Abstract

Methods and Strategies for Synthesis: (a) New methods for highly functionalized quinolines, (b) Synthetic studies toward Adriatoxin B, and (c) Total synthesis and structure assignment of Nosperin.

Jinsuop Youn

2014

This thesis describes the development of methods and strategies inspired by three natural products: the well-known anti-malarial quinine, the ladder polyether adriatoxin B, and nosperin – a natural product with unprecedented combinations of biosynthetic origins.

Chapter 1 details a novel method for constructing highly functionalized quinolones by CH-bond activation. This short, efficient, and scalable synthetic route begin C-H activation of aromatic carbonyl with Ru catalyst, oxime formation, and Beckmann rearrangement initiated LA is developed. This new method can be applied to synthesis of complex natural product including quinolines or small molecules in drug discovery.

Chapter 2 investigates plans for a total synthesis of Adriatoxin B and methodologies for ladder polyether compounds. Specific developments include a Ti-based subunit coupling method for pyran containing compounds, a ring-expansion reaction from pyrans to the 7-membered ring (oxepane), and from an oxepane to an oxocane (8-membered ring). In addition a new route for the synthesis of the *cis*-1, 3-dimethyl pyran ring found in polyethers has been developed.

Chapter 3 provides a full story of the total synthesis and structure assignment of nosperin. Nosperin, known as a metabolite in symbiosis of lichen (*Peltigera membranaces*) and

microorganism (*Nostoc sp.* cyanobacterium), was initially reported in 2013 with two unassigned stereocenters. A highly convergent synthetic route for Nosperin and its diastereomers has been developed that proceeds in 18 steps longest linear sequence. This synthesis provides the absolute and relative stereochemistry of the natural product, includes a revision of relative stereochemistry in the proline domain, and establishes the stereochemistry of the polyketide domain.

Methods and Strategies for Synthesis: (a) New methods for highly functionalized quinolines, (b) Synthetic studies toward Adriatoxin B, and (c) Total synthesis and structure assignment of Nosperin.

A Dissertation

Presented to the Faculty of the Graduate School of Arts and Sciences

Of

Yale University

In Candidacy for the Degree of

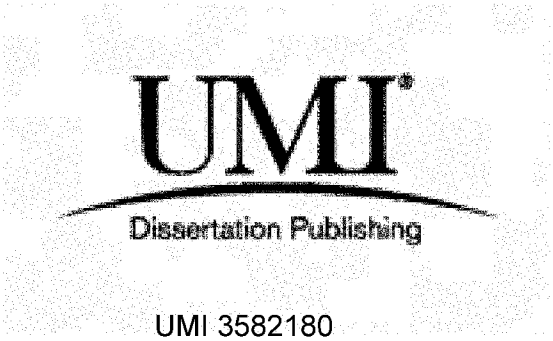
Doctor of Philosophy

By

Jinsuop Youn

Dissertation Director: Dr. Andrew J. Phillips

December, 2014



ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

Table of Contents

Figure, Table, and Scheme

List of Acronyms and Abbreviations

18-C-6	18-crown-6
3Å MS	3Å molecular sieves
4Å MS	4Å molecular sieves
Ac	acetyl
Acac	acetylacetonyl
AD	asymmetric dihydroxylation
AIBN	2,2'-azo *bis*(isobutyronitrile)
Aq.	aqueous
Ar	aryl (substituted aromatic ring)
BBN (9-BBN)	9-borabicyclo[3.3.1]nonane
Blechert-Hoveyda-Grubbs Catalyst	(1,3-bis-(2,4,6-trimethylphenyl)-imidazolidinylidene) dichloro(*o*-isopropoxyphenylmethylene)ruthenium
BHT	2,6-*di*-*tert*-butyl-*p*-cresol (butylated hydroxytoluene)
Bn	benzyl
Boc	*tert*-butoxycarbonyl
brsm	based on recovered starting material (for calculated yield)
Bz	benzoyl
CAN	cerium(IV) ammonium nitrate
CM	cross metathesis
^{13}C NMR	carbon nuclear magnetic resonance
COD	1,5-cyclooctadiene
COSY	correlation spectroscopy

Cp	cyclopentadienyl
CSA	camphorsulfonic acid
DET	diethyl tartrate
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DCE	dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de	diastereomeric excess
DEAD	diethyl azodicarboxylate
DEPC	diethyl cyanophosphonate
DHDQ	dihydroquinidine
DIBAL-H/DIBAL	diisobutylaluminum hydride
DIC	diisopropyl carbodiimide
DMAP	*N,N*-4-dimethylaminopyridine
DME	dimethoxyethane
DMF	*N,N*-dimethylformamide
DMP/Dess-Martin periodinane	1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethylsulfoxide
DPPBA	chiral ligand developed by the Trost group
EDC/EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
ee	enantiomeric excess

EI	electron impact ionization
ESI	positive ion electron spray ionization
Et	ethyl
FCC	flash column chromatography
GC	gas chromatography
Grubbs' catalyst	benzylidene bis(tricyclohexylphosphine)dichlororuthenium
Grubbs' II catalyst	(1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene) dichloro(phenylmethylene)-(tricyclohexylphosphine) ruthenium
^{1}H NMR	proton nuclear magnetic resonance
Hex	hexanes
HMBC	heteronuclear multiple bond correlation
HMPA	hexamethylphosphoramide
HMQC	heteronuclear multiple quantum coherence
HOBt	1-hydroxybenzotriazole
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
h or hr	hours (length of reaction time)
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
hv	irradiation with light
Hz	Hertz
IBCF	Isobutylchloroformate
IBX	1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide
IC_{50}	concentration at which 50% inhibition occurs

Imid (im)	imidazole
Ipc	isopinocamphenyl
HMPA	hexamethylphosphoramide
Hünig's base	diisopropylethylamine
IR	infrared spectroscopy
KHMDS	potassium hexamethyldisilazide
LA	general Lewis acid
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
LLS	longest linear sequence
2,6-lut	2,6-dimethylpyridine (2,6-lutidine)
m	*meta*
m-CPBA	*meta* chloroperoxybenzoic acid
Me	methyl
Mes	mesityl = 2,4,6-trimethylbenzenesulfonyl
MOM	methoxymethyl
MPO	4-methoxypyridine-*N*-oxide
Ms	mesyl = methanesulfonyl
MS	mass spectrometry
MS	molecular sieves
MST	mean survival time
MTBE	methyl *tert*-butyl ether
NaHMDS	sodium hexamethyldisilazide

NMM	*N*-methylmorpholine
NMO	*N*-methylmorpholine-*N*-oxide
NOESY	nuclear Overhauser effect spectroscopy
Nos or Ns	nosyl = 2-nitrobenzenesulfonyl
Nu or Nuc	general nucleophile
o	*ortho*
Oxone	potassium peroxymonosulfate
p	*para*
PCC	pyridinium chlorochromate
Ph	phenyl
Phth	phthaloyl
Piv	trimethylacetyl = pivaloyl
PMB or MPM	*para*-methoxybenzyl
PMP	4-methoxyphenyl
PPTS	pyridinium *para*-toluenesulfonate
p-TsOH	*para*-toluenesulfonic acid
py (pyr)	pyridine
RCM	ring-closing metathesis
Red-Al	sodium *bis*(2-methoxyethoxy) aluminum hydride
Rochelle's salt	potassium sodium tartrate
ROM	ring-opening metathesis
ROMP	ring-opening metathesis polymerization
r.t, rt, or RT	room temperature
SEM	2-(trimethylsilyl)ethoxymethyl

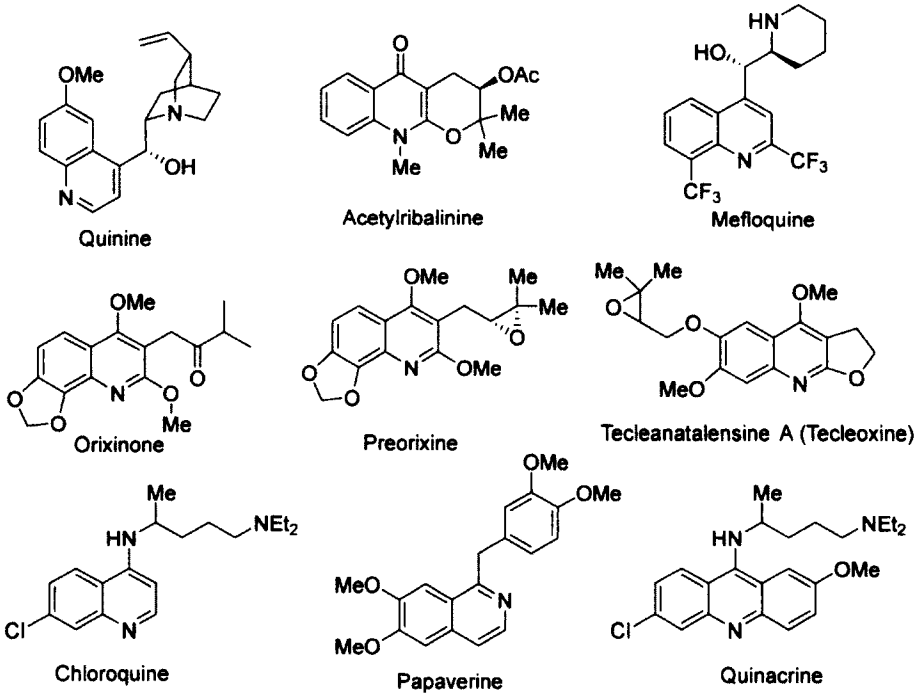
Sia	1,2-dimethylpropyl (secondary isoamyl)
TBAF	tetrabutylammonium fluoride
TBDPS	*t*-butyldiphenylsilyl
TES	triethylsilyl
TBHP	*tert*-butyl hydroperoxide
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMEDA	*N,N,N,N*-tetramethylethylenediamine
TMG	tetramethylguanidinium
TMS	trimethylsilyl
TPAP	tetra-*n*-propylammonium perruthenate
Tr	trityl (triphenylmethyl)
Ts or Tos	tosyl = toluenesulfonyl
Z (Cbz)	benzyloxycarbonyl

Chapter 1 – Synthetic studies motivated by quinine: a C-H bond activation approach to quinolines.

1.1 Introduction

Functionalized quinolines are found in a number of drugs, represent important compounds in drug discovery, and are also found in many natural products (Fig. 1-1). These small molecules and natural products exhibit a broad spectrum of antimicrobial activity[2], antitubercular activity, antimalarial activity,[3,4] and can also show antiasthmatic in addition to antiallergic activity.[4] The representative examples of the quinoline drug are chloroquine, quinacrine, mefloquine, and quinine (Figure 1-1). These compounds were the most effective methods to treat malaria until the emergence of drug resistance. Quinoline is also common core scaffold in the drug discovery programs. Their widespread presence underscores the need for effective methodologies to produce highly functionalized quinolines.[1]

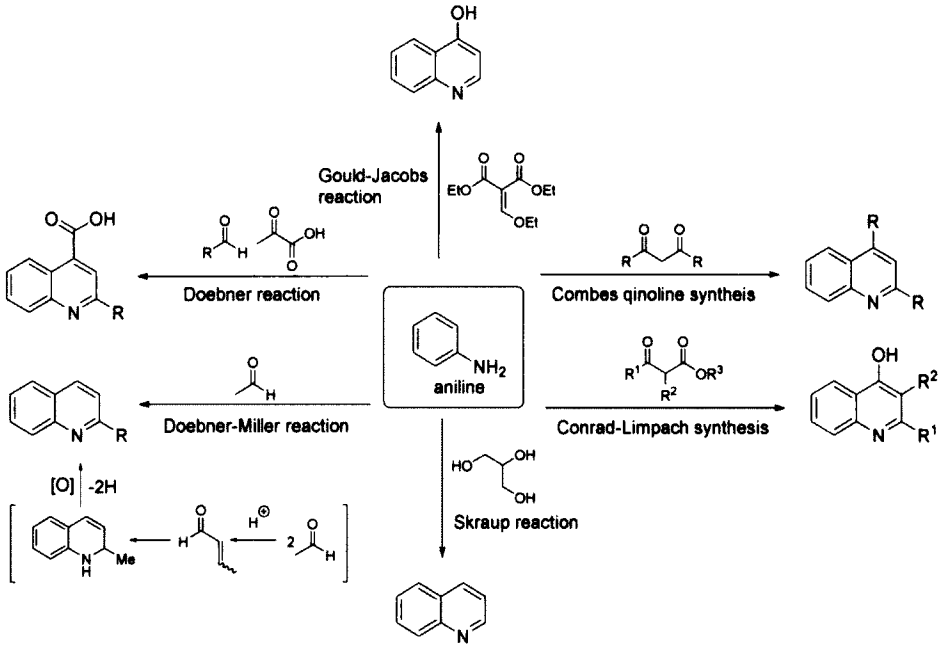
Figure 1-1 Representative quinoline natural product.



1.1.1 Previous Synthetic Studies for quinolines.

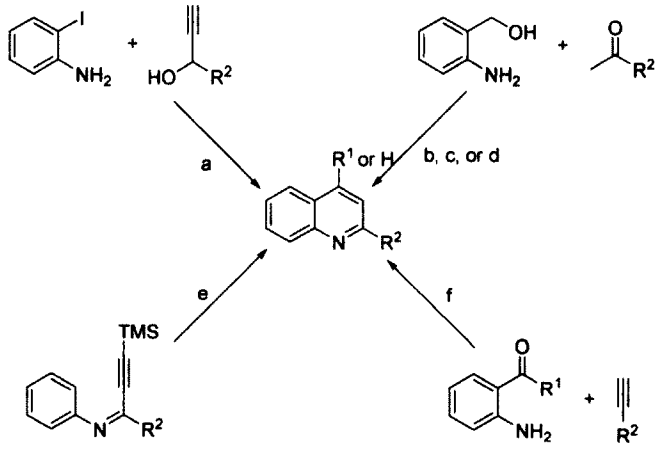
Many novel strategies to access functionalized quinolines are reported. The construction of the quinoline system by the classical methods[11-14] described in Scheme 1-1. These methods are based on the reaction of an aromatic amine containing at least one free *ortho* position with a reagent providing a source of the three-carbon fragment. These classical methods share mechanistic similarities and most occur under strong acidic conditions in which the aniline forms Schiff base or β-addition intermediate to α-β-unsaturated carbonyl system followed by intramolecular cyclization and oxidation. For example, the Doebner-Miller reaction is traditionally described as a process in which the first stage is probably an aldol condensation of two molecules of an aldehyde or ketone, resulting in the formation of α,β-unsaturated carbonyl compound. The α,β-unsaturated carbonyl compound then reacts with the aniline, forming a Schiff base and setting the stage for a cyclo-condensation that gives a 4-amino-1,2,3,4-tetrahydroquinoline. Oxidation gives the hydroquinoline and subsequent oxidation leads to the quinoline derivative (Scheme 1-1).[5] The Camps, Knorr, Niementowski, Pfitzinger, and Povarov quinolone synthesis[14-16] reactions that give quinolines also require also aniline or a substituted aniline as a substrate and proceed via similar reaction mechanisms.

Scheme 1-1. Classical quinoline synthesis.



Even a cursory evaluation points to the narrow substrate scope and functional group tolerance of the classical methods for quinolone synthesis. In light of these limitations, there has been sizeable activity in recent years exploring methods for quinoline formation using transition metal catalysis (Scheme 1-2).[5]

Scheme 1-2. Transition metal catalyzed quinoline formation.



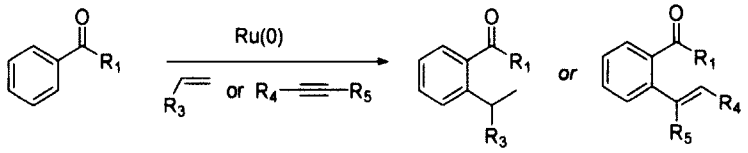
reagents; a. $PdCl_2(PPh_3)_2$, CuI, *aq.*Bu_4NOH, THF, 80 °C; b. PhCOMe, $RhCl(PPh_3)_3$ or $[Rh(DMSO)_4]Cl_2$, KOH,dioxnae, 80 °C; c. PhCOMe, $[IrCl(cod)_2]_2$ or $IrCl_3$, PPh_3, KOH, no solvent, 100 °C; d. ketone, 5%Pd/C, KOH, dioxane, 100 °C; e. $CpRu(PPh_3)_2Cl$, SPhos, NH_4PF_6, 105 °C; f. Au(II) salt, AgOTf, NH_4PF_6, CH_3CN, 150 °C(μw)

In these transition metal-mediated reactions (e.g. Pd, Rh, Ir, Ru, and Au)[6] an anilines is employed as a starting material, along with a coupling partner based on 2 or 3 carbon reagent (most commonly an alkyne). Although there are mechanistic nuances, most reactions using these transition metal catalysts proceed via an initial hydroamination that is followed by intra-molecular hydroarylation or cross coupling reaction followed by hydroamination under thermal conditions. However, these methodologies also have shortcomings: a) thermal conditions (>80 °C) with reactive transition metal catalysts are incompatible with many functional groups on substrates, b) the aniline often needs protection and deprotection steps, and c) one of the coupling partners must be an aniline.

1.1.2 Our approach and synthetic plan.

The goal of this project was a new efficient method to synthesize highly functionalized quinolone derivatives from non-aniline substrates using an *ortho*-selective CH-bond and alkenylation of aromatic ketones by transition metal catalysis followed by a Beckmann rearrangement including Lewis-acid initiated intramolecular cyclization. Central to our plans was a surprisingly little used 1993 report by Murai that described an *ortho*-selective alkylation of aromatic ketones with olefins using $RuH_2CO(PPh_3)_3$ or $Ru(CO)_2(PPh_3)_3$ catalysts.[7] This process was then extended to incorporate alkynes to form *ortho*-alkenylated products (Scheme 1-3).[8]

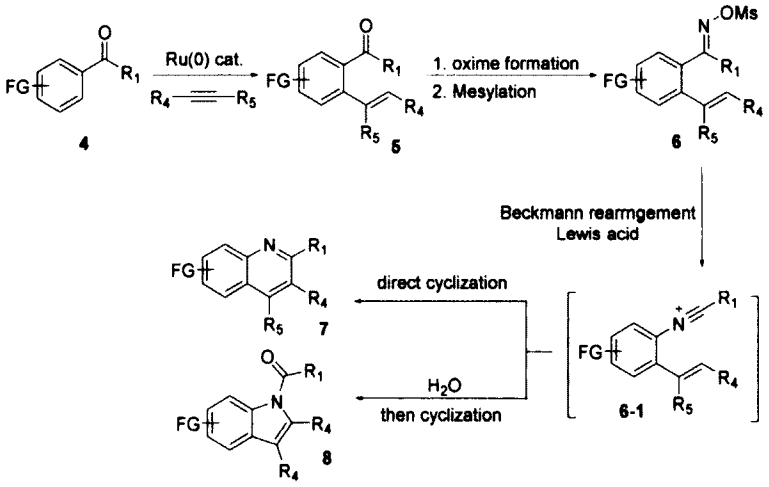
Scheme 1-3. Ru catalyzed CH activation.



We viewed this *ortho*-selective C-H bond alkenylation reaction as potentially very useful in the preparation of complex heterocycles (Scheme1-4). Murai's investigations had been well studied and there was good knowledge in terms of reactivity, regiochemistry of the addition, and catalysts

for these reactions.[9] After the alkenylation onto aromatic ketone **4** we planned for formation of an intermediate nitrilium ion by Beckmann rearrangement to produce a species that could be trapped by the silyl-alkene. The Beckmann rearrangement is the skeletal rearrangement of ketoximes in the presence of certain acids, including Lewis acids, to give amides or lactams.[10] In this situation, we hoped to trap the nitrilium ion with a nitrogen atom, forming quinolines or with water. Upon quenching with H_2O in the Beckmann rearrangement reaction we thought this reactive nitrile ion (**6-1**) can be directly cyclized by nucleophilic silyl-alkene group.

Scheme 1-4. Quinoline/indole formation inspired by CH activation.

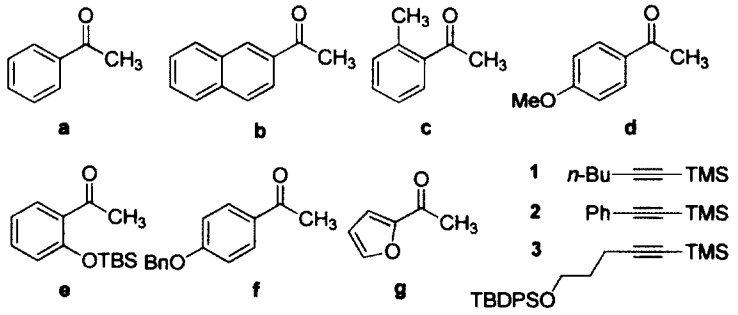


Since the first discovery of this rearrangement by Beckmann in 1886[10], successive investigations have largely clarified its scope, reaction mechanism, and the stereochemical configurations of the oximes employed. Accordingly, the Beckmann rearrangement has become an increasingly reliable synthetic tool in organic chemistry. The reaction has found broad application as a step in the manufacture of synthetic polyamides[17] and also in a variety of alkaloid syntheses.[18] We viewed these benefits of the Beckmann rearrangement as promising and that might help overcome limitations and substrate scope of current methodologies for quinoline and indole synthesis.

1.2 Results

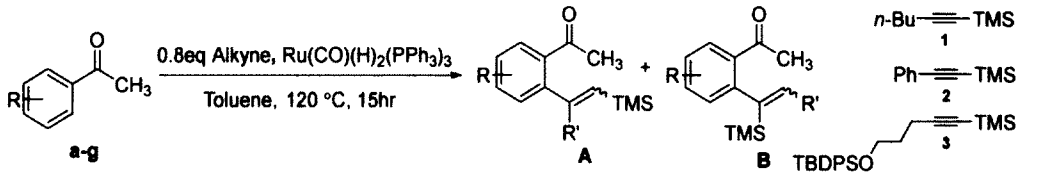
Our synthetic strategy to form functionalized pyridine and indole compounds commenced with C-H activation using Murai's conditions on seven aromatic ketones **1a-g** and three alkynes **2a-c** (Figure 1-2).

*Figure 1-2. Aromatic ketone **a-g** and alkyne **1-3**.*



Treatment of aromatic ketones **a-g** with a catalytic amount of $RuH_2CO(PPh_3)_3$ and alkynes **1-3** provided alkenylated aromatic ketones **1a-g, 2a-g, and 3a-g** in 32 - 90 % yields (Table 1-1). The ratio of *E/Z* isomers in this step varied from 1:1 to 20:1 depending on the substrates. The ratios of some substrates were different with reported ratios. This deviation might come from a purity of $RuH_2CO(PPh_3)_3$ catalyst. However, both the *E* and *Z* isomers gave the same desired products in our final cyclization step, thus there was no need to separate the isomers. The coupling between aromatic ketones **c**, **e** and alkynes **1-3** gave a mixture of regioisomers (**A** and **B**, Table 1-1) in addition to *E/Z* isomers and between aromatic ketones **a**, **d**, and **f** and alkynes **2** gave di-alkenylated products as major products.

Table 1-1 C-H activation with alkyne.

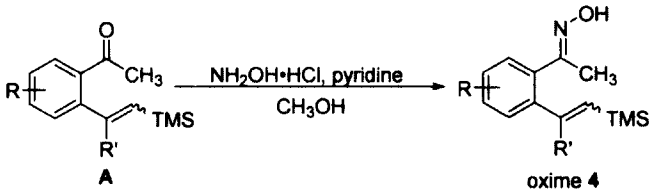


	n-Bu—≡—TMS 1	Ph—≡—TMS 2	TBDPSO—≡—TMS 3
a	38% (4.5:1)*	-	32% (1.9:1)*
b	81% (5.2:1)*	85% (1.6:1)*	81% (1.1:1)*
c	68% (A:B= 2.7:1) E/Z of A = 20.6:1	84% (2.3:1) Ref; 7.25:1	71% (A:B=1.8:1 E/Z of A = 2.2:1)
d	40% (2.4:1)*	-	38% (1.7:1)*
e	80% (A:B= 2.4:1) (E/Z of A = 11.6:1)	84% (5.9:1)* Ref; 10:1	90% (A:B=2.3:1) (E/Z of A = 26.4:1)*
f	43% (2.4:1)*	-	35% (1:2)*
g	62% (1:1)*	75% (4.9:1)* Ref; 5:1	58% (1:1)*

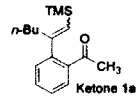
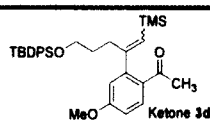
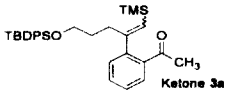
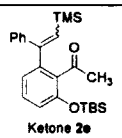
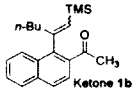
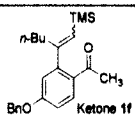
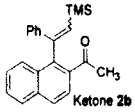
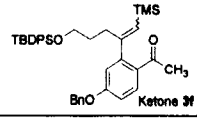
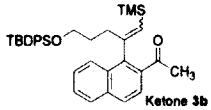
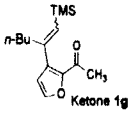
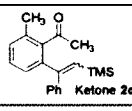
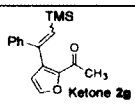
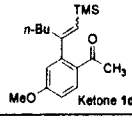
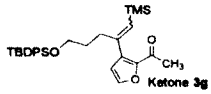
**E/Z* ratio determined by crude NMR spectrum. Isolated yields.

After introducing the alkenyl group onto the aromatic rings, treatment of alkenylated aromatic ketones **A** with hydroxylamine and pyridine provided oximes **4** in good yields for all examples except compound **2c** and **2e** (Table 1-2). Oxime formation of akenyl ketone **2c** and **2e** were very slow reaction due to intrinsic steric hindrance of two *ortho* substituents on the benzene ring at room temperature. Alkenylated aromatic ketones **2c** and **2e** had to be heated to 50 °C to overcome the inherent steric hindrance and yields were 45% and 30% respectively.

Table 1-2 Synthesis of oxime.



A oxime **4**

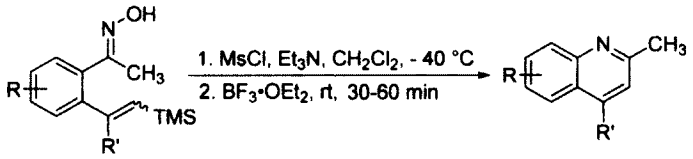
Substrate	Isolation yield	Substrate	Isolation yield
 Ketone 1a	83%	 Ketone 3d	89%
 Ketone 3a	79%	 Ketone 2e	30% [a]
 Ketone 1b	81%	 Ketone 1f	79%
 Ketone 2b	86%	 Ketone 3f	80%
 Ketone 3b	89%	 Ketone 1g	93%
 Ketone 2c	45% [a]	 Ketone 2g	85%
 Ketone 1d	85%	 Ketone 3g	84%

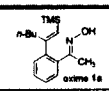
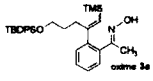
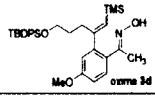
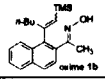
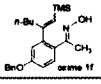
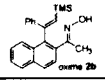
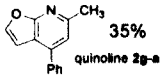
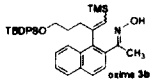
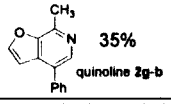
[a] reactions were carried at 50 °C. Isolation yields

Selected oximes **1a-g**, **2a-g**, and **3a-g** were mesylated and immediately treated to Lewis Acid conditions that spontaneously promoted the desired Beckmann rearrangement and subsequent cyclization to give the quinoline (Scheme 1-4). Various Lewis Acids (e.g. $TiCl_4$, $SnCl_2$, $AgClO_4$, $ZnCl_2$ etc.) and Bronsted acids (e.g. TFA, CSA, etc.) were tested and BF_3O-OEt_2 gave a best results in terms of yield and product purity. Under BF_3-OEt_2 condition mesylated oxime **4** rearranged to electrophilic iminium ion (**6-1**, Scheme 1-5). The resulting iminium ion reacts with a nucleophilc

TMS-vinyl group activated by silyl α and β effects. Using this approach we were able to prepare a variety of complex quinolines in good overall yields (Table 1-3). Interestingly, mesylated oxime **2-g** produced a separable 1:1 mixture of two isomers from the cyclization step (Table 1-3). In addition to Beckmann rearrangement, followed by intra-molecular cyclization (quinoline **2g-a**), direct cyclization by an intramolecular SN_2 cyclization between nucleophilic vinyl-TMS group and electrophilic mesylated oxime group produced isoquinoline **2g-b**.

Table 1-3 Mesylation and cyclization.

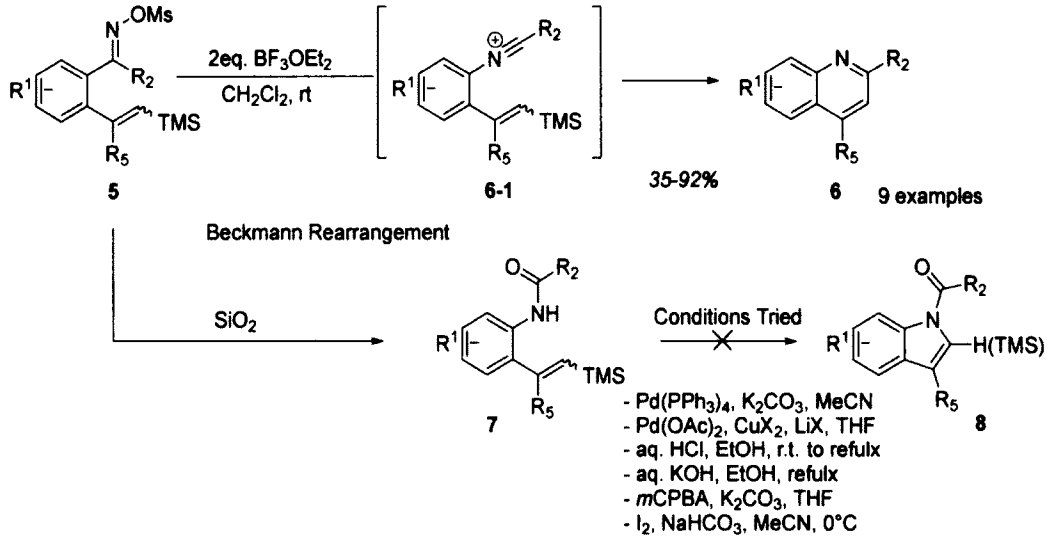


Substrate	Isolation yield	Substrate	Isolation yield
	92%		85%
	80%		89%
	88%		78%
	86%		 35% quinoline 2g-a
	91%		 35% quinoline 2g-b

Isolation yields

In contrast to our successes with the synthesis of quinolines, all efforts to make indoles were unsuccessful (Scheme 1-5). The mesylated oximes were smoothly arranged by simple stirring with SiO_2, The isolated amides **7** were tested for the cyclization under various conditions to produce indole **8**. However, a variety of conditions failed to produce the indole, and at this juncture we abandoned this approach.

Scheme 1-5. Final cyclization for quinolines and indoles.



As summarized in Scheme 1-6, we found a reliable and practical route to construct highly functionalized quinolines from non-aniline based substrates. This reaction sequence provide an alternative method to build functionalized quinolones which couldn't be accessed by other methods from non-aniline base substrates. Also, each step on this synthetic sequence is scalable.

Scheme 1-6. Synthesis of quinolines.

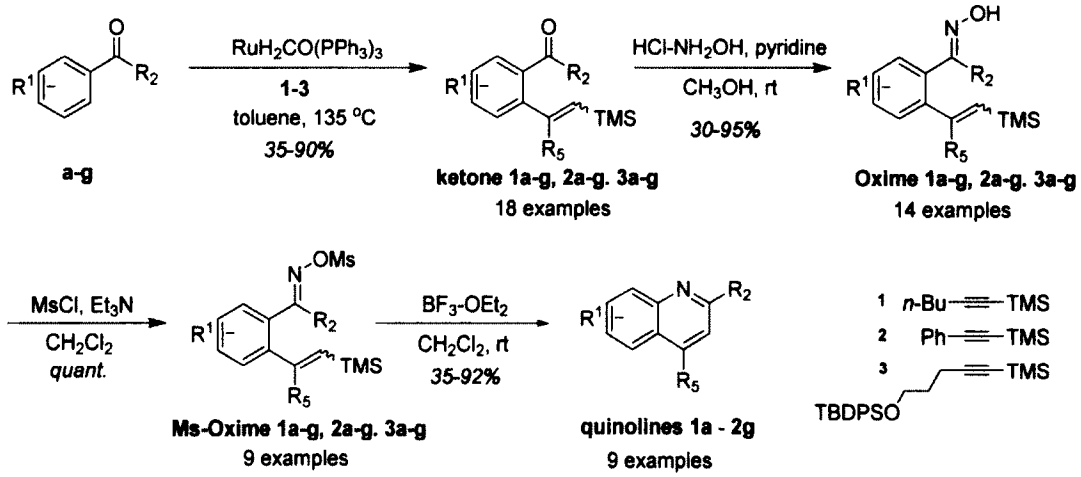
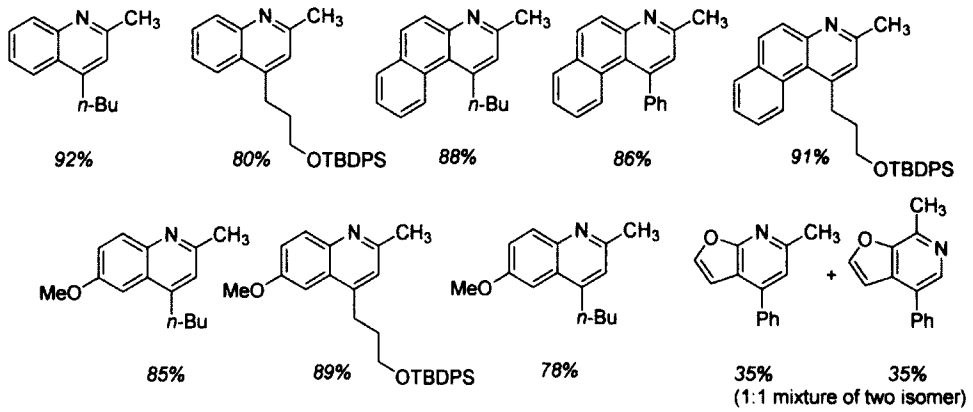


Figure 1-3. Selected final products.



1.3. Conclusion.

Using the newly developed synthetic sequence of C-H activation of aromatic ketone, oxime formation, and intramolecular cyclization, we were able to access to functionalized quinolones in a scalable, short, and efficient way from non-aniline substrates.

1.4 Experimental Procedures and Data

^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C on Varian Inova spectrometers at 500 or 400, and 125 or 100 MHz, respectively. Chemical shifts are quoted in ppm relative residual solvent as an internal reference[1]. The following abbreviations are used to describe signal multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), dt (doublet of triplets) etc. COSY, HMQC, and DEPT experiments were used when appropriate to aid structure assignment. Diastereotopic protons are labeled as H'-X and H''-X and imply no particular stereochemistry. Compounds were numbered according to their names as indicated in their structures.

[1] The following values were used as internal locks ($^{1}H/^{13}C$ NMR spectra, respectively): 7.26/77.16 ppm in $CDCl_3$, 7.16/128.06 ppm in C_6D_6, 1.94/118.26 ppm in CD_3CN, and 4.87/49.0 ppm in CD_3OD.

Mass spectral data were obtained with electron impact (EI) ionization or positive ion electron spray (ESI) ionization.

Infrared spectra were obtained using a Perkin Elmer FT-IR spectrometer. The spectra of solids were recorded using a thin film of the neat product whereas the spectra of oils were recorded using a thin liquid film of the product indicated by the bracketed solvent.

Optical rotations were measured in a 100 mm length cell using a Jasco P-1030 polarimeter fitted with a sodium source lamp and a Glan-Taylor polarizer.

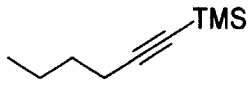
Melting points were recorded using a digital Stanford Research Systems OptiMelt automated melting point system. The reported values are an average of duplicate measurements which were takes by slowly increasing the temperature from 25 °C at a rate of 2.5 °C per min.

Analytical thin-layer chromatography was carried out on SiliCycle glass-backed extra hard layer 60 Å plates (20×20 cm particle, 250 μm thickness), using either aqueous potassium permanganate or aqueous cerium ammonium molybdate stains to aid visualization.

Flash column chromatography was carried out following the general principles of Still (W.C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.using SiliaFlash P60 silica (40-63 μm particle size, 230-400 mesh, SiliCycle). Preparative HPLC was performed on a Gilson HPLC consisting of a 215 liquid handler, 305/305 pump modules, and a 155 UV/VIS detector, all operating under control of Gilson's Trilution software. A Waters Sunfire silica column (10×250 mm, 5μm particle size) was used for purifications described herein

Non-aqueous reactions were carried out under an atmosphere of nitrogen, in flame-dried glassware, using solvents dried by passage though activated alumina as described by Bergman and Grubbs (P. J. Alaimo, D.W. Peters, J. Arnold and R.G. Bergman, *J. Chem. Educ.*, **2001**, *78*, 64;

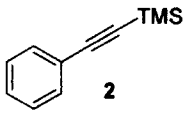
A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R.K. Rosen and F. J. Timmers, *Organometallics,* **1996**, *15*, 151) or obtained by distillation when more appropriate. Bases such as triethylamine, pyridine, and diisopropylamine (Hünig's base) were freshly distilled from CaH_2 prior to use. Brine refers to a saturated solution of sodium chloride and pH 2 sulfate buffer refers to an aqueous solution made of 1 M sodium bisulfate and 1 M sodium sulfate mixed in 1:1 v/v ratio.



1

hex-1-yn-1-yltrimethylsilane (1):

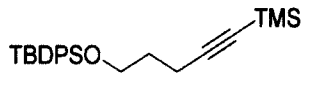
ν_{max} (neat)/cm^{-1} 2941, 2856, 2009; δ_H (500 MHz, $CDCl_3$) 2.92 (t, *J* = 7.2 Hz, 2H), 1.47 (m, 2H), 1.38 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H), 0.12 (s, 9H); δ_C (125 MHz, $CDCl_3$) 107.7, 84.3, 30.9, 22.1, 19.7, 13.7, 0.3.



2

trimethyl(phenylethynyl)silane (2):

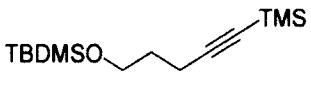
ν_{max} (neat)/cm^{-1} 3136, 3021, 1946; δ_H (500 MHz, $CDCl_3$) 7.45-7.48 (m, 2H), 7.27-7.33 (m, 3H), 0.25 (s, 9H); δ_C (125 MHz, $CDCl_3$) 132.1, 128.6, 128.3, 123.2, 105.2 94.2, 0.13.



3

tert-butyldiphenyl((5-(trimethylsilyl)pent-4-yn-1-yl)oxy)silane (3):

ν_{max}(neat)/cm^{-1} 3203, 3172, 3028, 2936, 2003; δ_H (500 MHz, $CDCl_3$) 7.68-7.75 (m, 4H), 7.37-7.46 (m, 6H), 3.78 (t, , *J* = 5.8 Hz, 2H), 2.41 (t, *J* = 7.2 Hz, 2H), 1.8 (m, 2H), 1.08 (s, 9H), 0.16 (s, 9H); δ_C (125 MHz, $CDCl_3$) 135.7, 134.0, 129.7, 127.8, 107.2, 84.6, 62.6, 31.7, 26.9, 19.4, 16.6, 0.32.

