *J* = 6.6 Hz, 1H), 4.04 (dt, *J* = 8.3, 3.0 Hz, 1H), 3.54 (d, *J* = 9.4 Hz, 1H), 2.51 (ddd, *J* = 15.9, 8.4, 3.3 Hz, 1H), 2.18 (dt, *J* = 15.9, 1.6 Hz, 1H), 2.04-1.86 (m, 4H), 1.35 (d, *J* = 6.6 Hz, 3H), 1.09 (d, *J* = 8.1 Hz, 3H), 1.05 (s, 9H), 1.00-0.94 (m, 18H), 0.76-0.70 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.19, 136.55, 136.09, 135.98, 129.86, 127.63, 122.63, 81.72, 69.09, 46.05, 42.93, 26.93, 19.25, 17.68, 17.55, 17.47, 12.72, 12.50, 10.61, 10.17; MS (APCI): *m/z* (M^+ - $OTIPS^F$) 407.

(*E*)-3-((Perfluoropentyl)diisopropylsilyloxy)-2,4-dimethylhex-4-enal ("M-"2.46)

PCC (4 g, 18.5 mmol) was added to a solution of alcohol **M-2.51** (3.0 g, 5.95 mmol) in CH_2Cl_2 (120 mL) at 0 °C. The reaction mixture was stirred for 5 h at room temperature and then filtered through a pad of silica gel. The filtrate was concentrated under vacuum and purified by column chromatography (hexane/EtOAc = 20:1) to afford the title compound "**M-"2.46** (5.38 g, 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (d, *J* = 1.8 Hz, 1H), 5.49 (q, *J* = 6.3 Hz, 1H), 4.37 (d, *J* = 6.3 Hz, 1H), 2.56 (quint, t, *J* = 6.3, 1.8 Hz, 1H), 2.18-1.98 (m, 2H), 1.61 (d, *J* = 7.2 Hz, 3H), 1.58 (s, 3H), 1.06 (d, *J* = 6.3 Hz, 3H), 1.06-1.03 (m, 2H), 1.04 (s, 12H), 0.88-1.81 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.83, 135.56, 122.91, 78.98, 51.42, 25.60-24.91 (m, 1C), 17.56, 17.45, 17.42, 12.74, 12.67, 11.95, 9.50; IR (neat) 2946, 2870, 1729, 1464, 1352, 1112, 1056; MS (APCI) for **2.46-C_3F_7**: *m/z* (M^+ - C_3H_5O) 395; for **2.46-C_4F_9**: *m/z* (M^+ - C_3H_5O) 445.

(R)-4-benzyl-3-((2S,3S,*E*)-3-Hydroxy-2,4-dimethylhex-4-enoyl)oxazolidin-2-one (2.49b-1)

Evans' auxiliary **2.48b** (11.65 g, 50 mmol) and CH_2Cl_2 (120 mL) were added to a 500 mL three-necked flask with mechanical stirrer. After cooling to –78 °C, $TiCl_4$ (23.7 g, 125 mmol) was then added to the reaction mixture in 1.5 h with syringe pump. The reaction was

stirred for another 5 min, then diisopropylethylamine (16.8 g, 130 mmol) was added. The reaction was stirred for 1.5 h, tiglic aldehyde (neat, 10.5 g, 125 mmol) was added in 40 min with syringe pump. The reaction was quenched with aqueous NH_4Cl solution after it was stirred for 6 h at –78 °C. The reaction mixture was extracted with ether (4 × 100 mL) and the combined organic extracts were washed with brine, and dried over $MgSO_4$. The crude product was purified by column chromatography (hexane/EtOAc = 3:1) to afford the title compound **2.49b-1** (10.52 g, 66%) as a white solid. Mp. 71-72 °C. $[\alpha]_D^{25}$ = - 60.0 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.20 (m, 5H), 5.61 (q, *J* = 6.6 Hz, 1H), 4.73-4.66 (m, 1H), 4.10 (d, *J* = 4.2 H, 1H), 4.18 (dd, *J* = 15.0 Hz, 9.0 Hz, 1H), 4.17 (dd, *J* = 15.0 Hz, 5.4 Hz, 1H), 4.05 (dt, *J* = 11.4 Hz, 4.8 Hz, 1H), 3.25 (dd, *J* = 13.4 Hz, 3.3 Hz, 1H), 2.72 (dd, *J* = 13.4 Hz, 9.6 Hz, 1H), 2.58 (brs, 1H), 1.66 (s, 3H), 1.63 (d, *J* = 6.9 Hz, 3H), 1.14 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.33, 153.06, 135.15, 134.76, 129.27, 128.84, 127.25, 120.64, 65.98, 55.04, 40.60, 37.84, 12.91, 12.64, 10.80; IR (neat) 3596, 2921, 1796, 1690, 1376, 1211, 1089, 993, 758, 701 cm^{-1}; MS (EI) for a: *m/z* 317 (M^+); HRMS (EI) *m/z* (M^+) calcd for $C_{18}H_{23}NO_4$ 317.1627, found 317.1621. Following the same procedure as above, compound **2.49a-1** was prepared (10.7 g, 67%) as a white solid. Mp 72-73 °C. $[\alpha]_D^{25}$ = +58.2 (c = 1.0, $CHCl_3$).

(R)-4-Benzyl-3-((2R,3S,*E*)-3-Hydroxy-2,4-dimethylhex-4-enoyl)oxazolidin-2-one (2.49b-2)

$[\alpha]_D^{25}$ = - 46.0 (c = 0.50, $CHCl_3$).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.17 (m, 5H), 5.53 (q, *J* = 6.6 Hz, 1H), 4.71-4.63 (m, 1H), 4.19-4.06 (m, 4H), 3.27 (dd, *J* = 13.5, 3.3 Hz, 1H), 2.76 (dd, *J* = 13.5, 9.3 Hz, 1H), 2.66 (brs, 1H), 1.66 (s, 3H), 1.62 (d, *J* = 6.8 Hz, 3H), 1.02 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.61, 153.60, 135.22, 129.32, 128.70, 127.04, 123.44, 81.06, 65.80, 55.37, 40.47, 37.49, 14.50, 12.93, 10.41;

(R)-4-benzyl-3-((2S,3S,*E*)-3-(Diisopropyl(3,3,4,4,5,5,6,6,6-nonafluorohexyl)silyloxy)-2,4-dimethylhex-4-enoyl)oxazolidin-2-one (2.50b)

Trifluoromethanesulfonic acid (neat, 7.47 g, 49 mmol) was added to silane **2.20a** (neat, 22.8 g, 63 mmol) at 0 °C in 40 min with syringe pump. The reaction mixture was stirred for 15 h at room temperature. Alcohol **2.49b-1** (14.2 g, 45 mmol) in CH_2Cl_2 (100 mL) and 2,6-lutidine (10.4 mL) was added at 0 °C in 40 min with syringe pump. The solution was stirred for another 30 min at 0 °C and then quenched with aqueous NH_4Cl solution. The reaction mixture was extracted with ether (4 × 100 mL) and the combined organic extracts were washed with brine, and dried over $MgSO_4$. The crude product was purified by column chromatography. Elution with (hexane/EtOAc = 10:1) provided the title compound **2.50b** (25.1 g, 82%) Elution with (hexane/EtOAc = 3:1) provided alcohol **2.49b-1** (1.01 g, 7%). $[\alpha]_D^{25}$ = - 15.0 (c = 0.50, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.25 (m, 3H), 7.18 (d, *J* = 6.5 Hz, 2H), 5.47 (q, *J* = 6.8 Hz, 1H), 2.64 (dq, *J* = 10.0, 3.8 Hz, 1H), 4.39 (d, *J* = 9.0 Hz, 1H), 4.26-4.07 (m, 3H), 3.17 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.52 (dd, *J* = 13.2, 9.6 Hz, 1H), 2.11-2.04 (m, 2H), 1.66 (s, 3H), 1.53 (d, *J* = 6.7 Hz, 3H), 1.28 (d, *J* = 6.7 Hz, 3H), 1.05 (d, *J* = 7.6 Hz, 14H), 0.88-0.82 (m, 2H); IR (neat) 2946, 2869, 1784, 1698, 1455, 1378, 1217, 1132, 886, 704 cm^{-1}; MS (ESI) *m/z* 650 (M^+ + Na); HRMS (ESI) *m/z* (M^+ + Na) calcd for $C_{29}H_{40}NaNF_7SiO_4$ 650.2513, found 650.2508.

(S)-4-benzyl-3-((2R,3R,*E*)-3-((3,3,4,4,5,5,5-heptafluoropentyl)diisopropylsilyloxy)-2,4-dimethylhex-4-enoyl)oxazolidin-2-one (2.50a)

Following the same procedure as above, the title compound **2.50a** was prepared (18.1 g, 78%) and starting alcohol **2.49a-1** (2.31 g, 20%). $[\alpha]_D^{25}$ = + 15.8 (c = 0.50, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29-7.19 (m, 5H), 6.13 (d, *J* = 7.2 Hz, 1H), 5.42 (q, *J* = 6.5 Hz, 1H), 4.26

(d, *J* = 8.2 Hz, 1H), 4.02-3.97 (m, 1H), 3.62-3.51 (m, 3H), 2.81 (d, *J* = 7.3 Hz, 2H), 2.38 (quin, *J* = 7.5 Hz, 1H), 2.15-1.95 (m, 2H), 1.49 (d, *J* = 6.8 Hz, 3H), 1.47 (s, 3H), 1.16 (d, *J* = 6.8 Hz, 3H), 1.03 (d, *J* = 5.2 Hz, 12H), 1.03-0.97 (m, 2H), 0.85-0.79 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.80, 137.79, 135.31, 129.12, 128.59, 126.58, 123.54, 81.10, 63.59, 53.19, 46.74, 36.70, 25.31-24.65 (m, 1C), 17.58, 17.47, 17.41, 14.37, 12.74, 12.55, 10.72; IR (neat) 2945, 1782, 1697, 1456, 1352, 1227, 1110, 972, 704 cm^{-1}; MS (ESI) *m/z* 700 (M^+ + Na); HRMS (ESI): *m/z* (M^+ + Na) calcd for $C_{30}H_{40}NaNF_9SiO_4$ 700.2481, found 700.2507.