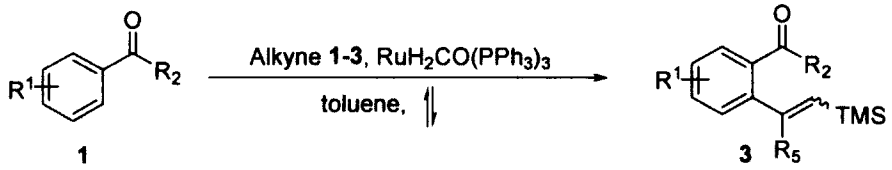


3-1

tert-butyldimethyl((5-(trimethylsilyl)pent-4-yn-1-yl)oxy)silane (3-1):

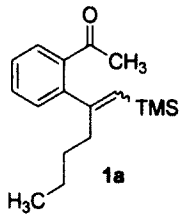
ν_{max}(neat)/cm^{-1} 3203, 3172, 3028, 2936, 2003; δ_H (500 MHz, $CDCl_3$) 3.69 (t, J = 6.2 Hz 2H), 2.30 (t, J = 7.0 Hz, 2H), 1.70 (m, 2H), 0.89 (s, 9H), 0.14 (s, 9H), 0.05 (s, 6H); δ_C (125 MHz, $CDCl_3$) 107.2, 84.7, 61.6, 31.7, 26.1, 18.5, 16.4, 0.3, -5.2.

General Procedure of ortho-alkenylation of aromatic ketone:



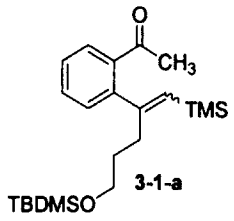
1 3

The aromatic ketone (1 mmol) and alkyne (0.8 mmol) were added under Ar to a solution of carbonyl(dihydrido)tris(triphenylphosphine)ruthenium(II) (0.1 mmol) in toluene (10 mL). Then the reaction mixture was stirred under reflux condition for 15 hr. The reaction was cooled to room temp, then concentrated under reduced pressure. The products were purified by flash column chromatography.



(E)-1-(2-(1-(trimethylsilyl)hex-1-en-2-yl)phenyl)ethanone (1a):

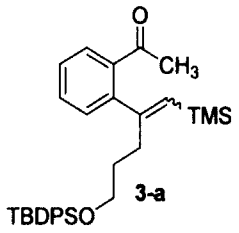
Isolation yield 38% (*E*/*Z* = 4.5:1) as a clear oil; ν_{max}(neat)/cm^{-1} 3060, 2956, 2861, 1691; *E*-form δ_H (500 MHz, $CDCl_3$) 7.46-7.47 (m, 1H), 7.37-7.40 (m, 1H), 7.27-7.31 (m, 1H), 7.22-7.24 (m, 1H), 5.45 (s, 1H), 2.47-2.50 (m, 5H), 1.27-1.32 (m, 4H), 0.85 (t, *J* = 7.1 Hz, 3H), 0.18 (s, 9H); δ_C (125 MHz, $CDCl_3$) 204.3, 158.7, 144.9, 139.5, 131.9, 130.8, 128.8, 128.3, 127.2, 37.3, 31.7, 30.5, 23.3, 14.2, 0.2; *Z*-form δ_H (500 MHz, $CDCl_3$) 7.67-7.69 (m, 1H), 7.40-7.43 (m, 1H), 7.32-7.36 (m, 1H), 7.08-7.09 (m, 1H), 5.60 (t, J = 1.3 Hz, 1H), 2.54 (s, 3H), 2.21-2.44 (m, 2H), 1.23-143 (m, 4H), 0.87 (t, , J = 7.4 Hz, 3H), -0.25 (s, 9H); δ_C (125 MHz, $CDCl_3$) 201.0, 159.8, 144.2, 137.4, 131.1, 131.0, 129.2, 127.2, 125.8, 42.5, 30.3, 29.6, 22.6, 14.2, 0.2.



(E)-1-(2-(5-((tert-butyldimethylsilyl)oxy)-1-(trimethylsilyl)pent-1-en-2-yl)phenyl)ethan-1-one (3-1-a):

Isolation yield 39% (*E*/*Z* = 2.4:1) as an yellow oil; ν_{max}(neat)/cm^{-1} 3060, 2953, 2894, 2857, 1692, 1593, 1248; δ_H (500 MHz, $CDCl_3$, * -minor isomer) 7.68-7.69* (m, 1H), 7.46-7.48 (m, 1H), 7.40-7.43* (m, 1H), 7.36-7.39 (m, 1H), 7.32-7.36* (m, 1H), 7.28-7.27 (m, 1H), 7.22-7.24 (m, 1H), 7.08-7.09* (m, 1H), 5.62* (s, 1H), 5.47 (m, 1H), 3.60* (t, *J* = 6.5 Hz, 2H), 3.56 (t, *J* = 6.4 Hz, 2H), 2.55-2.59 (m, 2H+1H*), 2.52* (s, 3H), 2.48 (s, 3H), 2.27-2.37* (m, 1H), 1.59-1.68* (m, 2H), 1.50-1.56 (m, 2H), 0.87 (s, 9H+9H*), 0.18 (s, 9H), 0.02* (s, 6H), 0.01 (s, 6H), -0.26* (s, 9H); δ_C (125 MHz, $CDCl_3$)

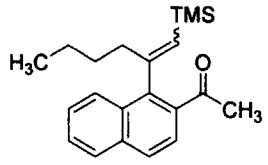
204.0, 200.8*, 159.2*, 158.1, 144.6, 144.0*, 139.5, 137.4*, 132.2, 131.2*, 131.0*, 130.7, 129.2*, 128.7, 128.3, 127.3*, 127.1, 126.1*, 63.2, 62.8*, 38.9*, 33.8, 32.5, 31.2*, 30.4, 29.5*, 26.1, 26.1*, 18.5, 18.5*, 0.1, -0.2*, -5.1*, -5.2.



3-a

(E)-1-(2-(5-((tert-butyldiphenylsilyl)oxy)-1-(trimethylsilyl)pent-1-en-2-yl)phenyl)ethan-1-one (3-a):

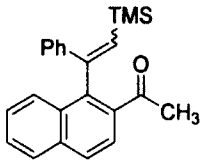
Isolation yield 32% (*E*/*Z* = 1.9:1) as an yellow oil; *E*-form ν_{max} (neat)/cm^{-1} 3059, 2934, 2892, 2849, 1695, 1256; δ_H (500 MHz, $CDCl_3$) 7.68-7.73 (m, 5H), 7.35-7.45 (m, 8H), 7.07 (dd, , *J* = 7.5, 1.4 Hz, 1H), 5.66 (t, , *J* = 1.4 Hz, 1H), 3.71 (t, *J* = 6.4 Hz, 1H), 2.56 (s, 3H), 1.08 (s, 9H), -0.21 (s, 9H); δ_C (125 MHz, $CDCl_3$)



1-b

(E)-1-(1-(1-(trimethylsilyl)hex-1-en-2-yl)naphthalen-2-yl)ethan-1-one (1-b):

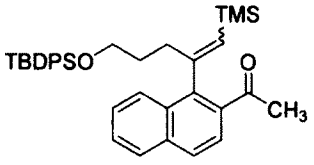
Isolation yield 81% (*E*/*Z* = 5.2:1) as an yellow oil; E-form ν_{max} (neat)/cm^{-1} 3058, 2955, 2860, 1687, 1597, 1246; δ_H (500 MHz, $CDCl_3$) 8.10-8.13 (m, 1H), 7.83-7.85 (m, 1H), 7.78 (d, , *J* = 8.5 Hz, 1H), 7.50-7.56 (m, 2H), 5.59 (s, 1H), 2.69-2.75 (m, 1H), 2.64 (s, 3H), 2.35-2.41 (m, 1H), 1.08-1.27 (m 4H), 0.75 (t, , *J* = 7.1 Hz, 3H), 0.28 (s, 9H); δ_C (125 MHz, $CDCl_3$) 204.1, 185.8, 143.3, 134.8, 134.7, 132.8, 131.6, 128.1, 127.8, 127.3, 127.1, 126.5, 124.6, 39.6, 31.2, 31.1, 23.3, 13.9, -0.2; Accurate mass (ES^+): Found 347.179863 (< -1.0 ppm), $C_{21}H_{28}NaOSi$ ($M+Na^+$) requires 347.180163.



2-b

(E)-1-(1-(1-phenyl-2-(trimethylsilyl)vinyl)naphthalen-2-yl)ethan-1-one (2-b):

Isolation yield 85% (*E*/*Z* = 1:1.6) as an yellow oil; ν_{max}(neat)/cm^{-1} 3045, 2921, 1946, 1573, 1553; δ_H (500 MHz, $CDCl_3$, * -minor isomer) 8.61 (d, *J* = 8.5 Hz, 1H), 8.56* (d, *J* = 8.5 Hz, 1H), 8.51* (d, *J* = 8.5 Hz, 1H), 8.45-8.47* (m, 2H), 8.41-8.45 (m, 2H), 8.18 (d, *J* = 8.5 Hz, 1H), 8.11-8.14* (m, 1H), 8.06-8.09 (m, 1H), 8.00-8.03 (m, 1H+1H*), 7.95-7.98 (m, 2H+2H*), 7.82-7.89 (m, 3H+3H*), 7.46* (s, 1H), 6.56 (s, 1H), 3.08* (s, 3H), 3.07 (s, 3H), 0.73 (s, 9H), 0.21* (s, 9H); δ_C (125 MHz, $CDCl_3$) 204.3, 201.9*, 154.7, 152.4*, 142.4, 142.2, 141.9*, 140.0*, 137.6*, 137.3, 136.3*, 134.9*, 134.8, 133.1*, 131.7, 131.6, 129.4, 128.7*, 128.5*, 128.3*, 128.3, 128.2, 128.2*, 128.1*, 128.1, 128.1, 127.9*, 127.8*, 127.3, 127.1*, 127.0, 126.6, 125.4*, 124.3, 31.0, 30.8*, 0.5, -0.9*.

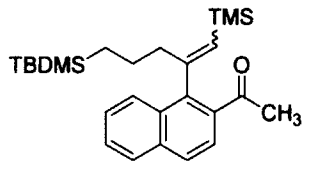


3-b

(E)-1-(1-(5-((tert-butyldiphenylsilyl)oxy)-1-(trimethylsilyl)pent-1-en-2-yl)naphthalen-2-yl)ethan-1-one (3-b):

Isolation yield 81% (*E*/*Z* = 1.1:1) as a clear oil; *E*-form ν_{max}(neat)/cm^{-1} 3032, 2891, 1954, 1583, 1562; δ_H (500 MHz, $CDCl_3$) 8.16 (d, *J* = 7.8 Hz, 1H), 7.88 (d, *J* = 7.8 Hz, 1H), 7.82 (d, *J* = 8.5 Hz, 1H), 7.66 *d, *J* = 8.5 Hz, 1H), 7.61-7.64 (m, 4H), 7.53-7.59 (m, 2H), 7.40-7.44 (m, 2H), 7.34-7.38 (m, 4H), 5.68 (s, 1H), 3.53-3.60 (m, 2H), 2.95-3.01 (m, 1H), 2.67 (s, 3H), 2.56-2.62 (m, 1H), 1.55-1.64 (m, 1H), 1.40-1.49 (m, 1H), 1.05 (s, 9H), 0.35 (s, 9H); δ_C (125 MHz, $CDCl_3$) 203.4, 155.4, 143.1, 135.6, 134.7,

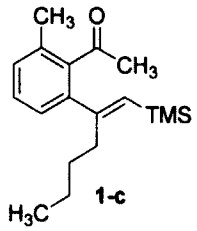
134.6, 133.9, 133.8, 132.9, 131.5, 129.6, 128.1, 127.7, 127.3, 127.2, 126.6, 124.6, 64.0, 36.2, 31.8, 31.1, 26.9, 19.2, 0.2.



3-1-b

1-(1-(5-(tert-butyldimethylsilyl)-1-(trimethylsilyl)pent-1-en-2-yl)naphthalen-2-yl)ethan-1-one (3-1-b):

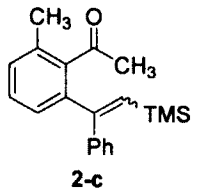
Isolation yield 83% (*E*/*Z* = 1.9:1) as a clear oil; ν_{max} (neat)/cm^{-1} 3059, 2953, 2894, 2857,2249, 1691, 1462; δ_H (500 MHz, $CDCl_3$ *-minor isomer) 8.10-8.13 (m, 1H), 8.03-8.05* (m, 1H), 7.80-7.84 (m, 1H, 2H*), 7.78 (d, *J* = 8.6 Hz, 1H), 7.74* (d, *J* = 8.6 Hz, 1H), 7.61 (d, *J* = 8.6 Hz, 1H), 7.49-7.56 (m, 2H, 2H*), 5.99* (t, *J* = 1.6 Hz, 1H), 5.62 (s, 1H), 3.63-3.71* (m, 2H), 3.41-3.49 (m, 2H), 2.84-2.90 (m, 1H), 2.65* (s, 3H), 2.54 (s, 3H), 2.58-2.62* (m, 1H), 2.43-2.51 (m, 1H, 1H*), 1.82-.191* (m, 2H), 1.45-1.53 (m, 1H), 1.29-1.37 (m, 1H), 0.87* (s, 9H), 0.83 (s, 9H), 0.30 (s, 9H), 0.03* (s, 3H), 0.02* (s, 3H), -0.04 (s, 3H), -0.05 (s, 3H), -0.45* (s, 9H); δ_C (125 MHz, $CDCl_3$) 203.7, 201.4*, 155.3, 155.3*, 143.1, 142.9*, 134.8, 134.7*, 134.7, 134.0*, 133.0, 131.9*, 131.5, 128.1, 128.1*, 128.0*, 127.7, 127.6*, 127.4*, 127.3, 127.2*, 127.2, 126.6, 126.6, 125.0*, 124.6, 63.2, 63.1*, 38.4*, 36.2, 32.0, 31.2, 30.7*, 30.4*, 26.1*, 26.0, 18.4*, 18.4, 0.1, -0.9, -.5.2*, -5.3*, -5.3*.



1-c

(E)-1-(2-methyl-6-(1-(trimethylsilyl)hex-1-en-2-yl)phenyl)ethan-1-one (1-c):

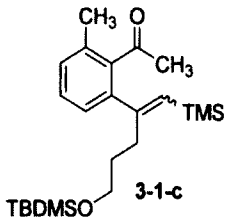
Isolation yield 68% (*E*/*Z* = 20.6:1) as a clear oil; ν_{max}(neat)/cm^{-1} 3062, 2885, 2872, 1932, 1696; δ_H (500 MHz, $CDCl_3$) 7.18-7.21 (m, 1H), 7.04-7.10 (m, 2H), 5.48 (s, 1H), 2.44-2.48 (m, 2H), 2.38 (s, 3H), 2.25 (s, 3H), 1.28-1.33 (m, 4H), 0.84-0.89 (m, 3H), 0.16 (s, 9H); δ_C (125 MHz, $CDCl_3$) 207.9, 157.7, 142.2, 140.9, 133.5, 132.8, 129.3, 128.4, 125.2, 37.1, 32.6, 31.5, 23.2, 19.8, 14.1, 0.1.



2-c

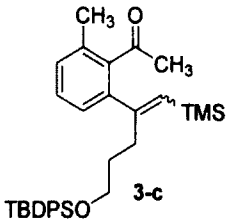
1-(2-methyl-6-(1-phenyl-2-(trimethylsilyl)vinyl)phenyl)ethan-1-one (2-c):

Isolation yield 84% (*E*/*Z* = 2.3:1) as a clear oil; ν_{max} (neat)/cm^{-1} 3053, 3.43, 1678, 1251; δ_H (500 MHz, $CDCl_3$, *-minor isomer) 7.32-7.37 (m, 2H, 2H*), 7.23-7.30 (m, 3H, 4H*), 7.14-7.20 (m, 2H, 2H*), 6.97 (d, *J* = 7.6 Hz, 1H), 6.42* (s, 1H), 5.96 (s, 1H), 2.32 (s, 3H), 2.31 (s, 3H), 2.30* (s, 3H), 2.09* (3H), 0.0 (s, 9H), -0.1* (s, 9H); δ_C (125 MHz, $CDCl_3$) 207.2, 206.1*, 156.4, 154.5*, 142.5, 142.5*, 142.4*, 141.9*, 141.7, 138.6*, 136.1, 133.5*, 133.3, 132.1, 130.0*, 129.8, 128.6*, 128.4*, 128.3, 128.2, 128.0, 128.0, 127.3, 127.1, 32.1, 31.8*, 19.7, 19.7*, -0.1, -0.4*.



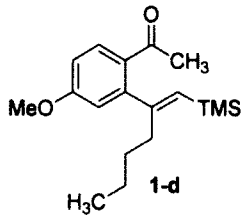
1-(2-(5-((tert-butyldimethylsilyl)oxy)-1-(trimethylsilyl)pent-1-en-2-yl)-6-methylphenyl)ethan-1-one (3-1c):

Isolation yield 74% (*E*/*Z* = 1.9:1) as a clear oil; ν_{max} (neat)/cm^{-1} 3052, 2953, 2895, 2858, 1914, 1698, 1251; δ_H (500 MHz, $CDCl_3$,) 7.16-7.20 (m, 1H), 7.05-7.09 (m, 2H), 5.51 (s, 1H), 3.67 (t, *J* = 6.8 Hz, 1H), 3.56-3.61 (m, 3H), 2.55-2.58 (m, 2H), 2.37 (s, 3H), 2.25 (s, 3H), 1.52-1.58 (m, 2H), 0.88 (s, 9H), 0.16 (s, 9H), 0.02 (s, 6H); δ_C (125 MHz, $CDCl_3$) 207.7, 157.0, 141.9, 133.5, 133.2, 129.3, 129.2, 128.4, 125.1, 63.2, 33.72, 32.6, 32.3, 26.1, 19.8, 18.4, 0.0, -5.2.



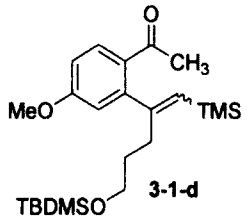
1-(2-(5-((tert-butyldiphenylsilyl)oxy)-1-(trimethylsilyl)pent-1-en-2-yl)-6-methylphenyl)ethan-1-one (3-c):

Isolation yield 71% (*E*/*Z* = 2.2:1) as a clear oil; ν_{max} (neat)/cm^{-1} 3048, 3003, 1682, 1232; δ_H (500 MHz, $CDCl_3$, *-minor isomer) 7.63 (m, 6H, 6H*), 7.35-7.44 (m, 7H, 7H*), 5.66* (s, 1H) 5.51 (s, 1H), 3.73* (t, *J* = 6.9 Hz, 2H), 3.63 (t, *J* = 6.3 Hz, 2H), 2.60-2.63 (m, 2H), 2.36* (s, 3H), 2.36-2.38* (m, 2H), 2.36 (s, 3H), 2.34* (s, 3H), 2.26 (s, 3H), 1.58-1.63 (m, 2H, 2H*), 1.05 (s, 9H), 1.05 (s, 9H), 0.16 (s, 9H), -0.11 (s, 6H), -0.15* (s, 9H), -0.19* (s, 6H); δ_C (125 MHz, $CDCl_3$)



(E)-1-(4-methoxy-2-(1-(trimethylsilyl)hex-1-en-2-yl)phenyl)ethan-1-one (1-d):

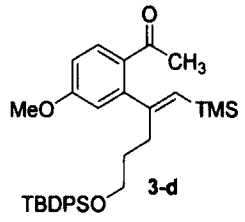
Isolation yield 40 % (*E*/*Z* = 2.4:1) as a clear oil; ν_{max} (neat)/cm^{-1} 3065, 3000, 2955, 1680, 1596, 1484; δ_H (500 MHz, $CDCl_3$) 7.75 (d, *J* = 8.6 Hz, 1H), 6.83 (dd, , *J* = 8.6, 2.8 Hz, 1H), 6.58 (d, , *J* = 2.8 Hz, 1H), 5.55 (s, 1H), 3.85 (s, 3H), 2.50 (s, 3H), 2.36-2.44 (m, 1H), 2.22-2.29 (m, 1H), 1.50-.1.57 (m, 1H), 1.25-.143 (m, 3H), 0.88 (t, *J* = 7.2 Hz, 3H), -0.24 (s, 9H); δ_C (125 MHz, $CDCl_3$) 198.4, 161.7, 160.6, 147.2, 132.1, 129.7, 124.5, 116.5, 112.0, 55.5, 42.0, 30.3, 29.1, 22.6, 14.2, 0.0; Accurate mass (ES$^+$): Found 327.174755 (<-1.0 ppm), $C_{18}H_{28}NaO_2Si$ (M+Na$^+$) requires 327.175078.



1-(2-(5-((tert-butyldimethylsilyl)oxy)-1-(trimethylsilyl)pent-1-en-2-yl)-4-methoxyphenyl)ethan-1-one (3-1-d):

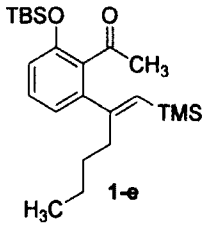
Isolation yield 43% (*E*/*Z* = 1.6:1) as a clear oil; ν_{max} (neat)/cm^{-1} 2953, 2895, 2857, 1680, 1596; δ_H (500 MHz, $CDCl_3$, *-minor isomer) 7.75* (d, *J* = 8.6 Hz, 1H), 7.58 (d, *J* = 8.6 Hz, 1H), 6.82* (dd, , *J* = 8.5, 2.8 Hz, 1H), 6.78 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.68 (d, *J* = 2.8 Hz, 1H), 6.57* (d, *J* = 2.8 Hz, 1H), 5.57* (s, 1H), 5.43 (s, 1H), 3.84* (s, 3H), 3.83 (s, 3H), 3.60* (m, 2H), 3.53 (t, *J* = 6.2 Hz, 2H), 2.51-2.54 (m, 2H), 2.50* (s, 3H), 2.46 (s, 3H), 2.25-2.36* (m, 2H), 1.60-1.70* (m, 2H), 1.47-1.53 (m, 2H), 0.86* (s, 9H), 0.86 (s, 9H), 0.19 (s, 9H), 0.00 (s, 6H), -0.24* (s, 6H); δ_C (125 MHz, $CDCl_3$)

201.1, 198.2*, 161.7, 161.6*, 159.9*, 159.3, 148.0, 147.0*, 132.2*, 131.3, 131.0*, 130.4, 129.7*, 124.9, 116.6*, 115.1, 112.0*, 111.8, 63.2, 62.9*, 55.5, 55.5*, 38.4*, 33.9, 32.6, 31.3*, 29.8, 29.0*, 26.1, 26.1*, 18.5*, 18.4.



(E)-1-(2-(5-((tert-butyldiphenylsilyl)oxy)-1-(trimethylsilyl)pent-1-en-2-yl)-4-methoxyphenyl)ethan-1-one (3-d):

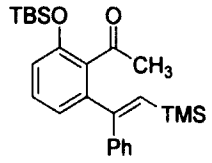
Isolation yield 38% (*E*/*Z* = 1.6:1) as a clear oil; ν_{max} (neat)/cm^{-1} 3034, 2933, 2875, 2863, 1663, 1547; δ_H (500 MHz, $CDCl_3$) 7.64-7.66 (m, 4H), 7.62 (d, , *J* = 8.6 Hz, 1H), 7.36-7.44 (m, 6H), 6.82 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.71 (d, , *J* = 2.4 Hz, 1H), 5.47 (s, 1H), 3.84 (s, 3H), 3.63 (t, *J* = 6.3 Hz, 2H), 2.59-2.63 (m, 2H), 2.48 (s, 3H), 1.57-1.63 (m, 2H), 1.06 (s, 9H), 0.22 (s, 9H); δ_C (125 MHz, $CDCl_3$) 201.0, 161.6, 159.2, 148.1, 135.6, 33.9, 131.4, 131.0, 130.4, 129.7, 127.7, 115.0, 111.8, 64.1, 55.5, 34.0, 32.4, 29.8, 27.0 19.3, 0.1.



(E)-1-(2-((tert-butyldimethylsilyl)oxy)-6-(1-(trimethylsilyl)hex-1-en-2-yl)phenyl)ethan-1-one (1-e):

Isolation yield 80% (*E*/*Z* = 11.6:1) as a clear oil; ν_{max} (neat)/cm^{-1} 3012, 2977, 2863, 2853, 1683, 1421; δ_H (500 MHz, $CDCl_3$) 7.12-7.15 (m, 1H), 6.77-6.80 (m, 1H), 6.60-6.72 (m, 1H), 5.43 (s, 1H), 2.41 (s, 3H), 1.27-1.33 (m, 4H), 0.96 (s, 9H), 0.83-0.88 (m, 5H), 0.22 (s, 6H), 0.14 (s, 9H); δ_C (125 MHz, $CDCl_3$)

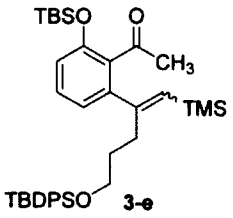
204.9, 157.3, 151.6, 144.2, 133.3, 131.5, 129.0, 120.6, 117.3, 37.0, 32.8, 31.4, 25.7, 23.1, 18.2, 14.1, 0.15, -4.18.



2-e

(E)-1-(2-((tert-butyldimethylsilyl)oxy)-6-(1-phenyl-2-(trimethylsilyl)vinyl)phenyl)ethan-1-one (1-e):

Isolation yield 84% (*E*/*Z* = 5.9:1) as a clear oil; ν_{max} (neat)/cm^{-1} 3059, 3025, 2953, 2896, 2859, 1932, 1704, 1568; δ_H (500 MHz, $CDCl_3$, *-minor isomer) 7.29-7.32 (m, 2H, 3H*), 7.19-7.25 (m, 3H, 4H*), 7.16 (m, 1H), 6.96-6.97* (m, 1H) 6.88-6.89 (m, 1H), 6.76-6.78 (m, 1H), 6.28* (s, 1H), 5.98 (s, 1H), 2.02 (s, 3H), 1.91* (s, 3H), 0.97 (s, 9H, 9H*), 0.23 (s, 6H, 6H*), -0.05 (s, 9H, 9H*); δ_C (125 MHz, $CDCl_3$) 205.6, 203.6*, 156.6, 154.3*, 152.1*, 151.7, 144.7, 142.7*, 142.4, 141.3*, 134.6, 134.0*, 133.9*, 133.7*, 131.6*, 130.1, 129.3*, 128.6*, 128.1, 129.2, 127.8, 127.7, 124.2*, 122.8, 119.2*, 118.1, 31.9, 31.5*, 25.8*, 25.7, 18.2, 18.2*, 0.1, -0.3*, -4.2, -4.2*.

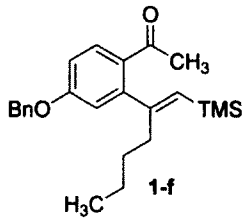


3-e

1-(2-((tert-butyldimethylsilyl)oxy)-6-(5-((tert-butyldiphenylsilyl)oxy)-1-(trimethylsilyl)pent-1-en-2-yl)phenyl)ethan-1-one (3-e):

Isolation yield 90% (*E*/*Z* = 26.4:1) as a clear oil; ν_{max} (neat)/cm^{-1} 3023, 3012, 2932, 2873, 1678; δ_H (500 MHz, $CDCl_3$) 7.64-7.66 (m, 4H), 7.35-7.43 (m, 6H), 7.12-7.15 (m, 1H), 6.77-6.79 (m, 1H), 6.71-6.73 (m, 1H), 5.45 (s, 1H), 3.63 (t, *J* = 5.78 Hz, 2H), 2.54-2.58 (m, 2H), 2.39 (s, 3H), 1.57-1.64 (m, 2H), 1.05 (s, 9H), 0.97 (s, 9H), 0.23 (s, 6H), 0.15 (s, 9H); δ_C (125 MHz, $CDCl_3$) 204.9, 156.6, 151.7,

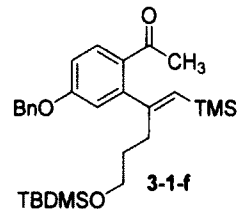
144.0, 135.7, 134.0, 133.5, 132.0, 129.7, 129.7, 129.1, 127.8, 127.7, 120.5, 117.4, 77.4, 64.2, 33.9, 32.9, 32.1, 27.0, 25.8, 25.8, 25.8, 19.3, 18.3, 0.1, -4.1.



1-f

(E)-1-(4-(benzyloxy)-2-(1-(trimethylsilyl)hex-1-en-2-yl)phenyl)ethan-1-one (1-f):

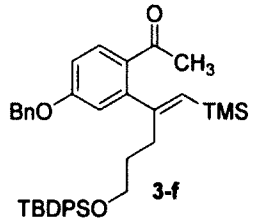
Isolation yield 43% (*E*/*Z* = 2.4:1) as a clear oil; ν_{max} (neat)/cm^{-} 2954, 2860, 1680, 1594, 1560, 1314; δ_H (500 MHz, $CDCl_3$) 7.57 (d, *J* = 8.4 Hz, 1H), 7.33-7.45 (m, 5H), 6.86-6.88 (dd, *J* = 8.4, 2.5 Hz, 1H), 6.78 (d, *J* = 2.5 Hz, 1H), 5.42 (s, 1H), 5.11 (s, 2H), 2.47 (s, 3H), 2.42-2.45 (m, 2H), 1.22-1.28 (m, 4H), 0.83 (t, *J* = 6.6 Hz, 3H), 0.18 (s, 9H); δ_C (125 MHz, $CDCl_3$) 201.4, 160.7, 159.7, 148,2 136.5, 131.3, 131.2, 130.3, 128.8, 127.7, 116.0, 112.6, 70.2, 37.3, 31.7, 29.9, 23.2, 14.1, 0.1.



3-1-f

(E)-1-(4-(benzyloxy)-2-(5-((tert-butyldimethylsilyl)oxy)-1-(trimethylsilyl)pent-1-en-2-yl)phenyl)ethan-1-one (3-1-f):

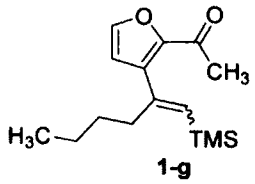
Isolation yield 40% (*E*/*Z* = 2.4:1) as a clear oil; ν_{max} (neat)/cm^{-} 2952,2930,2893, 2857, 1681, 1595; δ_H (500 MHz, $CDCl_3$) 7.74 (d, *J* = 8.8 Hz, 1H), 7.38-7.44 (m, 4H), 7.32-7.35 (m, 1H), 6.90 (dd, *J* = 8.8, 2.7 Hz, 1H), 6.65 (d, *J* = 2.7 Hz, 1H), 5.57 (s, 1H), 5.12 (d, *J* = 3.3 Hz, 2H), 3.56-3.61 (m, 2H), 2.50 (s, 3H), 2.42-2.49 (m, 1H), 2.25-2.32 (m, 1H), 1.58-1.69 (m, 2H), 0.87 (s, 9H), 0.02 (s, 6H), -0.25 (s, 9H); δ_C (125 MHz, $CDCl_3$)



3-f

(E)-1-(4-(benzyloxy)-2-(5-((tert-butyldiphenylsilyl)oxy)-1-(trimethylsilyl)pent-1-en-2-yl)phenyl)ethan-1-one (3-f):

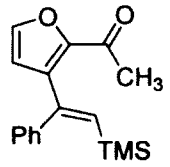
Isolation yield 35% (*E*/*Z* = 1:2) as a clear oil; ν_{max}(neat)/cm^{-} 3021, 2913, 2837, 1691, 1601; δ_H (500 MHz, $CDCl_3$) 7.61-7.63 (m, 4H), 8.04 (d, *J* = 8.7 Hz, 1H), 7.32-7.43 (m, 11H), 6.87 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.77 (d, *J* = 2.6 Hz, 1H), 5.43 (s, 1H), 5.08 (s, 2H), 3.57 (t, *J* = 6.3 Hz, 2H), 2.54-2.58 (m, 2H), 2.45 (s, 3H), 1.51-1.55 (m, 2H), 1.02 (s, 9H), 0.18 (s, 9H); δ_C (125 MHz, $CDCl_3$) 201.1, 160.7, 159.1, 148.0, 136.4, 135.7, 134.9, 133.9, 131.4, 131.3, 130.7, 129.7, 128.8, 128.3,127.7, 127.7, 116.0, 112.6, 70.2, 64.1, 33.9, 32.4, 29.8, 27.0, 19.3, 0.1.



1-g

1-(3-(1-(trimethylsilyl)hex-1-en-2-yl)furan-2-yl)ethan-1-one (1-g):

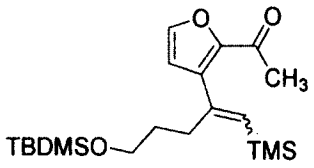
Isolation yield 62% (*E*/*Z* = 1:1) as a clear oil; ν_{max}(neat)/cm^{-1} 3117, 2956, 2872, 1938, 1679, 1561, 1478; δ_H (500 MHz, $CDCl_3$, *-isomer) 7.43 (d, *J* = 1.7 Hz, 1H), 7.39 (d, *J* = 1.7 Hz, 1H), 6.36 (d, *J* = 1.7 Hz, 1H), 6.28 (d, *J* = 1.7 Hz, 1H), 5.69 (s, 1H), 5.60 (s, 1H), 2.51 (t, *J* = 7.5 Hz, 2H), 2.41 (s, 3H), 2.40 (s, 3H), 2.33 (t, *J* = 7.5 Hz, 2H), 1.20-1.34 (m, 8H), 0.77-0.84 (m, 6H), 0.13 (s, 9H), -0.19 (s, 9H); δ_C (125 MHz, $CDCl_3$) 187.4, 186.9, 150.5, 147.4, 146.9, 144.3, 144.2, 137.1, 135.0, 132.1, 128.8, 15.8, 114.7, 41.6, 35.8, 31.4, 29.9, 27.4, 26.9, 22.7, 22.3, 13.9, 13.9, 0.1, -0.4.



2-g

(E)-1-(3-(1-phenyl-2-(trimethylsilyl)vinyl)furan-2-yl)ethan-1-one (2-g):

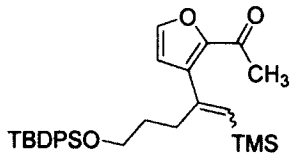
Isolation yield 75% (*E*/*Z* = 4.9:1) as a clear oil; ν_{max} (neat)/cm^{-1} 3320, 3139, 3115, 3023, 2995, 2897, 1940, 1684; δ_H (500 MHz, $CDCl_3$) 7.64 (d, *J* = 1.8 Hz, 1H), 7.37-7.39 (m, 2H), 7.26-7.31 (m, 3H), 6.57 (s, 1H), 6.50 (d, *J* = 1.8 Hz, 1H), 2.33 (s, 3H), -0.22 (s, 9H); δ_C (125 MHz, $CDCl_3$) 186.6, 148.6, 147.3, 145.1, 140.7, 133.3, 131.8, 128.4, 128.1, 126.1, 116.4, 27.2, -0.4.



3-1-g

1-(3-(5-((tert-butyldimethylsilyl)oxy)-1-(trimethylsilyl)pent-1-en-2-yl)furan-2-yl)ethan-1-one (3-1-g):

Isolation yield 60 % (*E*/*Z* = 1:1) as a clear oil; ν_{max} (neat)/cm^{-1} 3118, 2953, 2893, 2857, 17412, 1682, 1560; δ_H (500 MHz, $CDCl_3$, *-isomer) 7.44 (s, 1H), 7.40 (s, 1H), 6.38 (s, 1H), 6.29 (s, 1H), 5.71 (s, 1H), 5.65 (s, 1H), 3.57 (t, *J* = 6.2 Hz, 2H), 3.52 (t, *J* = 6.2 Hz, 2H), 2.57-2.61 (m, 2H), 2.39-2.44 (m, 2H), 2.42 (s, 3H), 2.41 (s, 3H), 1.56-1.61 (m, 2H), 1.44-1.50 (m, 2H), 0.84 (s, 9H), 0.83 (s, 9H), 0.15 (s, 9H), 0.0 (s, 6H), 0.0 (s, 6H), -0.2 (s, 9H); δ_C (125 MHz, $CDCl_3$) 187.6, 187.1, 150.0, 147.5, 147.1, 144.4, 144.3, 137.1, 134.9, 132.8, 129.4, 115.9, 114.8, 63.0, 62.6, 38.2, 32.7, 32.5, 31.0, 27.5, 27.1, 18.4, 0.1, -0.3, -5.2, -5.3.

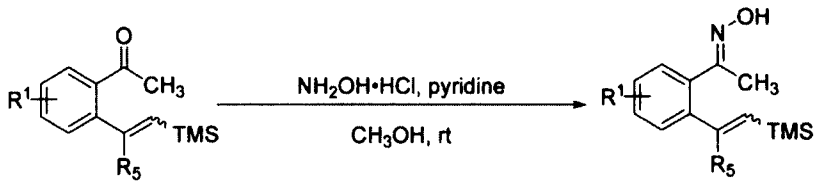


3-g

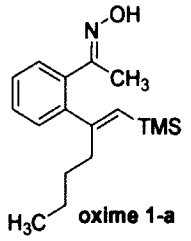
1-(3-(5-((tert-butyldiphenylsilyl)oxy)-1-(trimethylsilyl)pent-1-en-2-yl)furan-2-yl)ethan-1-one (3-g):

Isolation yield 58% (*E*/*Z* = 1:1) as a clear oil; ν_{max} (neat)/cm^{-1} 3115, 2950, 2896, 2832, 1740, 1654, 1568; δ_H (500 MHz, $CDCl_3$, *-isomer) 7.67-7.70 (m, 4H+4H*), 7.37-7.48 (m, 7H+7H*), 6.39 (d, *J* = 1.6 Hz, 1H), 6.28* (d, *J* = 1.6 Hz, 1H), 5.79 (s, 1H), 5.73* (s, 1H), 3.72 (t, *J* = 6.7 Hz, 2H), 3.67* (t, *J* = 6.7 Hz, 2H), 2.70-2.73 (m, 2H), 2.53-2.56* (m, 2H), 2.46 (s, 3H+3H*), 1.69-1.74 (m, 2H), 1.58-1.64* (m, 2H), 1.09 (s, 9H+9H*), 0.22 (s, 9H), -0.10* (s, 9H).

General procedure of oxime formation;

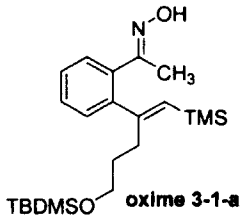


The NH_2OH-HCl (2 mmol) was added under Ar to a solution of aromatic ketone (1 mmol) and pyridine (3 mmol) in CH_2Cl_2 (5 mL). Then the reaction mixture was stirred at ambient temperature for 15 hr. The reaction was diluted with EtOAc. The organic layer was washed with 1 M hydrochloric acid in water and brine. The organic layer was then dried over sodium sulfate and filtered. The organic layer was concentrated under reduced pressure. The crude oil was purified by flash column chromatography.



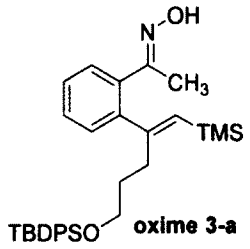
(E)-1-(2-((E)-1-(trimethylsilyl)hex-1-en-2-yl)phenyl)ethan-1-one oxime (oxme 1-a):

Isolation yield 83% as a clear oil; ν_{max}(neat)/cm^{-1} 3299, 3-60, 2955, 2928, 2859, 1599, 1247; δ_H (500 MHz, $CDCl_3$) 9.09 (bs, 1H), 7.20-7.32 (m, 4H), 5.55 (s, 1H), 2.41-2.44 (m, 2H), 2.14 (s, 3H), 1.18-1.28 (m, 4H), 0.82 (t, J = 7.6 Hz, 3H), 0.17 (s, 9H); δ_C (125 MHz, $CDCl_3$) 159.0, 158.6, 144.5, 135.4, 131.4, 129.2, 128.7 128.6, 127.0, 36.6, 31.5, 23.0, 15.9, 14.1, -0.2.



(E)-1-(2-((E)-5-((tert-butyldimethylsilyl)oxy)-1-(trimethylsilyl)pent-1-en-2-yl)phenyl)ethan-1-one oxime (oxime 3-1-a):

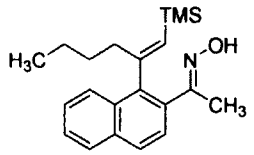
Isolation yield 81% as a clear oil; ν_{max}(neat)/cm^{-1} 3299, 3160, 2955, 2928, 2859, 1599, 1247; δ_H (500 MHz, $CDCl_3$) 8.58 (bs, 1H), 7.26-7.32 (m, 3H), 7.07-7.09 (m, 1H), 5.63 (s, 1H), 3.57 (t, J = 6.5 Hz, 2H), 2.27-2.41 (m, 2H), 2.17 (s, 3H), 1.50-1.65 (m, 2H), 0.87 (s, 9H), 0.02 (s, 6H), -0.19 (s, 9H); δ_C (125 MHz, $CDCl_3$) 158.2, 158.1, 142.6, 135.5, 130.5, 128.7, 128.5, 128.2, 127.4, 62.8, 38.1, 31.2, 26.1, 18.5, 15.2, -0.2, -5.1.



oxime 3-a

(E)-1-(2-((E)-5-((tert-butyldiphenylsilyl)oxy)-1-(trimethylsilyl)pent-1-en-2-yl)phenyl)ethan-1-one oxime (oxime 3-a):

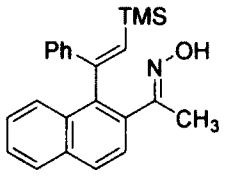
Isolation yield 79% as a clear oil; ν_{max}(neat)/cm^{-1} 3324, 3250, 2823, 2811, 1602; δ_H (500 MHz, $CDCl_3$) 8.52 (bs, 1H), 7.63-7.65 (m, 4H), 7.33-7.43 (m, 6H), 7.25-7.31 (m, 3H), 7.19-7.20 (m, 1H), 6.57 (s, 1H), 3.59 (t, *J* = 6.3 Hz, 2H), 2.54-2.58 (m, 2H), 2.11 (s, 3H), 1.50-1.55 (m, 2H), 1.04 (s, 9H), 0.17 (s, 9H).



oxime 1-b

(E)-1-(1-((E)-1-(trimethylsilyl)hex-1-en-2-yl)naphthalen-2-yl)ethan-1-one oxime (oxime 1-b):

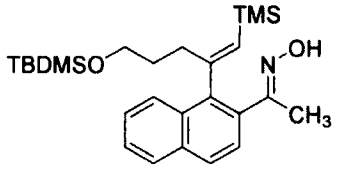
Isolation yield 81% as a clear oil; ν_{max}(neat)/cm^{-1} 3301, 2955, 2859, 1769, 1603, 1455; δ_H (500 MHz, $CDCl_3$) 7.97-7.99 (m, 1H), 7.90 (bs, 1H), 7.81-7.83 (m, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.46-7.49 (m, 2H), 7.39 (d, *J* = 8.4 Hz, 1H), 5.96 (s, 1H), 2.40-2.45 (m, 2H), 2.25 (s, 3H), 1.47-1.54 (m, 2H), 1.30-1.37 (m, 2H), 0.88 (t, *J* = 7.5 Hz, 3H), -0.43 (s, 9H); δ_C (125 MHz, $CDCl_3$) 158.9, 154.1, 140.9, 133.4, 132.2, 132.2, 129.4, 128.0, 127.2, 126.9, 126.2, 126.2, 42.2, 29.8, 27.8, 15.7, 14.2, -1.1; Accurate mass (ES$^+$): Found 362.190927 (<-1.0 ppm), $C_{21}H_{29}NNaOSi$ (M+Na$^+$) requires 362.191062.



oxime-2-b

(E)-1-(1-((E)-1-phenyl-2-(trimethylsilyl)vinyl)naphthalen-2-yl)ethan-1-one oxime (oxime-2-b):

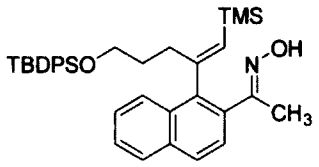
Isolation yield 86% as a clear oil; ν_{max} (neat)/cm^{-1} 3297, 3058, 2953, 2897, 1950, 1738, 1590, 1568; δ_H (500 MHz, $CDCl_3$) 9.11 (bs, 1H), 8.00 – 7.85 (m, 3H), 7.57 (d, *J* = 8.5 Hz, 1H), 7.52 (ddd, *J* = 8.1, 6.8, 1.3 Hz, 1H), 7.44 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 7.37 – 7.34 (m, 2H), 7.30 – 7.24 (m, 3H), 2.01, (s, 3H), -0.32 (s, 9H); δ_C (125 MHz, $CDCl_3$) 158.5, 150.9, 143.5, 138.2, 134.4, 133.4, 133.2, 133.1, 128.5, 128.0, 128.0, 127.7, 127.3, 126.6, 126.5, 126.4, 15.6, -1.2.



oxime-3-1-b

(E)-1-(1-((E)-5-((tert-butyldimethylsilyl)oxy)-1-(trimethylsilyl)pent-1-en-2-yl)naphthalen-2-yl)ethan-1-one oxime (oxime-3-1-b):

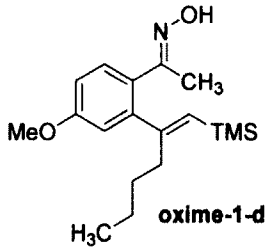
Isolation yield 92% as a clear oil; ν_{max} (neat)/cm^{-1} 3314, 3054, 2952, 2929, 2894, 2857, 1934, 1606, 1469, 1250; δ_H (500 MHz, $CDCl_3$) 8.87 (bs, 1H), 8.02 – 7.95 (m, 1H), 7.86 – 7.80 (m, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.51 – 7.45 (m, 2H), 7.42 (d, *J* = 8.4 Hz, 1H), 5.99 (t, *J* = 1.6 Hz, 1H), 3.64 (t, *J* = 6.5 Hz, 2H), 2.63 – 2.41 (m, 2H), 2.26 (s, 3H), 1.86 – 1.70 (m, 2H), 0.88 (s, 9H), 0.03 (s, 6H), -0.4 (s, 9H); δ_C (125 MHz, $CDCl_3$) 158.4, 153.6, 140.7, 133.4, 132.4, 132.2, 129.7, 128.0, 127.3, 126.9, 126.2, 126.2, 126.2, 63.1, 38.5, 30.8, 26.1, 18.5, 15.8, -1.1, -5.1.



oxime-3-b

(E)-1-(1-((E)-5-((tert-butyldiphenylsilyl)oxy)-1-(trimethylsilyl)pent-1-en-2-yl)naphthalen-2-yl)ethan-1-one oxime(oxime-3-b):

Isolation yield 89% as a clear oil; ν_{max} (neat)/cm^{-1} 3310, 3049, 2959, 2926, 2864, 1929, 1600, 1473, 1251; δ_H (500 MHz, $CDCl_3$) 8.19 – 8.14 (m, 1H), 7.89 – 7.86 (m, 1H), 7.82 (d, *J* = 8.6 Hz, 1H), 7.68 – 7.61 (m, 5H), 7.60 – 7.50 (m, 2H), 7.46 – 7.40 (m, 2H), 7.34-7.38 (m, 4H), 5.69 (s, 1H), 3.62 – 3.50 (m, 2H), 3.05 – 2.92 (m, 1H), 2.67 (s, 3H), 2.65 – 2.52 (m, 1H), 1.65 – 1.53 (m, 1H), 1.51 – 1.40 (m, 1H), 1.05 (s, 9H), 0.35 (s,9H); δ_C (125 MHz, $CDCl_3$) 203.6, 155.6, 143.3, 135.8, 135.8, 134.9, 134.8, 134.0, 134.0, 133.1, 131.7, 129.8, 128.3, 127.9, 127.8, 127.5, 127.5, 127.3, 126.8, 124.8, 77.7, 77.3, 77.0, 64.2, 36.4, 31.9, 31.3, 27.2, 27.1, 19.4, 0.4.

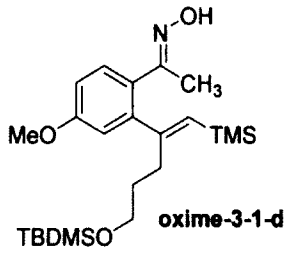


oxime-1-d

(E)-1-(4-methoxy-2-((E)-1-(trimethylsilyl)hex-1-en-2-yl)phenyl)ethan-1-one oxime (oxime-1-d):

Isolation yield 85% as a clear oil; ν_{max} (neat)/cm^{-1} 3220, 2956, 2930, 2871, 1700, 1678, 1603, 1564, 1248; δ_H (500 MHz, $CDCl_3$) 9.12 (bs, 1H), 7.26 (d, *J* = 8.5 Hz, 1H), 6.80 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.63 (d, *J* = 2.7 Hz, 1H), 5.60 (s, 1H), 3..82 (s, 3H), 2.8 (t, *J* = 7.4 Hz, 2H), 2.15 (s, 3H), 1.37 – 1.22 (m, 5H), 0.85 (t, *J* = 7.0 Hz, 3H), -0.15 (s, 9H); δ_C (125 MHz, $CDCl_3$) 159.4, 159.1, 157.7, 144.4, 130.1, 128.2,

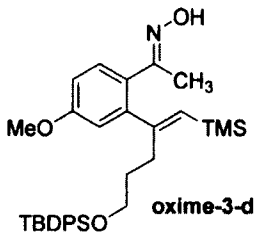
128.1, 116.4, 112.3, 77.6, 77.3, 76.9, 55.5, 41.6, 30.5, 22.6, 15.4, 14.2, 0.0; Accurate mass (ES^+): Found 342.185711 (<-1.0 ppm), $C_{18}H_{29}NNaO_2Si$ ($M+Na^+$) requires 342.185977.



oxime-3-1-d

(E)-1-(2-((E)-5-((tert-butyldimethylsilyl)oxy)-1-(trimethylsilyl)pent-1-en-2-yl)-4-methoxyphenyl)ethan-1-one oxime (oxime-3-1-d):

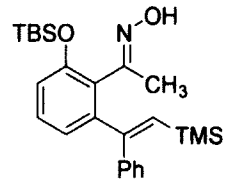
Isolation yield 85% as a clear oil; ν_{max} (neat)/cm^{-1} 3295, 2953, 2858, 1601, 1563, 1493, 1468, 1388, 1289; δ_H (500 MHz, $CDCl_3$) 8.35 (bs, 1H), 7.20 (d, J = 8.4 Hz, 1H), 6.77 (dd, J = 8.4, 2.7 Hz, 1H), 6.73 (d, J = 2.7 Hz, 1H), 5.57 (s, 1H), 3.81 (s, 3H), 3.52 (t, J = 6.3 Hz, 2H), 2.51 – 2.44 (m, 2H), 2.10 (s, 3H), 1.50 – 1.41 (m, 2H), 0.87 (s, 9H), 0.17 (s, 9H), 0.00 (s, 9H); δ_C (125 MHz, $CDCl_3$) 159.8, 158.6, 158.3, 145.8, 131.8, 130.2, 128.4, 114.9, 112.1, 76.9, 63.4, 55.6, 33.4, 32.5, 26.2, 18.6, 16.1, 0.2, -5.1.



oxime-3-d

(E)-1-(2-((E)-5-((tert-butyldiphenylsilyl)oxy)-1-(trimethylsilyl)pent-1-en-2-yl)-4-methoxyphenyl)ethan-1-one oxime (oxime-3-d):

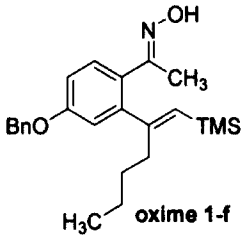
Isolation yield 89% as a clear oil; ν_{max} (neat)/cm^{-1} 3285, 2963, 2859, 1583, 1555, 1438, 1380, 1282; δ_H (500 MHz, $CDCl_3$) 8.04 (s, 1H), 7.66 – 7.56 (m, 4H), 7.45 – 7.32 (m, 6H), 7.19 (d, J = 8.4 Hz, 1H), 6.77 (dd, J = 8.4, 2.7 Hz, 1H), 6.72 (d, J = 2.7 Hz, 1H), 5.57 (s, 1H), 3.79 (s, 3H), 3.58 (t, J = 6.2 Hz, 2H), 2.55 – 2.49 (m, 2H), 2.08 (s, 3H), 1.53 (m, 2H), 1.03 (s, 9H), 0.15 (s, 9H); δ_C (125 MHz, $CDCl_3$)



oxime 2-e

(E)-1-(2-((tert-butyldimethylsilyl)oxy)-6-((E)-1-phenyl-2-(trimethylsilyl)vinyl)phenyl)ethan-1-one oxime (oxime-2-e):

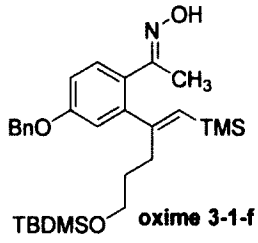
Isolation yield 30% as a clear oil; ν_{max} (neat)/cm^{-1} 3272, 2973, 2873, 1562, 1562, 1443, 1379, 1219; δ_H (500 MHz, $CDCl_3$) 8.06 (s, 1H), 7.30 – 7.24 (m, 3H), 7.20 (t, *J* = 7.9 Hz, 1H), 7.17 – 7.14 (m, 2H), 7.01 (dd, *J* = 7.9, 1.1 Hz, 1H), 6.79 (dd, *J* = 7.9, 1.1 Hz, 1H), 5.96 (s, 1H), 1.44 (s, 3H), 0.96 (s, 9H), 0.18 (s, 6H), -0.05 (s, 9H); δ_C (125 MHz, $CDCl_3$) 158.3, 157.1, 153.9, 147.4, 143.4, 133.4, 129.8, 128.8, 128.4, 127.7, 127.4, 123.3, 118.5, 25.9, 18.3, 15.8, 0.5, -4.1.



oxime 1-f

(E)-1-(4-(benzyloxy)-2-((E)-1-(trimethylsilyl)hex-1-en-2-yl)phenyl)ethan-1-one oxime (oxime 1-f):

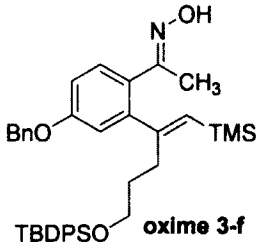
Isolation yield 79% as a clear oil; ν_{max} (neat)/cm^{-1} 3305, 3066, 3034, 2954, 2989, 2870, 1740, 1600, 1562; δ_H (500 MHz, $CDCl_3$) 8.87 (bs, 1H), 7.45 – 7.42 (m, 2H), 7.41 – 7.37 (m, 2H), 7.35 – 7.30 (m, 1H), 7.26 (d, *J* = 8.5 Hz, 1H), 6.88 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.71 (d, *J* = 2.7 Hz, 1H), 5.59 (t, *J* = 1.3 Hz, 1H), 5.09 (s, 2H), 2.28 (t, *J* = 6.8 Hz, 2H), 2.15 (s, 3H), 1.37 – 1.15 (m, 4H), 0.85 (t, *J* = 6.9 Hz, 3H), -0.16 (s, 9H); δ_C (125 MHz, $CDCl_3$) 158.87, 158.45, 157.77, 144.3, 136.9, 130.0, 128.7, 128.4, 128.1, 128.0, 127.5, 117.1, 113.3, 77.5, 77.2, 76.9, 70.1, 41.6, 30.4, 22.5, 15.3, 14.1, -0.1.



oxime 3-1-f

(E)-1-(4-(benzyloxy)-2-((E)-5-((tert-butyldimethylsilyl)oxy)-1-(trimethylsilyl)pent-1-en-2-yl)phenyl)ethan-1-one oxime (oxime 3-1-f):

Isolation yield 83% as a clear oil; ν_{max} (neat)/cm^{-1} 3303, 3034, 2952, 2929, 2895, 2857, 1599, 1563, 1250; δ_H (500 MHz, $CDCl_3$) 8.22 (bs, 1H), 7.49 – 7.43 (m, 2H), 7.43 – 7.38 (m, 2H), 7.37 – 7.32 (m, 1H), 7.28 (s, 1H), 6.89 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.71 (d, *J* = 2.8 Hz, 1H), 5.62 (t, *J* = 1.2 Hz, 1H), 5.10 (s, 2H), 3.58 (t, *J* = 6.7 Hz, 1H), 2.45 – 2.37 (m, 1H), 2.27-2.36 (m, 1H), 2.16 (s, 3H), 1.50-1.59 (m, 2H), 0.90 (s, 9H), 0.04 (s, 6H), -0.15 (s, 9H); δ_C (125 MHz, $CDCl_3$) 158.5, 158.1, 157.9, 144.2, 136.9, 130.1, 128.7, 128.5, 128.2, 128.1, 127.7, 127.5, 117.1, 113.3, 77.5, 70.1, 62.7, 38.0, 31.2, 26.1, 18.5, 15.2, -0.2, -5.1.

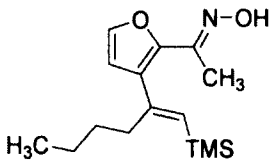


oxime 3-f

(E)-1-(4-(benzyloxy)-2-((E)-5-((tert-butyldiphenylsilyl)oxy)-1-(trimethylsilyl)pent-1-en-2-yl)phenyl)ethan-1-one oxime (oxime 3-f):

Isolation yield 80% as a clear oil; ν_{max} (neat)/cm^{-1} 3313, 3000, 2948, 2932, 2930, 2842, 1592, 1543, 1228; δ_H (500 MHz, $CDCl_3$, *E*/*Z* = 1.2:1, *-minor isomer) 8.21 (bs, 1H, 1H*), 7.62-7.67 (m, 4H+4H*), 7.48 – 7.31 (m, 10H, 10H*), 7.27 – 7.17 (m, 2H, 2H*), 6.92 – 6.79 (m, 2H, 2H*), 5.60* (s, 1H), 5.57 (s, 1H), 5.06* (s, 2H), 5.05 (s, 2H), 3.61* (t, *J* = 6.2 Hz, 2H), 3.57 (t, *J* = 6.2 Hz, 2H), 2.51 (m, 2H), 2.41-2.48* (m, 1H), 2.30-2.37* (m, 1H), 2.13* (s, 3H), 2.08 (s, 3H), 1.69 – 1.57* (m, 2H), 1.54 –

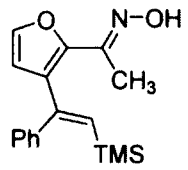
1.45 (m, 2H), 1.04 (s, 9H, 9H*), 0.15 (s, 9H), -0.18* (s, 9H); δ_C (125 MHz, $CDCl_3$) 158.4, 158.0, 144.1, 136.9, 135.7, 134.1, 130.0, 129.7, 128.7, 128.4, 128.2, 128.1, 127.8, 127.7, 127.5, 117.0, 113.3, 70.0, 63.4, 38.1, 30.9, 27.0, 19.4, 15.2, -0.2.



oxime 1-g

(E)-1-(3-((E)-1-(trimethylsilyl)hex-1-en-2-yl)furan-2-yl)ethan-1-one oxime (oxime 1-g):

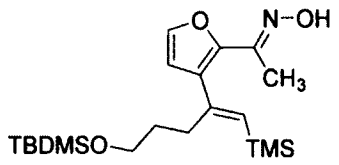
Isolation yield 93% as a clear oil; ν_{max} (neat)/cm^{-1} 3411, 2057, 2847, 1701, 1619, 1556; δ_H (500 MHz, $CDCl_3$) 9.46 (bs, 1H), 7.34 (s, 1H), 6.32 (s, 1H), 5.55 (s, 1H), 2.42 (t, *J* = 7.5 Hz, 2H), 2.18 (s, 3H), 1.35 – 1.24 (m, 4H), 0.86 (t, *J* = 7.3 Hz, 3H), 0.16 (s, 9H); δ_C (125 MHz, $CDCl_3$) 150.6, 149.1, 144.5, 142.0, 131.7, 129.9, 113.3, 36.1, 31.7, 23.0, 14.2, 12.5, 0.3, 0.3.



oxime 2-g

(E)-1-(3-((E)-1-phenyl-2-(trimethylsilyl)vinyl)furan-2-yl)ethan-1-one oxime (oxime 2-g):

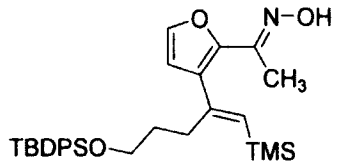
Isolation yield 85% as a clear oil; ν_{max} (neat)/cm^{-1} 3252, 2954, 2896, 1942, 1599, 1562, 1394, 1247; δ_H (500 MHz, $CDCl_3$) 10.16 (bs, 1H), 7.53 (d, *J* = 1.8 Hz, 1H), 7.50 – 7.40 (m, 2H), 7.38 – 7.24 (m, 3H), 6.56 (s, 1H), 6.41 (d, *J* = 1.8 Hz, 1H), 2.14 (s, 3H), 0.04 (s, 9H); δ_C (125 MHz, $CDCl_3$) 147.9, 147.8, 145.9, 142.2, 141.4, 132.1, 128.4, 128.0, 126.4, 125.6, 115.7, 11.5, -0.4.



oxime 3-1-g

(E)-1-(3-((E)-5-((tert-butyldimethylsilyl)oxy)-1-(trimethylsilyl)pent-1-en-2-yl)furan-2-yl)ethan-1-one oxime (oxime 3-1-g):

Isolation yield 80% as a clear oil; ν_{max} (neat)/cm^{-1} 3304, 2928, 2857, 1608, 1567, 1469, 1389, 1251; δ_H (500 MHz, $CDCl_3$) 9.27 (bs, 1H), 7.37 (d, *J* = 1.8 Hz, 1H), 6.22 (d, *J* = 1.8 Hz, 1H), 5.69 (t, *J* = 1.4 Hz, 1H), 3.59 (t, *J* = 6.2 Hz, 2H), 2.36 (ddd, *J* = 9.3, 6.2, 1.4 Hz, 2H), 2.20 (s, 3H), 1.63 (ddt, *J* = 9.3, 7.9, 6.2 Hz, 2H), 0.87 (s, 9H), 0.02 (s, 6H), -0.13 (s, 9H); δ_C (125 MHz, $CDCl_3$) 150.6, 148.7, 144.4, 141.7, 130.0, 127.0, 115.2, 62.8, 38.5, 31.1, 26.1, 18.5, 11.5, -0.3, -5.1.

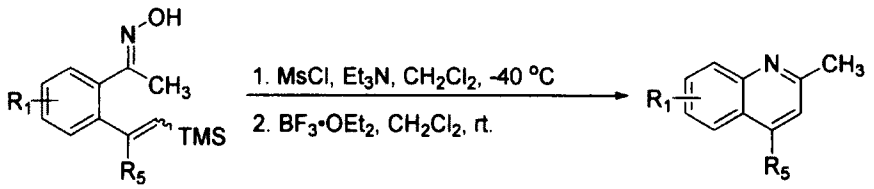


oxime 3-g

(E)-1-(3-((E)-5-((tert-butyldiphenylsilyl)oxy)-1-(trimethylsilyl)pent-1-en-2-yl)furan-2-yl)ethan-1-one oxime (oxime 3-g):

Isolation yield 84% as a clear oil; ν_{max} (neat)/cm^{-1} 3300, 2948, 2853, 1618, 1572, 1426, 1251; δ_H (500 MHz, $CDCl_3$) 9.09 (bs, 1H), 7.78 – 7.60 (m, 4H), 7.46 – 7.32 (m, 7H), 6.16 (d, *J* = 1.7 Hz, 1H), 5.69 (t, *J* = 1.3 Hz, 1H), 3.66 (t, *J* = 6.4 Hz, 2H), 2.42 (ddd, *J* = 9.2, 6.4, 1.4 Hz, 2H), 2.19 (s, 3H), 1.72 – 1.65 (m, 2H), 1.04 (s, 9H), -0.13 (s, 9H); δ_C (125 MHz, $CDCl_3$) 149.9, 149.0, 144.6, 142.1, 142.0, 135.7, 134.1, 133.9, 132.2, 129.7, 127.7, 113.2, 64.1, 63.5, 33.0, 32.4, 31.2, 27.0, 27.0, 19.3, 19.3, 12.5, 12.3, 0.2.

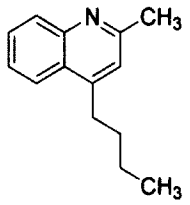
General procedure of mesylation and quinolone cyclization;



oxime quinoline

To a solution of oxime (0.9 mmol) and triethylamine (253 μL, 1.8 mmol) in dichloromethane (6 ml) was added methansulfonyl chloride (85 μL, 1.1 mmol) at -40 °C. The reaction mixture was stirred for 3 hr at this temperature. The reaction was quenched with 10% *aq.* sodium bicarbonate (5 ml) and warm to room temperature. The bi-phasic mixture was extracted with ethyl acetate (10 ml x 3) and the combined organic layer was washed with brine. The organic layer was dried over sodium sulfate and filtered. The organic layer was concentrated under reduced pressure. The crude material used to the next step without further purification.

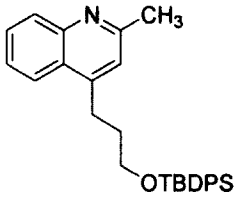
The mesylated oxime was dissolved in dichloromethane (18 ml) and cooled to 0 °C. A solution of BF_3-OEt_2 (222 μL, 1.8 mmol) was added to the reaction mixture and the whole mixture was warm to room temperature. The reaction mixture was stirred for 1 hr and quenched with saturated *aq.* sodium bicarbonate. The bi-phasic mixture was extracted with ethyl acetate (10 ml x 3) and the combined organic layer was washed with brine. The organic layer was dried over sodium sulfate and filtered. The organic layer was concentrated under reduce pressure. The crude was purified by flash column chromatography.



quinoline 1-a

4-butyl-2-methylquinoline (quinolone 1-a):

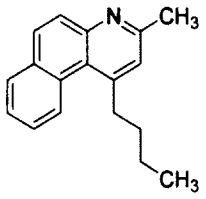
Isolation yield 92% as a clear oil; ν_{max} (neat)/cm^{-1} 3063, 2956, 2930, 2869, 1699, 1601, 1563, 1510; δ_H (500 MHz, $CDCl_3$) 8.08 – 7.96 (m, 2H), 7.64-7.67 (m, 1H), 7.47-7.50 (m, 1H), 7.13 (s, 1H), 3.10 – 2.97 (m, 2H), 2.70 (s, 3H), 1.78 – 1.66 (m, 2H), 1.52 – 1.41 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H); δ_C (125 MHz, $CDCl_3$) 158.8, 148.8, 148.2, 129.5, 129.1, 126.0, 125.5, 123.5, 121.8, 32.4, 32.0, 25.5, 23.0, 14.1.



quinoline 3-a

4-(3-((tert-butyldiphenylsilyl)oxy)propyl)-2-methylquinoline (quinolone 3-a):

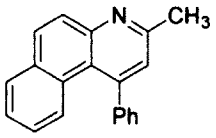
Isolation yield 80% as a clear oil; ν_{max} (neat)/cm^{-1} 3043, 2963, 2943, 2854, 1683, 1611, 1575, 1502; δ_H (500 MHz, $CDCl_3$) 8.08 – 7.99 (m, 2H), 7.73 – 7.67 (m, 4H), 7.67 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.50 – 7.46 (m, 2H), 7.46 – 7.36 (m, 5H), 7.13 (s, 1H), 3.77 (t, *J* = 5.9 Hz, 2H), 3.22 – 3.11 (m, 2H), 2.70 (s, 3H), 2.03 – 1.95 (m, 2H), 1.12 (s, 9H); δ_C (125 MHz, $CDCl_3$) 158.7, 148.3, 148.2, 135.7, 133.9, 129.8, 129.4, 129.1, 127.8, 125.9, 125.5, 123.6, 121.9, 63.1, 33.0, 28.5, 27.0, 25.4, 19.4.



quinoline 1-b

1-butyl-3-methylbenzo[f]quinolone (quinolone 1-b):

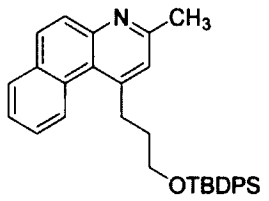
Isolation yield 88% as a clear oil; ν_{max} (neat)/cm^{-1} 3055, 2956, 2929, 2871, 1697, 1587, 1558, 1525, 1486; δ_H (500 MHz, $CDCl_3$) 8.66 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.96 – 7.90 (m, 3H), 7.59-7.66 (m, 2H), 7.27 (s, 1H), 3.44 – 3.35 (m, 2H), 2.74 (s, 3H), 1.93 – 1.82 (m, 2H), 1.54-1.62 (m, 2H), 1.04 (t, *J* = 7.4 Hz, 3H); δ_C (125 MHz, $CDCl_3$) 157.3, 149.8, 132.9, 131.0, 130.6, 129.3, 129.2, 127.3, 126.5, 126.3, 126.3, 124.8, 123.4, 37.6, 32.1, 24.7, 23.2, 14.2; Accurate mass (ES^+): Found 250.158848 (<-1.0 ppm), $C_{18}H_{19}NNa$ ($M+Na^+$) requires 250.15902.



quinoline 2-b

3-methyl-1-phenylbenzo[f]quinolone (quinolone 2-b):

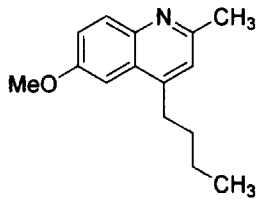
Isolation yield 86% as a clear oil; ν_{max} (neat)/cm^{-1} 3054, 2921, 2853, 1952, 1620, 1582, 1556, 1443, 1349; δ_H (500 MHz, $CDCl_3$) 8.03 – 7.95 (m, 2H), 7.86 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.63 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.54 – 7.48 (m, 3H), 7.45 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 7.43 – 7.39 (m, 2H), 7.24 (s, 1H), 7.14 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 2.78 (s, 3H); δ_C (125 MHz, $CDCl_3$) 157.2, 149.4, 148.8, 142.9, 132.7, 131.5, 129.9, 129.3, 128.7, 128.4, 128.4, 128.2, 128.0, 126.3, 125.6, 125.1, 122.0, 24.7.



quinoline 3-b

1-(3-((tert-butyldiphenylsilyl)oxy)propyl)-3-methylbenzo[f]quinolone (quinolone 3-b):

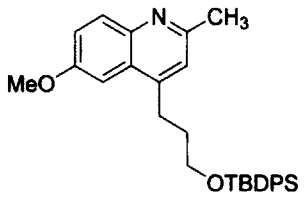
Isolation yield 91% as a clear oil; ν_{max} (neat)/cm^{-1} 3054, 2921, 2853, 1952, 1620, 1582, 1556, 1443, 1349; δ_H (500 MHz, $CDCl_3$) 8.79 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.98 – 7.91 (m, 3H), 7.75 – 7.70 (m, 4H), 7.62-7.55 (m, 2H), 7.47 – 7.43 (m, 2H), 7.42-7.38 (m, 4H), 7.29 (s, 1H), 3.87 (t, *J* = 5.8 Hz, 2H), 3.65 – 3.53 (m, 2H), 2.74 (s, 3H), 2.23 – 2.13 (m, 2H), 1.14 (s, 9H); δ_C (125 MHz, $CDCl_3$) 157.2, 149.7, 149.3, 135.7, 133.8, 132.8, 131.1, 130.4, 129.8, 129.2, 129.0, 127.9, 127.3, 126.7, 126.2, 125.0, 123.4, 77.5, 77.2, 76.8, 63.4, 34.4, 32.6, 27.1, 24.6, 19.5.



quinoline 1-d

4-butyl-6-methoxy-2-methylquinoline (1-d):

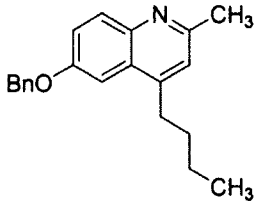
Isolation yield 85% as a clear oil; ν_{max} (neat)/cm^{-1} 2995, 2966, 2952, 2928, 2860, 1621, 1599, 1508, 1226; δ_H (500 MHz, $CDCl_3$) 7.92 (d, *J* = 9.1 Hz, 1H), 7.32 (dd, *J* = 9.1, 2.8 Hz, 1H), 7.21 (d, *J* = 2.8 Hz, 1H), 7.08 (s, 1H), 3.93 (s, 3H), 2.96 (t, J = 7.9 Hz, 2H), 2.66 (s, 3H), 1.79 – 1.69 (m, 2H), 1.50-1.42 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H); δ_C (125 MHz, $CDCl_3$) 157.0, 156.1, 147.3, 144.1, 130.8, 126.7, 121.9, 120.8, 102.2, 55.6, 32.0, 31.8, 25.1, 22.9, 14.1; Accurate mass (ES$^+$): Found 230.153226 (<-1.0 ppm), $C_{15}H_{19}NNaO$ (M+Na$^+$) requires 230.153941.



quinoline 3-d

4-(3-((tert-butyldiphenylsilyl)oxy)propyl)-6-methoxy-2-methylquinoline (quinolone 3-d):

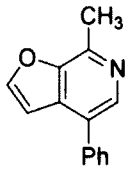
Isolation yield 89% as a clear oil; ν_{max} (neat)/cm^{-1} 2972, 2944, 2935, 2911, 2824, 1683, 1573, 1522, 1214; δ_H (500 MHz, $CDCl_3$) 7.94 (d, *J* = 9.1 Hz, 1H), 7.72 – 7.65 (m, 4H), 7.46 – 7.41 (m, 2H), 7.38 (dd, *J* = 7.9, 6.5 Hz, 4H), 7.32 (dd, *J* = 9.1, 2.8 Hz, 1H), 7.23 (d, *J* = 2.8 Hz, 1H), 7.09 (s, 1H), 3.86 (s, 3H), 3.78 (t, *J* = 5.9 Hz, 2H), 3.18 – 3.06 (m, 2H), 2.65 (s, 3H), 2.65 (s, 3H), 2.05 – 1.95 (m, 2H), 1.10 (s, 9H); δ_C (125 MHz, $CDCl_3$) 157.2, 156.1, 146.9, 144.0, 135.7, 133.9, 130.8, 129.8, 127.8, 126.7, 122.1, 121.1, 102.0, 63.3, 55.6, 32.5, 28.8, 27.1, 25.1, 19.4.



quinoline 1-f

6-(benzyloxy)-4-butyl-2-methylquinoline (quinolone 1-f):

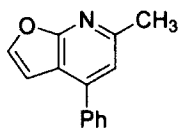
Isolation yield 78% as a clear oil; ν_{max} (neat)/cm^{-1} 3033, 2993, 2932, 2843, 1693, 1593, 1472, 1283; δ_H (500 MHz, $CDCl_3$) 7.94 (d, *J* = 9.1 Hz, 1H), 7.52 – 7.48 (m, 2H), 7.42-7.39 (m, 3H), 7.36 – 7.32 (m, 1H), 7.28 (d, *J* = 2.8 Hz, 1H), 7.08 (s, 1H), 5.20 (s, 2H), 2.92 (t, *J* = 7.9 Hz, 1H), 2.66 (s, 3H), 1.70 – 1.61 (m, 2H), 1.44-1.38 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H); δ_C (125 MHz, $CDCl_3$) 156.2, 136.9, 130.7, 128.8, 128.3, 128.3, 127.8, 127.6, 126.7, 122.0, 121.5, 104.1, 104.0, 70.5, 32.2, 31.9, 29.9, 23.0, 14.1.



quinoline 2-g-a

7-methyl-4-phenylfuro[2,3-c]pyridine (quinolone 2-g-a):

Isolation yield 35% as a clear oil; ν_{max} (neat)/cm^{-1} 3059, 3028, 2852, 1734, 1612, 1472, 1445, 1347; δ_H (500 MHz, $CDCl_3$) 8.41 (s, 1H), 7.79 (d, *J* = 2.1 Hz, 1H), 7.66 – 7.60 (m, 2H), 7.51 (dd, *J* = 8.4, 6.9 Hz, 2H), 7.46 – 7.41 (m, 1H), 6.98 (d, *J* = 2.1 Hz, 1H), 2.81 (s, 3H); δ_C (125 MHz, $CDCl_3$) 150.9, 147.8, 141.9, 140.6, 137.2, 131.7, 129.1, 128.8, 128.4, 128.0, 106.0, 18.7.



quinoline 2-g-b

6-methyl-4-phenylfuro[2,3-b]pyridine (quinolone 2-g-b):

Isolation yield 35% as a clear oil; ν_{max} (neat)/cm^{-1} 3116, 3058, 3032, 2923, 2853, 1727, 1601, 1528, 1445; δ_H (500 MHz, $CDCl_3$) 7.70 – 7.63 (m, 3H), 7.56 – 7.50 (m, 2H), 7.49 – 7.43 (m, 1H), 7.21 (s, 1H), 6.92 (d, *J* = 2.5 Hz, 1H), 2.69 (s, 3H); δ_C (125 MHz, $CDCl_3$) 154.1, 144.2, 144.1, 138.0, 129.2, 129.0, 128.4, 118.1, 114.7, 105.4, 24.5.

1.5 Reference.

1. J. O. Michael, *Nat. Prod. Rep.*, **2008**, *25*, 166-187
2. A. Raadt, H. Griengl, M. Petsch, P. Plachota, N. Schoo, H.Weber, G. Brauneg, I. Kopper, M. Kreiner, and A. Zeiser, *Tetraheron: Asymmetry*, **1996**, *7*, 473.
3. R. C. Storr, P. M. O'Neill, B. K. Park, *Tetrahedron.* **1998**, *54*, 4615.
4. S. Clavier, O. Rist, S. Hansen, L. O. Gerlach, T. Hogberg, J. Bergman, *Org. Biomolec. Chem.* **2003**, *1*, 2003.
5. A) K. H. Park, H. S. Joo, K. I. Ahn, K. Jun, *Tetrahedron Lett.* **1995**, *36*, 5943. B) O. Schindler, W. Michaelis, *Helv. Chim. Acta.***1970**, *53*, 766.
6. A) C.S. Cho, *J. Organomet. Chem.* **2005**, *690*, 4094. B) C. S. Cho, H. J. Seok, S. C. Shim, *J. Heterocycl. Chem.* **2005**, *42*, 1219. C) K. Taguchi, S. Sakaguchi, Y. Ishii, *Tetrahedron Lett.* **2005**, *46*, 4539. D) C. So. Cho, W. X. Ren, S. C. Shim, *Bull. Korean. Chem. Soc.*2005, 26, 1286. E) M. Movassaghi, M. D. Hill, *J, Am, Chem, Soc.* **2005**, *26*, 1286. F) R. Martinez, G. J. Brand, D. J. Ramon, M. Yus, *Tetrahedron Lett.* **2005**, *46*, 3683. G) K. Motokura, T. Mizugaki, K. Ebitani, K. Kaneda, *Tetrahedron Lett.* **2004**, *45*, 6029. H) X. Liu, P. Ding, J. Huang, C. Che, *Org. Lett.* **2007**, *9*, 2645.
7. A) S. Murai; F. Kakicuchi; S. Sekine; Y. Tanaka; A. Kamatani; M. Sonoda; N. Chatani; *Nature* **1993**, *366*, 529-531. B) C. Jia, T. Kitamura, Y. Fujiwara, *Acc. Chem. Res.* **2001**, *34*, 633-639. C) C. Jia, W. Lu, J. Oyamada, T. Kitamura, K. Matsuda, M. Irie, Y. Fujiwara, *J. Am. Chem. Soc.* **2000**, *122*, 7252-7263. D) M. A. Campo, R. C. Larock, *J. Am. Chem. Soc.* **2002**, *124*, 14327-14327. E) C. Jia, D. Piao, J. Oyamada, W. Lu, T. Kitamura, Y. Fujiwara, *Science*, **2000**, *287*, 1992-1995.
8. A) F. Kakiuchi; Y. Yamamoto; N. Chani; S. Murai, *Chem. Lett.* **1995**, 681-682. B) S. Sakaguchi, T. Kubo, Y. Ishi, *Angew. Chem. Int. Ed.* **2001**, *40*, 2534. C) B. Heller, M. Hapke, *Chem. Soc.*

Rev. **2007**, *36*, 1085-1094. D) T. Satoh, Y. Nishinaka, M. Miura, M. Nomura, Chem. Lett. 1999, 615-616. E) J. Oyamada, C. Jia, Y. Fujiwara, T. Kitamura, Chem. Lett. 2002, 380-381. F) Paul. W. R. Harris, C. E. F. Rickard, P. D. Woodgate, J. Org. Met. Chem. 1999, 589, 168-179. G) T. Hayashi, K. Inoue, N. Taniguchi, M. Ogasawara. *J. Am. Chem. Soc.* **2001**, *123*, 9918-9919. H) C. Jia, D. Piao, T. Kitamura, Y. Fujiwara, *J. Org. Chem.* **2000**, *65*, 7516-7522. I) T. M. Londergea, Y. You, M. E. Thompson, W. Weber, *Macromolecules*, **1998**, *31*, 2784, 2788. J) B. L. Gray, X. Wang, W. C. Brown, L. Kuai, S. L. Schreiber, *Org. Lett.* **2008**, *10*, 2621-2624. K) Y. Lim, K. Lee, B. T. Koo, J. Kang, Tetrahedron Lett. 2001, 42, 7609-7612.