(*E*)-3-((Perfluoropentyl)diisopropylsilyloxy)-2,4-dimethylhex-4-en-1-ol (“M-”2.51)

$LiBH_4$ (25.5 mL, 51 mmol) was dropwise added to a solution of compound “**M-”2.50** (12.5 g, 19.2 mmol) in THF (100 mL) and MeOH (6.9 mL) at 0 °C. After 1 h, the reaction mixture was quenched with sodium tartrate solution (100 mL 1.0 M) and stirred for another 1 h at 0 °C. The reaction mixture was then extracted with ether (4 × 100 mL) and the combined organic extracts were washed with brine, dried over $MgSO_4$. The crude product was purified by column chromatography (hexane/EtOAc = 10:1) to afford the title compound **M-2.51** (5.78 g, 70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.44 (q, *J* = 5.8 Hz, 1H), 4.03 (d, *J* = 6.5 Hz, 1H), 3.54 (dd, *J* = 10.9 Hz, 6.6 Hz, 1H), 3.40 (dd, *J* = 10.9 Hz, 5.4 Hz, 1H), 2.18-2.00 (m, 2H), 1.92-1.85 (m, 1H), 1.61 (s, 3H), 1.60 (d, *J* = 5.7 Hz, 3H), 1.04 (d, *J* = 5.7 Hz, 12H), 1.05-1.02 (m, 2H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.86-0.80 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.71, 122.01, 81.31, 65.72, 40.13, 17.66, 17.55, 17.51, 13.21, 12.78, 12.70, 12.16; IR (neat) 3368, 2946, 2870, 1464, 1352, 1228, 1027, 885 cm^{-1}; HRMS (ESI): *m/z* (M^+ - $OTIPS^F$) calcd for $C_8H_{15}O$ 127.1123, found 127.1127.

(*E*)-6-((Perfluoropentyl)diisopropylsilyloxy)-5,7-dimethylnona-1,7-dien-4-ol (“M-”2.52)

Me_2AlCl (35 mL, 35 mmol, 1.0 M in hexane) was added to a solution of aldehyde **M-2.46** (6.68 g, 14 mmol) in CH_2Cl_2 (140 mL) at –78 °C in 45 min with syringe pump. After 5 min, allylsilane (4.79 g, 42 mmol) was added to the reaction mixture in 20 min with syringe pump. The reaction was stirred for another 50 min and then quenched with aqueous NH_4Cl at –78 °C. After warmed to room temperature, the resulting suspension was extracted with ether (4 × 100 mL). The combined organic extracts were washed with brine and dried over $MgSO_4$. The crude product was purified by column chromatography. Elution with (hexane/EtOAc = 20:1) provided starting aldehyde “**M-”2.46** (405 mg, 6%). Elution with (hexane/EtOAc = 10:1) provided the title compound “**M-”2.52** (5.68 g, 78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91-5.79 (m, 1H), 5.45 (q, *J* = 6.6 Hz, 1H), 5.13 (d, *J* = 12.7 Hz, 2H), 4.25 (d, *J* = 4.4 Hz, 1H), 3.55 (td, *J* = 8.1, 3.0 Hz, 1H), 2.86 (brs, 1H), 2.39-2.30 (m, 1H), 2.11-2.01 (m, 3H), 1.78-1.72 (m, 1H), 1.63 (s, 3H), 1.59 (d, *J* = 8.0 Hz, 3H), 1.04 (d, *J* = 7.0 Hz, 14H), 0.87-0.83 (m, 2H), 0.80 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.12, 135.01, 121.73, 117.71, 80.42, 71.90, 42.82, 38.96, 25.64-24.85 (m, 1C), 17.61, 17.53, 17.48, 12.93, 12.78, 12.69, 11.20; IR (neat) 3493, 2945, 2869, 1464, 1352, 1231, 1133, 885 cm^{-1}; MS (ESI) for **2.52-C_3F_7**: *m/z* 517 (M^+ + Na); **2.52-C_4F_9**: *m/z* 567 (M^+ + Na); HRMS (ESI) for **2.52-C_3F_7**: *m/z* (M^+ + Na) calcd for $C_{22}H_{37}NaF_7SiO_2$ 517.2349, found 517.2341; **2.52-C_4F_9**: *m/z* (M^+ + Na) calcd for $C_{23}H_{37}NaF_9SiO_2$ 567.2317, found 567.2302.

(4S,5S,6R,*E*)-4-Allyl-6-(but-2-en-2-yl)-2,2,5-trimethyl-1,3-dioxane (“M-”2.53)

TBAF (0.5 mL in THF, 0.5 mmol) was added to a solution of compound “**M-”2.52** (100 mg, 0.196 mmol) in THF at 0 °C. The reaction was then warmed to room temperature and stirred for another 1 h. The reaction was quenched with water (5 mL) and extracted with ether (3 × 10

mL). The combined organic extracts were washed with brine, and dried over $MgSO_4$. The crude product was purified by column chromatography (hexane/EtOAc = 2:1) to afford the corresponding diol (20 mg, 59%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.92-5.78 (m, 1H), 5.53 (tq, *J* = 6.8, 1.4 Hz, 1H), 5.17 (d, *J* = 18.0 Hz, 1H), 5.16 (d, *J* = 12.1Hz, 1H), 4.37 (s, 1H), 3.69 (dt, *J* = 8.0, 5.0 Hz, 1H), 2.59 (brs, 1H), 2.50 (brs, 1H), 2.45-2.24 (m, 2H), 1.65 (d, *J* = 7.8 Hz, 3H), 1.56 (s, 3H), 0.88 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.22, 135.10, 118.78, 117.96, 75.53, 74.07, 39.84, 39.43, 13.50, 12.92, 10.43.

A mixture of the above diol (17.4 mg, 0.1 mmol), 2, 2-dimethoxypropane (26 mg, 0.25 mmol) and PPTS (10 mg, 0.04 mmol) in benzene (5 mL) was refluxing for 6 h. The solution was cooled to room temperature and diluted with ether (30 mL). The resulting solution was washed with water and dried over $MgSO_4$. The crude product was purified by column chromatography (hexane/EtOAc = 40:1) to afford the title compound "**M-"2.53** (6 mg, 27%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95-5.81 (m, 1H), 5.51 (tq, *J* = 6.8, 1.4 Hz, 1H), 5.11 (d, *J* = 18.0 Hz, 1H), 5.06 (d, *J* = 11.6 Hz, 1H), 4.23 (d, *J* = 1.5 Hz, 1H), 3.33 (q, *J* = 6.9 Hz, 1H), 2.31 (t, *J* = 5.8 Hz, 2H), 1.85-1.78 (m, 1H), 1.63 (d, *J* = 6.7 Hz, 3H), 1.54 (s, 3H), 1.36 (d, *J* = 3.3 Hz, 6H), 0.69 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.34, 132.72, 118.13, 116.38, 100.68, 74.63, 72.03, 39.10, 38.70, 25.11, 24.03, 13.66, 12.66, 12.43; IR (neat) 2975, 2924, 2853, 1731, 1463, 1377, 1120 cm^{-1}.

(*E*)-5-allyl-7-(But-2-en-2-yl)-perfluoro-9,9-diisopropyl-2,2,6-trimethyl-3,3-diphenyl-4,8-dioxa-3,9-disilatetradecane ("**M-"2.55)**

TBDPSCl (6.88 g, 25 mmol) was added to a solution of alcohol "**M-"2.52** (5.19 g, 10 mmol) and imidazole (3.4 g, 50 mmol) in DMF (8 mL). The reaction mixture was stirred for 70 h

at room temperature. Water (20 mL) was added to quench the reaction. The resulting suspension was extracted with ether (4 × 30 mL), washed with water and dried over $MgSO_4$. The crude product was purified by column chromatography. Elution with (100% hexane) provided the title compound "**M-"2.55** (5.85 g, 77 %) Elution with (hexane/EtOAc = 10:1) provided recovered starting alcohol "**M-"2.52** (910 mg, 17%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65-7.61 (m, 4H), 7.42-7.30 (m, 6H), 5.66-5.52 (m, 1H), 5.15 (q, *J* = 6.4 Hz, 1H), 4.86 (d, *J* = 15.3 Hz, 1H), 4.82 (d, *J* = 8.7 Hz, 1H), 3.67 (d, *J* = 9.7 Hz, 1H), 3.52 (dt, *J* = 8.1, 3.2 Hz, 1H), 2.16 (quin, *J* = 7.5 Hz, 1H), 2.10-1.93 (m, 3H), 1.86-1.75 (m, 1H), 1.35 (d, *J* = 6.6 Hz, 3H), 1.08 (d, *J* = 7.5 Hz, 3H), 1.04 (s, 9H), 1.00-0.94 (m, 18Hz), 0.76-0.70 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.99, 136.87, 136.20, 134.50, 134.19, 129.54, 129.41, 127.39, 127.25, 122.35, 116.06, 81.84, 73.72, 43.45, 36.71, 27.11, 19.43, 17.75, 17.62, 17.53, 12.86, 12.51, 10.72, 10.23; IR (neat) 2932, 2865, 1427, 1230, 1111, 1046, 702 cm^{-1}; MS (APCI): *m/z* (M^+ - $OTIPS^F$) 405.