9. A) T. Matsubara, N. Koga, D. G. Musaev, K. Morokuma, *Organimetallics*, **2000**, *19*, 2318-2329. B) T. Matsubara, N. Koga, D. G. Musaev, K. Morokuma, *J. Am. Chem. Sco.* **1998**, *120*, 12692-12693. C) U. R. Aulwurm, J. U. Melchinger, H. Kisch, *Organometallic*, **1995**, *14*, 3385-3395.
10. E. Beckmann, *Ber. Dtsch. Chem.Rev.* **1886**, *19*, 988.
11. F. W. Bergstrom, *Chem. Rev.* **1944**, *35*, 156.
12. J. Brouet, S. Gu, N. P. Peet, J. D. Williams, *Synthetic Communication* **2009**, *39*, 1563-1569.
13. R. G. Gould, W. A. Jacobs, *J. Am. Chem. Soc.* **1939**, *61*, 2890-2895.
14. R. F. Manske, *Chem. Rev.* **1942**, *30*, 113-144.
15. J. M. Contelles, E. P. Mayoral, A. Samadi, M. C. Carreiras, E. Soriano, *Chem. Rev.* **2009**, **109**, 2652-2671.
16. M. Wang, Y. Liu, Z. Huang, *Tetrahedron Letters*, **2001**, *42*, 2553-2555.
17. A) J. C. Eck, C. S. Marvel, *Organic Syntheses Coll.* **1939**, *19*, 20, B) J. C. Eck, C. S. Marvel, *Organic Syntheses Coll.* **1943**, *2*, 76.
18. A) B. S. Lee, S. Chu, I. Y. Lee, B. S. Lee, C. E. Song, D. Y. Chi, *Bull. Korean Chem. Soc.* **2000**, *21*, 860-866, B) N. S. Mani, M. Wu, *Tetrahedron: Asymmetry* **2000**, *11*, 4687-4691, C) J. D.

White, P. Hrnciar, F. Stappenbeck, *J. Org, Chem.* **1999**, *64*, 7871-7884, D) J. D. white, Y. Choi, *Org. Lett.* **2000**, *2*, 2372-2376, E) B. T. Smith, J. A. Wendt, J, Aube, *Org. Lett.* **2002**, *4*, 2577-2579.

Chapter 2 – Synthetic studies toward Adriatoxin

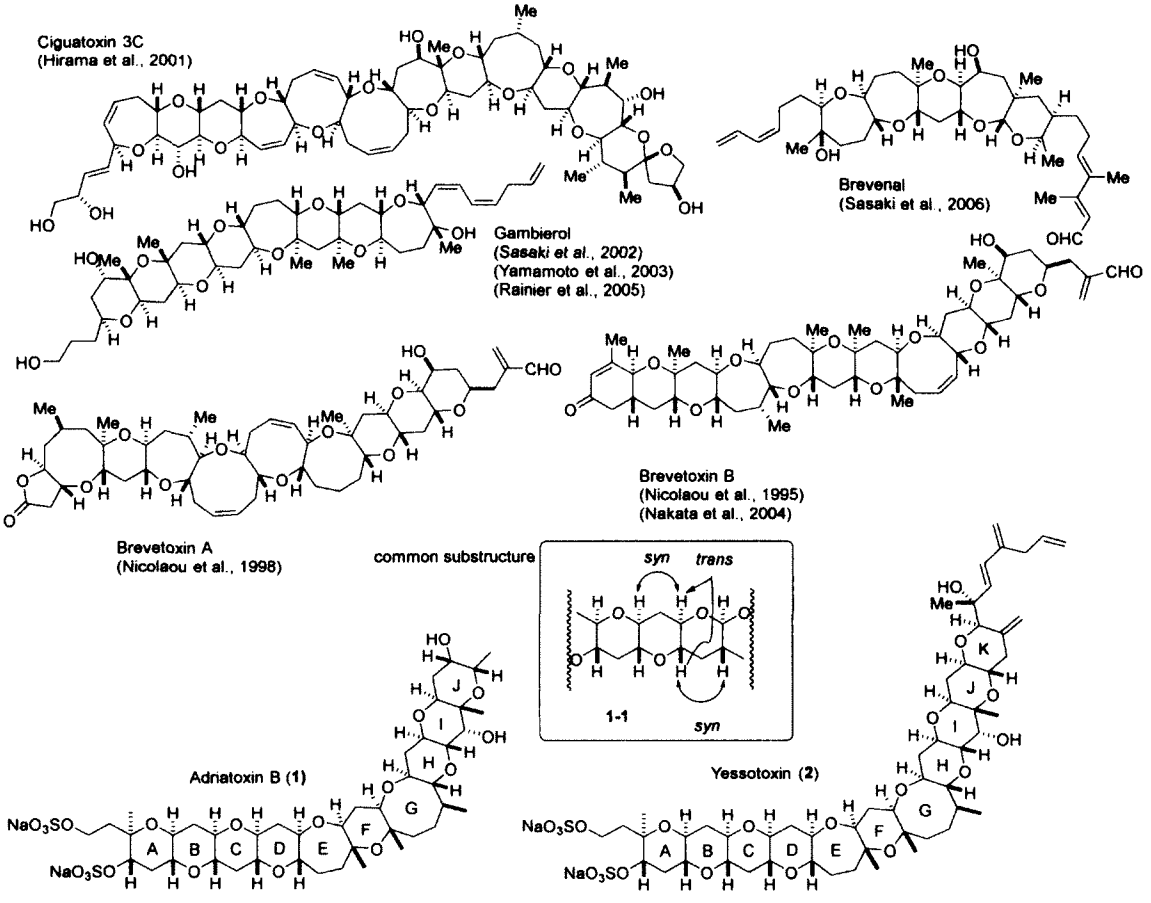
2.1 Introduction

Marine organisms have proven to be one of the richest reservoirs of interesting natural products in terms of molecular architectures and potent biological activities.[1] One class of that stands out in terms of structure and activity are the ladder polyethers (Figure 2-1).[2] This family of marine natural products has spawned a large field involving chemists and biologists interested in probing biological activities including toxic effects from red-tide and seafood poisoning, as well as the pursuit of complex structures from the point of view of synthetic chemists.[3] Each natural product in this class is identified by the presence of *syn-trans-syn*-fused cyclic ethers (**1-1**) in an alternating fashion, with ring sizes from 5- to 9-membered cyclic ethers (Figure 2-1).

Adriatoxin B (**1**), a member of the yessotoxin family of ladder polyether natural products, was isolated in 2010 by North, Daranas, and Fernandez.[5] Adriatoxin was isolated from dianoflagellate *Protoceratium reticulatum* and is distributed through the food-chain readily. Many of the yessotoxin family have been associated with diarrhetic shellfish poisoning (DSP), although the data is equivocal with regard to cause, while other members have shown potent anti-cancer activity.[6] Adriatoxin is also known to have an apoptotic effect that is mediated by a mitochondrial signal transduction pathway although details are lacking.[5] Although some studies point to a mechanism related to phosphodiesterase interaction, the precise mode of action is still unknown and there is little biological coherency to the current phenotypic effects observed.[7] Adriatoxin shares a common *trans-syn-trans* polycyclic framework all other members of the polyether family, but is most similar to yessotoxin, having the identical backbone frameworks from ring A to J except ring K and the unsaturated side chain (Figure 2-1). The ladder shape polyether backbone decorated with saturated or unsaturated aliphatic chain, oxygenated, or spirocyclic functionalities.

An efficient synthesis of adriatoxin, and other related natural products, would provide an excellent platform to understand mode of action questions for the marine ladder polyether toxins. Indeed, this general idea has been widely accepted with the synthesis community and a large number of synthetic studies directed at the synthesis of these compounds as potential therapeutics or to molecules that may illuminate biology have been published.[4]

Figure 2-1 Marine ladder-shape polyether.

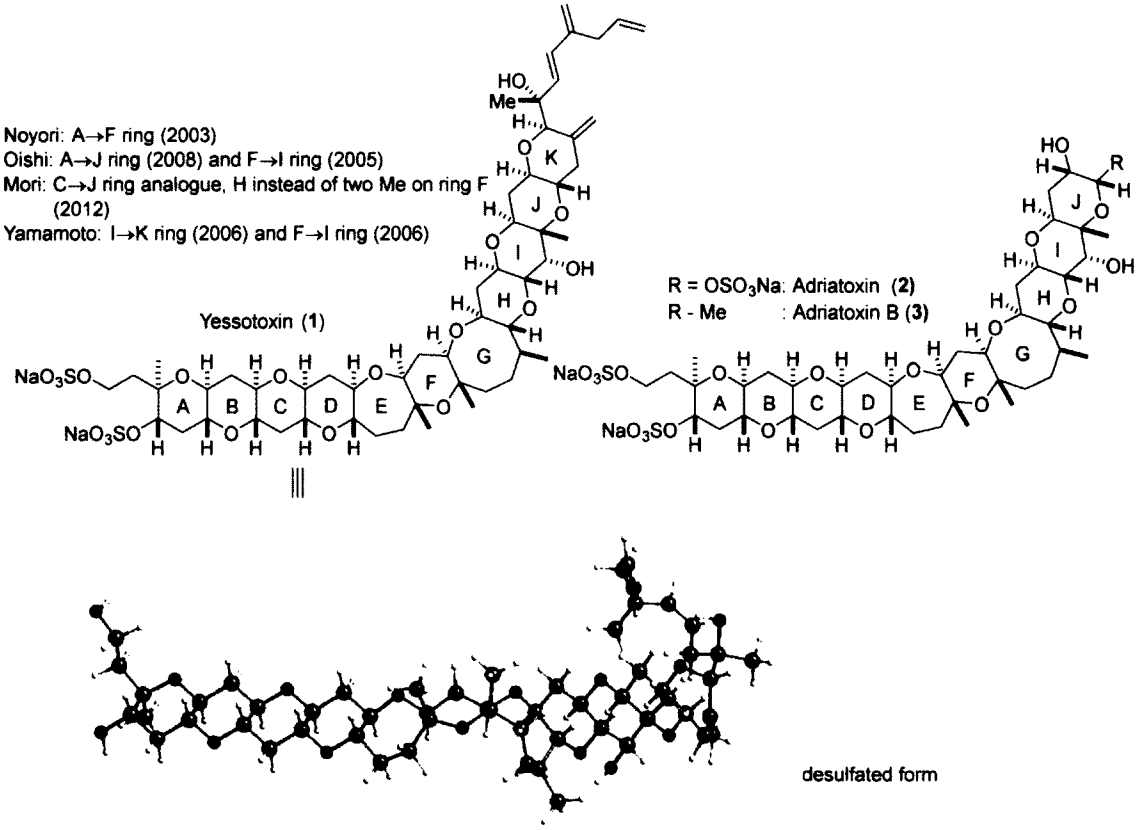


2.2 Other synthetic studies directed at Yessotoxin and Adriatoxin

To date no total syntheses of Adriatoxin and Yessotoxin have been reported. However, syntheses of various subunits containg 2 or 3 of the fused rings have been published.[12] The most

significant work has been by Noyori[8], Oishi[9], Mori[10], and Yamamoto[11] (Figure 2-2). Although these studies have provided some foundations, the synthesis community still has several major challenges to address in order to complete these molecules. Our analysis of the features of the yessotoxin-adriatoxin family identified three main challenges: (a) the need for streamlined subunit couplings, (b) the 2,6-*syn*-dimethylpyran (F ring), and (c) the likelihood of a lengthy overall synthesis. In order to consider these challenges fully, some background is provided in the next 3 sections.

Figure 2-2 Synthetic studies by others on adriatoxin and yessotoxin and calculated conformation.[28]



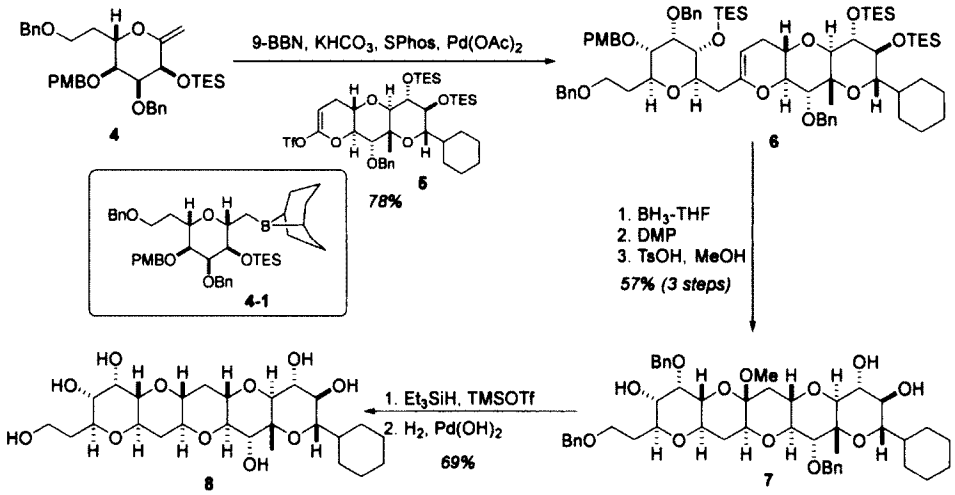
2.2.1 Synthetic precedents for subunit coupling

The ladder polyethers have provided numerous examples and opportunities for the development of subunit coupling stratgeies. An exhaustive review has been provided by Nakata and Sasaki[30] and here only selected examples are given so as to provide context for our studies. Simialr material is also provided for worth the impacts the other two key questions above.

a. Subunit couplings by Pd-mediated *B*-alkyl Suzuki coupling

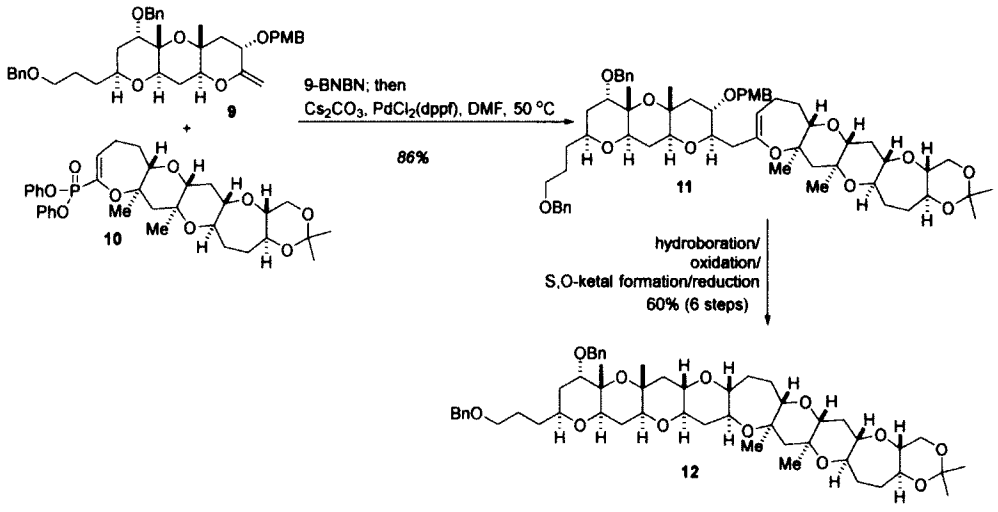
The Nicolaou group used a Pd-catalyzed cross coupling to connect the G-ring (**4**) and IJK subunit **5** in a report directed toward the synthesis of maitotoxin.[13] The key transformation and steps needed to complete the synthesis of the GHIJK ring system **8** are shown in Scheme 2-1 Hydroboration of the G-ring alkene **4** with 9-BBN in THF at 50 °C furnished an intermediate alkylborane (**4-1**) which underwent smoothly a *B*-alkyl Suzuki-Miyaura coupling with vinyl triflate **5** in the presence of catalytic $Pd(OAc)_2$, SPhos ligand, and $KHCO_3$ to afford tetracycle **6** in 78% yield. Subsequent hydropboration, oxidation, acetalization and reduction steps led to compound **8**.

Scheme 2-1 Nicolaou's Pd cross coupling.



In a related example, the Sasaki group also used a Pd-catalyzed cross coupling in their synthesis of Gambierol. Hydroboration of exocyclic enol ether **9** with 9-BBN generated the intermediate alkylborane, which reacted in situ with the EFGH-ring ketene acetal phosphate **10** in the presence of $PdCl_2(PPh_3)$ and aqueous Cs_2CO_3 in THF/DMF at 50 °C.[14] The desired crucial cross-coupling product **11** obtained in 86% yield. Six steps that parallel the Nicolaou work above then advanced **11** to **8** in 60% overall yield.

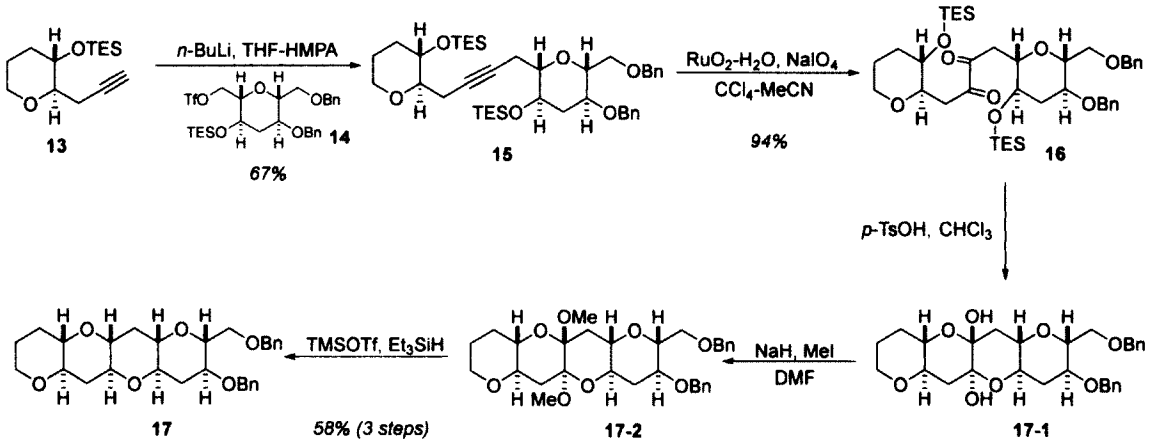
Scheme 2-2 Sasaki's Pd cross coupling.



b. S_N2 alkylation

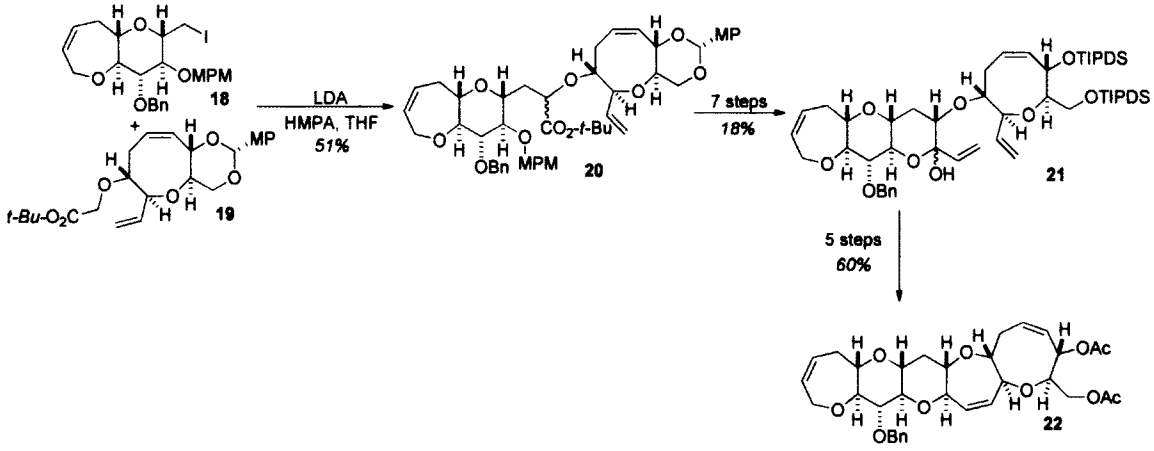
In early work directed at developing new ways to produce poly-pyran containing systems, Mori developed a highly convergent method for the synthesis of *tran*-fused polyethers. This method involves three keys steps that are exemlified in Scheme 2.3: i. coupling of triflate **14** with an acetylide derived from **13,** ii. oxidation of the acetylene **15** to 1,2-diketone **16** using RuO_2 and $NaIO_4$ and iii, the formation of a *trans*-fused bis-hemiacetal, **17-1**. Subsequent *O*-methylation (**17-2**) and ionic reduction produced t*rans*-fused tetrapyran **17**.[15]

Scheme 2-3. Mori's alkyne alkylation with tliflate and terminal alkyne.



The Hirama group has also reported a subunit coupling method based alkylation as a central transformation.[16] The lithium enolate of *t*-butyl ester **19**, generated by treatment with LDA, reacts with iodide **18** in the presence of HMPA to give alkylated adduct **20** in 51% yield. Although a nice approach to the formation of a difficult bond, the product requires significant manipulations to arrive at the fully-formed tetracycle. This 12 step sequence begins with lactone formation and includes the addition of a vinyl group to give a hemi-ketal. Ring-closing metathesis is an effective approach to the ring-closure and ultimately leads to the fully-formed A→E ring system (**22**) of ciguatoxin CTX3C.

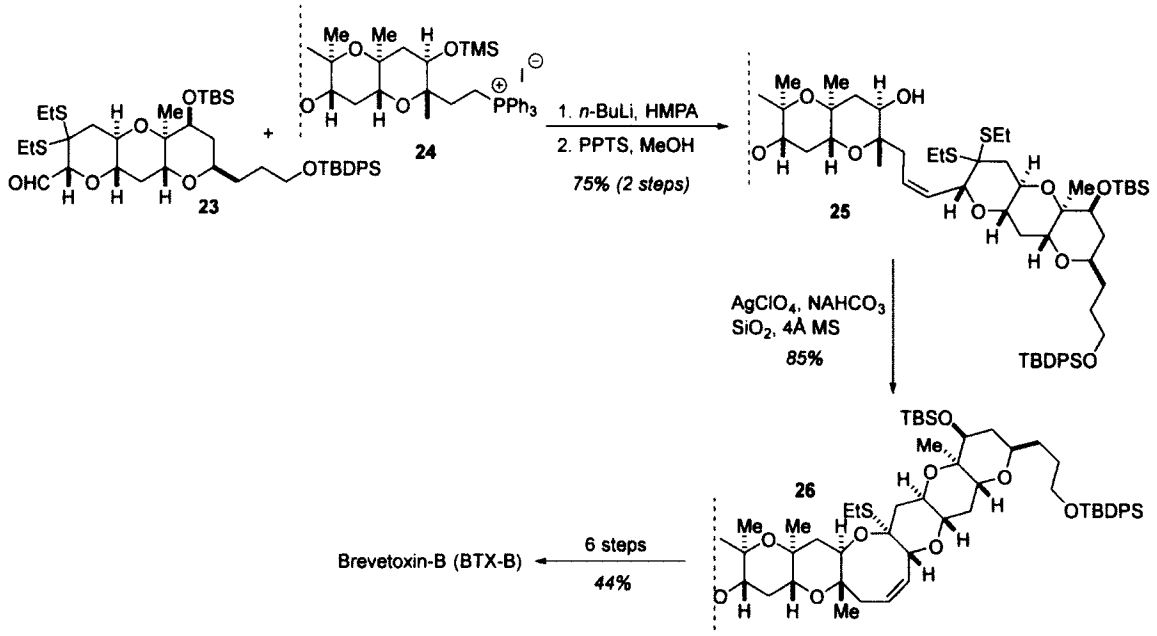
Scheme 2-4 Hirama's enolate alkylation strategy.



c. Other methods

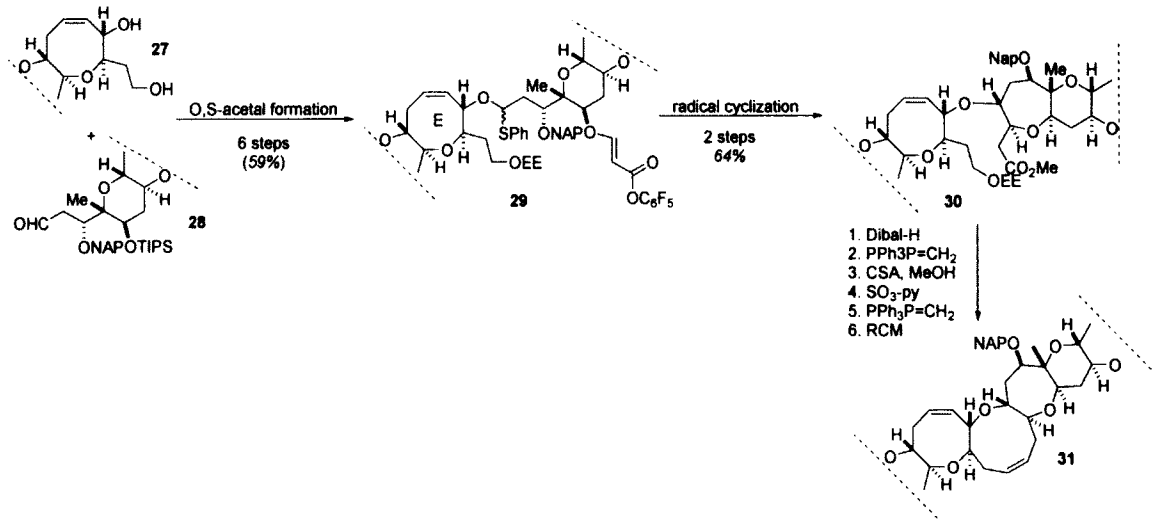
In one of the most direct approaches known (and also one of the earliest published), Nicolaou used a Wittig olefination between the phosphonium salt **24** and aldehyde **23** to produce (*Z*)-olefin **25** in 75% yield (over two steps including TMS deprotection). This reaction played a central role in Nicolaou's prototypical total synthesis of brevetoxin, BTX-B.[16] The most major drawback of this approach is the lack of general applicability to other ring sizes, and the additional challenges of forming moisture sensitvie phosphonium salts from complex molecules and engaging them in Wittig olefinations can not be overlooked.

Scheme 2-5 Nicolaou's Wittig olefination coupling.



Hirama has reported a novel coupling method using a sequence of *O,S*-acetal formation, radical cyclization, and RCM as a part of his ciguatoxin, CTX3C synthesis (Scheme 2-6).[18] Diol **27** and aldehyde **28** can be connected by acetalization during a 6 steps sequence that leads to linear *O,S*-acetal **29,** which can be readily cyclized by a 7-exo radical cyclization to form **30.** Further manipulations over 5 steps including RCM gave **31.** This compound was ultimately integrated into the complete total synthesis, a landmark acheivement in the field of polyether synthesis (65 steps LLS, 119 steps overall).[18b-d]

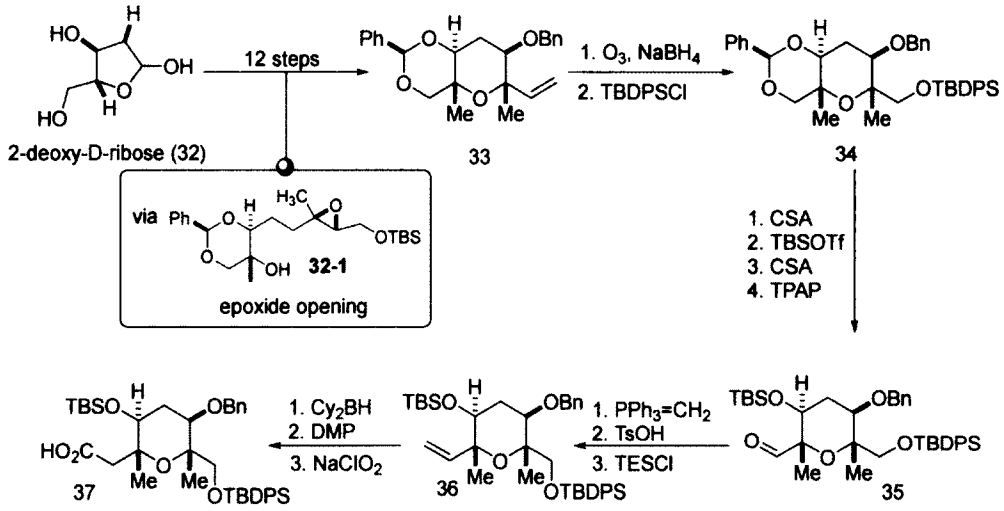
Scheme 2-6 Hirama's O,S-acetal formation coupling.



2.2.2. Construction of 2,6-*syn*-dimethylpyrans

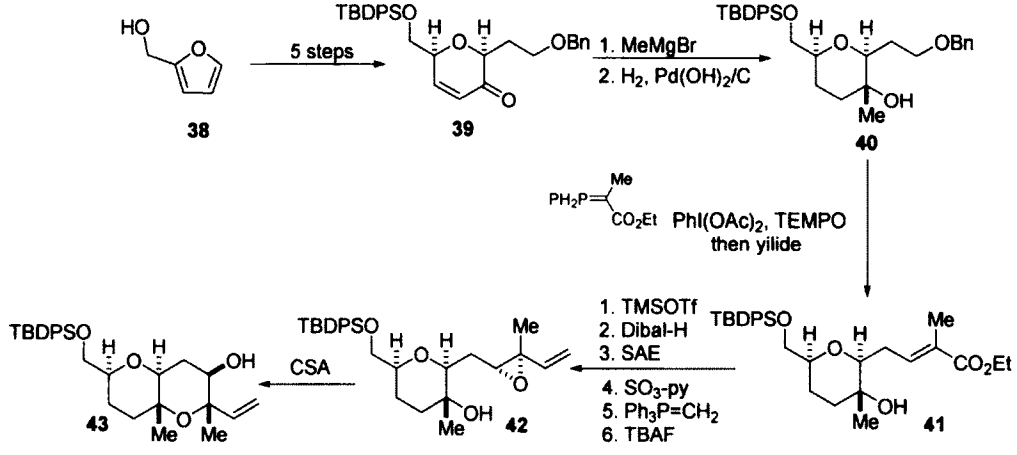
The 2,6-syn-dimethyl pyran ring found in adriatoxin as the F-ring, and in other polyethers, is a susbtantial challenge for synthetic chemistry, and there are only two published strategies/ methods for the synthesis of this type of compound. A sugar-derived strategy is found in Nicolaou's synthetic studies directed at a synthesis of Maitotoxin.[19] Construction of the fully functionalized 2,6-dimethyl pyran **37** was accomplished by a sequence of 24 steps (8% overall yield) from 2-deoxy-D-ribose **32** described in Scheme 2-7. The initial steps of the synthesis involve extensive manipulations of 2-deoxy-D-ribose to arrive at intermediate **32-1**, which is poised for an intramolecular 6-exo S_N2 reaction to form the pyran, **33**. Straightforward manipulations advance **33** to a substrate competent for subunit coupling, compound **37**. Beyond the length of the synthetic sequence, it is worth noting the cost of 2-deox-D-ribose (~$10 per gram, Sigma-Aldrich, April 2, 2014).

Scheme 2-7. Nicolaou's 1,3-dimethyl pyran formation.



Nicolaou has also provided a related example as part of the CDEF-ring subunit synthesis of Maitotoxin.[20] This strategy leverages the Phillips-Jackson-Henderson strategy for the conversion of furans to 2,6-*syn* pyranones in the early stages of the synthesis, which embarks in earnest from compound **39** (Scheme 2-8). Addition of methylmagnesium bromide and reduction gives compound **40**, which is readily advanced to **41.** At this juncture, the stage is set to install a vinyl epoxide for a stereoselective epoxide opening reaction with an adjacent oxane as a template. The key reaction involving CSA-catalyzed conversion of **42** to **43** proceeds in 94% yield.

Scheme 2-8. Nicolaou's epoxide opening for 1,3-dimethyl pyran.



These two examples underscore the challenge, and to date all cases for the functionalized 2,6-*syn*-dimethyl pyran ring in a synthesis of ladder polyether relies on a sequence of Sharpless asymmetric epoxidation on allylic alcohol followed by intramolecular epoxide opening reaction with tertiary alcohol derived ultimately from sugar or furfuryl alcohol starting materials. There are no concise solutions to this problem and the current strategies present practical challenges as well as underscoring inefficiencies in step count.

2.2.3. Overall length of polyether syntheses.

Based on published syntheses for related molecules, the biggest challenge to constructing targets of the complexity of Adriatoxin or Yessotoxin will be step count on the longest linear sequence. Although the polyethers have attracted substantial attention from the synthesis community, questions that relate structure to biology cannot at this juncture be answered: the simplest members require ~40 steps (longest linear sequence) and ~10 steps per ring defines the current state of the art (Figure 2-3). For example, Isobe's CTX-1B synthesis required 175 total steps, at a cost of 13.5 steps on average for each of the 13 rings, and involved a 77 steps longest linear sequence. A molecule of the complexity of adriatoxin, although not yet synthesized, could be expected to require ~100 steps (longest linear sequence) based on 10 rings and ~10 steps per ring. This analysis provided much imeptus for us to define goals directed at developing new, scalable, and convergent methodologies for polyether synthesis and ultimately we aimed at ~5 steps per ring for adriatoxin B. Investments made in this development phase provide a foundation from which explorations along biological lines with the class of interesting molecules will hopefully become possible.

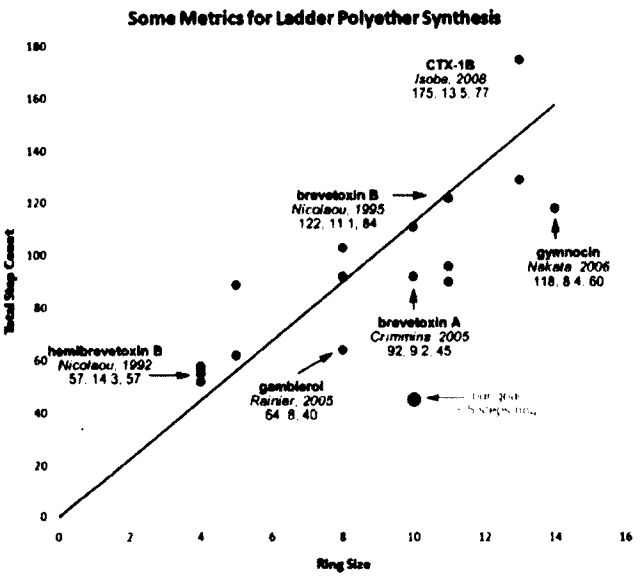


Figure 2-3 Ladder Polyether metrics. Completed total syntheses are described by total steps/steps per ring/longest linear sequence.

2.3. Preliminary study toward polyether compound.

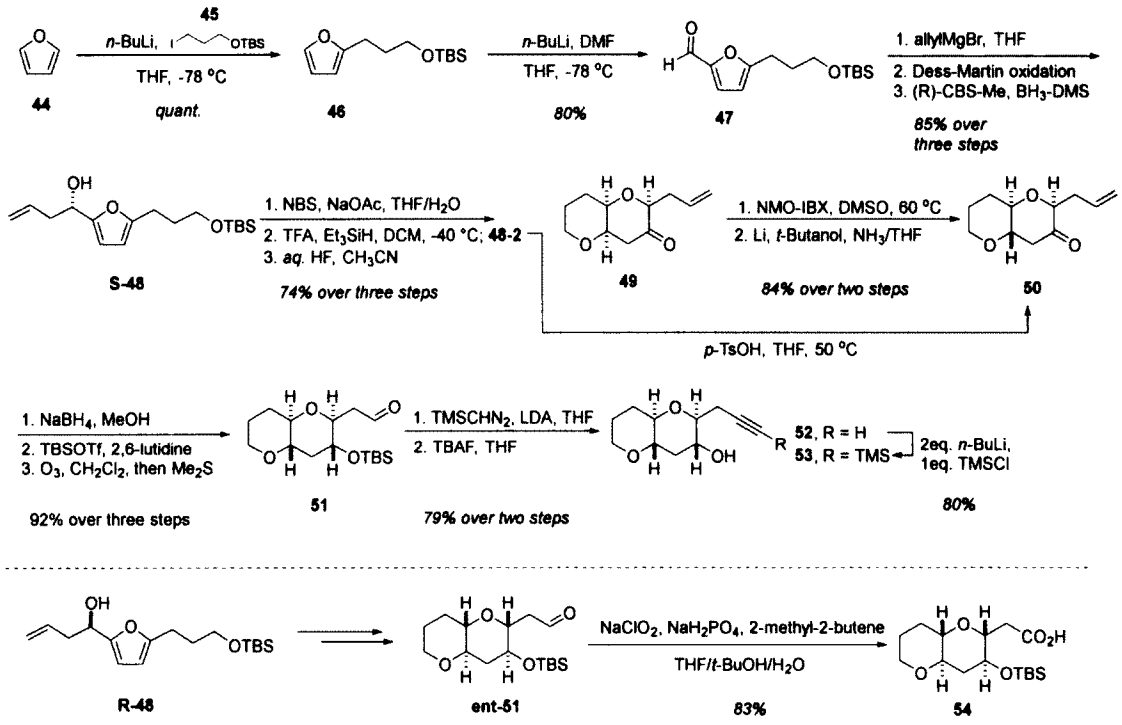
2.3.1. Construction of model systems by Achmatowiz and ionic reduction.

The underlying technology for the construction of building blocks for model studies used here is a combination of an Achmatowicz reaction and ionic reduction (Kishi reduction) to convert furans to saturated heterocycles. James Henderson, a former Phillips group member (PhD, 2007), discovered in the spring of 2005 that a reaction sequence of Achmatowiz oxidation and Kishi's ionic reduction is a highly efficient and direct way to construct pyranones. Subsequent work by Nolan Griggs (PhD, 2008) expanded the utility of this process to the synthesis of *cis*- and *trans*-pyranopyrans. The overall strategic utility of these reactions in complex molecule synthesis was shown by Katrina Jackson (PhD, 2007) in the total synthesis of norhalichondrin B.

The model system to explore subunit coupling and other methodologies for polyether molecules was synthesized easily as shown in Scheme 2-9. Compounds (*S*)-**48** and (*R*)-**48** were derived from furan in five known steps including alkylation, lithiation-formylation of furan, and

asymmetric reduction in 72% overall yield. An equally viable approach is to employ asymmetric Brown allylation of aldehyde **46**. Sequential treatment of furan **48** with NBS, TFA-Et_3SiH, and finally acid provided **49** in 75% overall yield. The final step of this sequence - deprotection of the TBS ether with HF and acid-mediated hetero-conjugate addition - produces a single *cis-syn*-diastereomer of the product. Transformation to the *trans*-pyranopyran **50,** albeit in a poor yield, could be accomplished by haeating for exteded periods in the presence of p-TsOH or by a two step protocol developed earlier by Noan Griggs. Treatment of *cis*-pyranopyran **50** to NMO-IBX complex gave α-β unsaturated ketone.[21] The resulting crude material was then subjected to Birch-type reducition conditions to form the *trans*-pyranopyran **50**. Pyranopyran **50** was then reduced with $NaBH_4$ to give the hydroxyl group having *trans-cis* relative stereochemistry. The hydroxyl group was then protected as the TBS ether and the resulting material was ozonized to give aldehyde **51** in a 72% yield over three steps. Alkyne **53**, a projected partner for a coupling reaction between an alkyne and an ester, was made in three steps from aldehyde **51** with 51% overall yield. Carboxylic acid **54**, the other coupling subunit, was derived from aldehyde **ent-51**, which came from **(R)-48** using the same sequence, and a final step Lindgren-Pinnick oxidation to form carboxylic acid **54**.

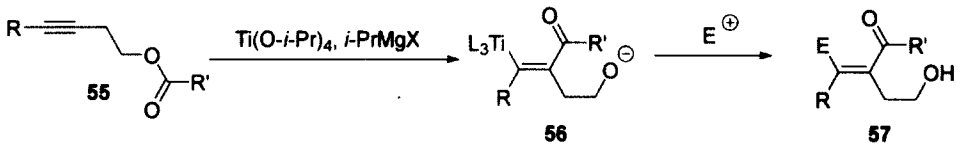
Scheme 2-9. Pyranopyran synthesis.



2.3.2. Subunit couplings to make polyethers using Ti(II)-mediated reactions.

The overall goal of intial studies in this area was to establish the Sato-type intramolecular nucleophilic acyl substitution (INAS)[22] as a method for the coupling of complex pyran subunits. In this reaction, a Ti(II) species formed in situ by reduction of a Ti(IV) alkoxide presumably coordinates to the alkyne and generates a strained titanacyclopropene intermediate (Scheme 2-10). The presumed strain in the intermediate is typically invoked to explain the higher than expected nucleophilicty of organotitanium reagents of this type – a characteristic that extends to esters as electrophiles. The reaction conditions are very mild and extensive work by Sato has shown the excellent selectivity for alkynes and esters as reacting functional group. Despite these features, the INAS reaction has seen little use in complex molecule in the period since it was first described by Sato in the late 1990's.

Scheme 2-10 Ti(II)-mediated INAS.

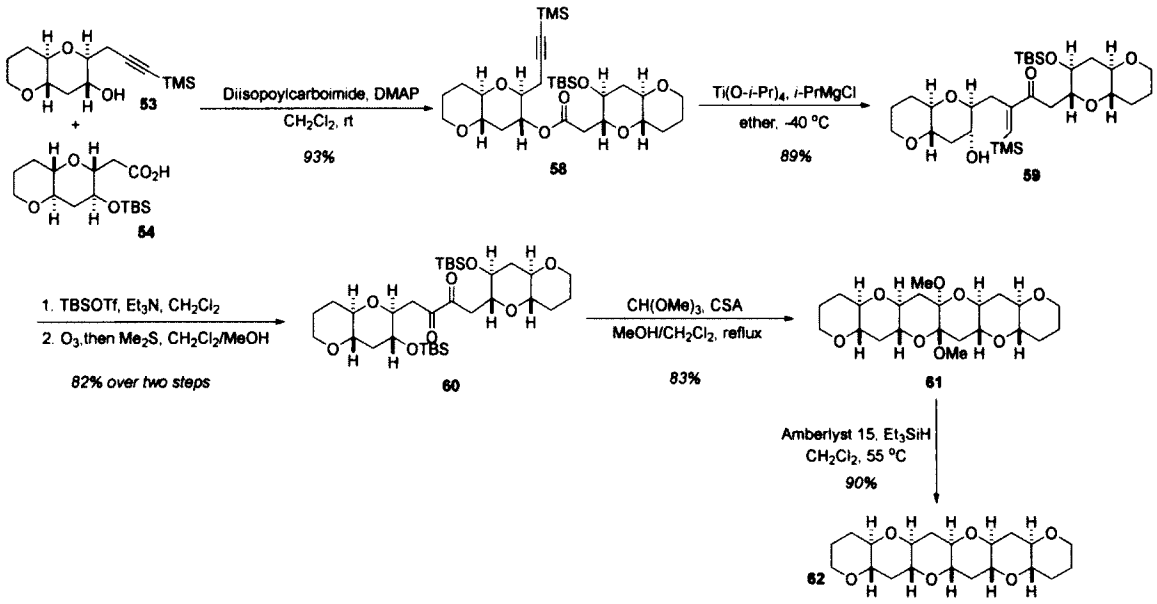


We imagined that this reaction might provide an excellent overall way to fashion a crucial CC bond between two polyether subunits that has been previously connected by ester formation. The implementation of this plan is shown in Scheme 2-11. A simple esterification between alkyne **53** and carboxylic acid **54** gave ester **58**, and when subjected to Ti(II)-mediated intramolecular nucleophilic acyl substitution (INAS), enone **59** was produced in excellent yield.

This reaction was studied extensively during the work described in this chapter, and a number of observations can be summarized here: (a) freshly prepared *i*-PrMgCl was the best reducing reagent among *c*-HexMgBr, EtMgBr, and *n*-BuLi, (b) $Ti(O\text{-}i\text{-}Pr)_4$ consistently gives better yields than $TiCl(O\text{-}i\text{-}Pr)_3$, (c) the reaction was sensitive to the reaction temperature: formation of the Ti(II) species should be commenced at -40 °C and after addition of the Grignard reaction, the reaction should be allowed to warm to 0 °C over 40 min; after recooling to -40 °C the alkyne ester **58** can be added and the overall dark mixture was allowed to warm to -10 °C and stirred for 3hr.

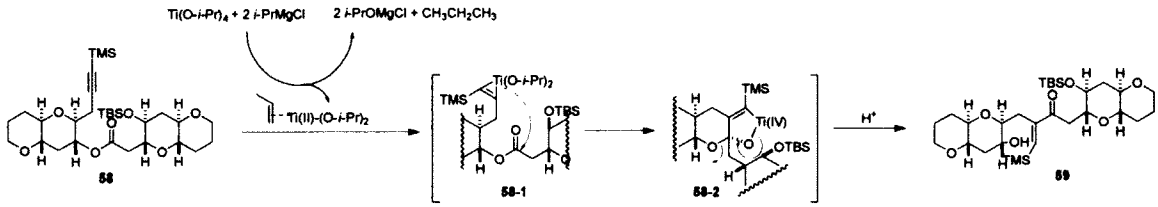
The enone produced by the INAS reaction could be readily advanced to a polycyclic ether (Scheme 2-11). An alcohol protection and ozonolytic cleavage of the enone **59** gave diketone **60**, which yielded the mixed methyl acetal **61** after treatment to CSA and $CH(OMe)_3$. Hexapyran **62** was then obtained by ionic reduction of the mixed methyl acetal **61** with Amberlyst 15 ion exchange resin and Et_3SiH. Overall, two further pyran rings are formed and importantly this strategy provides complex polyethers at an average step count of ~2.5-3 steps per ring. This represents a substantial improvement over the current state of the art.

Scheme 2-11. Coupling reaction by Ti(II)-mediated INAS.



Although mechanistic studies on Ti(II)-based organometallics are scant, it is possible to hypothesize that the reduction of Ti(O-*i*-Pr)$_4$ by *i*-PrMgCl forms an active Ti(II)-species (Scheme 2-12). Subsequent addition of an alkynyl ester as substrate presumably results in an titanocyclopropene complex **58-1** (at an alternative limiting description, this could be imagined as an η^2-acetylene-titanium complex) which acts as nucleophile toward the adjacent ester. Enone **59** is ultimately formed by protonation of the intermediate vinyltitanium species.

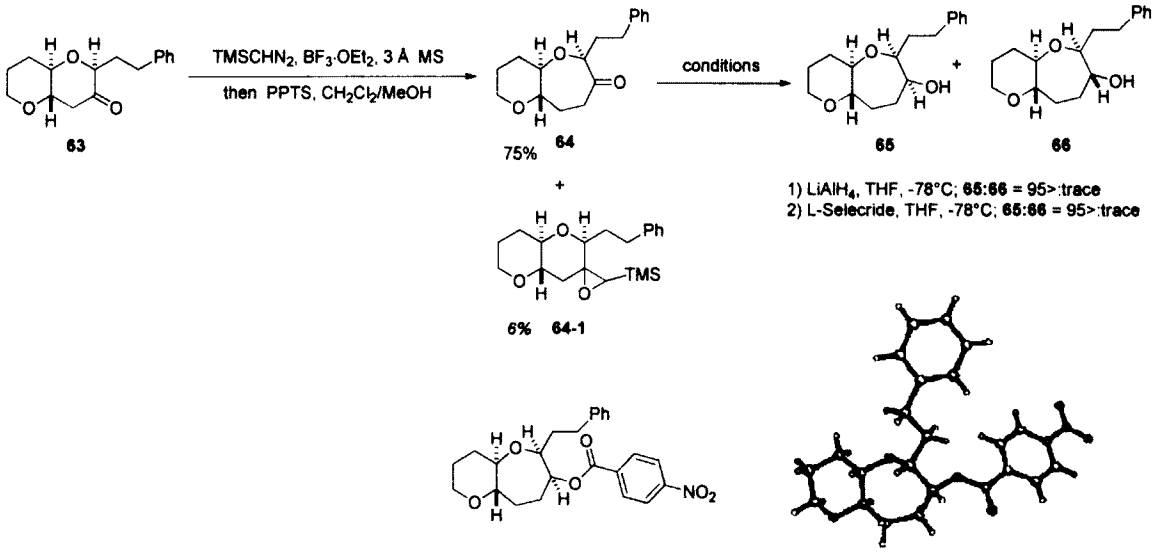
Scheme 2-12. Mechanism of Ti(II)-mediated INAS.



2.3.3. Connecting straightforward pyranone synthesis with larger rings: strategies for ring expansion.

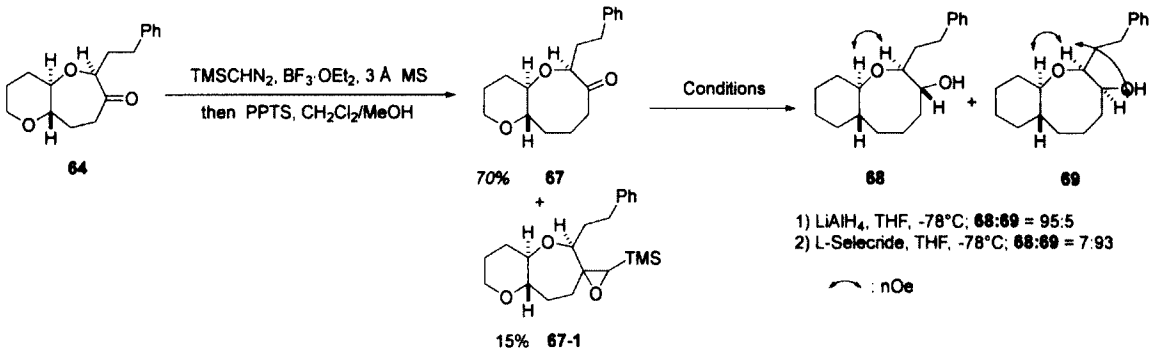
With a strategy to couple subunits together established, attention turned to examining ways to expand pyranone rings to larger ring systems. It was envisaged that success in this direction would provide an excellent way to build on the direct synthesis of pyranones available from furans. Pyranopyran **63**, which prepared by the sequence of Achmatowicz oxidation and ionic reduction can be readily expanded to the pyranooxepane ring system **64** by using TMS-diazomethane (Scheme 2.13).[23] Reduction of ketone **64** using LAH or L-Selectride® gave alcohol **65** in a *trans-cis* relationship. The stereochemistry of this compound was determined by X-ray analysis on the *p*-nitrobenzoyl derivative.

Scheme 2-13. Ring expansion using $TMSCHN_2$.



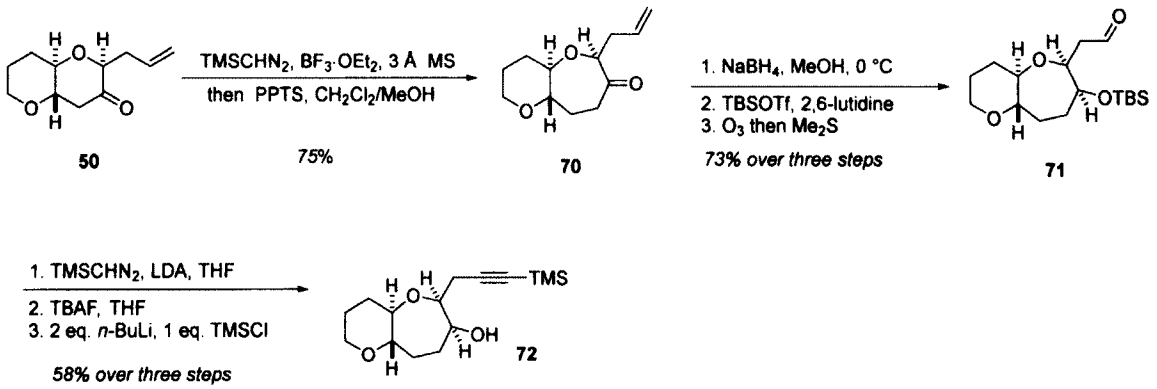
In related work, it was also established that the ring expansion of the pyranooxepane **64** to pyranooxocane **67** is possible (Scheme 2-14). Reduction of ketone **67** using LAH and L-Selectride® gave alcohol **68** and **69** as a major products respectively (as determined by nOe experiments).

Scheme 2-14. Ring expansion using $TMSCHN_2$.



We these results in hand, studies were initiated to connect ring-expansion strategies with the INAS-subunit coupling strategy. Pyranopyran **50** was treated to the ring expansion condition and produced the desired pyranooxepane **70** in 75% yield (Scheme 2-15). Reduction of ketone **70** with $NaBH_4$ gave a *tran-cis-cis* pyranooxepane that was protected and then ozonized to give 71 (73% over three steps). Alkyne formation, deprotection, and alkyne protection with TMS produced alkyne coupling subunit **72**.

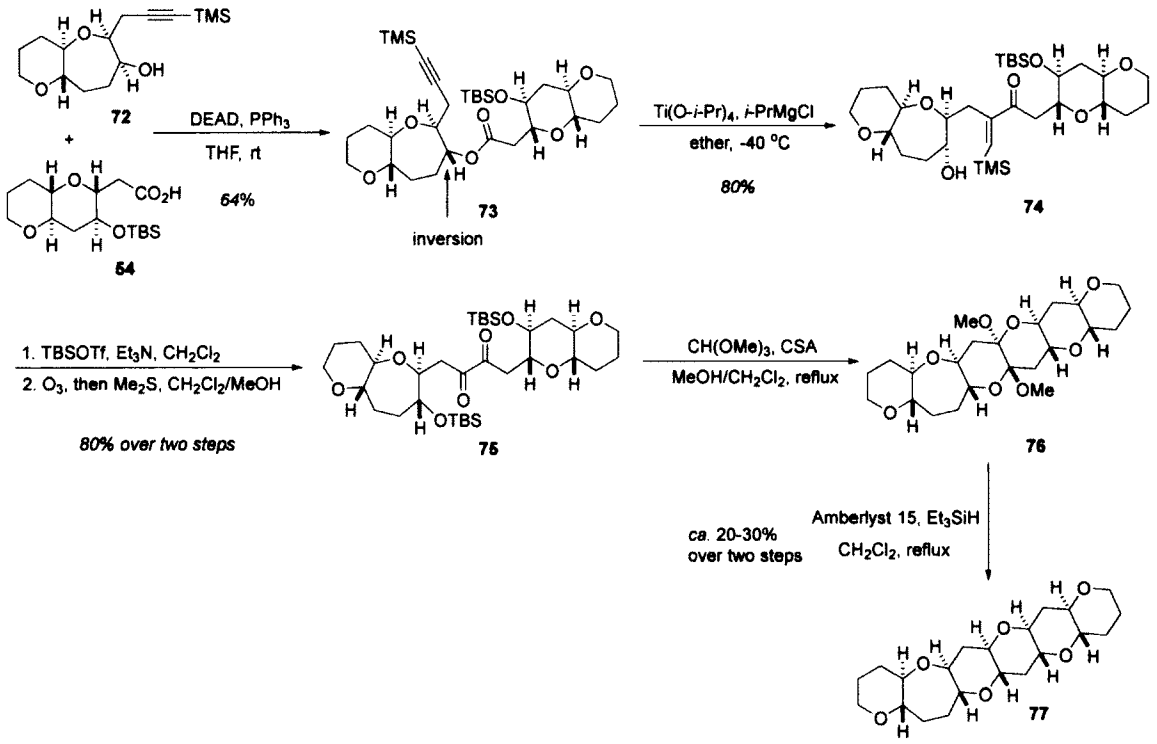
Scheme 2-15 Model system-pyranooxepane.



The application of the Ti(II)-mediated strategy to the connection of pyranooxepane **72** and pyranopyran **54** also occurs smoothly (Scheme 2-16). In this case, the connection of the two subunits initially occurs by Mitsunobu reaction to set the desired *cis-trans* stereochemistry on oxepane system. Subsequent Ti(II)-mediated INAS under the conditions developed earlier gives

enone **74** in an excellent 80% yield. The enone **74** was advanced to dikeotn **75** by TNS protection and ozonolysis reaction. The two step procedure including cyclix ketal formation (**76**) and inonic reduction provided hexacyclic system **77** in 20-30% yield. The last ionic reduction step needs an optimization in terms of LA, solvent, and reaction temperature for better yield and selectivity.

Scheme 2-16. Coupling reaction using INAS.



2.3.4. Novel strategies for the syntehsis of 2,6-*syn*-dimethyl pyrans

2,6-*syn*-dimethyl pyran is a common moiety in many ladder polyether toxins (Figure 2-4). The current practical synthetic method for the *syn*-dimethyl pyran from 2-deoxy-D-ribose or furfuryl alcohol (Scheme 2-7 and 2-8) is based on epoxide opening chemistry which was developed by Nicolaou.[19, 20] The difficulty involved in setting two *syn*-dimethyl groups on a pyran subunit adds length the overall synthetic sequence and necessitates complex retrosynthetic strategy for this class of molecules.

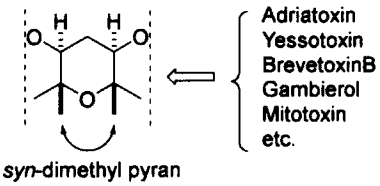
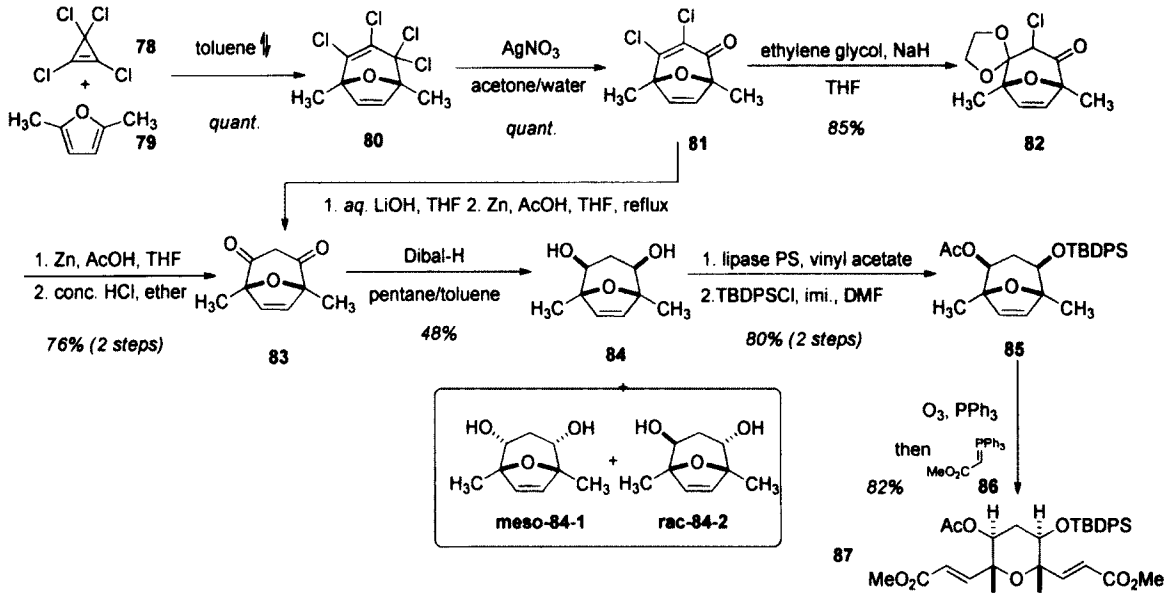


Figure 2-4. Subunit of syn-dimethyl pyran in polyether natural products

In this section, a very short and efficient route to access this subunit is described that exploits the cycloaddition of dimethylfuran with tetrachlorocyclopropene (Scheme 2-17). Tandem Diels-Alder cycloaddition and electrocyclic ring-opening of tetrachlorocyclopropene **78** and 2,5-dimethylfuran **79** gave compound **80** in quantitative yield.[24] Compound **80** is advanced to the 1,3-diketone **83** by a four step sequence consisting of: (i) solvolysis and trapping of the carbocation intermediate by use of $AgNO_3$ and water (**80** -> **81**)[24], (ii) protection of ketone with 1,3-dioxolane (**81** -> **82**), (iii) dechlorination with Zn and acetic acid, (iv) deprotection of 1,3-dioxolane. Although not as direct as some possible alternatives e.g. hydrolysis to the chlorodiketone and direct reduction, this sequence can be scaled to >10g and is reliable and robust.

Scheme 2-17. Synthetic route for 1,3-dimethyl pyran.



Stereoselective reduction of diketone **83** with DIBAL-H in pentane and toluene gave the *meso-syn*-diol **84** as a major diastereomer. The use of pentane and toluene (v/v = 10:1) was essential in ensuring a reasonable amount of the desired diastereomer (2.4:0.9:1 = desired *syn*-diol **84**: undesired *syn*-diol **84-1**: *anti*-diol **84-2**). Nucleophilic hydride reagents (e.g. L-Selectride®, Red-Al®, $LiBH_4$, $LiEt_3BH$, and $NaBH_4$ without $CeCl_3$) resulted in both poor stereoselectivities and yields (Table 2-1).

Table 2-1 Stereoselectivity of diketone reduction.

	Meso - **84**	Meso - **84-1**	Racemic - **84-2**
LAH, ether	1	1	1
NaBH4, $CeCl_3$, MeOH	trace	7.7	1
$TiCl_4$, Et_3SiH, CH_2Cl_2	trace	22	1
DIBAL-H, CH_2Cl_2	1	1	1
DIBAL-H, toluene/pentane (1:10)	2.4	0.9	1

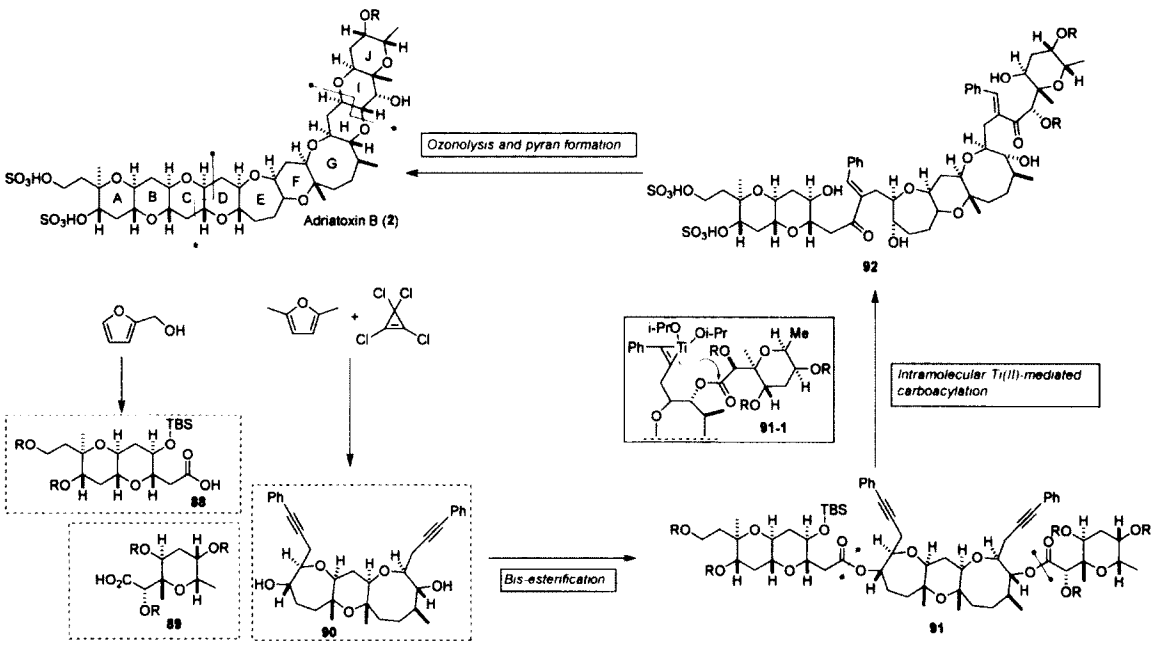
All reactions at -78 °C. Ratio of diastereomers from analysis of crude NMR.

In order to differentiate between the two alcohols in *meso*-diol **84**, enzymatic resolution was employed using of Lipase PS and vinyl acetate to yield the enantiomerically pure mono-acetylated alcohol. After TBDPS protection (**85**) of the remaining alcohol, a simple one-pot reaction of ozonolytic cleavage, followed by either Wittig or Horner-Wadsworth-Emmons olefination (**86**) afforded functionalized *syn*-dimethyl pyran **87**. The synthetic protocol (**78**+**79**→**85**) described in Scheme 2-17 can be applied to other combinations of reactions to produce obvious derivatives (e.g. ozonolysis/$NaBH_4$, ozonolysis/alkyne formation with Bestmman's reagent etc.). This newly developed synthetic sequence stands as the shortest and most practical method for the synthesis of 2,6-syn-dimethylpyrans of the type found in adriatoxin and other polyethers. The sequence as shown proceeds in 9 steps and is capable of producing amounts of compounds in excess of 10 grams without problem.

2.3.5. Overall length of synthesis.

Strategic analysis of adriatoxin B suggests that the most direct synthesis will likely explore the recognition of elements of local symmetry. Our approach is outlined in Scheme 2-18 and involves plans to implement a highly convergent coupling of subunits **88**, **89**, and **90** to give the bis-alkynyl ester **91**. Preliminary work described above supports the idea that it may be possible to implement a two-directional Ti(II)-mediated INAS reaction (via intermediates of general type **91-1**), followed by pyran formation to give the full carbon framework of adriatoxin B (**2**). Such an overall plan could be expected to provide adriatoxin by a route of ~25 steps. Studies toward this goal are described in the balance of this chapter.

Scheme 2-18. Two directional synthetic plan.



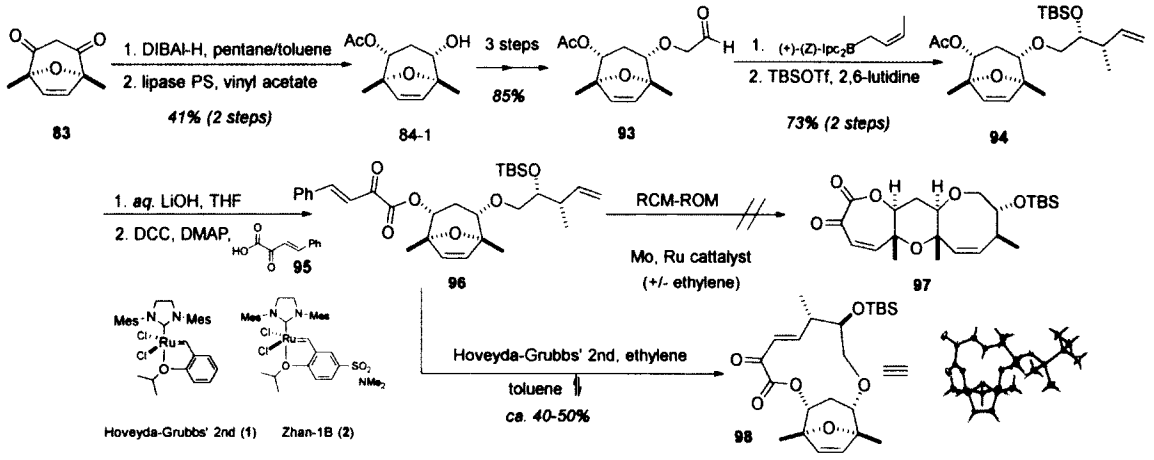
2.4 - Toward the synthesis of adriatoxin

2.4.1 - Study towards the synthesis of EFG ring system.

Efforts to capitalize on preliminary studies and move toward an adriatoxin total syntehsis commenced with studies of two-directional ROM-RCM strategies designed to connect the opening of oxabicyclo[3.2.1]octenes with the synthesis of adjacent rings. Our first strategy for the formation of EFG ring system was began with oxabicyclo[3.2.1]octene **96** (Scheme 2-19). If successfully implemented, this strategy would provide a remarkably rapid route to the desired central tri-cyclic precursor for the Ti(II)-mediated INAS coupling. Aldehyde **93** was synthesized in a three step sequence involving reductive etherification (cinnamaldehyde, Et_3SiH, FeCl3)[26], dihydroxylation (AD mix-α), and oxidative cleavage ($NaIO_4$) from enantiomerically pure alcohol **84-1**. Brown crotylation , followed by silyl protection gave compound **94** which was treated with *aq*. LiOH and a subsequent DCC coupling with acid **95** to afford two-directional ring-opening-ring-closing metathesis precursor **96**. It was envisioned that the two-directional ring-opening-ring-closing metathesis conditions derived using the model substrate in our lab would afford 7,6,8 tri-

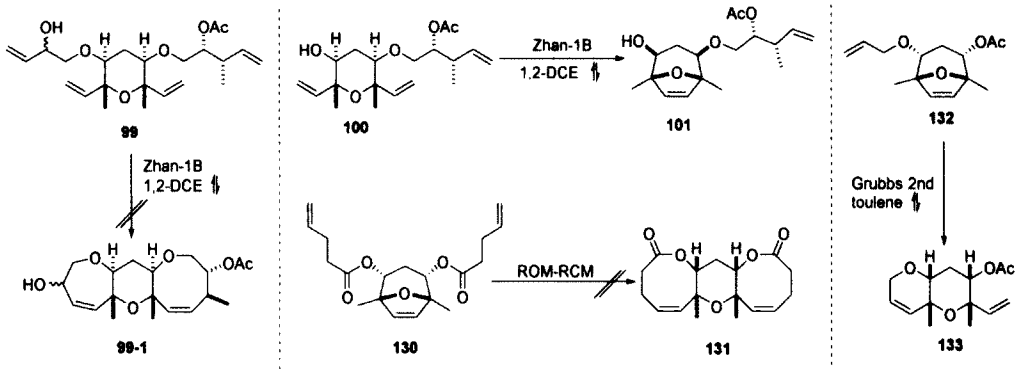
cyclic system **97**. However, all attempts to effect this transformation were unsuccessful, returning either **96** or producing undesired product **98**.

Scheme 2-19. Two directional ROM-RCM.



Efforts toward a two-directional RCM (**99→99-1**) were also unsuccessful (Scheme 2-20). Interestingly, the truncated compound **100** yielded bicyclo[3.1.2]octene **101** under Zhan-1B catalyst condition – underscoring the delicate balance of thermodynamics in these systems. The only successful result in ROM-RCM strategy was one directional ROM-RCM with octene **132** (not the needed stereochemistry for polyether natural products) to produce bis-pyran **133**. Overall, these studies delineated the lack of viability to an approach using an oxabicyclo[3.2.1.]octene, or compounds downstream, as starting materials for tandem metathesis or RCM reactions.

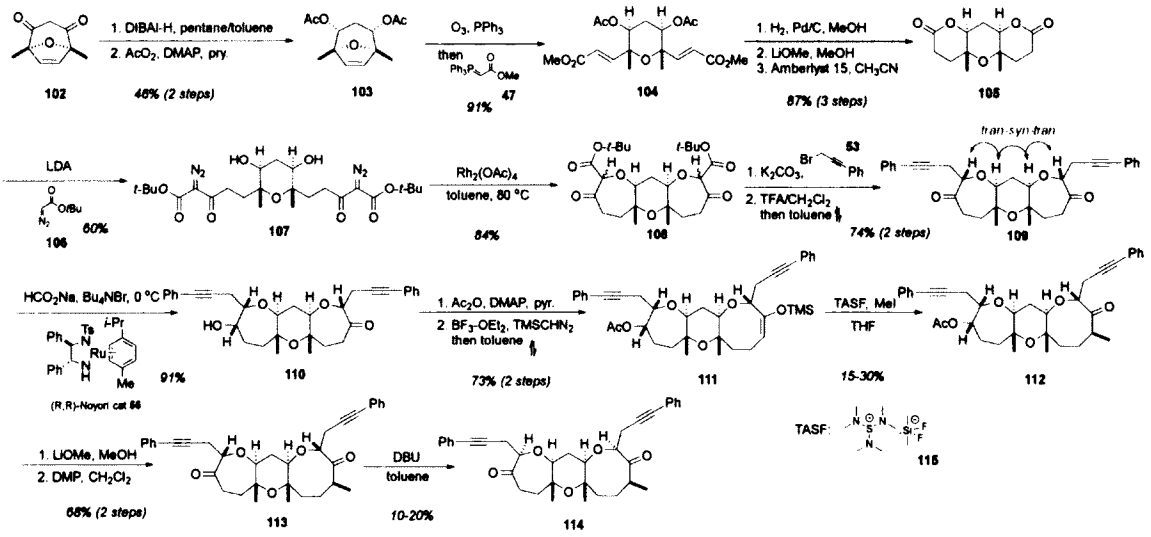
Scheme 2-20. RCM.



An alternative route utilizing Rh carbenoid cyclization and desymmetrization with asymmetric reducing condition, was also studied. This approach was based on the obervation that Moody had described the synthesis of 3-oxo-oxapanes using rhodium carbenoid mediated cyclization of ω-hydroxy-α-diazo-β-keto esters.[27] A simple one-pot ozonolysis and HWE olefination procedure to diacetate **103** yields *bis*-unsaturated ester **104** (Scheme 2-21). A four step procedure involving hydrogenation, hydrolysis of acetate, bis-lactone formation, and lithiated *tert*-butyl diazoacetate addition afforded ω-hydroxy-α-diazo-β-keto ester **107**. Based on Moody's condition, rhodium-catalyzed etherification gave key building block **108** in 84% yield. Treatment of **108** with phenyl propargyl bromide **53** and potassium carbonate, followed by decarboxylation with trifluoroacetic acid in CH_2Cl_2 yielded *meso*-diketone **109**. The *trans-syn-trans* stereochemistry of *meso*-diketone **109** was assigned according to the 2D-NOESY experiment. With *meso*-diketone **109** in hand, the planed desymmetrization was explored using a variety of asymmetric reductions. The best results were obtained using the Noyori Ru catalyst **55** along with HCO_2Na and *n*-Bu_4NBr. The combination of substrate-based stereocontrol and catalyst stereochemical preferences are presumably matched here in producing a high level of stereoselectivity. After acetylation of alcohol **110**, a ring expansion of the acetylated compound, utilizing the conditions developed for the model system **67** and **70** describe in Schemes 2-14 and 2-15, followed by silyl migration under thermal condition gave enol-silyl ether **111**. Methylation with TASF and iodomethane, hydrolysis of acetate,

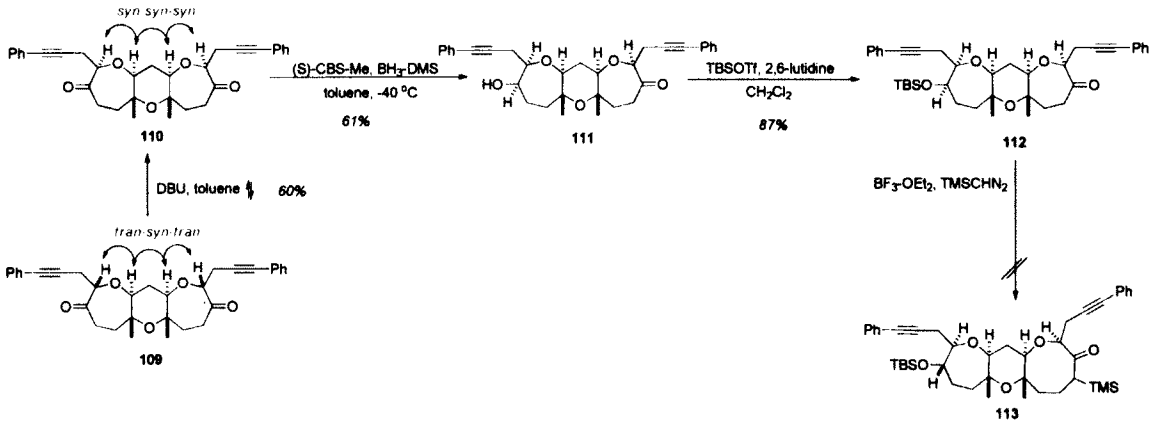
and oxidation provided diketone **113**. The methylation step with TASF and iodomethane needs to be optimized to produce a higher yield. Epimerization to reach the desired *syn-syn-syn* diastereomer **114** were explored under various basic and acidic conditions. Although the isolated yield was poor (10-20%), the desired diastereomer **114** was obtained using DBU and refluxing toluene.

Scheme 2-21.Two directional Rh mediated cyclization.



An alternative route to ketone **113** was also studied. Epimerization of *trans-syn-trans* diketone **109** with DBU yielded a mixture of diastereomers (2.5:1 = **110**: the other diastereomers, Scheme 2-22). Diketone **110** was desymmetrized with (*S*)-CBS-Me and BH_3-DMS in toluene. It turned out that the CBS-Me catalyst for desymmetrization of **110** was better than Noyori's system in this case. After TBS protection to alcohol **111**, ketone **112** was treated to ring expansion conditions. However, all attempts to expand the oxepane **112** were unsuccessful. The reasons for this failure are unclear although subtle differences in a conformation of ketone **112** and model system **64** (Scheme 2-14) caused by 1,3-*syn*-dimethyl group may have profound effects on the outcome of the ring expansion reaction.

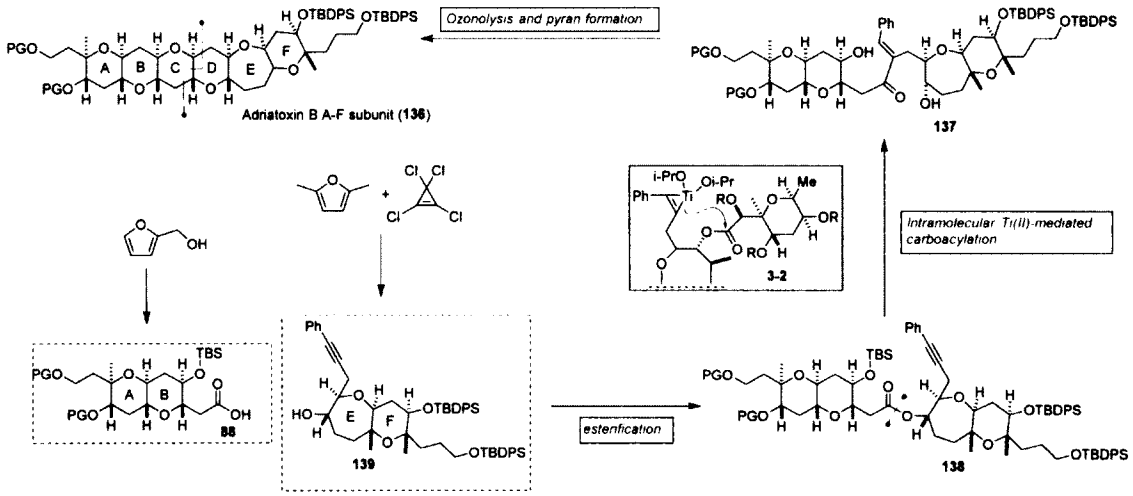
Scheme 2-22. Epimerization to syn-syn-syn stereochemistry.



The combined efforts described here, and the repeated late-stage failures of key reactions provide sufficient perspective to abandon two directional approaches at this stage.