(*E*)-4-(tert-Butyldiphenylsilyloxy)-6-((perfluoropentyl)diisopropylsilyloxy)-5,7-dimethylnon-7-ene-1,2-diol ("M-"2.56)

A mixture of alkene "**M-"2.55** (6.3 g, 8.3 mmol), AD-mix α (25.6 g, 18.3 mmol) in *t*-BuOH (41.5 mL) and water (41.5 mL) was stirred for 20 h at room temperature. Na_2S (27.4 g, 35.2 mmol) was added and the reaction was stirred for another 1 h. The reaction mixture was extracted with EtOAc (4 × 40 mL). The organic extracts were washed with brine and dried over $MgSO_4$. The crude product was purified by column chromatography (hexane/EtOAc = 3:1) to afford the title compound "**M-"2.56** (6.2 g, 94 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69-7.63 (m, 4H), 7.47-7.34 (m, 6H), 5.17-5.11 (m, 1H), 3.71-2.97 (m, 6H), 2.03-1.65 (m, 4H), 1.38 (d, *J* =

6.6 Hz, 3H), 1.15 (s, 3H), 1.08 (d, *J* = 7.5 Hz, 3H), 1.07 (s, 9H), 1.01-0.90 (m, 18H), 0.77-0.67 (m, 2H).

(*E*)-7-(But-2-en-2-yl)-5-(3,3-dibromoallyl)-perfluoro-9,9-diisopropyl-2,2,6-trimethyl-3,3-diphenyl-4,8-dioxa-3,9-disilatetradecane ("**M-"2.57)**

Ph_3P (9.06 g, 34.6 mmol) in CH_2Cl_2 (20 mL) was dropwise added to a solution of CBr_4 (5.73 g, 17.28 mmol) in CH_2Cl_2 (20 mL) at 0°C. After the reaction mixture was cooled to –78 °C, aldehyde "**M-"2.45** (5.48 g, 7.2 mmol) in CH_2Cl_2 (15 mL) was added quickly. The resulting mixture was stirred for 30 min and warmed to 0 °C, then stirred for another 30 min. The reaction mixture was quenched with water, extracted with ether (3 × 60 mL) and dried over $MgSO_4$. The crude product was purified by column chromatography (hexane/EtOAc = 50:1) to afford the title compound "**M-"2.57** (5.35 g, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65-7.61 (m, 4H), 7.44-7.33 (m, 6H), 6.20 (t, *J* = 7.1 Hz, 1H), 5.20 (q, *J* = 6.6 Hz, 1H), 3.63 (d, *J* = 9.7 Hz, 1H), 3.56-3.52 (m, 1H), 2.23 (quin, J = 7.3 Hz, 1H), 2.05-1.86 (m, 4H), 1.36 (d, *J* = 6.6 Hz, 3H), 1.12 (d, *J* = 8.1 Hz, 3H), 1.06 (s, 9H), 1.00-10.97 (brs, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.02, 136.63, 136.14, 136.07, 133.84, 133.71, 129.76, 129.67, 127.60, 122.93, 89.13, 81.72, 71.77, 43.35, 35.62, 27.04, 25.60-24.95 (m, 1C), 19.33, 17.75, 17.62, 17.54, 12.82, 12.60, 10.60, 10.13; IR (neat) 2942, 2866, 1463, 1428, 1230, 1043, 702 cm^{-1}.

(*E*)-Trimethyl(4-methyl-5-phenylpent-4-en-1-ynyl)silane (2.59)

$Pd(PhP_3)_4$ (58 mg, 0.05 mmol) was added to a suspension of dry CuI (28.7 mg, 0.15 mmol) and LiCl (85 mg, 2 mmol) in THF (4 mL) at room temperature. After 5 min, iodobenzene (102 mg, 0.5 mmol) and vinylstannane **2.43** were added. The reaction mixture was refluxing for

4 h. After cooling to room temperature, the resulting mixture was diluted with ether (30 mL), washed with water, dried over $MgSO_4$. The crude product was purified by column chromatography (100% hexane) to afford the title compound **2.59** (50 mg, 44%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.20 (m, 6H), 6.57 (s, 1H), 3.11 (s, 2H), 1.89 (s, 3H), 0.18 (s, 9H).

7-((*E*)-But-2-en-2-yl)-5-((2*E*,4*E*)-3,5-dimethyl-8-(trimethylsilyl)octa-2,4-dien-7-ynyl)-perfluoro-9,9-diisopropyl-2,2,6-trimethyl-3,3-diphenyl-4,8-dioxa-3,9-disilatetradecane (“M-”2.60)

t-BuLi (5.8 mL, 9.9 mmol) was added to a solution of vinyl iodide **2.42** (1.25 g, 4.5 mmol) in ether (7 mL) at –78 °C. After the reaction was stirred for 1.5 h at the same temperature, $ZnBr_2$ (1.01 g, 4.5 mmol) in ether (6 mL) was added. The resulting solution was stirred for 15 min at –78 °C, then warmed to 0 °C and stirred for another 1 h

The above zinc reagent **2.61** was added to a solution of $Pd(OAc)_2$ (34.3 mg, 0.153 mmol), Ph_3P (80.1 mg, 0.306 mmol) and the vinyl iodide “**M-”2.4a** (1.38 g, 1.53 mmol) in ether (40 mL) at 0 °C. The resulting mixture was stirred for 4 h at room temperature. Water (20 mL) was added and the solution was extracted with ether (3 × 40 mL). The organic extracts were washed with brine and dried over $MgSO_4$. The crude product was purified by column chromatography (hexane/EtOAc = 100:1) to afford the title compound “**M-”2.60** (1.31 g, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (t, *J* = 7.8 Hz, 4H), 7.46-7.31 (m, 6H), 5.72 (s, 1H), 5.15 (q, *J* = 6.3 Hz, 1H), 5.08 (t, J = 7.0 Hz, 1H), 3.70 (d, *J* = 9.9 Hz, 1H), 3.57-3.49 (m, 1H), 2.92 (s, 2H), 2.26-2.16 (m, 1H), 2.15-1.98 (m, 3H), 1.90-1.75 (m, 1H), 1.70 (s, 3H), 1.58 (s, 3H), 1.37 (d, *J* = 6.5 Hz, 3H), 1.11-0.98 (m, 29H), 0.77-0.71 (m, 2H); MS (APCI): *m/z* (M^+ - $OTIPS^F$) 569.

7-((*E*)-But-2-en-2-yl)-5-((2*E*,4*E*)-3,5-dimethylocta-2,4-dien-7-ynyl)-perfluoro-9,9-diisopropyl-2,2,6-trimethyl-3,3-diphenyl-4,8-dioxa-3,9-disilatetradecane (“M-”2.62)

KOH (700 mg, 12.6 mmol) was added to a solution of compound “**M-”2.60** (1.16 g, 1.26 mmol) in methanol (150 mL). After the reaction mixture was stirred for 3 h, most of the organic solvent was removed under reduced pressure. The residue was diluted with ether (50 mL), washed with water, and dried over $MgSO_4$. The crude product was purified by column chromatography (hexane/EtOAc = 50:1) to afford the title compound “**M-”2.62** (780 mg, 73%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 8.1, 3.3 Hz, 4H), 7.41-7.32 (m, 6H), 5.73 (s, 1H), 5.16 (q, *J* = 6.6 Hz, 1H), 5.10 (t, *J* = 7.2 Hz, 1H), 3.71(d, *J* = 9.7 Hz, 1H), 3.53 (dt, *J* = 7.4, 3.3 Hz, 1H), 2.88 (s, 2H), 2.24-2.19 (m, 1H), 2.12 (t, *J* = 2.5 Hz, 1H), 2.07-1.97 (m, 3H), 1.90-1.85 (m, 1H), 1.69 (s, 3H), 1.58 (s, 3H), 1.37 (d, *J* = 6.6 Hz, 3H), 1.10 (d, *J* = 6.8 Hz, 3H), 1.09 (s, 3H), 1.04 (s, 9H), 1.00-0.98 (m, 2H), 1.00 (d, *J* = 7.3 Hz, 6H), 0.98 (d, *J* = 7.3 Hz, 6H), 0.75 (t, *J* = 8.7 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.02, 136.17, 136.15, 134.33, 134.08, 132.83, 130.27, 129.48, 129.27, 128.88, 128.24, 127.37, 127.22, 122.41, 81.95, 81.76, 73.52, 70.31, 19.34, 17.76, 17.75, 17.62, 17.53, 17.52, 16.77, 12.79, 12.56, 10.88, 10.17; IR (neat) 3314, 2932, 2865, 1463, 1428, 1230, 1110, 1044, 741, 703 cm^{-1}; MS (APCI): *m/z* (M^+ - $OTIPS^F$) 497.

7-((*E*)-But-2-en-2-yl)-perfluoro-5-((2*E*,4*E*,7*E*)-8-iodo-3,5,7-trimethylocta-2,4,7-trienyl)-9,9-diisopropyl-2,2,6-trimethyl-3,3-diphenyl-4,8-dioxa-3,9-disilatetradecane (“M-”2.63)

Me_3Al (1.5 mL in hexane, 3.0 mmol) was added to a solution of Cp_2ZrCl_2 (112 mg, 0.382 mmol) in CH_2Cl_2 (5 mL) at –23 °C. After the reaction was stirred for 10 min at the same temperature, alkyne “**M-”2.62** (680 mg, 0.764 mmol) in CH_2Cl_2 (5 mL) was added. The solution was stirred for another 2 h and I_2 (762 mg, 3 mmol) in THF (3 mL) was added. The reaction

mixture was stirred for another 10 min at -23 °C before warmed to room temperature. Water (20 mL) was added and the reaction mixture was extracted with ether (3 × 30 mL). The combined organic extracts were washed with sodium thiosulfate solution and water, and dried over $MgSO_4$. The crude product was purified by column chromatography (100% hexane) to afford the title compound "**M-"2.63** (530 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (td, *J* = 7.9, 1.3Hz, 4H), 7.43-7.29 (m, 6H), 5.90 (s, 1H), 5.48 (s, *J* = 7.3 Hz, 1H), 5.17-5.09 (m, 2H), 4.22 (d, *J* = 9.6 Hz, 1H), 3.69 (d, *J* = 9.7 Hz, 1H), 3.51 (dt, *J* = 8.3, 3.1 Hz, 1H), 2.80 (t, *J* = 6.7 Hz, 2H), 2.25-2.16 (m, 1H), 2.08-1.96 (m, 3H), 1.88-1.80 (m, 1H), 1.71 (s, 3H), 1.57 (s, 3H), 1.52 (s, 3H), 1.34 (d, *J* = 6.5 Hz, 3H), 1.10-0.93 (m, 29H), 0.77-0.71 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.31, 137.09, 136.18, 136.11, 134.44, 134.34, 134.09, 133.06, 131.68, 131.25, 129.52, 129.34, 128.14, 127.38, 127.22, 122.41, 81.86, 75.82, 73.62, 50.79, 43.60, 30.68, 27.03, 25.70-24.90 (m, 1C), 23.24, 19.36, 17.75, 17.62, 17.53, 17.09, 16.84, 12.84, 12.53, 10.80, 10.20; IR (neat) 3071, 2932, 2865, 1463, 1428, 1353, 1230, 1111, 1044, 741, 703 cm^{-1}; MS (APCI): *m/z* (M^+ - $OTIPS^F$) 639.