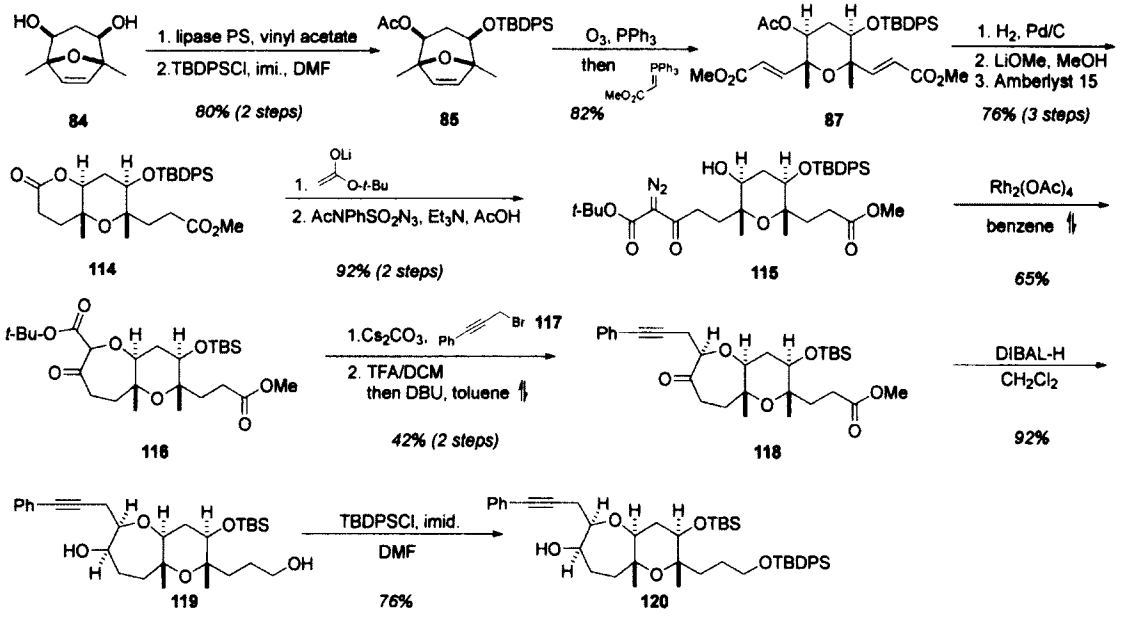
Our attention was directed toward an initial exploration of one directional stepwise coupling strategies as described in Scheme 2-23. The coupling in between acid **88** and EF ring **139** would provide Ti(II)-INAS precursor **138**. The same synthetic sequence including INAS and acetal cyclization followed by reduction will be applied to the ester **138**. It is fully expected that the A-F ring system of adriatoxin shown as compound **136** will be a viable launching point for the later stages of the total synthesis.

Scheme 2-23 Stepwise coupling strategy.



The synthesis of key building block **139** is shown in Scheme 2-24. Bis-ester **87** was prepared by a three step sequence descried in Scheme 2-17 in 68% yield. A subsequent five step procedure involving hydrogenation, hydrolysis of acetate, lactone formation, lithiated *tert*-butyl diazoacetate addition, and diazo transfer reaction afforded ω-hydroxy-α-diazo-β-keto ester **115**. The previously developed reaction sequence in the two directional synthesis was applied to the ester **115**: Rh-catalyzed etherification gave key building block **116** in 92% yield, treatment of **116** with phenylpropargyl bromide **117** and cesium carbonate, followed by decarboxylation with trifluoroacetic acid in dichloromethane yielded ketone **118**. Reduction of ketone **118** with DIBAL-H produced diol **119** and subsequent selective TBDPS protection of the primary alcohol furnished **120** in 70% yield over two steps

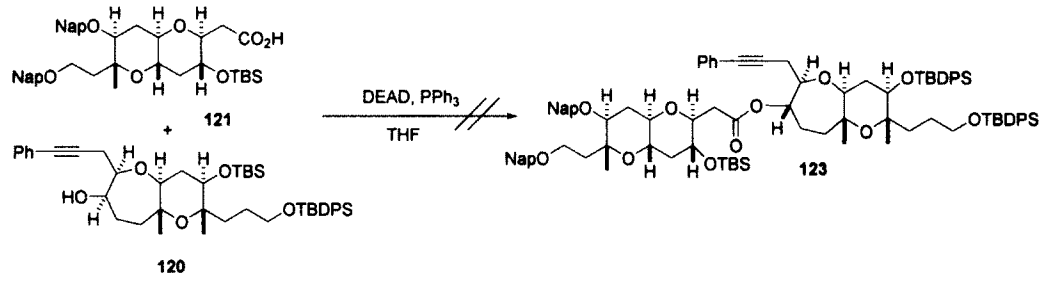
Scheme 2-24. One directional Rh mediated cyclization.



With acid **121** and alcohol **120** in hand, esterification by Mitsunobu reaction was examined as an approach to connect these two fragments with the desired stereochemical outcome (Scheme 2-25). Disappointingly, this reaction failed to provide any desired product under standard

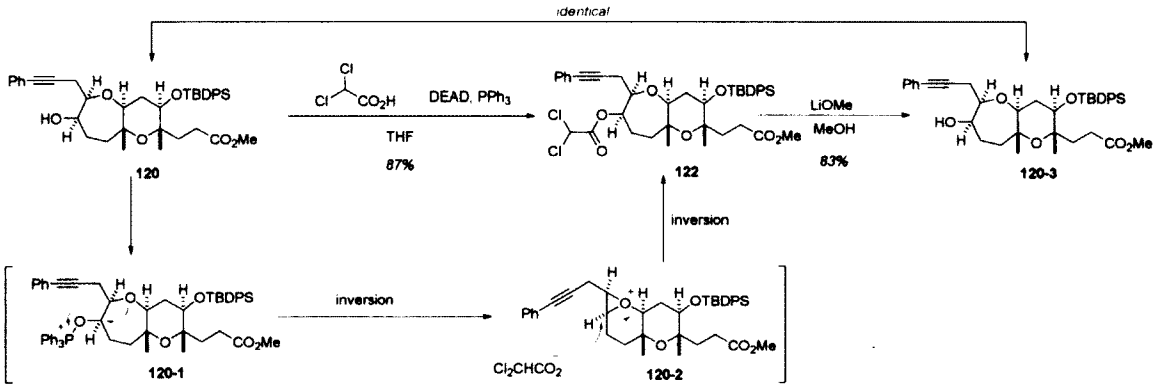
conditions - DEAD, PPh_3, THF, 25 °C - that had smoothly worked with the model system (Scheme 2-16).

Scheme 2-25. Mitsunobu reaction.



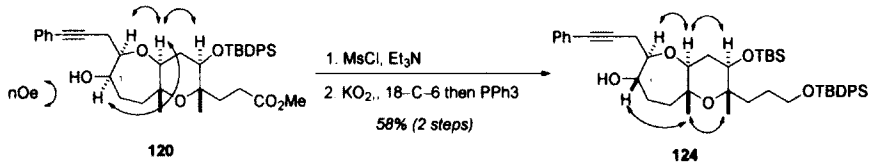
Alternatively, Mitsunobu inversion was possible using excess dichloroacetic acid as a nucleophile (Scheme 2-26). The reaction gave ester **122** in 87% yield and hydrolysis conditions (LiOMe, MeOH) provied the desired alcohol. To our surprise, the resulting alcohol **120-3** was identical to alcohol **120**. Clearly, the overall stereochemical outcome from the two step sequence of Mistunobu and hydrolysis was retention, and presumably reflects participation of functional groups in the substrate (Scheme 2-26). An explanation of this observation is a double inversion process in the Mitsunobu reaction in which phosphonium ion **120-1** is displaced (with inversion) by the adjacent oxygen to form oxonium ion **120-2**. This oxonium ion **120-2** is opened (with inversion) by dichloroacetate to give ester **122**.

Scheme 2-26 Mitsunobu reaction_double inversion.



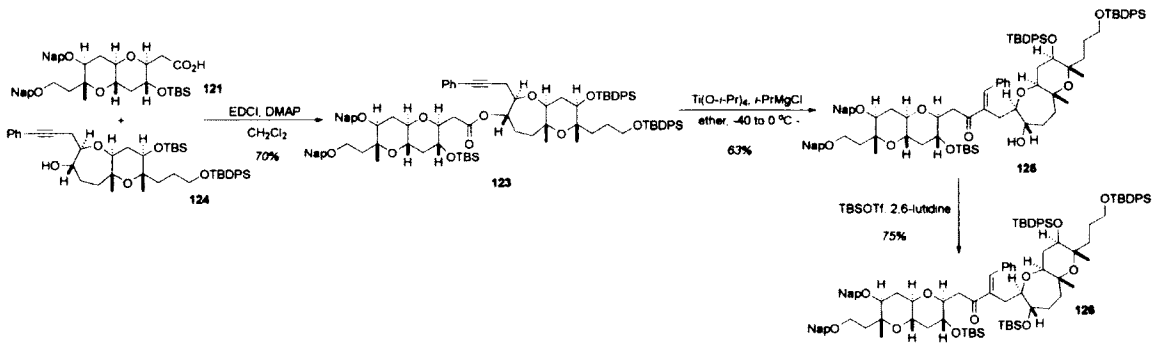
Extensive efforts to identify an alternative produced a solution. Alcohol **120** can be mesylated under standard conditions and SN_2 inversion with KO_2 in the present of [18-crown-6] gave the desired alcohol **124** in 53% yield over two steps (Scheme 2-27).[28]

Scheme 2-27. Stereochemistry inversion.



With the challenges of stereochemistry solved, the two subunits, alcohol **124** and acid **121**, were coupled to produce ester **123** using standard conditions of EDCI and DMAP (Scheme2-28). The resulting ester **123** was then treated to the Ti(II)-INAS conditions, producing the desired enone **125** in an excellent 63% yield. The free alcohol on the enone **125** was readily protected at the TBS ether using TBSOTf and 2,6-lutidine to give **126**.

Scheme 2-28. EDCI coupling and Ti(II)-INAS.

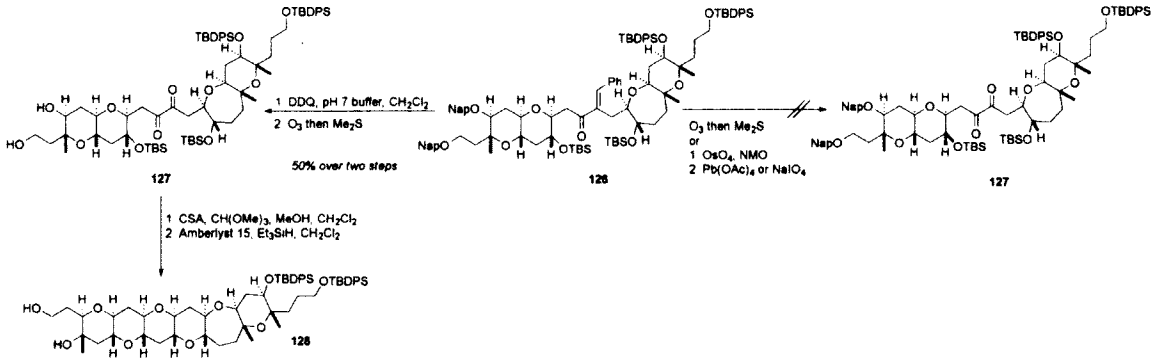


At this juncture problems were encountered with moving material forward. Subjecting **126** to routine ozonolysis conditions produced a complex mixture (Scheme 2-29). Efforts to alter the reaction outcome (reaction times; alternative reducing agents e.g. Me_2S, PPh_3, and Zn) failed to provide any indication of the desired product. Dihydroxylation and oxidative cleavage also produced complex mixtures. Although firm evidence was not available, the Nap (naphthylmethyl

ether) protecting groups were suspected to be the cause of difficulties and this idea was examined by removal of the Nap protecting groups from enone **126** using *aq.* DDQ. Direct ozonolysis of this materail produced the desired diketone **127** in 47% yield over two steps. At this stage material was very limited and although the two step sequence of ketal formation and reduction was examined, it was not possible to obtain the desired product **128** cleanly.

Future studies in this area demand a careful analysis of suitable protecting groups for the completion of the A→F ring system of adriatoxin. On the presumption that this issue can be addressed, it seems likely that the chemistry described here will result in a synthesis of this ring system in a sequence that is 25 steps on the longest linear sequence (~4 steps per ring). Streamlining a number of operations in the sequence could lead to a <20 step LLS for the A→F ring system, and would bode well for a synthesis of adriatoxin on the order of 30 steps.

Scheme 2-29. Ozonolysis, ketalization, and reduction.



2.5 - Conclusion.

In summary, we found that the Ti(II)-mediated INAS is a robust and an efficient coupling method for polyether synthesis. A sequence of Ti(II)-mediated INAS, ozonolysis and ketal formation, and finally reductive etherification allows for the rapid construction of polyethers and

has been demonstrated in the context of several model systems. The strategy is also applicable to the total synthesis, although protecting group issues require re-evaluation. In addition, the studies in this chapter have resulted in a novel, scaleable, and direct route to synthesize the 2,6-*syn*-dimethylpyran that is found in a number of polyethers, including adriatoxin. Ring expansion from 6- and 7-membered cyclic ether to 7- and 8-membered cyclic ether, respectively, have also been examined and results underscore opportunities for the use of these approaches to the synthesis of ladder polyether toxins.

2.6 Experimental Procedures and Data

^{1}H NMR and ^{13}C NMR spectra were recorded using the following spectrometers: Bruker Avance 500 (500/125 MHz), Bruker Avance 400 (400/100 MHz), or an Agilent DD2 400 (400/100 MHz). Chemical shifts are quoted in ppm relative residual solvent as an internal reference[2]. The following abbreviations are used to describe signal multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), dt (doublet of triplets) etc. COSY, HMQC, and DEPT experiments were used when appropriate to aid structure assignment. Diastereotopic protons are labeled as H'-X and H''-X and imply no particular stereochemistry. Compounds were numbered according to their names as indicated in their structures.

Accurate mass spectra were recorded on a Waters Synapt G1 qTOF spectrometer equipped with a Waters Acquity UPLC (fitted with a BEH C18 Column, 130 Å, 1.7 μm, 2.1× 50 mm). Positive electrospray was used for ionization unless otherwise indictaed.

Infrared spectra were obtained using a Thermo Nicolet 6700 FTIR spectrometer fitted with a diamond ATR. The spectra of solids were recorded using a thin film of the neat product whereas the spectra of oils were recorded using a thin liquid film of the product indicated by the bracketed solvent.

Optical rotations were measured in a 100 mm length cell using a Perkin Elmer 341 Polarimeter fitted with a sodium source lamp and a Glan-Taylor polarizer.

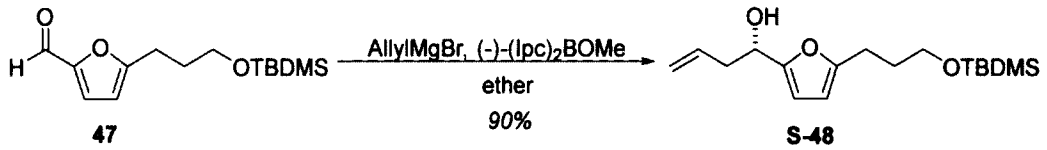
[2] The following values were used as internal locks ($^{1}H/^{13}C$ NMR spectra, respectively): 7.26/77.16 ppm in $CDCl_3$, 7.16/128.06 ppm in C_6D_6, 1.94/118.26 ppm in CD_3CN, and 4.87/49.0 ppm in CD_3OD.

Melting points were recorded using a digital Stanford Research Systems OptiMelt automated melting point system. The reported values are an average of duplicate measurements which were takes by slowly increasing the temperature from 25 °C at a rate of 2.5 °C per min.

Analytical thin-layer chromatography was carried out on SiliCycle glass-backed extra hard layer 60Å plates (20×20 cm particle, 250μm thickness), using either aqueous potassium permanganate or aqueous cerium ammonium molybdate stains to aid visualization.

Flash column chromatography was carried out following the general principles of Still (W.C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.using SiliaFlash P60 silica (40-63 μm particle size, 230-400 mesh, SiliCycle). Preparative HPLC was performed on a Gilson HPLC consisting of a 215 liquid handler, 305/305 pump modules, and a 155 UV/VIS detector, all operating under control of Gilson's Trilution software. A Waters Sunfire silica column (10×250 mm, 5μm particle size) was used for purifications described herein

Non-aqueous reactions were carried out under an atmosphere of nitrogen, in flame-dried glassware, using solvents dried by passage though activated alumina as described by Bergman and Grubbs (P. J. Alaimo, D.W. Peters, J. Arnold and R.G. Bergman, *J. Chem. Educ.*, **2001**, *78*, 64; A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R.K. Rosen and F. J. Timmers, *Organometallics*, **1996**, *15*, 151) or obtained by distillation when more appropriate. Bases such as triethylamine, pyridine, and diisopropylamine (Hünig's base) were freshly distilled from CaH_2 prior to use. Brine refers to a saturated solution of sodium chloride and pH 2 sulfate buffer refers to an aqueous solution made of 1 M sodium bisulfate and 1 M sodium sulfate mixed in 1:1 v/v ratio.



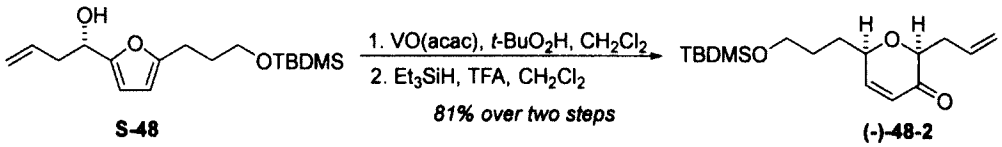
47 **S-48**

(S)-1-(5-(3-((tert-butyldimethylsilyl)oxy)propyl)furan-2-yl)but-3-en-1-ol:

(-)-Ipc_2BOMe (6.07 g, 19.18 mmol) and THF (40 ml) were added to a flame dried 250 ml round bottom flask under argon. A solution of freshly prepared AllylMgBr (19.18 ml, 19.18 mmol, 1.0 M solution in ether) was added dropwise to the reaction solution at -78 °C. The reaction was slowly warm to room temperature and stirred for 1 hr. The reaction mixture was then cooled to -78 °C. A solution of furylaldehyde **47** (3.96 g, 14.75 mmol) in ether (10 ml) was added to the reaction solution. The reaction was allowed to stir for 2 hr at -78 °C, then 1 hr at 0 °C. The reaction was quenched with addition of solution of sodium hydroxide (8.7 ml, 26.1 mmol, 3.0 M solution in water) and hydrogen peroxide (3.9 ml, 14.75 mmol, 30% solution in water) through additional funnel. Then the reaction mixture was stirred for 16 hr. The reaction was diluted with ether and extracted with ether (x3). The combined organic solution was washed with brine, dried with sodium sulfate and filtered. The organic layer was concentrated *in vacuo*. The crude oil was purified by flash column chromatography to give pure alcohol **S-48** (4.1 g, 13.20 mmol, 90%).

$[\alpha]^{20}_D$ -20.0 (c = 1.0 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3468, 3330, 2982, 2956, 1473, 1283; δ_H (500 MHz, $CDCl_3$) 6.13 (dd, *J* = 3.1, 0.6 Hz, 1H), 5.92 (dd, *J* = 3.1, 0.9 Hz, 1H), 5.81 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1H), 5.18 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.14 (ddt, *J* = 10.2, 2.0, 1.6 Hz, 1H), 4.69 (dt, *J* = 7.2, 5.4 Hz, 1H), 3.65 (t, *J* = 6.2 Hz, 2H), 2.71 – 2.64 (m, 2H), 2.64 – 2.56 (m, 2H), 1.84 (ddt, *J* = 8.4, 7.5, 6.3 Hz, 2H), 0.90 (s, 9H), 0.05 (s, 6H); δ_C (125 MHz, $CDCl_3$) 155.8, 154.2, 134.1, 134.1, 118.6, 106.9, 105.5, 67.1,

62.3, 40.2, 31.1, 26.1, 24.6, 18.5, -5.2; Accurate mass (ES^+): Found 333.1891 (+8.7 ppm), $C_{17}H_{30}O_3SiNa$ ($M+Na^+$) requires 333.1869



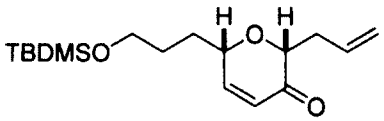
S-48 **(-)-48-2**

(2S,6R)-2-allyl-6-(3-((tert-butyldimethylsilyl)oxy)propyl)-2H-pyran-3(6H)-one:

To a stirred solution of furyl alcohol **S-48** (3.99 g, 12.85 mmol, 1eq) in CH_2Cl_2 (64 ml) at 0 °C was added vanadyl acetylacetonate (341 mg, 1.285 mmol, 0.1 eq) followed by dropwise *tert*-butylhydroperoxide (2.81 ml, 21.85 mmol, 1.7 eq). The solution was stirred for 40 minutes at 0 °C, then 1 hr at room temperature. Saturated aqueous sodium sulfite was added, and stirred was continued for 20 min. the resultant biphasic mixture was poured into EtOAc. The layer was separated and the aqueous extracted with EtOAc. The combined organic phase was washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated. The crude residue was taken directly on the following reaction.

The crude residue was dissolved in CH_2Cl_2 (129 ml) and cooled to -40 °C. Triethylsilane (10.27 ml, 64.3 mmol, 5 eq) was added dropwise, followed by dropwise addition of trifluoroactic acid (14.87 ml, 193 mmol, 15 eq). The resultant solution was stirred at -40 °C for 2 hr. The reaction mixture was carefully poured into cold saturated aqueous $NaHCO_3$. The layers was separated, and the aqueous extracted with EtOAc. The combined organic phase was washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography to yield enone (-)-**48-2** as a pale yellow oil (3.25 g, 10.47 mmol, 81% yield for 2 steps).

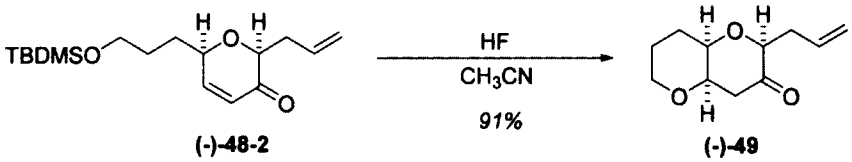
$[\alpha]^{20}_D$ -41.2 (c = 0.5 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 2988, 2847, 2834, 1701, 1682, 1583; δ_H (500 MHz, $CDCl_3$) 6.92 (dd, *J* = 10.3, 1.5 Hz, 1H), 6.09 (dd, *J* = 10.2, 2.5 Hz, 1H), 5.88 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H), 5.14 (dd, *J* = 17.1, 1.1 Hz, 1H), 5.07 (ddd, *J* = 10.2, 2.1, 1.1 Hz, 1H), 4.38 – 4.32 (m, 1H), 3.98 (ddd, *J* = 8.1, 3.7, 2.0 Hz, 1H), 3.71 – 3.61 (m, 2H), 2.73 (dddt, *J* = 15.1, 6.8, 3.7, 1.4 Hz, 1H), 2.73 (dddt, *J* = 15.1, 6.8, 3.7, 1.4 Hz, 1H), 1.86 – 1.76 (m, 1H), 1.76 – 1.59 (m, 3H), 0.89 (s, 9H), 0.05 (s, 6H); δ_C (125 MHz, $CDCl_3$) 196.4, 151.8, 134.3, 127.1, 117.3, 80.2, 74.0, 62.9, 34.1, 31.3, 28.4, 26.1, 26.0, 18.5, 6.7, 5.9, -5.2; Accurate mass (ES^+): Found 333.1843 (+5.7 ppm) $C_{17}H_{30}O_3SiNa$ ($M+Na^+$) requires 333.1862.



(+)-48-2

(2R,6S)-2-allyl-6-(3-((tert-butyldimethylsilyl)oxy)propyl)-2H-pyran-3(6H)-one:

$[\alpha]^{20}_D$ +15.4 (c = 1.0 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 2989, 2845, 2834, 1703, 1682, 1579; δ_H (500 MHz, $CDCl_3$) 6.93 (ddd, *J* = 10.2, 1.5, 0.6 Hz, 1H), 6.09 (dd, *J* = 10.3, 2.5 Hz, 1H), 5.89 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H), 5.18 – 5.11 (m, 1H), 5.11 – 5.02 (m, 1H), 4.35 (tt, *J* = 5.0, 2.3 Hz, 1H), 3.98 (ddd, *J* = 8.1, 3.7, 2.0 Hz, 1H), 3.72 – 3.60 (m, 2H), 2.74 (dddt, *J* = 15.0, 6.8, 3.6, 1.4 Hz, 1H), 2.41 (dddt, *J* = 14.9, 8.0, 6.7, 1.4 Hz, 1H), 1.79 (ddt, *J* = 9.2, 8.2, 3.1 Hz, 1H), 1.76 – 1.61 (m, 3H), 0.89 (s, 9H), 0.05 (s, 6H); δ_C (125 MHz, $CDCl_3$) 196.4, 151.8, 134.3, 127.1, 117.4, 80.2, 74.0, 62.9, 34.1, 31.4, 28.4, 26.1, 26.1, 18.5, -5.1; Accurate mass (ES^+): Found 333.1860 (-0.6 ppm) $C_{17}H_{30}O_3SiNa$ ($M+Na^+$) requires 333.1862.

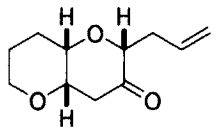


(-)-48-2 (-)-49

(2S,4aR,8aR)-2-allylhexahydropyrano[3,2-b]pyran-3(2H)-one:

A solution of silyl ether **(-)-48-2** (4 g, 12.88 mmol, 1 eq) in acetonitrile (107 ml) was treated to HF (2.68 ml, 48% aqueous solution) in a Teflon® vial, and the reaction was allowed to stir overnight at room temperature. The reaction was then quenched with cold saturated aqueous $NaHCO_3$, and the mixture was then extracted with ether (x3), washed with brine, dried over $MgSO_4$, and the solvent was removed *in vacuo* to give pure product **(-)-49** (2.3 g, 11.72 mmol, 91%) as a clear oil.

$[\alpha]^{20}_D$ -26.3 (c = 1.0 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 2989, 2863, 2823, 1718, 1682, 1572; δ_H (500 MHz, $CDCl_3$) 5.86 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H), 5.10 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.03 (ddt, *J* = 10.2, 2.1, 1.2 Hz, 1H), 3.96 (ddt, *J* = 11.5, 4.1, 1.8 Hz, 1H), 3.86 (td, *J* = 4.7, 3.2 Hz, 2H), 3.80 (t, *J* = 3.1 Hz, 1H), 3.43 (ddd, *J* = 12.5, 11.4, 2.3 Hz, 1H), 3.43 (ddd, *J* = 12.5, 11.4, 2.3 Hz, 1H), 2.65 – 2.50 (m, 3H), 2.44 – 2.33 (m, 1H), 2.06 (dtd, *J* = 13.8, 4.9, 4.1, 2.1 Hz, 1H), 2.02 – 1.90 (m, 1H), 1.70 (tdd, *J* = 13.5, 4.7, 3.0 Hz, 1H), 1.30 (ddd, *J* = 13.5, 4.5, 2.2 Hz, 1H); δ_C (125 MHz, $CDCl_3$) 205.5, 134.4, 134.4, 117.0, 117.0, 81.7, 76.0, 71.4, 68.4, 44.8, 33.7, 28.4, 20.3; Accurate mass (ES^+): Found 219.0990 (-3.2 ppm), $C_{11}H_{16}O_3Na$ ($M+Na^+$) requires 219.0997.

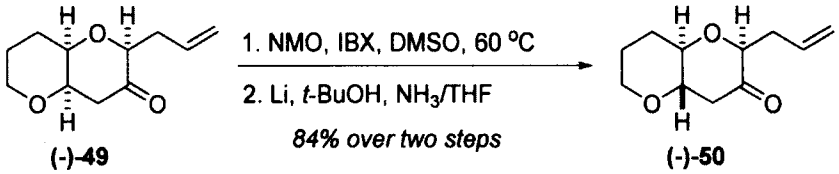


(+)-49

(2R,4aS,8aS)-2-allylhexahydropyrano[3,2-b]pyran-3(2H)-one:

$[\alpha]^{20}_D$ +24.5 (c = 1.0 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 2982, 2917, 2832, 1710, 1634, 1452; δ_H (500 MHz, $CDCl_3$) 5.89 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 5.13 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.06 (ddt, *J* = 10.2, 1.9,

1.1 Hz, 1H), 3.99 (ddt, *J* = 11.6, 3.9, 1.8 Hz, 1H), 3.89 (td, *J* = 4.3, 2.4 Hz, 2H), 3.81 (t, *J* = 3.1 Hz, 1H), 3.45 (ddd, *J* = 12.5, 11.4, 2.3 Hz, 1H), 2.69 – 2.55 (m, 4H), 2.42 (dddt, *J* = 15.2, 7.8, 6.7, 1.4 Hz, 1H), 2.16 – 2.05 (m, 1H), 2.05 – 1.89 (m, 1H), 1.72 (tdd, *J* = 13.4, 4.7, 3.0 Hz, 1H), 1.32 (ddq, *J* = 13.5, 4.2, 2.1 Hz, 1H); δ_C (125 MHz, $CDCl_3$) 205.6, 134.5, 134.5, 117.1, 81.9, 76.0, 71.5, 68.5, 44.9, 33.8, 28.5, 20.4; Accurate mass (ES^+): Accurate mass (ES^+): Found 219.0995 (-0.9 ppm), $C_{11}H_{16}O_3Na$ ($M+Na^+$) requires 219.0997.



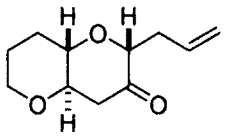
(2S,4aS,8aR)-2-allylhexahydropyrano[3,2-b]pyran-3(2H)-one:

To a solution of NMO (1.55 g, 13.25 mmol, 2 eq) in DMSO (38 ml) was added IBX (3.71 g, 13.25 mmol, 2 eq), and the mixture was stirred until homogeneous. A solution of ketone **(-)-49** (1.3 g, 6.62 mmol, 1eq) in DMSO (2 ml) was then added dropwise, and the reaction mixture was heated to 60 °C and stirred in the dark for 4 hr. The reaction was then quenched with saturated aqueous $Na_2S_2O_3$ doped with saturated aqueous $NaHCO_3$, and the mixture was extracted with ether (x3). The combined organic layers were washed with brine, dried with $MgSO_4$, and the solvent was removed *in vacuo*. The crude material obtained was immediately taken to the next reaction.

At -78 °C, NH_3 was condensed in a two-neck flask to the approx. volume of 15 ml. A solution of vinyligous ether (1.29 g, 6.63 mmol) in THF (22 ml) and *t*-BuOH (1.84 ml, 17.14 mmol) was added slowly. The resulting solution was stirred for 10 min., a small piece of lithium metal was then added, and the reaction turned to dark blue. The reaction was stirred an additional 10 min., and then quenched with solid NH_4Cl. The suspension was allowed to warm to room temperature open

to the air. H_2O was then added, and the mixture was extracted with EtOAc (x3). The combined organic layers was washed with brine, dried over $MgSO_4$, and the solvent was removed *in vacuo*. The crude material was purified by flash column chromatography to give the pure product **(-)-50** (1.09 g, 5.55 mmol 84% over two steps) as a clear oil.

$[\alpha]^{20}_D$ -40.9 (c = 1.0 in $CHCl_3$); ν_{max} (neat)/cm^{-1} 2976, 2843, 1716, 1663, 1472; δ_H (500 MHz, $CDCl_3$) 5.80-5.88 (m, H), 5.13 (ddd, *J* = 17.2, 2.0, 1.1 Hz, 1H), 5.06 (ddt, *J* = 10.2, 2.1, 1.1 Hz, 1H), 3.93 (dtd, *J* = 11.5, 3.6, 1.7 Hz, 1H), 3.85 (dd, *J* = 7.6, 4.3 Hz, 1H), 3.45 – 3.38 (m, 1H), 3.37 – 3.26 (m, 2H), 2.89 (dd, *J* = 15.8, 4.6 Hz, 1H), 2.63 (dddt, *J* = 15.1, 6.8, 4.2, 1.4 Hz, 1H), 2.48 – 2.39 (m, 1H), 2.34 (dddt, *J* = 15.2, 7.7, 6.8, 1.3 Hz, 1H), 2.23 – 2.16 (m, 1H), 1.80-1.74 (m, 2H), 1.61 – 1.46 (m, 1H); δ_C (125 MHz, $CDCl_3$) 205.3, 134.1, 117.5, 83.1, 77.3, 77.0, 67.7, 45.5, 33.8, 29.3, 25.3; Accurate mass (ES^+): Accurate mass (ES^+): Found 219.1003 (+2.7 ppm), $C_{11}H_{16}O_3Na$ ($M+Na^+$) requires 219.0997.

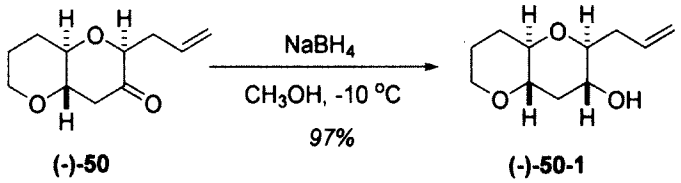


(+)-50

(2R,4aR,8aS)-2-allylhexahydropyrano[3,2-b]pyran-3(2H)-one:

$[\alpha]^{20}_D$ +35.1 (c = 1.0 in $CHCl_3$) ; ν_{max} (neat)/cm^{-1} 2976, 2843, 1716, 1663, 1472; δ_H (500 MHz, $CDCl_3$) 5.82 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H), 5.11 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.04 (dq, *J* = 10.2, 1.4 Hz, 1H), 3.97 – 3.87 (m, 1H), 3.97 – 3.87 (m, 1H), 3.83 (dd, *J* = 7.6, 4.3 Hz, 1H), 3.45 – 3.35 (m, 1H), 3.35 – 3.22 (m, 2H), 2.92 – 2.81 (m, 1H), 2.61 (dddt, *J* = 15.2, 7.1, 4.4, 1.4 Hz, 1H), 2.49 – 2.37 (m, 1H), 2.37 – 2.24 (m, 1H), 2.17 (dddd, *J* = 12.5, 5.0, 3.6, 1.7 Hz, 1H), 1.74 (ddt, *J* = 10.8, 6.1, 3.7 Hz, 2H), 1.51 (dddd, *J* = 19.9, 10.5, 5.9, 2.0 Hz, 1H); δ_C (125 MHz, $CDCl_3$) 205.3, 134.1, 117.5, 83.1, 77.3,

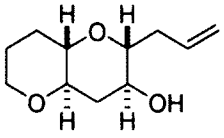
77.0, 67.7, 45.5, 33.8, 29.3, 25.3; Accurate mass (ES^+): Found 219.1006 (+4.1 ppm), $C_{11}H_{16}O_3Na$ ($M+Na^+$) requires 219.0997.



(2S,3R,4aS,8aR)-2-allyloctahydropyrano[3,2-b]pyran-3-ol:

To a solution of ketone **(-)-50** (103 mg, 0.525 mmol, 1 eq) in MeOH (6 ml) at -10 °C was added $NaBH_4$ (59.6 mg, 1.575 mmol, 3 eq) slowly. The reaction was stirred for 30 min and then quenched with saturated aqueous NH_4Cl. The suspension was allowed to warm to room temperature. H_2O was then added, and the mixture was extracted with EtOAc (x3). The combined organic layers was washed with brine, dried with $MgSO_4$ and filtered. The solvent was removed *in vacuo*. The crude material was purified by flash column chromatography to give the pure product **(-)-50-1** (101 mg, 0.509 mmol, 97%) as a clear oil.

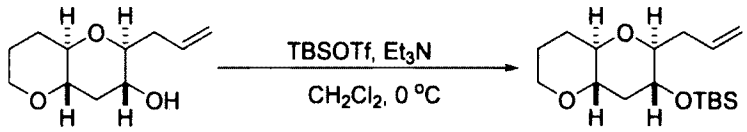
$[\alpha]^{20}_D$ -34.3 (c = 1.0 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3402, 2938, 2873, 1639, 1622, 1562; δ_H (500 MHz, $CDCl_3$) 5.91 (ddt, *J* = 17.1, 10.0, 6.9 Hz, 1H), 5.18 – 5.08 (m, 1H), 5.05 (dt, *J* = 10.5, 1.4 Hz, 1H), 3.93 – 3.83 (m, 1H), 3.49 – 3.40 (m, 1H), 3.34 (ddt, *J* = 14.8, 11.2, 7.2 Hz, 1H), 3.15 (ddd, *J* = 8.7, 7.3, 3.8 Hz, 1H), 3.00 – 2.90 (m, 2H), 2.54 (dddd, *J* = 14.2, 7.0, 3.6, 1.7 Hz, 1H), 2.40 – 2.23 (m, 2H), 2.18 (bs, 1H), 2.02 (ddt, *J* = 11.9, 4.5, 2.3 Hz, 1H), 1.68 (ddt, *J* = 12.2, 8.0, 4.0 Hz, 2H), 1.49 – 1.31 (m, 2H); δ_C (125 MHz, $CDCl_3$) 135.0, 117.0, 81.5, 77.8, 76.9, 69.6, 67.9, 39.0, 36.6, 29.3, 25.5; Accurate mass (ES^+): Found 221.1159 (+2.3 ppm), $C_{11}H_{18}O_3Na$ ($M+Na^+$) requires 221.1154.



(+)-50-1

(2R,3S,4aR,8aS)-2-allyloctahydropyrano[3,2-b]pyran-3-ol:

$[\alpha]^{20}_D$ +14.9 (c = 1.0 in $CHCl_3$); ν_{max} (neat)/cm^{-1} 3402, 2938, 2873, 1639, 1622, 1562; δ_H (500 MHz, $CDCl_3$) 5.93 (ddt, *J* = 17.2, 10.1, 7.0 Hz, 1H), 5.14 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.07 (ddt, *J* = 10.2, 2.2, 1.2 Hz, 1H), 3.89 (ddq, *J* = 11.4, 4.0, 1.7 Hz, 1H), 3.54 – 3.44 (m, 1H), 3.40 – 3.32 (m, 1H), 3.18 (ddd, *J* = 9.1, 7.2, 4.0 Hz, 1H), 2.97 (ddt, *J* = 8.8, 6.4, 3.2 Hz, 2H), 2.55 (dddt, *J* = 14.2, 7.0, 4.0, 1.4 Hz, 1H), 2.36 – 2.24 (m, 2H), 2.08 – 1.97 (m, 1H), 1.87 (d, *J* = 5.3 Hz, 1H), 1.70 (dddd, *J* = 9.8, 7.2, 6.0, 2.6 Hz, 2H), 1.50 – 1.31 (m, 2H); δ_C (125 MHz, $CDCl_3$) 135.0, 117.0, 81.5, 77.8, 76.9, 69.6, 67.9, 39.0, 36.6, 29.3, 25.5; Accurate mass (ES^+): Found 221.1162 (+3.6 ppm), $C_{11}H_{18}O_3Na$ ($M+Na^+$) requires 221.1154.



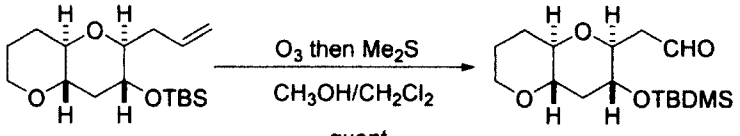
(-)-50-1 **(-)-50-2**

(((2S,3R,4aS,8aR)-2-allyloctahydropyrano[3,2-b]pyran-3-yl)oxy)(tert-butyl)dimethylsilane:

The alcohol **(-)-50-1** (102 mg, 0.514 mmol, 1 eq) was dissolved in CH_2Cl_2 (3.4 ml) and cooled to 0 °C. To this solution was added Et_3N (181 µL, 1.286 mmol) followed by the slow addition of *t*-butyldimethylsilyltrifluoromethane sulfonate (130 µL, 0.566 mmol, 1.1 eq). After 1 hr of stirring at 0 °C, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (x3). The combined organic layers were washed with brine, dried $MgSO_4$, filtered and

concentrated *in vacuo*. The crude was purified by flash column chromatography to provide silyl ether **(-)-50-2** (153 mg, 0.490 mmol, 95%) as a clear oil.

$[\alpha]^{20}_{D}$ -64.5 (c = 1.0 in $CHCl_3$), enantiomer; +18.1 (c = 1.0 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 2994, 2887, 2813, 1683, 1653, 1483; δ_H (500 MHz, $CDCl_3$) 5.89 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H), 5.08 (dq, *J* = 17.1, 1.8 Hz, 1H), 5.03 (ddt, *J* = 10.2, 2.1, 1.8 Hz, 1H), 3.90-3.86 (m, 1H), 3.42 (ddd, *J* = 10.8, 8.9, 4.7 Hz, 1H), 3.39 – 3.30 (m, 1H), 3.16 (td, *J* = 8.6, 2.8 Hz, 1H), 3.02 – 2.88 (m, 2H), 2.55 (dddt, *J* = 14.8, 6.3, 3.0, 1.6 Hz, 1H), 2.24 (dt, *J* = 11.5, 4.2 Hz, 1H), 2.11 (dtt, *J* = 15.1, 8.4, 1.3 Hz, 1H), 2.07 – 1.96 (m, 1H), 1.73 – 1.63 (m, 2H), 1.48 (q, *J* = 11.1 Hz, 1H), 1.44 – 1.31 (m, 1H), 0.87 (s, 9H), 0.06 (s, 6H); δ_C (125 MHz, $CDCl_3$) ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.5, 135.4, 116.5, 82.1, 77.8, 76.9, 70.2, 67.9, 39.8, 36.1, 29.4, 25.9, 25.6, 18.1, -3.9, -4.6; Accurate mass (ES^+): Found 335.2010 (-2.4 ppm), $C_{17}H_{32}O_3SiNa$ ($M+Na^+$) requires 335.2018.

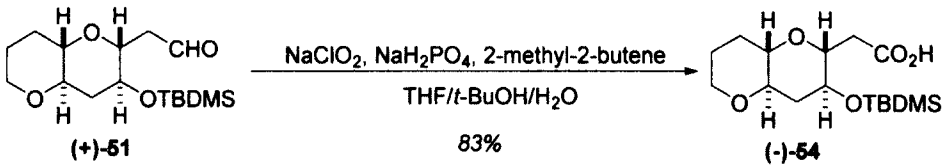


(-)-50-2 **(-)-51**

2-((2S,3R,4aS,8aR)-3-((tert-butyldimethylsilyl)oxy)octahydropyrano[3,2-b]pyran-2-yl)acetaldehyde:

To alkene **(-)-50-2** (70 mg, 0.224 mmol) was dissolved in MeOH-CH_2Cl_2 (v:v = 1:1, 8 ml) and cooled to -78 °C. O_3/O_2 was bubbled through the solution for 5 minutes, at which point a steel blue color persisted. Stirring was continued 5 minutes at -78 °C, then N_2 gas was bubbled through the solution until the steel blue color dissipated. Dimethyl sulfide (200 µL) was added and the reaction mixture was warm to room temperature, and stirring was continued for 12 hr. The solution was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography to give aldehyde **(-)-51** (71 mg, 0.224 mmol, *quant.*).

$[\alpha]^{20}_D$ -40.0 (c = 1.0 in $CHCl_3$), enantiomer +40.1 (c = 1.0 in $CHCl_3$); ν_{max} (neat)/cm^{-1} 2983, 2834, 1726, 1632, 1583; δ_H (500 MHz, $CDCl_3$) 9.73 (dd, *J* = 3.1, 1.7 Hz, 1H), 3.94 – 3.80 (m, 1H), 3.65 (td, *J* = 8.9, 3.6 Hz, 1H), 3.42 (ddd, *J* = 10.7, 8.9, 4.6 Hz, 1H), 3.38 – 3.25 (m, 1H), 3.02 (ddd, *J* = 11.0, 8.9, 4.3 Hz, 1H), 2.93 (ddd, *J* = 11.5, 8.9, 4.2 Hz, 1H), 2.72 (ddd, *J* = 16.2, 3.6, 1.7 Hz, 1H), 2.41 (ddd, *J* = 16.2, 8.8, 3.0 Hz, 1H), 2.25 (dt, *J* = 11.7, 4.3 Hz, 1H), 2.06 – 1.92 (m, 1H), 1.76 – 1.62 (m, 2H), 1.50 (q, *J* = 11.4 Hz, 1H), 1.45 – 1.27 (m, 1H), 0.83 (d, *J* = 2.5 Hz, 9H), 0.04 (s, 3H), 0.02 (s, 3H); δ_C (125 MHz, $CDCl_3$) 201.4, 78.1, 78.0, 76.7, 70.6, 68.0, 46.4, 39.7, 29.4, 25.9, 25.6, 18.1, -3.9, -4.6.



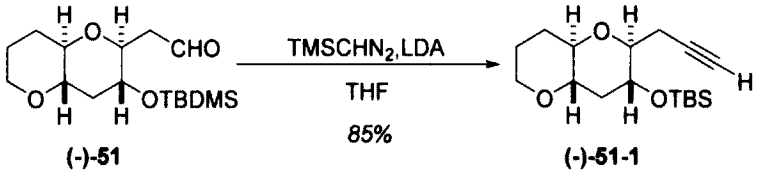
(+)-51 (-)-54

2-((2S,3R,4aS,8aR)-3-((tert-butyldimethylsilyl)oxy)octahydropyrano[3,2-b]pyran-2-yl)acetic acid:

To a reaction mixture of aldehyde **(+)-51** (40 mg, 0.127 mmol, 1 eq) in THF/*t*-BuOH (v:v = 1:1, 2 ml) was added a solution of 2-methyl-2-butene (1.7 ml, 3.43 mmol, 2.0 M solution in THF) followed by a solution of NaH_2PO_4 (35.1 mg, 0.254 mmol) and $NaClO_2$ (43.1 mg, 0.382 mmol) in H_2O (0.5 ml) at room temperature. The reaction mixture was stirred for 5 hr at room temperature. After the reaction completion, the reaction was diluted with additional H_2O. The bi-layer mixture was extracted with EtOAc (x3). The organics was washed with brine, dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was pure enough to use to the next step without further purification, **(-)-54** (35 mg, 0.105 mmol, 83%).

$[\alpha]^{20}_D$ -26.6 (c = 1.0 in $CHCl_3$), enantiomer +30.1 (c = 1.0 in $CHCl_3$); ν_{max} (neat)/cm^{-1} 2973, 2834, 1682, 1589; δ_H (500 MHz, $CDCl_3$) 11.05 (bs, 1H), 3.93 – 3.85 (m, 1H), 3.60 (td, *J* = 9.1, 3.0 Hz, 1H), 3.45 (ddd, *J* = 10.7, 9.0, 4.6 Hz, 1H), 3.41 – 3.32 (m, 1H), 3.07 (ddd, *J* = 11.0, 8.9, 4.3 Hz, 1H), 2.97 (ddd, *J* = 11.5, 9.0, 4.1 Hz, 1H), 2.84 (dd, *J* = 15.7, 3.1 Hz, 1H), 2.39 (dd, *J* = 15.7, 9.1 Hz, 1H), 2.27

(dt, *J* = 11.7, 4.4 Hz, 1H), 2.10 – 1.99 (m, 1H), 1.75 – 1.62 (m, 2H), 1.58 – 1.44 (m, 1H), 1.45 – 1.33 (m, 1H), 1.31 – 1.17 (m, 1H), 0.86 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); δ_C (125 MHz, $CDCl_3$) 176.5, 79.0, 78.0, 76.7, 70.2, 68.0, 39.5, 37.5, 29.3, 25.8, 25.5, 18.0, -3.9, -4.7; Accurate mass (ES^+): Found 353.1769 (+2.5 ppm), $C_{16}H_{30}O_5SiNa$ ($M+Na^+$) requires 353.1760.



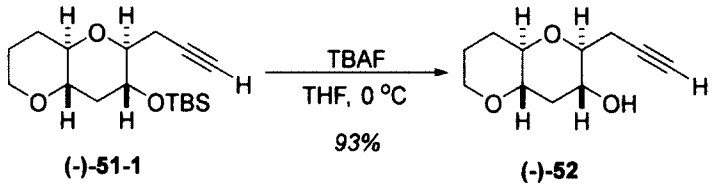
(-)-51 **(-)-51-1**

tert-butyldimethyl(((2S,3R,4aS,8aR)-2-(prop-2-yn-1-yl)octahydropyrano[3,2-b]pyran-3-yl)oxy)silane:

A solution of *n*-BuLi (1.29 ml, 0.397 mmol, 1.6 M solution in hexane) was added dropwise to a solution of diisopropylamine (57 µL, 0.397 mmol) in THF (4 ml) at 0 °C, and stirred for 30 min. After cooling down to -78 °C, $TMSCHN_2$ (244 µL, 0.488 mmol, 2.0 M solution in hexane) was added to the reaction mixture. The resulting reaction mixture was stirred for 30 min. A solution of aldehyde **(-)-51** (96 mg, 0.305 mmol) in THF (2 ml) was added and stirring was maintained for additional 1hr at -78 °C. The reaction solution was slowly warn to room temperature and stirred for 2 hr. The reaction mixture was quenched with ice-cooled water, and extracted with ether (x3). The combined organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude oil was purified by flash column chromatography to give pure alkyne **(-)-51-1** (81 mg, 0.261 mmol, 85%).

$[\alpha]^{20}_D$ -35.9 (c = 1.0 in $CHCl_3$), enantiomer +42.3 (c = 1.0 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 2973, 2953, 2858, 2082, 1643, 1587; δ_H (500 MHz, $CDCl_3$) 3.89 (ddt, *J* = 11.5, 3.9, 1.9 Hz, 1H), 3.62 (tdd, *J* = 10.3, 4.8, 1.2 Hz, 1H), 3.43 – 3.33 (m, 1H), 3.24 (ddd, *J* = 9.1, 6.1, 3.2 Hz, 1H), 3.02 (dddd, *J* = 24.4, 11.5, 9.0, 4.2 Hz, 2H), 2.64 (dt, *J* = 17.0, 3.0 Hz, 1H), 2.45 (ddd, *J* = 17.0, 6.1, 2.6 Hz, 1H), 2.27 (dt, *J* = 11.6,

4.4 Hz, 1H), 2.16 – 2.05 (m, 1H), 1.99 (t, *J* = 2.7 Hz, 1H), 1.76 – 1.64 (m, 2H), 1.57 – 1.34 (m, 2H), 0.87 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); δ_C (125 MHz, $CDCl_3$) 81.1, 80.1, 78.0, 76.6, 69.9, 69.1, 67.9, 39.5, 29.3, 25.9, 25.8, 25.6, 21.9, 18.0, -4.0, -4.7; Accurate mass (ES^+): Found 333.1860 (-0.6 ppm), $C_{17}H_{30}O_3SiNa$ ($M+Na^+$) requires 333.1862.

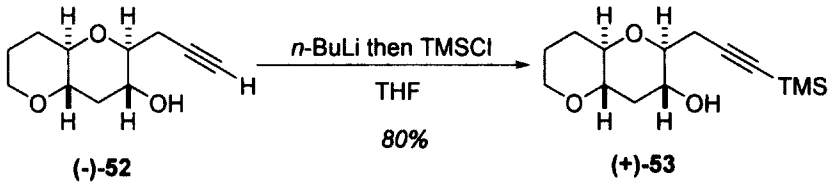


(-)-51-1 (-)-52

(2S,3R,4aS,8aR)-2-(prop-2-yn-1-yl)octahydropyrano[3,2-b]pyran-3-ol:

The silyl ether **(-)-51-1** (70 mg, 0.225 mmol) was dissolved in THF (1 ml) and TBAF (2.2 ml of 1.0 M THF solution, 2.254 mmol) was added at 0 °C. The reaction mixture was stirred for 3 hr at room temperature. The reaction mixture was diluted with EtOAc and the organic layer was washed with water (x2) and brine. The organic layer was dried with $MgSO_4$ and filtered. The organic layer was concentrated under reduced pressure. The crude oil was purified by flash column chromatography to pure alcohol **(-)-52** (41 mg, 0.209 mmol, 93%).

$[\alpha]^{20}_D$ -6.8 (c = 1.0 in $CHCl_3$), enantiomer +12.2 (c = 1.0 in $CHCl_3$); ν_{max} (neat)/cm^{-1} 3421, 2943, 2861, 2092, 1621, 1561; δ_H (500 MHz, $CDCl_3$) 3.89 (ddt, *J* = 11.8, 3.8, 1.8 Hz, 1H), 3.66 (dddd, *J* = 11.0, 9.2, 4.8, 1.4 Hz, 1H), 3.42 – 3.32 (m, 1H), 3.27 (dtd, *J* = 9.2, 5.2, 4.6, 1.0 Hz, 1H), 3.08 – 2.96 (m, 2H), 2.69 – 2.51 (m, 2H), 2.35 (dt, *J* = 11.7, 4.4 Hz, 1H), 2.05 (t, *J* = 2.8 Hz, 1H), 1.76 – 1.65 (m, 2H), 1.55 – 1.34 (m, 2H); δ_C (125 MHz, $CDCl_3$) δ 80.7, 79.6, 78.0, 76.6, 70.6, 69.2, 67.9, 38.7, 29.2, 25.5, 22.2; Accurate mass (ES^+): Found 219.1003 (+2.7 ppm), $C_{11}H_{16}O_3Na$ ($M+Na^+$) requires 219.0997.

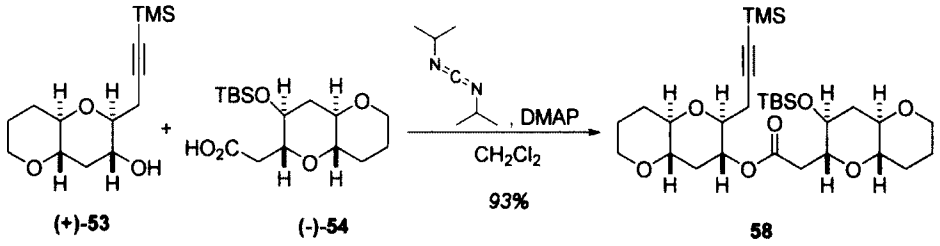


(-)-52 (+)-53

(2S,3R,4aS,8aR)-2-(3-(trimethylsilyl)prop-2-yn-1-yl)octahydropyrano[3,2-b]pyran-3-ol:

To a solution of alcohol **(-)-52** (21.9 mg, 0.112 mmol) in THF (1.1 ml) *n*-Butyllithium solution (173 µL, 0.223 mmol) was added at -78 °C. The reaction mixture was stirred for 30 min and TMSCl (18.5 µL, 15.76 mmol) was added. The reaction mixture was stirred for 1 hr at -78 °C and quenched with few drops of methanol at -78 °C. The reaction mixture was warmed to room temperature and diluted with water. The bi-layer mixture was extracted with EtOAc (x3). The combined organic layer was washed with brine, dried with sodium sulfate, filtered, and concentrated *in vacuo*. The crude material was purified by flash column chromatography to give pure product **(+)-53** (24 mg, 0.089 mmol, 80%).

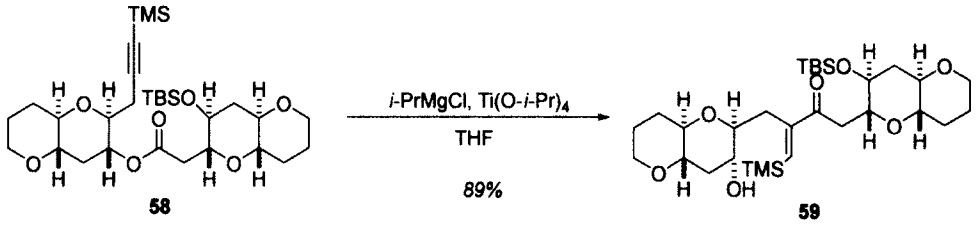
$[\alpha]^{20}_{D}$ +8.1 (c = 1.0 in $CHCl_3$), enantiomer +12.2 (c = 1.0 in $CHCl_3$); ν_{max} (neat)/cm^{-1} 3426, 2982, 2832, 2059, 1634, 1598; δ_H (500 MHz, $CDCl_3$) 3.90 (ddt, *J* = 11.4, 4.2, 1.6 Hz, 1H), 3.74 – 3.59 (m, 1H), 3.42 – 3.28 (m, 2H), 3.06 – 2.94 (m, 2H), 2.72 – 2.50 (m, 3H), 2.34 (dt, *J* = 11.5, 4.4 Hz, 1H), 2.10 – 2.00 (m, 1H), 1.75 – 1.66 (m, 2H), 1.50 (q, *J* = 11.3 Hz, 1H), 1.46 – 1.34 (m, 1H), 0.15 (s, 9H); δ_C (125 MHz, $CDCl_3$) 102.9, 88.2, 79.3, 77.8, 76.6, 70.6, 67.9, 38.3, 29.2, 25.5, 24.3, 0.1; Accurate mass (ES^+): Found 291.1387 (-1.7 ppm), $C_{14}H_{24}O_3SiNa$ ($M+Na^+$) requires 291.1392.



(2S,3R,4aS,8aR)-2-(3-(trimethylsilyl)prop-2-yn-1-yl)octahydropyrano[3,2-b]pyran-3-yl 2-((2R,3S,4aR,8aS)-3-((tert-butyldimethylsilyl)oxy)octahydropyrano[3,2-b]pyran-2-yl)acetate:

The acid **(-)-54** (36.9 mg, 0.112 mmol) and alcohol **(+)-53** (16.5 mg, 0.061 mmol) was dissolved in CH_2Cl_2 (1.2 ml). DMAP (13.7 mg, 0.112 mmol) and diisopropylcarboimide (21 μL, 16.93 mmol) were added to the reaction mixture. The reaction mixture was stirred for 14 hr. The reaction mixture was diluted with EtOAc and washed with aqueous 1N HCl solution (x2) and brine. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude oil was purified by flash column chromatography to give ester product **58** (30.7 mg, 0.057 mmol, 93%) as a clear oil.

$[\alpha]^{20}_D$ +14.10 (c = 1.0 in $CHCl_3$); ν_{max} (neat)/cm^{-1} 2992, 2889, 2001, 1682, 1564; δ_H (500 MHz, $CDCl_3$); 4.72 (ddd, *J* = 11.2, 9.5, 4.8 Hz, 1H), 3.94 – 3.82 (m, 2H), 3.56 (td, *J* = 9.3, 3.1 Hz, 1H), 3.47 (ddt, *J* = 11.3, 9.0, 3.5 Hz, 2H), 3.36 (dddd, *J* = 19.7, 15.0, 9.4, 4.9 Hz, 2H), 3.13 – 2.89 (m, 4H), 2.80 (dd, *J* = 14.5, 3.1 Hz, 1H), 2.57 (dd, *J* = 17.4, 2.7 Hz, 1H), 2.41 (dt, *J* = 11.2, 4.4 Hz, 1H), 2.38 – 2.30 (m, 2H), 2.30 – 2.21 (m, 1H), 2.15 – 2.07 (m, 1H), 2.07 – 1.99 (m, 1H), 1.79 – 1.62 (m, 5H), 1.53-1.44 (m, 3H), 0.86 (s, 9H), 0.13 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); δ_C (125 MHz, $CDCl_3$) 170.4, 103.0, 86.2, 79.4, 78.2, 78.0, 77.9, 76.7, 76.7, 76.4, 70.2, 70.1, 68.0, 68.0, 39.6, 38.1, 36.8, 35.4, 29.8, 29.2, 25.9, 25.6, 25.5, 24.8, 23.5, 23.4, 18.0, 0.3, -4.0, -4.6; Accurate mass (ES^+): Found 603.3155 (+1.0 ppm) $C_{30}H_{52}O_7Si_2Na$ ($M+Na^+$) requires 603.3149.



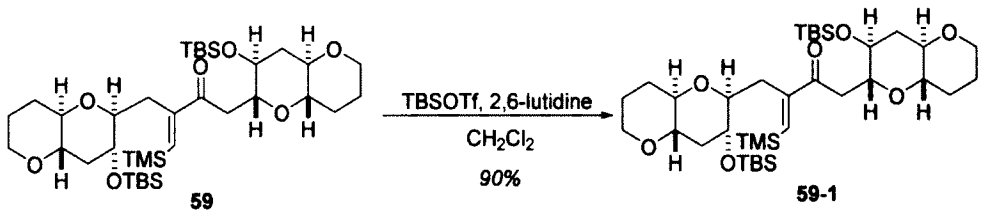
58 59

(E)-1-((2R,3S,4aR,8aS)-3-((tert-butyldimethylsilyl)oxy)octahydropyrano[3,2-b]pyran-2-yl)-3-(((2S,3R,4aS,8aR)-3-hydroxyoctahydropyrano[3,2-b]pyran-2-yl)methyl)-4-(trimethylsilyl)but-3-en-2-one:

Freshly prepared *i*-PrMgCl (570 µL, 0.627 mmol, 1.1 M solution in ether) was dissolved in ether (1 ml). The reaction solution was cooled to -40 °C and Ti(O-*i*-Pr)$_4$ (97 µL, 0.313 mmol) was added to the solution dropwise. The reaction mixture was stirred for 30 min at -40 °C and warm to 0 °C. The solution stirred for additional 10min at 0 °C and re-cooled to -40 °C. The ester substrate **58** (91 mg, 0.157 mmol) in ether (1.5 ml) was added to the reaction mixture by cannular. The reaction mixture was stirred for 1 hr at -40 °C and slowly warm to 0 °C. The reaction mixture was stirred for additional 1 hr at 0 °C and quenched with aqueous 1N HCl solution. The biphasic mixture was extracted with EtOAc (x3) and organic layer was washed with aqueous 10% sodium bicarbonate and brine. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude oil was purified by flash column chromatography to give pure product **59** (81 mg, 0.139 mmol, 89%)

$[\alpha]^{20}_D$ +10.2 (c = 1.0 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3472, 2927, 2843, 1693, 1623, 1526; δ_H (500 MHz, $CDCl_3$) 6.63 (s, 1H), 3.92 – 3.81 (m, 3H), 3.67 (td, *J* = 9.5, 2.1 Hz, 1H), 3.51 – 3.42 (m, 2H), 3.33 (tdd, *J* = 11.1, 6.3, 3.2 Hz, 3H), 3.29 – 3.19 (m, 2H), 3.19 – 3.08 (m, 1H), 3.01 (ddd, *J* = 10.9, 8.8, 4.2 Hz, 1H), 2.92 (dddt, *J* = 11.3, 9.0, 4.6, 2.7 Hz, 2H), 2.89 – 2.79 (m, 2H), 2.76 – 2.66 (m, 2H), 2.20-2.25 (m, 3H), 2.04 – 1.91 (m, 2H), 1.75 – 1.61 (m, 2H), 1.52 (q, *J* = 11.5 Hz, 1H), 1.47 – 1.31 (m, 2H), 0.87 (s, 9H), 0.19 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); δ_C (125 MHz, $CDCl_3$) 202.3, 151.6, 143.7, 81.7, 79.6, 77.8, 77.7, 76.7, 70.3, 68.6, 67.9, 40.4, 39.6, 38.8, 36.8, 32.4, 29.4, 29.2, 25.9, 25.9, 25.5, 25.5,

18.0, -0.1, -3.9, -4.7; Accurate mass (ES^+): Found 605.3310 (+0.7 ppm), $C_{30}H_{54}O_7Si_2Na$ ($M+Na^+$) requires 605.3306.

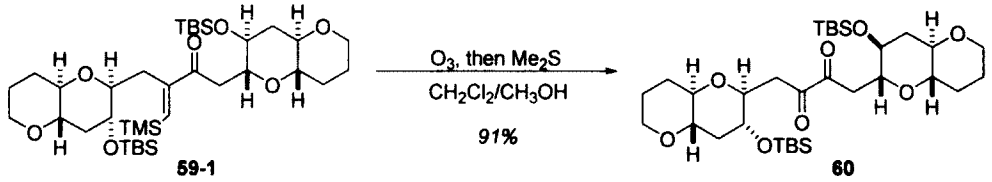


(E)-1-((2R,3S,4aR,8aS)-3-((tert-butyldimethylsilyl)oxy)octahydropyrano[3,2-b]pyran-2-yl)-3-(((2S,3R,4aS,8aR)-3-((tert-butyldimethylsilyl)oxy)octahydropyrano[3,2-b]pyran-2-yl)methyl)-4-(trimethylsilyl)but-3-en-2-one:

The alcohol **59** (50 mg, 0.086 mmol, 1 eq) was dissolved in CH_2Cl_2 (1.6 ml) and cooled to 0 °C. To this solution was added 2, 6-lutidine (26 µL, 0.214 mmol, 2.5 eq.), followed by a slow addition of *t*-butyldimethylsilyltrifluoromethane sulfonate (22 µl, 0.094 mmol, 1.1eq). After 1hr of stirring at 0 °C, the reaction mixture was quenched with saturated 10 % aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (x3). The combined organic layers were washed with brine, dried $MgSO_4$, filtered and concentrated *in vacuo*. The crude was purified by flash column chromatography to provide silyl ether **59-1** (54 mg, 0.077 mmol, 90 %) as a clear oil.

$[\alpha]^{20}_D$ +20.09 (c = 1.0 in $CHCl_3$); ν_{max} (neat)/cm^{-1} 2930, 2839, 1696, 1611, 1589; δ_H (500 MHz, $CDCl_3$) 6.44 (s, 1H), 3.93 – 3.81 (m, 3H), 3.63 (td, *J* = 9.4, 2.1 Hz, 1H), 3.45 (ddd, *J* = 10.8, 9.0, 4.5 Hz, 1H), 3.42 – 3.26 (m, 4H), 3.13 (ddd, *J* = 11.2, 8.6, 2.8 Hz, 1H), 3.04 – 2.86 (m, 6H), 2.83 – 2.77 (m, 1H), 2.74 (dd, *J* = 15.8, 9.7 Hz, 1H), 2.45 (dd, *J* = 13.2, 10.9 Hz, 1H), 2.26 (dt, *J* = 11.8, 4.4 Hz, 1H), 2.20 (dt, *J* = 11.7, 4.5 Hz, 1H), 1.99 (dt, *J* = 12.6, 4.1 Hz, 1H), 1.94 – 1.84 (m, 2H), 1.77 – 1.57 (m, 7H), 1.38 – 1.18 (m, 3H), 1.56 – 1.41 (m, 3H), 0.89 (s, 9H), 0.86 (s, 9H), 0.17 (s, 9H), 0.07 (s, 3H); δ_C (125 MHz, $CDCl_3$) 202.1, 154.9, 138.4, 82.2, 79.3, 77.7, 77.0, 72.1, 70.5, 68.0, 41.1, 39.8, 36.8,

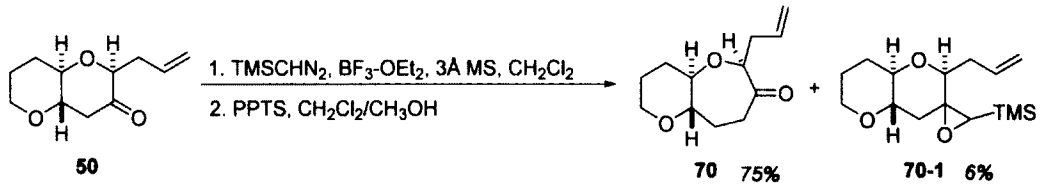
34.2, 29.9, 29.3, 29.2, 26.0, 25.9, 25.5, 25.5, 24.8, 18.1, 18.1, 0.1, -3.9, -4.2, -4.4, -4.6; Accurate mass (ES^+): Found 719.4182 (+1.5 ppm), $C_{36}H_{68}O_7Si_3Na$ ($M+Na^+$) requires 719.4171.



1-((2R,3S,4aR,8aS)-3-((tert-butyldimethylsilyl)oxy)octahydropyrano[3,2-b]pyran-2-yl)-4-((2S,3R,4aS,8aR)-3-((tert-butyldimethylsilyl)oxy)octahydropyrano[3,2-b]pyran-2-yl)butane-2,3-dione:

The enone **59-1** (50 mg, 0.072 mmol) was dissolved in MeOH-CH_2Cl_2 (v:v = 1:1, 5 ml) and cooled to -78 °C. O_3/O_2 was bubbled through the solution for 5 minutes, at which point a steel blue color persisted. Stirring was continued 5 minutes at -78 °C, then N_2 gas was bubbled through the solution until the steel blue color dissipated. Dimethyl sulfide (0.5 ml) was added and the reaction mixture was warm to room temperature, and stirring was continued for 12 hrs. The solution was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography to give aldehyde **60** (41 mg, 0.065 mmol, 91%)

$[\alpha]^{20}_D$ +9.89 (c = 1.0 in $CHCl_3$); ν_{max} (neat)/cm^{-1} 2913, 2880, 1712, 1683, 1562; δ_H (500 MHz, $CDCl_3$) 3.88 (dddd, *J* = 9.7, 7.8, 5.1, 3.1 Hz, 1H), 3.75 – 3.62 (m, 1H), 3.46 (ddd, *J* = 10.7, 9.0, 4.6 Hz, 1H), 3.34 (ddt, *J* = 14.8, 5.9, 3.8 Hz, 1H), 3.05 (dd, *J* = 16.5, 3.0 Hz, 1H), 3.02 – 2.89 (m, 2H), 2.83 (dd, *J* = 16.5, 9.6 Hz, 0H), 2.26 (dt, *J* = 11.7, 4.3 Hz, 1H), 2.00 – 1.91 (m, 1H), 1.76 – 1.60 (m, 2H), 1.51 (q, *J* = 11.3 Hz, 1H), 1.36 – 1.23 (m, 1H), 0.85 (s, 18H), 0.07 (s, 6H), 0.06 (s, 6H); δ_C (125 MHz, $CDCl_3$) ; Accurate mass (ES+): Found 649.3572 (+0.6 ppm), $C_{32}H_{58}O_8Si_2Na$ (M+Na+) requires 649.3568.

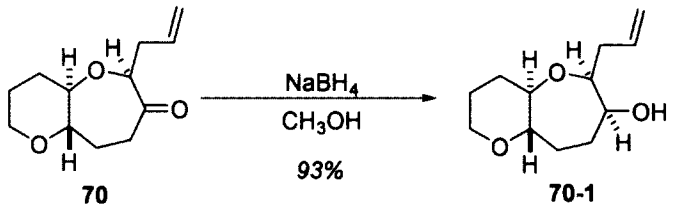


50 **70** *75%* **70-1** *6%*

(4aR,6S,9aS)-6-allylhexahydro-2H-pyrano[3,2-b]oxepin-7(6H)-one:

To a reaction solution of ketone **50** (150 mg, 0.764 mmol) and activated 3 Å MS (0.3 g) in CH_2Cl_2 (3.8 ml) was added $TMSCHN_2$ (459 µL, 0.917 mmol, 2.0 M solution in hexane), followed by BF_3-OEt_2 (376 µL, 3.06 mmol) at 0 °C. The reaction mixture was allowed to room temperature and stirred for 3hr. The reaction was quenched with 10% aqueous $NaHCO_3$ and extracted with EtOAc (x3).The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vaccuo*. The crude oil was dissolved in MeOH and CH_2Cl_2 (v:v = 1:1, 5 ml). PPTS (38.4 mg, 0.153 mmol) was added to the reaction solution. The reaction mixture was stirred for 3hr at room temperature. Triethylamine (few drops) was added to the reaction mixture and concentrated *in vacuo*. The crude material was purified by flash column chromatography to give pure ketone **70** (123 mg, 0.585 mmol, 75%) and epoxide **70-1** (side product, 12mg, 0.042 mmol, 6%).

$[\alpha]^{20}_D$ -109.2 (c = 1.0 in $CHCl_3$); ν_{max} (neat)/cm^{-1} 2920, 2892, 1719, 1662, 1593; δ_H (500 MHz, $CDCl_3$) 5.81 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.14 – 5.02 (m, 2H), 3.91 – 3.82 (m, 2H), 3.34 (td, *J* = 11.3, 3.3 Hz, 1H), 3.23 (ddd, *J* = 11.0, 9.1, 4.5 Hz, 1H), 2.96 (ddd, *J* = 10.8, 9.1, 4.7 Hz, 1H), 2.96 (ddd, *J* = 10.8, 9.1, 4.7 Hz, 1H), 2.42 (dddt, *J* = 12.7, 7.0, 4.6, 1.4 Hz, 1H), 2.37 – 2.27 (m, 2H), 2.10 (ddtd, *J* = 14.2, 7.0, 4.6, 2.1 Hz, 2H), 1.76 – 1.61 (m, 2H), 1.60 – 1.46 (m, 2H); δ_C (125 MHz, $CDCl_3$) 215.8, 133.5, 133.5, 117.8, 86.6, 81.9, 81.3, 67.7, 37.2, 37.1, 31.1, 29.8, 25.8.; Accurate mass (ES^+): Found 233.1149 (-2.1 ppm), $C_{12}H_{18}O_3Na$ ($M+Na^+$) requires 233.1154.



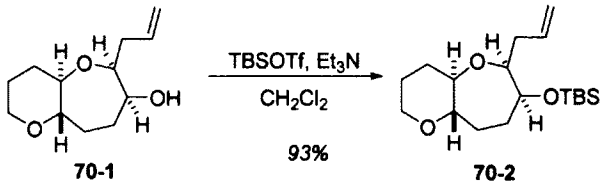
70 70-1

(4aR,6S,7R,9aS)-6-allyloctahydro-2H-pyrano[3,2-b]oxepin-7-ol:

To a solution of ketone **70** (80 mg, 0.380 mmol, 1e q) in MeOH (3.8 ml) at -10 °C was added $NaBH_4$ (72 mg, 1.902 mmol, 5eq.) slowly. The reaction was stirred for 30 min and then quenched with saturated aqueous NH_4Cl. The suspension was allowed to warm to room temperature. H_2O was then added, and the mixture was extracted with EtOAc (x3). The combined organic layers was washed with brine, dried with $MgSO_4$ and filtered. The solvent was removed *in vacuo*. The crude material was purified by flash column chromatography to give the pure product **70-1** (75 mg, 0.353 mmol, 93%) as a clear oil.

-LAH and L-selectride® gave a same major product.

$[\alpha]^{20}_D$ -62.9 (c = 1.0 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3402, 2982, 2883, 1639, 1611, 1557; δ_H (500 MHz, $CDCl_3$) 5.94 – 5.77 (m, 1H), 5.12 (dt, *J* = 17.3, 1.7 Hz, 1H), 5.05 (dt, *J* = 10.4, 1.7 Hz, 1H), 3.87-3.77 (m, 1H), (dt, *J* = 3.9, 1.8 Hz, 1H), 3.80 (q, *J* = 7.0 Hz, 1H), 3.50 (ddd, *J* = 8.1, 5.3, 2.3 Hz, 1H), 3.38 – 3.26 (m, 1H), 3.05 – 2.95 (m, 2H), 2.42 (dddt, *J* = 16.4, 8.1, 6.3, 1.5 Hz, 1H), 2.31 – 2.19 (m, 2H), 2.08 (ddt, *J* = 11.8, 4.3, 2.3 Hz, 1H), 1.94 (ddd, *J* = 13.4, 5.5, 3.0 Hz, 1H), 1.86-1.81 (m, 1H), 1.71 – 1.54 (m, 4H), 1.52 – 1.41 (m, 1H); δ_C (125 MHz, $CDCl_3$); Accurate mass (ES^+): Found 235.1319 (+3.8 ppm), $C_{12}H_{20}O_3Na$ ($M+Na^+$) requires 235.1310.

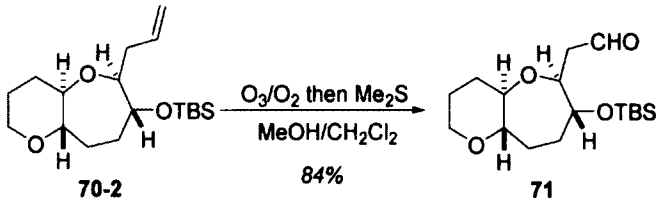


70-1 70-2

(((4aR,6S,7R,9aS)-6-allyloctahydro-2H-pyrano[3,2-b]oxepin-7-yl)oxy)(tert-butyl)dimethylsilane:

The alcohol **70-1** (52 mg, 0.245 mmol, 1 eq) was dissolved in CH_2Cl_2 (1.6 ml) and cooled to 0 °C. To this solution was added Et_3N (86 µL, 0.612 mmol) followed by the slow addition of *t*-butyldimethylsilyltrifluoromethane sulfonate (62 µL, 0.269 mmol, 1.1 eq). After 1hr of stirring at 0 °C, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (x3). The combined organic layers were washed with brine, dried $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography to provide silyl ether **70-2** (74 mg, 0.227 mmol, 93%) as a clear oil.

$[\alpha]^{20}_D$ -26.5 (c = 1.0 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3018, 2942, 2803, 2093, 1630, 1602, 1582; δ_H (500 MHz, $CDCl_3$) 5.95 – 5.82 (m, 1H), 5.12 – 5.03 (m, 1H), 5.03 – 4.96 (m, 1H), 3.88 – 3.79 (m, 2H), 3.46 (dt, *J* = 9.8, 3.4 Hz, 1H), 3.34 – 3.25 (m, 1H), 3.03 (td, *J* = 9.1, 4.0 Hz, 1H), 2.97 – 2.89 (m, 1H), 2.37 (dddt, *J* = 14.8, 9.6, 6.4, 1.4 Hz, 1H), 2.13 – 1.92 (m, 4H), 1.71 (ddd, *J* = 9.6, 7.5, 4.2 Hz, 1H), 1.68 – 1.56 (m, 3H), 1.54 – 1.38 (m, 2H), 0.87 (s, 9H), 0.03 (s, 3H), 0.03 (s, 3H); δ_C (125 MHz, $CDCl_3$) 136.7, 116.1, 85.3, 83.6, 82.4, 73.7, 68.0, 36.6, 31.2, 30.9, 28.7, 26.1, 25.9, 18.3, -4.1, -4.8; Accurate mass (ES^+): Found 349.2183 (+2.3 ppm), $C_{18}H_{34}O_3SiNa$ ($M+Na^+$) requires 349.2175.