(*E*)-5-Allyl-7-(but-2-en-2-yl)-perfluoro-9,9-diisopropyl-2,2,3,3,6-pentamethyl-4,8-dioxa-3,9-disilatetradecane ("M-"2.65)

TBSCl (3.14 g, 20 mmol) was added to a solution of alcohol **M-2.52** (5.19 g, 10 mmol) and imidazole (2.72 g, 40 mmol) in DMF (40 mL). The reaction mixture was stirred for 15 h at room temperature. Water (20 mL) was added to quench the reaction. The resulting suspension was extracted with ether (4 × 30 mL) and the combined organic extracts were washed with water and dried over $MgSO_4$. The crude product was purified by column chromatography (hexane/EtOAc = 100:1) to afford the title compound "**M-"2.65** (5.06 g, 75 %). ^{1}H NMR (300

MHz, $CDCl_3$) δ 5.82-5.69 (m, 1H), 5.38 (q, *J* = 6.6Hz, 1H), 4.97 (d, *J* = 11.4 Hz, 1H), 4.96 (d, *J* = 16.0 Hz, 1H), 3.79 (d, *J* = 9.5, 1H), 3.43 (dt, *J* = 9.0, 3.1 Hz, 1H), 2.15-1.97 (m, 4H), 1.85-1.80 (m, 1H), 1.60 (brs, 6H), 1.04-1.00 (m, 12H), 0.99 (d, *J* = 6.6 Hz, 3H), 0.88 (s, 9H), 0.84-0.79 (m, 2H), 0.02 (s, 3H), 0.00 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.12, 136.95, 122.67, 115.97, 81.80, 72.77, 43.98, 36.17, 25.87, 26.0-25.0 (m, 1C), 18.08, 17.79, 17.66, 17.58, 12.90, 12.74, 10.99, 10.37, -4.37, -4.44; IR (neat) 3077, 2930, 2867, 1641, 1463, 1353, 1231, 1046, 911, 885 cm^{-1}; MS (APCI): *m/z* (M^+ - $OTIPS^F$) 281.

(*E*)-3-(tert-Butyldimethylsilyloxy)-5-((perfluoropentyl)diisopropylsilyloxy)-4,6-dimethyloct-6-enal (“M-”2.66)

A mixture of alkene “**M-”2.65** (4.9 g, 7.7 mmol), AD-mix α (27 g, 19.3 mmol) in *t*-BuOH (80 mL) and water (80 mL) was stirred for 20 h at room temperature. Most of the organic solvent was removed under reduced pressure. The residue was extracted with EtOAc (4 × 40 mL). The organic extracts were washed with brine, and dried over $MgSO_4$ and concentrated under vacuum to give the crude product as pale yellow oil which was used for the next step without further purification.

$NaIO_4$ (8.24 g, 38.5 mmol) was added to the solution of the above crude diol in acetone (300 mL) and water (60 mL). The reaction mixture was stirred for 8 h at room temperature. Most of the organic solvent was removed under reduced pressure. The resulting suspension was then extracted with ether (4 × 50 mL). The combined organic extracts were washed with brine and dried over $MgSO_4$. The crude product was purified by column chromatography (hexane/EtOAc = 20:1) to afford the title compound “**M-”2.66** (4.01 g, 80% for two steps). ^1H NMR (300 MHz, $CDCl_3$) δ 9.71 (s, 1H), 5.35 (q, *J* = 6.5 Hz, 1H), 4.03 (dt, *J* = 9.6, 3.0Hz, 1H), 3.67 (d, *J* = 9.4 Hz,

1H), 2.49 (ddd, *J* = 15.6, 9.6, 3.3 Hz, 1H), 2.20 (d, *J* = 15.6 Hz, 1H), 2.11-1.81 (m, 3H), 1.62 (s, 3H), 1.60 (d, *J* = 7.8 Hz, 3H), 1.02 (brs, 17H), 0.86 (s, 9H), 0.85-0.78 (m, 2H), 0.07 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.32, 136.44, 123.31, 81.73, 67.88, 45.45, 43.40, 25.67, 25.72-25.87 (m, 1C), 17.91, 17.74, 17.62, 17.54, 12.82, 12.77, 10.91, 10.36, -4.36, -4.87; MS (APCI): *m/z* (M^+ - $OTIPS^F$) 283

(*E*)-7-(But-2-en-2-yl)-5-(3,3-dibromoallyl)-perfluoro-9,9-diisopropyl-2,2,3,3,6-pentamethyl-4,8-dioxa-3,9-disilatetradecane (“M-”2.67)

Ph_3P (7.68 g, 29.3 mmol) in CH_2Cl_2 (20 mL) was dropwise added to a solution of CBr_4 (4.86 g, 14.6 mmol) in CH_2Cl_2 (20 mL) at 0 °C. After the reaction mixture was cooled to –78 °C, aldehyde **M-2.66** (3.9 g, 6.1 mmol) in CH_2Cl_2 (15 mL) was added quickly. After 2 h at the same temperature, the reaction mixture was quenched with water, extracted with ether (3 × 60 mL), and dried over $MgSO_4$. The crude product was purified by column flash chromatography. Elution with (hexane/EtOAc = 50:1) provided the title compound “**M-”2.67** (3.75 g, 76%). Elution with (hexane/EtOAc = 20:1) provided starting aldehyde “**M-”2.66** (405 mg, 10%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.39 (t, *J* = 7.4 Hz, 1H), 5.44 (q, *J* = 6.6Hz, 1H), 3.76 (d, *J* = 9.6 Hz, 1H), 3.52 (dt, *J* = 9.2, 3.3 Hz, 1H), 2.21-1.98 (m, 4H), 1.90-1.83 (m, 1H), 1.61 (d, *J* = 5.7Hz, 3H), 1.60 (s, 3H), 1.04-1.00 (m, 15H), 0.90 (s, 9H), 0.85-0.79 (m, 2H), 0.04 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.18, 136.41, 123.50, 88.82, 81.66, 70.72, 43.77, 35.00, 25.76, 19.96, 17.80, 17.67, 17.58, 12.95, 12.81, 10.80, 10.27, -4.54, -4.74.

(*E*)-7-(But-2-en-2-yl)-5-(but-2-ynyl)-perfluoro-9,9-diisopropyl-2,2,3,3,6-pentamethyl-4,8-dioxa-3,9-disilatetradecane (“M-”2.68)

BuLi (6.2 mL, 9.9 mmol) was added to a solution of dibromide “**M-”2.67** (3.65 g, 4.5 mmol) in THF (40 mL) at –78 °C. After one hour, the reaction mixture was warmed to room temperature and stirred for another 1 h. After the resulting mixture was recooled to –78 °C, MeI (1.92, 13.5mmol) was dropwise added. The reaction mixture was warmed to room temperature and stirred for another 1 h. Aqueous NH_4Cl solution was added and resulting suspension was extracted with ether (4 × 40 mL). The combined organic extracts were washed with brine and dried over $MgSO_4$. The crude product was purified by column flash chromatography (hexane/EtOAc = 50:1) to afford the title compound “**M-”2.68** (2.76 g, 95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.41 (q, *J* = 6.6Hz, 1H), 3.90 (d, *J* = 9.3 Hz, 1H), 3.52 (dt, *J* = 9.2, 3.3 Hz, 1H), 2.15-2.12 (m, 2H), 2.12-2.00 (m, 2H), 1.91-1.85 (m, 1H), 1.75 (t, *J* = 2.4Hz, 3H), 1.61 (d, *J* = 6.4Hz, 3H), 1.60 (s, 3H), 1.02 (s, 12H), 0.97 (d, *J* = 6.9Hz, 3H), 0.90 (s, 9H), 0.84-0.78 (m, 2H), 0.08 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.12, 122.83, 80.91, 72.25, 43.66, 25.80, 25.78-25.00 (m, 1C), 22.79, 18.07, 17.77, 17.65, 17.58, 12.90, 12.84, 11.12, 10.64, 3.45, -4.46, -4.77; IR (neat) 2929, 2869, 1464, 1352, 1230, 1047, 885 cm^{-1}; MS (APCI): *m/z* (M^+ - $OTIPS^F$) 293.

7-((*E*)-But-2-en-2-yl)-perfluoro-5-((*E*)-3-iodobut-2-enyl)-9,9-diisopropyl-2,2,3,3,6-penta methyl-4,8-dioxa-3,9-disilatetradecane (“M-”2.69)

Cp_2ZrClH (1.85 g, 6.34 mmol) was added to a solution of alkyne “**M-”2.68** (2.05 g, 3.17 mmol) in THF (40 mL) at 0 °C, the resulting suspension was then stirred for 3 h at room temperature in the dark. I_2 (2.54 g, 10 mmol) in THF (10 mL) was added at 0 °C and the

resulting mixture was stirred for another 2 h at the same temperature. Water was added and the reaction mixture was extracted with ether (3 × 40 mL). The combined organic extracts were washed with sodium thiosulfate solution and brine, and dried over $MgSO_4$. The crude product was purified by column flash chromatography (100% hexane) to afford the title compound "**M-" 2.69** (960 mg, 40%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.08 (t, *J* = 7.2 Hz, 1H), 5.38 (q, *J* = 6.6 Hz, 1H), 3.76 (d, *J* = 9.6 Hz, 1H), 3.43 (dt, *J* = 9.6, 3.0 Hz, 1H), 2.34 (s, 3H), 2.13-2.03 (m, 3H), 1.93-1.84 (m, 2H), 1.61 (s, 6H), 1.04-1.00 (m, 17H), 0.90 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.38, 137.06, 123.04, 94.58, 81.94, 71.61, 43.97, 32.43, 27.49, 25.80, 25.65-24.90 (m, 1C), 17.96, 17.78, 17.65, 17.57, 12.88, 10.86, 10.31, -4.51, -4.63. IR (neat) 2956, 2867, 1668, 1639, 1463, 1352, 1229, 1047, 838 cm^{-1}; MS (APCI): *m/z* (M^+ - $OTIPS^F$) 421.

7-((*E*)-But-2-en-2-yl)-5-((2*E*,4*E*)-3,5-dimethylocta-2,4-dien-7-ynyl)-perfluoro-9,9-diiso propyl-2,2,3,3,6-pentamethyl-4,8-dioxa-3,9-disilatetradecane ("**M-"2.70)**

BuLi (8 mL, 12.8 mmol) was added to a solution of vinyl iodide **2.42** (1.67 g, 6 mmol) in ether (10 mL) at –78 °C. After the reaction was stirred for 2 h at the same temperature, $ZnBr_2$ (1.5 g, 6.7 mmol) in ether (10 mL) was added. The resulting solution was stirred for 1 h at –78 °C, then warmed to room temperature and stirred for another 1 h.

The above zinc reagent **2.61** (20 mL, 4 mmol) was added to the solution of $Pd(PPh_3)_4$ (120 mg, 0.1 mmol) and vinyl iodide "**M-"2.69** (762 mg, 1 mmol) in THF (10 mL) at 0 °C. The resulting mixture was warmed to room temperature and stirred at the same temperature for 3 h. Water (20 mL) was added and the solution was extracted with ether (3 × 30 mL). The organic extracts were washed with brine and dried over $MgSO_4$. The crude product was purified by

column flash chromatography (hexane/EtOAc = 100:1) to afford TMS protected alkyne (670 mg, 85%).

KOH (280 mg, 5 mmol) was added to a solution of above alkyne (650 mg, 0.827 mmol) in methanol (50 mL). After the reaction mixture was stirred for 3 h, most of the organic solvent was removed under reduced pressure. The residue was diluted with ether (50 mL), washed with water, dried over $MgSO_4$. The crude product was purified by column flash chromatography (hexane/EtOAc = 50:1) to afford the title compound "**M-"2.70** (550 mg, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91 (s, 1H), 5.39 (q, *J* = 6.3Hz, 1H), 5.28 (t, *J* = 6.9 Hz, 1H), 3.85 (d, *J* = 9.3 Hz, 1H), 3.47 (dt, *J* = 8.9, 3.0 Hz, 1H), 2.93 (s, 2H), 2.15-2.01 (m, 4H), 2.12 (t, *J* = 2.7 Hz, 1H), 1.88-1.82 (m, 1H), 1.83 (s, 3H), 1.71 (s, 3H), 1.60 (s, 3H), 1.59 (d, *J* = 5.4 Hz, 3H), 1.05-1.01 (m, 17H), 0.88 (s, 9H), 0.86-0.80 (m, 2H), 0.02 (s, 3H), -0.02 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.13, 132.98, 130.41, 129.17, 128.01, 122.71, 81.90, 81.71, 72.70, 70.31, 44.06, 30.40, 29.37, 25.84, 25.75-24.95 (m, 1C), 18.03, 17.79, 17.66, 17.58, 16.91, 12.92, 12.75, 10.99, 10.50, -4.53; IR 3315, 2930, 1463, 1384, 1352, 1224, 1046, 886, 740 cm^{-1}.

7-((*E*)-But-2-en-2-yl)-perfluoro-5-((2*E*,4*E*,7*E*)-8-iodo-3,5,7-trimethylocta-2,4,7-trienyl)-9,9-diisopropyl-2,2,3,3,6-pentamethyl-4,8-dioxa-3,9-disilatetradecane ("M-"2.72)

Me_3Al (2.13 mL in hexane, 4.26 mmol) was added to a solution of Cp_2ZrCl_2 (207 mg, 0.71 mmol) in CH_2Cl_2 (5 mL) at –23 °C. Water (26 mg, 1.42 mmol) was added very carefully. After the reaction was stirred for 10 min at the same temperature, alkyne "**M-"2.70** (500 mg, 0.71 mmol) in CH_2Cl_2 (5 mL) was added. The solution was stirred for another 15 min and I_2 (762 mg, 3 mmol) in THF (3 mL) was added. The reaction mixture was stirred for another 10 min at -23 °C before warmed to room temperature. Water (20 mL) was added and the reaction mixture

was extracted with ether (3 × 30 mL). The combined organic extracts were washed with sodium thiosulfate solution and water, dried over $MgSO_4$. The crude product was purified by column flash chromatography (100% hexane) to afford the title compound "**M-"2.72** (452 mg, 74%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94 (d, *J* = 1.0 Hz, 1H), 5.68 (s, 1H), 5.39 (q, *J* = 6.6 Hz, 1H), 5.25 (t, *J* = 7.3 Hz, 1H), 3.83 (d, *J* = 9.4 Hz, 1H), 3.45 (dt, *J* = 9.0, 3.3 Hz, 1H), 2.87 (s, 2H), 2.20-2.03 (m, 4H), 1.87-1.80 (m, 1H), 1.77 (d, *J* = 1.0 Hz, 3H), 1.70 (s, 3H), 1.66 (d, *J* = 1.0 Hz, 3H), 1.60 (s, 3H), 1.59 (d, *J* = 6.6 Hz, 3H), 1.05-1.00 (m, 17H), 0.87 (s, 9H), 0.88-0.80 (m, 2H), 0.01 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.35, 137.00, 133.11, 131.87, 131.34, 128.09, 122.77, 81.78, 75.89, 72.53, 50.78, 43.98, 30.04, 25.82, 23.21, 18.03, 17.81, 17.68, 17.59, 17.21, 16.94, 12.84, 10.93, 10.45, -4.51, -4.56; IR (neat) 3071, 2930, 2865, 1463, 1428, 1230, 1111, 1043, 886, 740, 702 cm^{-1}; MS (APCI): *m/z* (M^+ - $OTIPS^F$) 515.

(2R,4S,5R,*E*)-8-Acetoxy-5-(diisopropyl(3,3,4,4,5,5,6,6,6-nonafluorohexyl)silyloxy)-4,6-dimethyl-3-oxooct-6-en-2-yl benzoate (2.73)

DDQ (69 mg, 0.304 mmol) was added to a solution of compound **2.18b** (120 mg, 0.152 mmol) in CH_2Cl_2 (4 mL) and water (0.2 mL). After 3 h at room temperature, the reaction mixture was diluted with ether (40 mL) and washed with brine, dried over $MgSO_4$. The crude product was purified by column chromatography (hexane/EtOAc = 2:1) afford the corresponding alcohol (83 mg, 83%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (dd, *J* = 8.4Hz, 1.4 Hz, 2H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 5.63 (t, *J* = 6.3 Hz, 1H), 5.46 (q, *J* = 7.1 Hz, 1H), 4.39 (d, *J* = 9.5 Hz, 1H), 4.20 (d, *J* = 6.2 Hz, 2H), 3.06-3.00 (m, 1H), 2.15-2.05 (m, 2H), 1.63 (s, 3H), 1.54 (d, *J* = 7.0 Hz, 3H), 1.00 (brs, 17H), 0.85-0.78 (m, 2H).

Acetic anhydride (31 mg, 0.3 mmol) was added to the solution of the above alcohol (80 mg, 0.12 mmol), pyridine (32 mg, 0.4 mmol) and DMAP (12 mg, 0.1 mmol) in CH_2Cl_2 (4 mL) at room temperature. After 2 h at the same temperature, the reaction mixture was diluted with ether (30 mL) and washed successively with water, $CuSO_4$ solution, water, and dried over $MgSO_4$. The solution was concentrated under vacuum to afford the title compound **2.73** (84 mg, 99%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10-8.06 (m, 2H), 7.61-7.56 (m, 1H), 7.48-7.43 (m, 2H), 5.58 (t, *J* = 6.7 Hz, 1H), 5.45 (q, *J* = 7.0 Hz, 1H), 4.60 (d, *J* = 6.9 Hz, 2H), 4.39 (d, *J* = 9.6 Hz, 1H), 3.04-2.99 (m, 1H), 2.15-2.02 (m, 1H), 2.04 (s, 3H), 1.68 (s, 3H), 1.54 (d, *J* = 7.0 Hz, 3H), 1.03-0.95 (m, 14H), 0.85-0.79 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.84, 165.65, 139.84, 133.23, 129.72, 129.51, 128.36, 123.79, 80.47, 74.96, 60.33, 46.14, 20.62, 17.48, 17.45, 15.16, 14.46, 12.62, 12.53, 10.87; IR (neat) 2922, 2851, 1718, 1601, 1452, 1368, 1268, 1117, 713 cm^{-1}; MS (ESI) *m/z* 731 (M^+ + Na); HRMS (ESI) *m/z* (M^+ + Na) calcd for $C_{31}H_{41}KF_9SiO_5$ 731.2217, found 731.2249.

(*E*)-trimethyl(2-phenylprop-1-enyl)stannane (2.75)

Me_3Al (20 mL in hexane, 40 mmol) was added to a solution of Cp_2ZrCl_2 (1.17 g, 4 mmol) in CH_2Cl_2 (20 mL) at –23°C. Water (216 mg, 12 mmol) was then added very carefully. After the reaction was stirred for 10 min at the same temperature, alkyne **2.74** (816 mg, 8 mmol) in CH_2Cl_2 (10 mL) was added. The solution was stirred for another 15 min and I_2 (3.81 g, 15 mmol) in THF (15 mL) was added. The reaction mixture was stirred for another 10 min at -23 °C before warmed to room temperature. Water (40 mL) was added and the reaction mixture was extracted with ether (3 × 50 mL). The combined organic extracts were washed with sodium

thiosulfate solution and water, and dried over $MgSO_4$. The crude vinyl iodide (1.91 g, 98%) was conducted to the next step without further purification.

t-BuLi (10 mL in pentane, 17 mmol) was dropwise added to the solution of vinyl iodide above (977 mg, 4 mmol) in Et_2O (20 mL) at –78 °C. After 35 min at the same temperature, Me_3SnCl (6 mL in THF, 6 mmol) was added and the reaction was stirred for another 30 min before warmed to temperature. Ether (50 mL) and aqueous $NaHCO_3$ solution was added. The resulting mixture was washed water, dried over $MgSO_4$ and concentrated under vacuum to afford the title compound **2.75** (995 mg, 89%).

(2R,4S,5R,*E*)-8-Acetoxy-5-hydroxy-4,6-dimethyl-3-oxooct-6-en-2-ylbenzoate (2.77)

HF pyridine (0.4 mL) was added to a solution of compound **2.73** (80 mg, 0.11 mmol) in THF (3 mL) at room temperature. After 4 h at the same temperature, the reaction mixture was quenched with aqueous $NaHCO_3$ solution and extracted with ether (3 × 10 mL) and dried over $MgSO_4$. The crude product was purified by column chromatography (hexane/EtOAc = 2:1) to afford the title compound **2.77** (33 mg, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11-8.08 (m, 2H), 7.63-7.57 (m, 1H), 7.49-7.44 (m, 2H), 5.58 (t, *J* = 6.5 Hz, 1H), 4.55 (q, *J* = 7.1 Hz, 1H), 4.63 (d, *J* = 6.7 Hz, 2H), 4.25 (d, *J* = 8.9 Hz, 1H), 3.10-3.00 (m, 1H), 2.06 (s, 3H), 1.70 (s, 3H), 1.59 (d, *J* = 7.1 Hz, 3H), 1.09 (d, *J* = 7.1 Hz, 3H); IR (neat) 3500, 2923, 2852, 1718, 1452, 1268, 1117, 1071, 1025, 714 cm^{-1}; MS (ESI) *m/z* 371 (M^+ + Na); HRMS (ESI) *m/z* (M^+ + Na) calcd for $C_{19}H_{24}NaO_6$ 371.1471, found 371.1483.

(*E*)-3-Methyl-4-oxobut-2-enyl acetate (2.81)

A mixture of allylic acetate **2.80** (6.4 g, 50 mmol) and SeO_2 (5.55 g, 50 mmol) in ethanol (200 mL, 95%) was refluxing for 2 h. Most of the solvent was removed under reduced pressure and the residue was diluted with ether (150 mL), washed with water, and dried over $MgSO_4$. The crude product was conducted to next step without further purification.

PCC (12.9 g, 60 mmol) was added to the solution of the above crude alcohol in CH_2Cl_2 (150 mL) at room temperature. After 1 h, the reaction mixture was filtered and the filtrate was concentrated under vacuum. The resulting residue was purified by column chromatography (hexane/EtOAc = 2:1) to afford the title compound **2.81** (1.23 g, 17% for two steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.46 (s, 1H), 6.52-6.48 (m, 1H), 4.90 (d, *J* = 6.0 Hz, 2H), 2.13 (s, 3H), 1.80 (d, *J* = 1.1 Hz, 3H).

(*E*)-4-Hydroxy-3-methyloct-2-enyl acetate (2.82a)

BuMgCl (1.5 mL, 3 mmol) was dropwise added to a solution of aldehyde **2.81** (284 mg, 2 mmol) in THF (10 mL) at –78 ºC. After 2 h at the same temperature, the reaction mixture was quenched by aqueous NH_4Cl solution, extracted with ether (3 × 15 mL), and dried over $MgSO_4$. The crude product was purified by column flash chromatography (hexane/EtOAc = 2:1) to afford the title compound **2.82a** (372 mg, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.56 (t, *J* = 5.6 Hz, 1H), 4.63 (d, *J* = 6.9 Hz, 2H), 4.02 (t, *J* = 6.5 Hz, 1H), 2.05 (s, 3H), 1.67 (s, 3H), 1.54 (q, *J* = 6.9 Hz, 2H), 1.39-1.21 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.37, 119.50, 76.93, 60.94, 34.57, 27.82, 22.56, 20.91, 13.95, 11.88; IR (neat) 3435, 2957, 2933, 2861, 1742, 1459, 1379, 1234, 1023, 959 cm^{-1}; MS (EI) *m/z* 225 (M^+); HRMS (EI) *m/z* (M^+) calcd for $C_{14}H_{25}O_2$ 225.1855, found 225.1849.

(6*E*,9*E*)-6-Methyl-10-phenylundeca-6,9-dien-5-ol (2.83a)

A mixture of $Pd_2(dba)_3$ (11 mg, 0.012 mmol), vinylstannane **2.75** (34 mg, 0.12 mmol), allylic acetate **2.82a** (12 mg, 0.06 mmol) and dry LiCl (13 mg, 0.3 mmol) in dry DMF (2 mL) was stirred for 3 h at room temperature. The reaction mixture was diluted with ether (20 mL), washed with water, and dried over $MgSO_4$. The crude product was purified by column flash chromatography (hexane/EtOAc = 5:1) to afford the title compound **2.83a** (13 mg, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.30 (m, 5H), 5.74 (td, *J* = 7.2 Hz, 1.3 Hz, 1H), 5.45 (t, *J* = 7.0 Hz, 1H), 4.00 (td, *J* = 6.6 Hz, 2.7 Hz, 1H), 2.94 (t, *J* = 7.1 Hz, 2H), 2.06 (s, 3H), 1.67 (s, 3H), 1.56 (q, *J* = 7.0 Hz, 2H), 1.40-1.18 (m, 4H), 0.90 (t, *J* = 7.1 Hz, 3H); IR (neat) 3428, 2956, 2924, 2853, 1614, 1448, 1376, 1072, 764, 669 cm^{-1}

Trimethyl((6*E*,9*E*)-6-methyl-10-phenylundeca-6,9-dien-5-yloxy)silane (2.83b)

A mixture of $Pd_2(dba)_3$ (6.8 mg, 0.0074 mmol), vinylstannane (15 mg, 0.053 mmol), allylic acetate (10 mg, 0.037 mmol) and dry LiCl (13 mg, 0.3 mmol) in dry DMF (2 mL) was stirred for 20 h at 40 ºC. The reaction mixture was diluted with ether (20 mL), washed with water, and dried over $MgSO_4$. The crude product was purified by column chromatography (100% hexane) to afford the title compound **2.83b** (6.5 mg, 50%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.19 (m, 5H), 5.74 (td, *J* = 7.2 Hz, 1.3 Hz, 1H), 5.36 (t, *J* = 7.2 Hz, 1H), 3.95 (t, *J* = 6.6 Hz, 1H), 2.91 (t, *J* = 6.9 Hz, 2H), 2.06 (s, 3H), 1.62 (s, 3H), 1.55-1.47 (m, 2H), 1.34-1.25 (m, 4H), 0.90 (t, *J* = 7.2 Hz, 3H).

(*E*)-3-Methyl-4-(triisopropylsilyloxy)oct-2-enyl acetate (2.83c)

TIPSCl (193 mg, 1 mmol) was added to a solution of alcohol **2.82a** (100 mg, 0.5 mmol) and imidazole (102 mg, 1.5 mmol) in DMF (4 mL) at room temperature. After 2 h at the same temperature, the reaction mixture was diluted with ether (30 mL), washed with water, dried over $MgSO_4$. The crude product was purified by column flash chromatography (hexane/EtOAc = 20:1) to afford the title compound **2.82c** (166 mg, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.48 (t, *J* = 6.9 Hz, 1H), 4.61 (d, *J* = 6.9 Hz, 2H), 4.10 (t, *J* = 6.5 Hz, 1H), 2.04 (s, 3H), 1.66 (s, 3H), 1.58-1.50 (m, 2H), 1.35-1.23 (m, 2H), 1.19-1.02 (m, 23H), 0.88 (t, *J* = 7.3 Hz, 3H).

(4R,5S,*E*)-4-Hydroxy-3-methyl-5-(6-oxo-5-propyl-6H-pyran-2-yl)hex-2-enyl acetate (2.84a)

(4S,5R,*E*)-4-Hydroxy-3-methyl-5-(6-oxo-5-propyl-6H-pyran-2-yl)hex-2-enyl acetate (2.84b)

HF (0.4 mL 48% solution) was dropwise added to a solution of compound **2.2a** (50 mg, 0.065 mmol) in acetonitrile (2 mL) at room temperature. After 1 h at the same temperature, the reaction mixture was quenched by aqueous sodium bicarbonate solution, extracted with ether, dried over $MgSO_4$. The crude product was purified by column flash chromatography (hexane/EtOAc = 2:1) to afford the title compound **2.84a** (18.8 mg, 94%) as an oil. $[\alpha]_D^{25}$ = + 23.0 (c = 0.30, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (d, *J* = 6.7 Hz, 1H), 6.03 (d, *J* = 6.7 Hz, 1H), 5.62 (t, *J* = 6.5 Hz, 1H), 4.63 (d, *J* = 6.6 Hz, 2H), 4.26 (d, *J* = 9.2 Hz, 1H), 2.72-2.68 (m, 1H), 2.41 (t, *J* = 7.6 Hz, 2H), 2.07 (s, 3H), 1.72 (s, 3H), 1.69-1.56 (m, 2H), 1.09 (d, *J* = 7.1 Hz, 3H), 0.96 (d, *J* = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.84, 164.01, 163.58, 140.22, 138.80, 127.12, 123.40, 103.85, 78.88, 60.64, 42.32, 32.43, 21.08, 20.85, 15.49, 13.72, 11.19; IR (neat) 3435, 2958, 2924, 2854, 1714, 1640, 1576, 1378, 1231, 1021 cm^{-1}; MS (ESI) *m/z* 331 (M^+ + Na); HRMS (ESI) *m/z* (M^+ + Na) calcd for $C_{17}H_{24}NaO_5$ 331.1521, found 331.1531. Following

the same procedure, compound **2.84b** was synthesized from compound **2.2b**. $[\alpha]_D^{25}$ = -24 (c = 0.30, $CHCl_3$).

6-((2S,3R,4*E*,7*E*,10*E*,12*E*,15S,16S,17R,18*E*)-15-(tert-Butyldiphenylsilyloxy)-17-((3,3,4,4,5,5,5-heptafluoropentyl)diisopropylsilyloxy)-3-hydroxy-4,8,10,12,16,18-hexamethylicosa-4,7,10,12,18-pentaen-2-yl)-3-propyl-2H-pyran-2-one (2.85a)

BuLi (0.2 mL in hexane, 0.32 mmol) was dropwise added to a solution of vinyl iodide **M-2.63** (160 mg, 0.161 mmol) in ether at –78 °C. Me_3SnCl (0.32 mL in THF, 0.32 mmol) was added after the solution was stirred for 1.5 h at –78 °C. The reaction was stirred for 30 min then warmed to room temperature and stirred for another 15 min at room temperature before quenched with water and extract with ether (3 × 10 mL). The organic extracts were washed with water, dried over $MgSO_4$ and concentrated under reduced pressure to afford the crude vinyl tin compound "**M-"2.64**. The crude product was used in the next step without purification.

The mixture of the crude vinylstannane "**M-"2.64**, allylic acetate **2.84b** (13 mg, 0.041 mmol) and dry LiCl (17 mg, 0.4 mmol) in DMF was degassed for 5 min with argon. $Pd_2(dba)_3$ (7.5 mg, 0.082 mmol) was then added to the solution and the mixture was stirred overnight at room temperature. The reaction was quenched with water and extracted with ether (3 × 10 mL). The organic extracts were washed with water and dried over $MgSO_4$. The crude product was purified by column chromatography (hexane/EtOAc = 5:1) to afford compound "**M-"2.85** (27 mg, 59%). Compound "**M-"2.85** was then demixed by preparative fluorous HPLC to afford **2.85a** (14 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (td, *J* = 8.1, 1.5Hz, 4H), 7.41-7.31 (m, 6H), 7.05 (d, *J* = 6.6 Hz, 1H), 6.04 (d, *J* = 6.6 Hz, 1H), 5.50 (s, 1H), 5.48 (t, *J* = 7.3 Hz, 1H), 5.16-5.12 (m, 3H), 4.22 (d, *J* = 9.6 Hz, 1H), 3.70 (d, *J* = 9.7 Hz, 1H), 3.51 (dt, *J* = 8.3, 3.4 Hz, 1H),

2.78 (t, *J* = 6.7 Hz, 2H), 2.72-2.66 (m, 1H), 2.62 (s, 2H), 2.42 (t, *J* = 7.8 Hz, 2H), 2.24-2.16 (m, 1H), 2.08-1.96 (m, 2H), 1.88-1.82 (m, 1H), 1.66 (s, 3H), 1.65-1.59 (m, 1H), 1.58 (s, 3H), 1.57 (s, 3H), 1.53 (s, 3H), 1.51 (s, 3H), 1.34 (d, *J* = 6.5 Hz, 3H), 1.10-0.93 (m, 32H), 0.76-0.71 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.70, 163.72, 138.87, 137.10, 136.18, 134.46, 134.34, 134.26, 133.48, 132.97, 130.78, 129.48, 129.28, 129.06, 127.45, 127.37, 127.22, 126.94, 123.79, 122.46, 103.65, 81.84, 79.78, 73.69, 51.40, 43.60, 42.45, 32.46, 30.78, 27.08, 26.82, 25.26 (m, 1C), 21.12, 19.39, 17.76, 17.63, 17.55, 17.00, 16.96, 13.75, 12.87, 12.54, 10.85, 10.54, 10.21; IR (neat) 3340, 2960, 2927, 2856, 1722, 1641, 1579, 1462, 1220, 1043 cm^{-1}; MS (ESI) for 1111 (M^+ + Na), HRMS (ESI) *m/z* (M^+ + Na) calcd for $C_{61}H_{87}NaF_7Si_2O_5$ 1111.5878, found 1111.5872.

6-((2S,3R,4*E*,7*E*,10*E*,12*E*,15R,16R,17S,18*E*)-15-(tert-Butyldiphenylsilyloxy)-17-(diisopropyl(3,3,4,4,5,5,6,6,6-nonafluorohexyl)silyloxy)-3-hydroxy-4,8,10,12,16,18-hexamethylicosa-4,7,10,12,18-pentaen-2-yl)-3-propyl-2H-pyran-2-one (2.85b)

Compound "**M-"2.85** was demixed by preparative fluorous HPLC to afford **2.85b** (10 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (td, *J* = 8.1, 1.5Hz, 4H), 7.41-7.31 (m, 6H), 7.05 (d, *J* = 6.3 Hz, 1H), 6.04 (d, *J* = 6.4 Hz, 1H), 5.50 (s, 1H), 5.48 (t, *J* = 7.3 Hz, 1H), 5.16-5.12 (m, 3H), 4.22 (d, *J* = 9.6 Hz, 1H), 3.70 (d, *J* = 9.7 Hz, 1H), 3.51 (dt, *J* = 8.3, 3.4 Hz, 1H), 2.78 (t, *J* = 6.7 Hz, 2H), 2.72-2.66 (m, 1H), 2.62 (s, 2H), 2.42 (t, *J* = 7.8 Hz, 2H), 2.24-2.16 (m, 1H), 2.08-1.96 (m, 2H), 1.88-1.82 (m, 1H), 1.66 (s, 3H), 1.65-1.59 (m, 1H), 1.58 (s, 3H), 1.57 (s, 3H), 1.53 (s, 3H), 1.51 (s, 3H), 1.34 (d, *J* = 6.5 Hz, 3H), 1.10-0.93 (m, 32H), 0.76-0.71 (m, 2H); IR (neat) 3340, 2960, 2927, 2856, 1722, 1641, 1579, 1462, 1220, 1043 cm^{-1}; MS (ESI) *m/z* 1161 (M^+ + Na), HRMS (ESI) *m/z* (M^+ + Na) calcd for $C_{62}H_{87}NaF_9Si_2O_5$ 1161.5846, found 1161.5881.

6-((2R,3S,4*E*,7*E*,10*E*,12*E*,15R,16R,17S,18*E*)-15-(tert-Butyldimethylsilyloxy)-17-diisopropyl(3,3,4,4,5,5,6,6,6-nonafluorohexyl)silyloxy)-3-hydroxy-4,8,10,12,16,18-hexamethylicosa-4,7,10,12,18-pentaen-2-yl)-3-propyl-2H-pyran-2-one (2.86b)

BuLi (0.23 mL in hexane, 0.36 mmol) was dropwise added to a solution of vinyl iodide "**M-"2.72** (154 mg, 0.18 mmol) in ether at –78 °C. Me_3SnCl (0.36 mL in THF, 0.36 mmol) was added after the solution was stirred for another 1.5 h at –78 °C. The solution was stirred for 30 min then warmed to room temperature and stirred for 15 min at room temperature. The reaction was quenched with water and extract with ether (3 × 10 mL). The organic extracts were washed with water, dried over $MgSO_4$ and concentrated under reduced pressure to afford the crude vinylstannane "**M-"2.71**. The crude product was used in the next step without purification.

A mixture of the crude vinylstanne "**M-"2.71**, allylic acetate **2.84a** (14 mg, 0.044 mmol) and dry LiCl (17 mg, 0.4 mmol) in DMF was degassed for 5 min with argon. $Pd_2(dba)_3$ (8.0 mg, 0.088 mmol) was then added to the solution and the mixture was stirred for 3 h at room temperature. The reaction was quenched with water and extracted with ether (3 × 10 mL). The organic extracts were washed with water and dried over $MgSO_4$. The crude product was purified by column chromatography (hexane/EtOAc = 5:1) to afford compound "**M-"2.86** (32 mg, 74%). Compound "**M-"2.86** was then demixed by preparative fluorous HPLC to afford **2.86b** (11 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (d, *J* = 6.6 Hz, 1H), 6.04 (d, *J* = 6.6 Hz, 1H), 5.66 (s, 1H), 5.48 (t, *J* = 6.3 Hz, 1H), 5.40 (q, *J* = 6.4 Hz, 1H), 5.23 (t, *J* = 7.1Hz, 1H), 5.16 (t, *J* = 7.1 Hz, 1H), 4.22 (d, *J* = 9.6 Hz, 1H), 3.83 (d, *J* = 9.4 Hz, 1H), 3.47-3.41 (m, 1H), 2.78 (t, *J* = 6.9 Hz, 2H), 2.74-2.66 (m, 1H), 2.67 (s, 2H), 2.41 (t, *J* = 7.8 Hz, 2H), 2.17-1.99 (m, 4H), 1.88-1.82 (m, 1H), 1.70 (s, 3H), 1.66 (s, 3H), 1.64 (s, 3H), 1.59 (s, 3H), 1.58 (d, *J* = 6.5 Hz, 3H), 1.55 (s, 3H), 1.08-0.99 (m, 20H), 0.94 (t, *J* = 7.5 Hz, 3H), 0.87 (s, 9H), 0.86-0.78 (m, 2H), 0.00 (s, 3H), -0.04

(s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.72, 163.72, 138.87, 137.11, 134.44, 134.35, 133.50, 133.08, 130.90, 129.04, 127.34, 126.93, 123.81, 122.75, 103.64, 81.80, 79.77, 72.74, 51.29, 44.11, 42.45, 32.46, 30.24, 26.81, 25.86, 25.78-25.16(m, 1C), 21.11, 18.05, 17.78, 17.68, 17.59, 17.11, 17.07, 15.65, 15.34, 13.75, 12.93, 12.78, 10.97, 10.52, -4.52; IR (neat) 3340, 2959, 2929, 2858, 1717, 1613, 1450, 1230, 1110, 1041, 701; MS (ESI) for *m/z* 1037 (M^+ + Na), HRMS (ESI) *m/z* (M^+ + Na) calcd for $C_{52}H_{83}NaF_9Si_2O_5$ 1037.5533, found 1037.5585.

6-((2R,3S,4*E*,7*E*,10*E*,12*E*,15S,16S,17R,18*E*)-15-(tert-Butyldimethylsilyloxy)-17 ((3,3,4,4,5,5, 5-heptafluoropentyl)diisopropylsilyloxy)-3-hydroxy-4,8,10,12,16,18-hexamethylicos-4,7,10, 12,18-pentaen-2-yl)-3-propyl-2H-pyran-2-one (2.86a)

Compound "**M-"2.86** was demixed by preparative fluorous HPLC to afford **2.86a** (18 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (d, *J* = 6.6 Hz, 1H), 6.04 (d, *J* = 6.6 Hz, 1H), 5.66 (s, 1H), 5.48 (t, *J* = 6.3 Hz, 1H), 5.40 (q, *J* = 6.4 Hz, 1H), 5.23 (t, *J* = 7.1Hz, 1H), 5.16 (t, *J* = 7.1 Hz, 1H), 4.22 (dd, *J* = 9.6, 2.3 Hz, 1H), 3.83 (d, *J* = 9.4 Hz, 1H), 3.47-3.41 (m, 1H), 2.78 (t, *J* = 6.9 Hz, 2H), 2.74-2.66 (m, 1H), 2.67 (s, 2H), 2.41 (t, *J* = 7.8 Hz, 2H), 2.17-1.99 (m, 4H), 1.88-1.82 (m, 1H), 1.70 (s, 3H), 1.66 (s, 3H), 1.64 (s, 3H), 1.59 (s, 3H), 1.58 (d, *J* = 6.5 Hz, 3H), 1.55 (s, 3H), 1.08-0.99 (m, 20H), 0.94 (t, *J* = 7.5 Hz, 3H), 0.87 (s, 9H), 0.86-0.78 (m, 2H), 0.00 (s, 3H), -0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.69, 163.73, 138.87, 137.09, 134.40, 134.32, 133.48, 133.06, 130.89, 129.06, 127.34, 126.92, 123.79, 122.75, 103.65, 81.78, 79.76, 72.70, 51.29, 44.08, 42.42, 32.45, 30.20, 26.81, 25.85, 25.78-25.16(m, 1C), 21.09, 18.04, 17.80, 17.70, 17.59, 17.11, 17.06, 15.65, 15.33, 13.74, 12.90, 12.78, 10.96, 10.49, -4.53; IR (neat) 3340, 2959, 2929, 2858, 1717, 1613, 1450, 1230, 1110, 1041, 701 cm^{-1}; MS (ESI) *m/z* 987 (M^+ + Na), HRMS (ESI) *m/z* (M^+ + Na) calcd for $C_{51}H_{83}NaF_7Si_2O_5$ 987.5565, found 987.5612.

3-Propyl-6-((2S,3R,4*E*,7*E*,10*E*,12*E*,15S,16S,17R,18*E*)-3,15,17-trihydroxy-4,8,10,12,16,18-hexamethylicosa-4,7,10,12,18-pentaen-2-yl)-2H-pyran-2-one (2.1a)

TASF (15 mg) in DMF (0.2 mL) was added to a solution of **2.85a** (11.5 mg) in DMF (1 mL) at 0 °C. The solution was stirred for 2 h after warming to room temperature. The reaction mixture was diluted with ethyl acetate (30 mL), washed with water, dried over $MgSO_4$. The crude product was purified by column chromatography (hexane/EtOAc = 2:1) to afford the title compound **2.1a** (5.5 mg, 96%). $[\alpha]_D^{25}$ = - 18.0 (c = 0.20, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.05 (d, *J* = 6.6 Hz, 1H), 6.04 (d, *J* = 6.6 Hz, 1H), 5.70 (s, 1H), 5.55 (q, *J* = 6.3 Hz, 1H), 5.48 (t, *J* = 6.4 Hz, 1H), 5.32 (t, *J* = 7.3 Hz, 1H), 5.17 (t, *J* = 6.4 Hz, 1H), 4.39 (s, 1H), 4.22 (dd, *J* = 9.6, 1.8 Hz, 1H), 3.74-3.71 (m, 1H), 2.79 (t, *J* = 9.6 Hz, 1H), 2.69 (s, 2H), 2.70-2.68 (m, 1H), 2.46-2.38 (m, 6H), 1.80-1.78 (m, 1H), 1.78 (s, 3H), 1,68 (s, 3H), 1.67 (s, 3H), 1.66 (d, *J* = 6.3 Hz, 3H), 1.60 (tq, *J* = 7.3, 7.3 Hz, 2H), 1.57 (brs, 6H), 1.07 (t, *J* = 7.1 Hz, 3H), 0.97 (t, *J* = 7.3 Hz, 3H), 0.90 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.62, 163.84, 138.98, 136.12, 136.03, 134.34, 134.09, 134.06, 130.29, 129.07, 126.87, 124.65, 123.98, 118.72, 103.76, 79.72, 75.52, 75.15, 50.96, 42.32, 39.37, 34.15, 32.42, 26.76, 21.06, 17.41, 17.33, 15.66, 15.56, 13.77, 13.56, 12.98, 10.55, 10.42; IR (neat) 3367, 2926, 2855, 1698, 1637, 1576, 1445, 1378, 1231, 1116, 861 cm^{-1}; MS (ESI) *m/z* 563 (M^++Na); HRMS (ESI) *m/z* (M^++Na) calcd for $C_{34}H_{52}O_5Na$ 563.3712, found 563.3719.

3-Propyl-6-((2S,3R,4*E*,7*E*,10*E*,12E,15R,16R,17S,18*E*)-3,15,17-trihydroxy-4,8,10,12,16,18-hexamethylicosa-4,7,10,12,18-pentaen-2-yl)-2H-pyran-2-one (2.1b)

Following the same procedure as above, the title compound **2.1b** (4.2 mg, 92%) was obtained. $[\alpha]_D^{25}$ = - 12.0 (c = 0.20, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.06 (d, *J* = 6.6 Hz,

1H), 6.04 (d, *J* = 6.6 Hz, 1H), 5.70 (s, 1H), 5.55 (q, *J* = 6.3 Hz, 1H), 5.48 (t, *J* = 6.4 Hz, 1H), 5.32 (t, *J* = 7.3 Hz, 1H), 5.17 (t, *J* = 6.4 Hz, 1H), 4.39 (s, 1H), 4.22 (dd, *J* = 9.6, 1.8 Hz, 1H), 3.73 (m, 1H), 2.79 (t, *J* = 9.6 Hz, 1H), 2.69 (s, 2H), 2.69-2.68 (m, 1H), 2.46-2.38 (m, 6H), 1.80-1.78 (m, 1H), 1.78 (s, 3H), 1,68 (s, 3H), 1.67(s, 3H), 1.66 (d, *J* = 6.3 Hz, 3H), 1.60 (tq, *J* = 7.3, 7.3 Hz, 2H), 1.57 (brs, 6H), 1.07 (t, *J* = 7.1 Hz, 3H), 0.97 (t, *J* = 7.3 Hz, 3H), 0.90 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.58, 163.89, 139.02, 136.04, 134.28, 134.07, 130.26, 129.13, 126.85, 124.64, 123.96, 118.70, 103.79, 79.71, 75.49, 75.14, 50.96, 42.27, 39.28, 34.13, 32.40, 26.75, 21.04, 17.41, 17.34, 15.66, 15.55, 13.79, 13.57, 12.99, 10.55, 10.37; IR (neat) 3367, 2926, 2855, 1698, 1637, 1576, 1445, 1378, 1231, 1116, 861 cm^{-1}; MS (ESI) *m/z* 563 (M^++Na); HRMS (ESI) *m/z* (M^++Na) calcd for $C_{34}H_{52}O_5Na$ 563.3712, found 563.3742.

3-Propyl-6-((2R,3S,4*E*,7*E*,10*E*,12*E*,15S,16S,17R,18*E*)-3,15,17-trihydroxy-4,8,10,12,16,18-hexamethylicosa-4,7,10,12,18-pentaen-2-yl)-2H-pyran-2-one (2.1c)

Following the same procedure as above, the title compound **2.1c** (6.0 mg, 95%) was obtained. $[\alpha]_D^{25}$ = + 11.5 (c = 0.20, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.06 (d, *J* = 6.6 Hz, 1H), 6.04 (d, *J* = 6.6 Hz, 1H), 5.70 (s, 1H), 5.55 (q, *J* = 6.3 Hz, 1H), 5.48 (t, *J* = 6.4 Hz, 1H), 5.32 (t, *J* = 7.3 Hz, 1H), 5.17 (t, *J* = 6.4 Hz, 1H), 4.39 (s, 1H), 4.22 (dd, *J* = 9.6, 1.8 Hz, 1H), 3.73 (m, 1H), 2.79 (t, *J* = 9.6 Hz, 1H), 2.69 (s, 2H), 2.69-2.68 (m, 1H), 2.46-2.38 (m, 6H), 1.80-1.78 (m, 1H), 1.78 (s, 3H), 1,68 (s, 3H), 1.67(s, 3H), 1.66 (d, *J* = 6.3 Hz, 3H), 1.60 (tq, *J* = 7.3, 7.3 Hz, 2H), 1.57 (brs, 6H), 1.07 (t, *J* = 7.1 Hz, 3H), 0.97 (t, *J* = 7.3 Hz, 3H), 0.90 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.61, 163.84, 139.00, 136.11, 136.03, 134.33, 134.09, 134.06, 130.29, 129.08, 126.87, 124.66, 123.98, 118.72, 103.76, 79.72, 75.52, 75.15, 50.96, 42.32, 39.37, 34.15, 32.42, 26.76, 21.06, 17.41, 17.34, 15.66, 15.56, 13.78, 13.56, 12.98, 10.55,

10.42; IR (neat) 3367, 2926, 2855, 1698, 1637, 1576, 1445, 1378, 1231, 1116, 861 cm^{-1}; MS (ESI) *m/z* 563 (M^++Na); HRMS (ESI) *m/z* (M^++Na) calcd for $C_{34}H_{52}O_5Na$ 563.3712, found 563.3738.

3-Propyl-6-((2R,3S,4*E*,7*E*,10*E*,12*E*,15R,16R,17S,18*E*)-3,15,17-trihydroxy-4,8,10,12,16,18-hexamethylicosa-4,7,10,12,18-pentaen-2-yl)-2H-pyran-2-one (2.1d)

Following the same procedure as above, the title compound **2.1d** (5.1 mg, 94%) was obtained. $[\alpha]_D^{25}$ = + 19.0 (c = 0.20, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.05 (d, *J* = 6.6 Hz, 1H), 6.04 (d, *J* = 6.6 Hz, 1H), 5.70 (s, 1H), 5.55 (q, *J* = 6.3 Hz, 1H), 5.48 (t, *J* = 6.4 Hz, 1H), 5.32 (t, *J* = 7.3 Hz, 1H), 5.17 (t, *J* = 6.4 Hz, 1H), 4.39 (s, 1H), 4.22 (dd, *J* = 9.6, 1.8 Hz, 1H), 3.73 (m, 1H), 2.79 (t, *J* = 9.6 Hz, 1H), 2.69 (s, 2H), 2.70-2.68 (m, 1H), 2.45-2.39 (m, 6H), 1.80-1.78 (m, 1H), 1.78 (s, 3H), 1,68 (s, 3H), 1.67 (s, 3H), 1.66 (d, *J* = 6.3 Hz, 3H), 1.60 (tq, *J* = 7.3, 7.3 Hz, 2H), 1.57 (brs, 6H), 1.07 (t, *J* = 7.1 Hz, 3H), 0.97 (t, *J* = 7.3 Hz, 3H), 0.90 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.62, 163.84, 139.00, 136.12, 136.04, 134.34, 134.09, 134.06, 130.29, 129.08, 126.88, 124.65, 123.99, 118.72, 103.76, 79.73, 75.52, 75.16, 50.97, 42.33, 39.37, 34.15, 32.42, 26.77, 21.07, 17.41, 17.34, 15.66, 15.56, 13.78, 13.56, 12.98, 10.55, 10.43; IR (neat) 3367, 2926, 2855, 1698, 1637, 1576, 1445, 1378, 1231, 1116, 861 cm^{-1}; MS (ESI) *m/z* 563 (M^++Na); HRMS (ESI) *m/z* (M^++Na) calcd for $C_{34}H_{52}O_5Na$ 563.3712, found 563.3709.

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