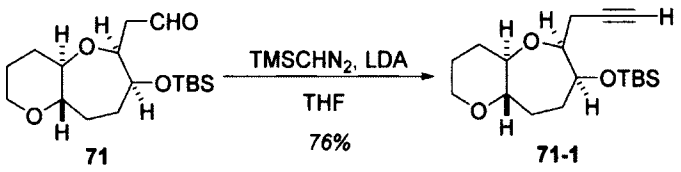


70-2 71

2-((4aR,6S,7R,9aS)-7-((tert-butyldimethylsilyl)oxy)octahydro-2H-pyrano[3,2-b]oxepin-6-yl)acetaldehyde:

The alkene **70-2** (80 mg, 0.245 mmol) was dissolved in MeOH-CH_2Cl_2 (v:v = 1:1, 5 ml) and cooled to -78 °C. O_3/O_2 was bubbled through the solution for 5 minutes, at which point a steel blue color persisted. Stirring was continued 5 minutes at -78 °C, then N_2 gas was bubbled through the solution until the steel blue color dissipated. Dimethyl sulfide (0.5 ml) was added and the reaction mixture was warm to room temperature, and stirring was continued for 12 hrs. The solution was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography to give aldehyde **71** (68 mg, 0.206 mmol, 84%)

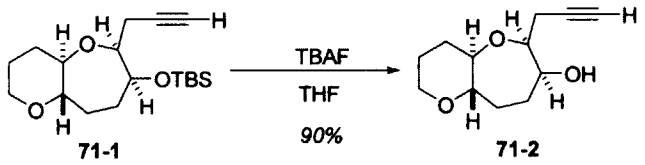
$[\alpha]^{20}_D$ -18.6 (c = 1.0 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 2973, 1895, 1720, 1630, 1582, 1528; δ_H (500 MHz, $CDCl_3$) 9.79 (t, *J* = 1.8 Hz, 1H), 4.13 (dt, *J* = 8.6, 4.1 Hz, 1H), 3.93 – 3.82 (m, 2H), 3.35 – 3.24 (m, 1H), 3.04 (dtt, *J* = 22.4, 9.2, 4.2 Hz, 3H), 2.75 (ddd, *J* = 17.1, 8.8, 2.1 Hz, 1H), 2.47 (ddd, *J* = 17.1, 4.1, 1.6 Hz, 1H), 2.06 – 1.92 (m, 4H), 1.76 – 1.57 (m, 4H), 1.53 – 1.36 (m, 3H), 0.87 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); δ_C (125 MHz, $CDCl_3$) 201.9, 83.1, 81.7, 79.5, 73.6, 68.0, 46.0, 31.3, 30.4, 29.2, 26.1, 26.1, 26.0, 26.0, 18.3, -4.2, -4.8.



tert-butyldimethyl(((4aR,6S,7R,9aS)-6-(prop-2-yn-1-yl)octahydro-2H-pyrano[3,2-b]oxepin-7-yl)oxy)silane:

A solution of *n*-BuLi (200 µL, 0.321 mmol, 1.6 M solution in hexane) was added dropwise to a solution of diisopropylamine (46 µL, 0.321 mmol) in THF (4 ml) at 0 °C, and stirred for 30 min. After cooling down to -78 °C, $TMSCHN_2$ (197 µL, 0.394 mmol, 2.0 M solution in hexane) was added to the reaction mixture. The resulting reaction mixture was stirred for 30 min. A solution of aldehyde **71** (81 mg, 0.247 mmol) in THF (2 ml) was added and stirring was maintained for additional 1 hr at -78 °C. The reaction solution was slowly warn to room temperature and stirred for 2 hr. The reaction mixture was quenched with ice-cooled water, and extracted with ether (x3). The combined organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude oil was purified by flash column chromatography to give pure alkyne **71-1** (61 mg, 0.188 mmol, 76%).

$[\alpha]^{20}_D$ -15.8 (c = 1.0 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 2983, 2849, 2833, 2542, 1629, 1582, 1529; δ_H (500 MHz, $CDCl_3$) 3.95 (ddd, *J* = 8.5, 5.2, 3.3 Hz, 1H), 3.86 (ddt, *J* = 11.4, 4.3, 1.8 Hz, 1H), 3.66 (ddd, *J* = 7.5, 6.2, 3.3 Hz, 1H), 3.38 – 3.27 (m, 1H), 3.09 – 3.02 (m, 2H), 2.52 – 2.37 (m, 2H), 2.15 – 2.07 (m, 1H), 2.08 – 1.97 (m, 2H), 1.94 (t, *J* = 2.6 Hz, 1H), 1.72 – 1.59 (m, 3H), 1.55-1.44 (m, 2H); δ_C (125 MHz, $CDCl_3$) ; Accurate mass (ES^+): Found 347.2010 (-2.3 ppm), $C_{18}H_{32}O_3SiNa$ ($M+Na^+$) requires 347.2018.

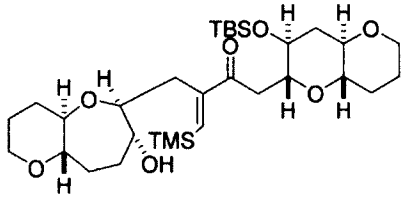


71-1 71-2

(4aR,6S,7R,9aS)-6-(prop-2-yn-1-yl)octahydro-2H-pyrano[3,2-b]oxepin-7-ol:

The silyl ether **71-1** (54.8 mg, 0.169 mmol) was dissolved in THF (1 ml) and TBAF (847 µL of 1.0 M THF solution, 0.847 mmol) was added at 0 °C. The reaction mixture was stirred for 3 hr at room temperature. The reaction mixture was diluted with EtOAc and the organic layer was washed with water (x2) and brine. The organic layer was dried with $MgSO_4$ and filtered. The organic layer was concentrated under reduced pressure. The crude oil was purified by flash column chromatography to pure alcohol **71-2** (32 mg, 0.152 mmol, 90%).

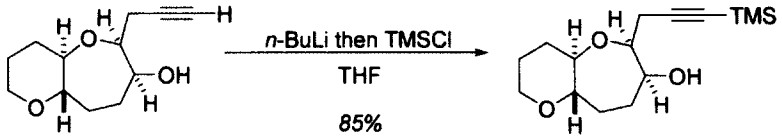
$[\alpha]^{20}_D$ +17.3 (c = 1.0 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3449, 2984, 2958, 2847, 1648, 1582, 1530; δ_H (500 MHz, $CDCl_3$) 3.99 (td, *J* = 6.7, 2.4 Hz, 1H), 3.89 – 3.83 (m, 1H), 3.70 (td, *J* = 7.2, 2.4 Hz, 1H), 3.36 – 3.26 (m, 1H), 3.11 – 2.98 (m, 2H), 2.51 (dt, *J* = 7.3, 2.6 Hz, 2H), 2.32 – 2.20 (m, 1H), 2.10 (dtd, *J* = 12.6, 3.7, 1.7 Hz, 1H), 2.01 – 1.92 (m, 2H), 1.72 – 1.56 (m, 5H), 1.51-1.42 (m, 1H); δ_C (125 MHz, $CDCl_3$) ; Accurate mass (ES^+): Found 233.1159 (+ 2.1 ppm), $C_{12}H_{18}O_3Na$ ($M+Na^+$) requires 233.1154.



(E)-1-((2R,3S,4aR,8aS)-3-((tert-butyldimethylsilyl)oxy)octahydropyrano[3,2-b]pyran-2-yl)-3-(((4aR,6S,7R,9aS)-7-hydroxyoctahydro-2H-pyrano[3,2-b]oxepin-6-yl)methyl)-4-(trimethylsilyl)but-3-en-2-one:

$[\alpha]^{20}_D$ +37.3 (c = 1.0 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3472, 2995, 2948, 2863, 1692, 1639, 1557; δ_H (500 MHz, $CDCl_3$) 6.42 (s, 1H), 3.87 (dd, *J* = 13.5, 9.8 Hz, 2H), 3.81 – 3.74 (m, 1H), 3.69 (dt, *J* =

8.5, 4.3 Hz, 1H), 3.45 (ddd, *J* = 10.6, 9.0, 4.5 Hz, 1H), 3.45 (ddd, *J* = 10.6, 9.0, 4.5 Hz, 1H), 3.40 – 3.25 (m, 2H), 3.21 (td, *J* = 7.6, 5.7 Hz, 1H), 3.14 – 2.87 (m, 7H), 2.80 (dd, *J* = 16.2, 10.2 Hz, 1H), 2.54 (dd, *J* = 12.9, 5.7 Hz, 1H), 2.26 (dt, *J* = 11.6, 4.4 Hz, 1H), 2.09 – 1.90 (m, 2H), 1.88 – 1.60 (m, 8H), 1.50 – 1.17 (m, 4H), 0.87 (s, 9H), 0.21 (s, 9H), 0.08 (s, 3H), 0.08 (s, 3H); δ_C (125 MHz, $CDCl_3$) 201.2, 154.4, 139.5, 86.5, 84.1, 83.7, 79.3, 77.8, 76.7, 73.8, 70.3, 68.0, 67.9, 40.6, 39.6, 37.0, 36.8, 31.5, 31.5, 29.9, 29.3, 27.5, 26.1, 25.9, 25.4, 24.8, 18.1, -0.1, -3.9, -4.6; Accurate mass (ES^+): Found 619.3472 (+1.6 ppm), $C_{31}H_{56}O_7Si_2Na$ ($M+Na^+$) requires 619.3462.



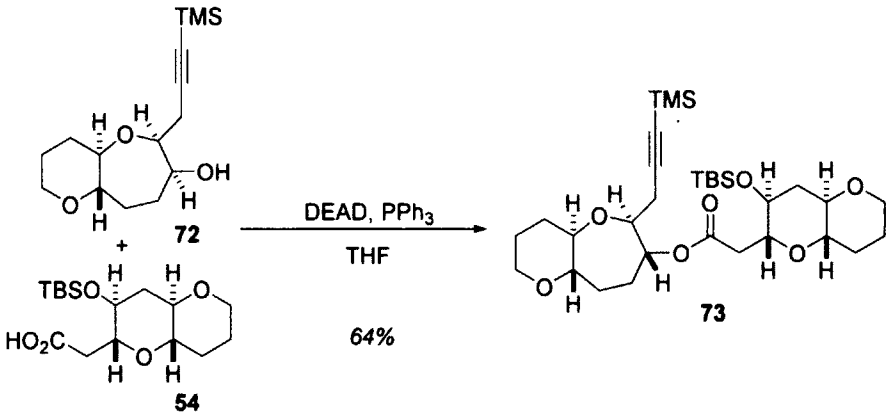
71-2 72

(4aR,6S,7R,9aS)-6-(3-(trimethylsilyl)prop-2-yn-1-yl)octahydro-2H-pyrano[3,2-b]oxepin-7-ol:

To a solution of alcohol **71-2** (27.3 mg, 0.130 mmol) in THF (1.3 ml) *n*-Butyllithium solution (162 µL, 0.260 mmol) was added at -78 °C. The reaction mixture was stirred for 30 min and TMSCl (26 µL, 0.203 mmol) was added. The reaction mixture was stirred for 1 hr at -78 °C and quenched with few drops of methanol at -78 °C. The reaction mixture was warmed to room temperature and diluted with water. The bi-layer mixture was extracted with EtOAc (x3). The combined organic layer was washed with brine, dried with sodium sulfate, filtered, and concentrated *in vacuo*. The crude material was purified by flash column chromatography to give pure product **72** (31 mg, 0.110 mmol, 85%).

$[\alpha]^{20}_D$ +25.4 (c = 1.0 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3428, 2930, 283, 2849, 2393, 1629, 1611, 1583, 1520; δ_H (500 MHz, $CDCl_3$) 3.97 (bs, 1H), 3.87 (ddt, *J* = 12.9, 4.1, 1.9 Hz, 1H), 3.69 (td, *J* = 7.3, 2.4

Hz, 1H), 3.37 – 3.23 (m, 1H), 3.12 – 2.97 (m, 2H), 2.54 (qdd, *J* = 16.9, 7.3, 0.9 Hz, 2H), 2.33 – 2.22 (m, 1H), 2.15 – 2.05 (m, 1H), 2.01 – 1.92 (m, 1H), 1.91 – 1.83 (m, 1H), 1.74 – 1.54 (m, 5H), 1.53 – 1.42 (m, 1H), 0.14 (s, 9H); δ_C (125 MHz, $CDCl_3$) ; Accurate mass (ES^+): Found 305.1540 (-2.9 ppm), $C_{15}H_{26}O_3SiNa$ ($M+Na^+$) requires 305.154.

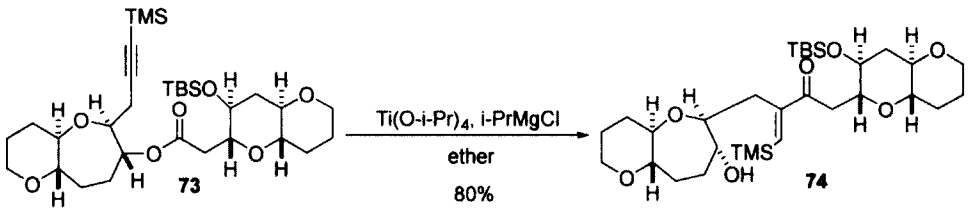


(4aR,6S,7R,9aS)-6-(3-(trimethylsilyl)prop-2-yn-1-yl)octahydro-2H-pyrano[3,2-b]oxepin-7-yl 2-((2R,3S,4aR,8aS)-3-((tert-butyldimethylsilyl)oxy)octahydropyrano[3,2-b]pyran-2-yl)acetate:

DEAD (37 µL, 0.236 mmol) and triphenylphosphine (61.8 mL, 0.236 mmol) were dissolved in THF (1 ml). A solution of acid **54** (30 mg, 0.091 mmol) and alcohol **54** (22.2 mg, 0.079 mmol) was added to the reaction mixture at room temperature. The reaction mixture was stirred for 14 hrs. The reaction mixture was diluted with EtOAc and washed with water and brine. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude oil was purified by flash column chromatography to give ester product **73** (30 mg, 0.050 mmol, 64%) as a clear oil.

$[\alpha]^{20}_D$ +44.9 (c = 1.0 in $CHCl_3$); ν_{max} (neat)/cm^{-1} 2983, 2840, 1689, 1620, 1583, 1520; δ_H (500 MHz, $CDCl_3$) 4.95 (td, *J* = 4.7, 3.0 Hz, 1H), 4.34 – 4.16 (m, 1H), 3.66 (dt, *J* = 7.8, 4.9 Hz, 1H), 3.58 (td, *J* = 9.4, 3.1 Hz, 1H), 3.47 (ddd, *J* = 10.7, 8.9, 4.5 Hz, 1H), 3.41 – 3.26 (m, 3H), 3.15 (ddd, *J* = 11.0, 9.2,

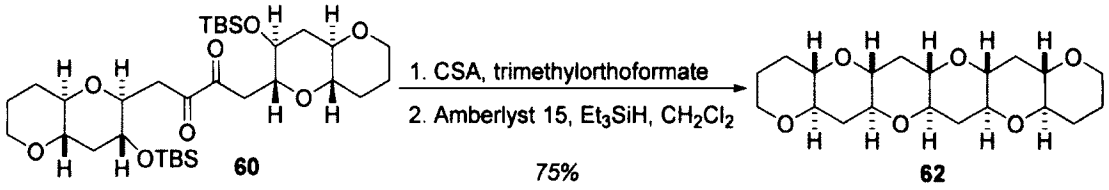
4.5 Hz, 1H), 3.05 – 2.92 (m, 3H), 2.82 (dd, *J* = 14.7, 3.1 Hz, 1H), 2.52 – 2.36 (m, 2H), 2.36 – 2.21 (m, 2H), 2.07 (d, *J* = 27.6 Hz, 2H), 1.99 (ddd, *J* = 17.5, 10.6, 3.4 Hz, 1H), 1.95 – 1.79 (m, 4H), 1.71-1.64 (m, 6H), 1.57 – 1.45 (m, 3H), 1.29 – 1.22 (m, 2H), 0.87 (s, 9H), 0.13 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H);δ_C (125 MHz, $CDCl_3$) ; Accurate mass (ES^+): Found 617.3298 (-1.3 ppm), $C_{31}H_{54}O_7Si_2Na$ ($M+Na^+$) requires 617.3306.



(E)-3-(((4aR,6S,7R,9aS)-7-((tert-butyldimethylsilyl)oxy)octahydro-2H-pyrano[3,2-b]oxepin-6-yl)methyl)-1-((2R,3S,4aR,8aS)-3-((tert-butyldimethylsilyl)oxy)octahydropyrano[3,2-b]pyran-2-yl)-4-(trimethylsilyl)but-3-en-2-one:

Freshly prepared *i*-PrMgCl (109 µL, 0.202 mmol, 1.85 M solution in ether) was dissolved in THF (1 ml). The reaction solution was cooled to -40 °C and Ti(O-*i*-Pr)$_4$ (30 µL, 0.101 mmol) was added to the solution dropwise. The reaction mixture was stirred for 30 min at -40 °C and warm to 0 °C. The solution stirred for additional 10 min at 0 °C and re-cooled to -40 °C. The ester substrate **73** (30 mg, 0.050 mmol) in THF (1 ml) was added to the reaction mixture by cannular. The reaction mixture was stirred for 1 hr at -40 °C and slowly warm to 0 °C. The reaction mixture was stirred for additional 1 hr at 0 °C and quenched with aqueous 1N HCl solution. The biphasic mixture was extracted with EtOAc (x3) and organic layer was washed with aqueous 10% sodium bicarbonate and brine. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude oil was purified by flash column chromatography to give pure product **74** (24 mg, 0.040 mmol, 80%).

$[\alpha]^{20}_D$ +41.0 (c = 1.0 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 2930, 2912, 2882, 2840, 1688, 1620, 1592; δ_H (500 MHz, $CDCl_3$) 6.54 (s, 1H), 3.92 – 3.79 (m, 3H), 3.72 (q, *J* = 3.9 Hz, 1H), 3.65 (td, *J* = 9.3, 2.2 Hz, 1H), 3.45 (ddt, *J* = 9.0, 6.6, 4.4 Hz, 2H), 3.39 – 3.32 (m, 1H), 3.30 – 3.18 (m, 2H), 3.06 – 2.86 (m, 7H), 2.75 (dd, *J* = 15.5, 9.6 Hz, 1H), 2.64 (dd, *J* = 13.2, 4.5 Hz, 1H), 2.45 (dd, *J* = 13.2, 9.9 Hz, 1H), 2.26 (dt, *J* = 11.5, 4.3 Hz, 1H), 2.03 – 1.94 (m, 1H), 1.93 – 1.80 (m, 3H), 1.75-1.64 (m, 8H), 1.63 – 1.43 (m, 6H), 1.37 – 1.17 (m, 9H), 0.89 (s, 9H), 0.87 (s, 9H), 0.19 (s, 9h), 0.08 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H), 0.04 (s, 3H); δ_C (125 MHz, $CDCl_3$) 201.5, 154.5, 140.2, 85.6, 82.5, 79.9, 79.5, 77.7, 77.4, 77.0, 75.3, 70.6, 68.0, 67.7, 41.1, 39.8, 36.8, 36.0, 31.2, 29.9, 29.4, 28.5, 27.0, 26.0, 26.0, 25.9, 25.8, 25.5, 24.8, 23.5, 18.1, 18.1, 0.1, -3.9, -4.4, -4.6; Accurate mass (ES^+): Found 733.4369 (+5.7 ppm), $C_{37}H_{70}O_7Si_3Na$ ($M+Na^+$) requires 733.4327.

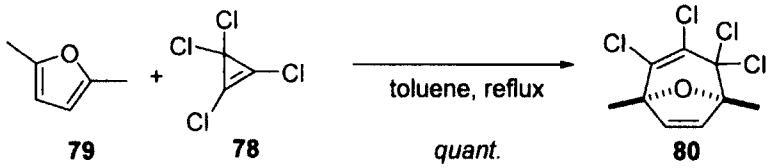


(4aR,5aS,6aR,7aS,8aR,12aS,13aR,14aS,15aR,16aS)-icosahydropyrano[2'',3'':5',6']pyrano[2',3':5,6]pyrano[3,2-b]pyrano[2',3':5,6]pyrano[2,3-e]pyran:

To a solution of diketone **60** (31.6 mg, 0.050 mmol) in MeOH (0.5 ml) and CH_2Cl_2 (0.5 ml) were added trimethylorthoformate (557 µL, 5.04 mmol) and CSA (46.8 mg) at room temperature. The reaction mixture was stirred for 36 hr at 50 °C. The reaction was quenched with Et_3N and concentrated *in vacuo*. The crude material was passed through short pad of silica and washed with 50% EtOAc in Hexane. The filtrate was concentrated *in vacuo* and used to the next step without further purification.

The crude ketal was dissolved in CH_2Cl_2 (1 ml). Triethylsilane (145 µL, 0.907 mmol) and Amberlyst 15 ion exchange resin (100 mg) were added to the reaction mixture. The reaction mixture was stirred for 16 hr under gentle reflux condition. The reaction mixture was filtered through Celite and the filtrate was concentrated *in vacuo*. The crude material was purified by flash column chromatography to give pure hexa-polyether compound **62** (13.9 mg, 0.038 mmol, 75%).

ν_{max} (neat)/cm^{-1} 2983, 2969, 1672, 1630, 1574; δ_H (500 MHz, $CDCl_3$) 3.91 (ddt, J = 11.7, 4.3, 1.8 Hz, 2H), 3.68 (t, J = 3.1 Hz, 2H), 3.49 – 3.33 (m, 4H), 3.16 – 2.96 (m, 6H), 2.33 – 2.19 (m, 4H), 2.11 – 1.97 (m, 2H), 1.78 – 1.66 (m, 4H), 1.66 – 1.53 (m, 4H), 1.48 – 1.34 (m, 2H); δ_C (125 MHz, $CDCl_3$) 78.3, 77.5, 77.4, 74.3, 73.7, 68.1, 35.9, 34.6, 29.5, 25.7; Accurate mass (ES^+): Found 389.1927 (-2.0 ppm), $C_{20}H_{30}O_6Na$ ($M+Na^+$) requires 389.1935.

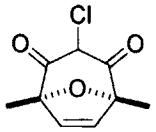


79 **78** *quant.* **80**

(1S,5R)-2,3,4,4-tetrachloro-1,5-dimethyl-8-oxabicyclo[3.2.1]octa-2,6-diene:

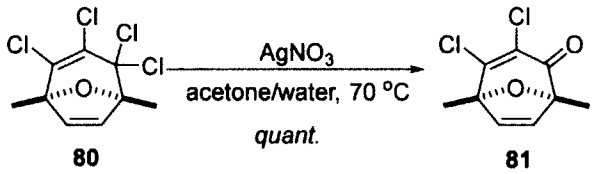
2,5-Dimethylfuran **79** (11.2 ml, 103.9 mmol) was added to a solution of tetrachlorocyclopropene **78** (10 ml, 79.9 mmol) in toluene (267 ml). The resulting mixture was heated to 110 °C and stirred for 12hr. The volatile material was removed *in vacuo*. The crude material (21.9 g, 79.9 mmol, quantitative) as a pale brown semisolid **80** was treated to the next step without further purification.

ν_{max} (neat)/cm^{-1} 3094, 2990, 2940, 2871, 1592, 1448, 1379, 1379, 1177, 1112; δ_H (500 MHz, $CDCl_3$) 6.53 (d, J = 5.5 Hz, 1H), 6.17 (d, J = 5.5 Hz, 1H), 1.82 (s, 3H), 1.62 (s, 3H); δ_C (125 MHz, $CDCl_3$) 141.8, 141.8, 140.9, 133.7, 133.7, 128.8, 92.9, 88.2, 20.1, 19.6.



(1R,5S)-3-chloro-1,5-dimethyl-8-oxabicyclo[3.2.1]oct-6-ene-2,4-dione:

ν_{max} (neat)/cm^{-1} 3097, 2987, 2936, 2909, 1723, 1444, 1372, 1222, 1130; δ_H (500 MHz, $CDCl_3$) 6.07 (s, 2H), 5.90 (s, 1H), 1.73 (s, 6H); δ_C (125 MHz, $CDCl_3$) 195.1, 136.2, 93.7, 71.8, 18.1; Accurate mass (ES^+): Found (ppm), $C_9H_9ClO_3Na$ ($M+Na^+$) requires 223.0138.

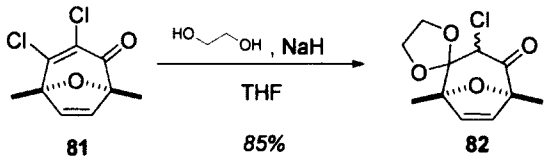


80 **81**

(1R,5S)-3,4-dichloro-1,5-dimethyl-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one:

To a stirred solution of tetrachlorooctene **80** (24.09 g, 87.93 mmol) in water and acetone (600 ml, v:v = 1:1) was added silver nitrate (32.86 g, 193.44 mmol). The whole mixture was stirred for 15 hr at 70 °C then cooled to room temperature. The biphasic mixture was filtered through celite and the filtrate was extracted with EtOAc (x3), washed with brine, and dried over sodium sulfate. The organic layer was concentrated *in vacuo*. The resulting crude **81** (19 g, 87.93 mmol, *quant.*) was used to the next step without further purification.

ν_{max} (neat)/cm^{-1} 2992, 2939, 1710, 1566, 1446, 1377, 1275, 1216, 1175; δ_H (500 MHz, $CDCl_3$) 6.65 (d, J = 5.4 Hz, 1H), 6.22 (d, J = 5.4 Hz, 1H), 1.73 (s, 3H), 1.59 (s, 3H); δ_C (125 MHz, $CDCl_3$) 187.1, 157.2, 142.4, 135.4, 123.9, 93.0, 90.2, 20.7, 17.7; Accurate mass (ES^+): Found (ppm), $C_9H_8Cl_2O_2Na$ ($M+Na^+$) requires 240.9799.

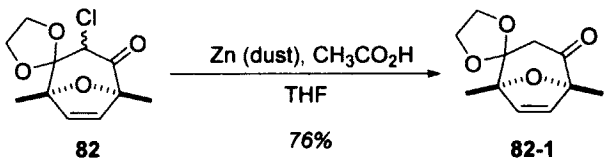


81 82

(1S,5R)-3-chloro-1,5-dimethyl-8-oxaspiro[bicyclo[3.2.1]octane-2,2'-[1,3]dioxolan]-6-en-4-one:

To a solution of ethylene glycol (23.2 ml, 0.42 mol) in THF (500 ml) was added NaH (11.09 g, 0.28 mol, 60% in oil) at 0 °C. The reaction mixture was stirred for 30 min at this temperature, and then enone **81** (30.38 g, 0.140 mol) solution in THF (140 ml) was added to the reaction solution via cannula. The whole mixture was allowed to warm to room temperature and stirred for 2 hr. The reaction was quenched with saturated ammonium chloride, extracted with EtOAC (x3), washed with brine, dried over magnesium sulfate and filtered. The organic layer was concentrated *in vacuo*. The crude oil was purified by flash column chromatography to give pure product **82** (29 g, 0.119 mol, 85%).

ν_{max} (neat)/cm^{-1} 2981, 2948, 1719, 1683, 1583, 1482, 1372, 1313, 1128, 1118; δ_H (500 MHz, $CDCl_3$, *-minor isomer) 6.31 (d, *J* = 5.8 Hz, 1H), 6.17* (d, *J* = 5.6 Hz, 1H), 6.13 (d, *J* = 5.8 Hz, 1H), 5.88* (d, *J* = 5.6 Hz, 1H), 5.30 (s, 1H), 5.17* (s, 1H), 4.44 – 4.36 (m, 1H), 4.35 – 4.27 (m, 1H, 1H*), 4.23 – 4.03 (m, 2H, 2H*), 3.95* (dt, *J* = 8.6, 7.0 Hz, 1H), 1.57* (s, 3H), 1.50 (s, 3H), 1.48 (s, 3H, 3H*); δ_C (125 MHz, $CDCl_3$) 197.5*, 192.6, 140.1*, 138.7, 136.7, 132.1*, 112.8*, 111.6, 92.6*, 91.4*, 91.3, 90.5, 77.4*, 71.2, 68.3, 67.3, 67.1*, 66.6*, 18.0*, 17.5*, 17.5, 16.9; Accurate mass (ES$^+$): Found (ppm), $C_{11}H_{13}ClO_4Na$ (M+Na$^+$) requires 267.0400.

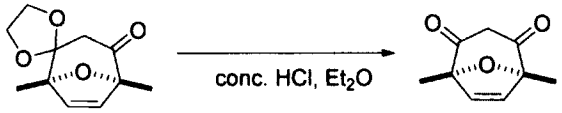


82 82-1

(1S,5R)-1,5-dimethyl-8-oxaspiro[bicyclo[3.2.1]octane-2,2'-[1,3]dioxolan]-6-en-4-one:

To a reaction mixture of chloroketone **82** (23.05 g, 94.21 mmol) in THF were added Zn dust (18.48 g, 282.62 mmol) and acetic acid (53.9 ml, 942.08 mmol). The reaction mixture was stirred for 3 hr under gentle reflux. The reaction mixture was cooled to room temperature and filtered through celite. The resulting filtrate was concentrated *in vacuo*. The crud oil was purified by flash column chromatography to give de-chlorinated product **82-1** (15.0 g, 73.63 mmol, 76%).

ν_{max} (neat)/cm^{-1} 2985, 2936, 2889, 1726, 1446, 1376, 1310, 1108; δ_H (500 MHz, $CDCl_3$) 6.24 (d, J = 5.7 Hz, 1H), 5.99 (d, J = 5.7 Hz, 1H), 4.06 – 3.99 (m, 2H), 3.99 – 3.92 (m, 2H), 3.03 (d, J = 17.7 Hz, 1H), 2.69 (d, J = 17.6 Hz, 1H), 1.45 (s, 3H), 1.43 (s, 3H); δ_C (125 MHz, $CDCl_3$) 201.3, 139.2, 135.1, 109.2, 91.4, 90.4, 65.6, 65.5, 47.5, 17.1, 16.5; Accurate mass (ES^+): Found 211.0970 (0.0 ppm), $C_{11}H_{15}O_4$ ($M+H^+$) requires 211.0970.

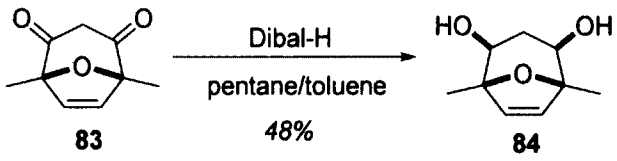


82-1 *quant.* 83

(1R,5S)-1,5-dimethyl-8-oxabicyclo[3.2.1]oct-6-ene-2,4-dione:

To a reaction mixture of dioxolane **82-1** (19.0 g, 90.38 mmol) in ether (180 ml) was added *conc.* HCl (90 ml) at 0 °C. The reaction mixture was allowed to room temperature and stirred overnight. The reaction mixture was diluted with water and EtOAc and washed with water (x3) and brine. The organic layer was dried over sodium sulfate and concentrated *in vacuo*. The crude material **83** (15.02 g, 90.38 mmol) used to the next step without further purification.

ν_{max} (neat)/cm^{-1} 2987, 2937, 1819, 1444, 1373, 1287, 1141, 1111, 1049; δ_H (500 MHz, $CDCl_3$) 6.03 (s, 2H), 3.66 (d, *J* = 19.9 Hz, 1H), 3.43 (d, *J* = 19.9 Hz, 1H), 1.58 (s, 6H); δ_C (125 MHz, $CDCl_3$) 200.5, 135.9, 93.1, 51.0, 17.3; Accurate mass (ES^+): Found 167.0709 (+0.6 ppm), C9H11O3 ($M+H^+$) requires 167.0708.

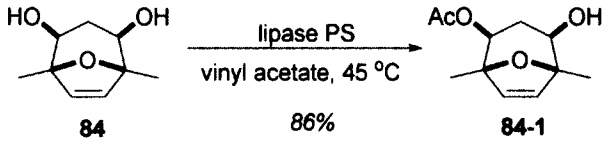


83 **84**

(1R,2S,4R,5S)-1,5-dimethyl-8-oxabicyclo[3.2.1]oct-6-ene-2,4-diol:

To a reaction mixture of diketone **83** (13.8 g, 83.05 mmol) in toluene (55 ml) was added DIBAL-H in pentane (550 ml) dropwise over 20 min. at -78 °C. The whole mixture was stirred for 3 hr at -78 °C. The reaction mixture was quenched with MeOH at -78 °C and then warm to room temperature. The mixture was concentrated *in vacuo* and the residual mixture was dissolved in EtOAc. Saturated aqueous Rochelle salt was added to the solution and stirred for 5 hr. The clear biphasic mixture was extracted with EtOAc (x3), washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated *in vacuo*. The crude oil was purified by flash column chromatography to give pure *meso*-diol **84** (the desired diastereomer; 6.8 g, 39.9 mmol, 48%).

ν_{max} (neat)/cm^{-1} 3396, 2973, 2931, 1716, 1445, 1373, 1262, 1192, 1098, 1067; δ_H (500 MHz, $CDCl_3$) 5.98 (s, 2H), 3.48 (dd, *J* = 4.8, 1.5 Hz, 2H), 2.97 (s, 2H), 2.34 (dt, *J* = 15.4, 4.7 Hz, 1H), 1.81 (dt, *J* = 15.4, 1.4 Hz, 1H), 1.41 (s, 6H); δ_C (125 MHz, $CDCl_3$) 136.8, 88.3, 67.3, 36.2, 20.1; Accurate mass (ES^+): Found 171.1024 (+1.8 ppm), $C_9H_{15}O_3$ ($M+H^+$) requires 171.1021.

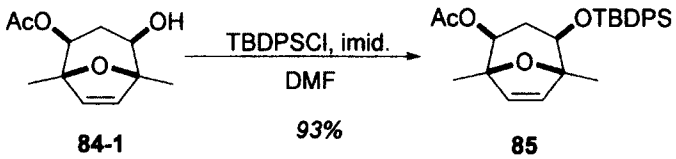


84 *86%* **84-1**

(1S,2R,4S,5R)-4-hydroxy-1,5-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-2-yl acetate:

To a solution of *meso*-diol **84** (15.0 g, 88.13 mmol) in vinyl acetate (294 ml) was added Lipase PS (15.0 g). The reaction mixture was stirred for 3 days at 45 °C. The reaction was filtered through a celite pad and concentrated *in vacuo*. The crude material was purified by flash column chromatography to give pure product **84-1** (16.1 g, 75.77 mmol, 86%).

ν_{max} (neat)/cm^{-1} 3494, 2978, 2935, 1733, 1374, 1267, 1239, 1102, 1043; $[\alpha]^{20}_{D}$ -+49.6 (c = 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 6.08 (d, *J* = 6.0 Hz, 1H), 5.97 (d, *J* = 6.0 Hz, 1H), 4.77 (dd, *J* = 5.1, 1.1 Hz, 1H), 3.41 (d, *J* = 4.6 Hz, 1H), 2.42 (dtd, *J* = 15.9, 4.9, 0.9 Hz, 1H), 2.13 (s, 3H), 1.79 (dd, *J* = 15.9, 1.2 Hz, 1H), 1.44 (s, 3H), 1.32 (s, 3H); δ_C (125 MHz, $CDCl_3$) 170.8, 138.2, 135.6, 88.5, 87.0, 68.7, 66.8, 33.9, 21.4, 20.0, 20.0; Accurate mass (ES$^+$): Found 213.1151 (+11.3 ppm), $C_{11}H_{17}O_4$ (M+H$^+$) requires 213.1127.



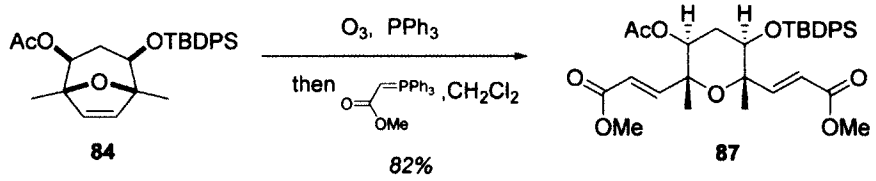
84-1 *93%* **85**

(1S,2R,4S,5R)-4-((tert-butyldiphenylsilyl)oxy)-1,5-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-2-yl acetate:

To a solution of alcohol **84-1** (10.9 g, 51.50 mmol) in DMF (25 ml) were added TBDPSCl (16.07 ml, 61.80 mmol) and imidazole (7.01 g, 103.00 mmol) at room temperature. The reaction mixture was stirred for 14 hr. The reaction solution was diluted with EtOAc and washed with water (x3) and brine. The organic layer was dried with sodium sulfate and filtered. The organic layer was

concentrated *in vacuo*. The crude material was purified by flash column chromatography to give pure product **85** (21.59 g, 47.90 mmol, 93%).

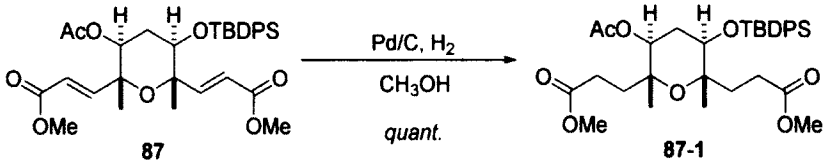
ν_{max}(neat)/cm^{-1} 2932, 2858, 1731, 1473, 1372, 1265, 1246, 1104, 1162; $[\alpha]^{20}_{D}$ -83.0 (c = 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 7.78 – 7.65 (m, 3H), 7.48 – 7.32 (m, 6H), 5.91 (s, 2H), 4.62 (dd, *J* = 5.7, 1.2 Hz, 1H), 3.59 (dd, *J* = 5.5, 1.1 Hz, 1H), 2.15 (dt, *J* = 16.5, 5.7 Hz, 1H), 2.11 (d, *J* = 1.0 Hz, 3H), 1.66 – 1.59 (m, 1H), 1.35 (s, 3H), 1.34 (s, 3H), 1.11 (d, *J* = 0.9 Hz, 9H); δ_C (125 MHz, $CDCl_3$) 171.3, 138.3, 136.3, 136.2, 136.2, 134.3, 133.9, 129.8, 127.7, 127.6, 127.6, 88.5, 86.2, 68.4, 67.1, 33.6, 27.3, 21.4, 21.0, 20.0, 19.8; Accurate mass (ES$^+$): Found 451.2292 (-2.9 ppm), $C_{27}H_{35}O_4Si$ (M+Na$^+$) requires 451.2305.



dimethyl 3,3'-((2R,3S,5R,6S)-3-acetoxy-5-((tert-butyldiphenylsilyl)oxy)-2,6-dimethyltetrahydro-2H-pyran-2,6-diyl)(2E,2'E)-diacrylate:

The alkene reactant **84** (15.26 g, 33.86 mmol) was dissolved in CH_2Cl_2 (330 ml) and cool to -78 °C. The reaction solution was bubbled with ozone until the solution changed into metallic blue color (*ca.* 15 min). After removing ozone source, the solution was stirred for additional 10 min at -78 °C. The reaction was quenched with PPh_3 (8.88 g, 33.86 mmol) and allowed to room temperature. The reaction was stirred for additional 3 hr. Ylide (34.07 g, 101.59 mmol) was added and stirred for additional 14 hr at room temperature. The solvent was removed under reduced pressure. The crude material was purified by flash column chromatography to give bis-enone **87** (16.51 g, 27.77 mmol, 82%).

ν_{max} (neat)/cm^{-1} 3067, 3004, 2952, 2884, 2859, 1723, 1660, 1429, 1305; $[\alpha]^{20}_D$ +104.3 (c = 3.0 in CH_3Cl); δ_H (500 MHz, $CDCl_3$) 7.70 – 7.60 (m, 4H), 7.48 – 7.33 (m, 6H), 7.08 (d, *J* = 15.7 Hz, 1H), 6.72 (d, *J* = 15.7 Hz, 1H), 5.99 (d, *J* = 15.7 Hz, 1H), 5.96 (d, *J* = 15.7 Hz, 1H), 4.45 – 4.36 (m, 1H), 3.75 (s, 3H), 3.70 (s, 3H), 3.66 – 3.58 (m, 1H), 1.96 (s, 3H), 1.90 – 1.81 (m, 2H), 1.53 (s, 3H), 1.40 (s, 3H), 1.06 (s, 9H); δ_C (125 MHz, $CDCl_3$) 169.4, 167.1, 167.0, 152.7, 151.2, 136.0, 135.8, 133.9, 132.1, 130.3, 123.0, 128.0, 127.8, 127.8, 119.1, 118.8, 77.5, 74.9, 73.1, 71.8, 51.7, 51.7, 30.4, 27.1, 27.1, 27.1, 21.1, 21.1, 20.5, 19.4.; Accurate mass (ES$^+$): Found 595.2648 (-13.3 ppm), $C_{33}H_{43}O_8Si$ ($M+H^+$) requires 595.2727.

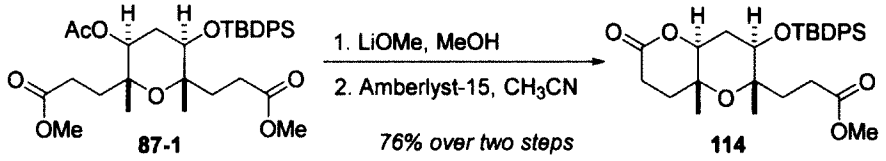


dimethyl 3,3'-((2R,3S,5R,6S)-3-acetoxy-5-((tert-butyldiphenylsilyl)oxy)-2,6-dimethyltetrahydro-2H-pyran-2,6-diyl)dipropionate:

To a reaction solution of enone **87** (14.13 g, 23.76 mmol) in MeOH (240 ml) was added 10% Pd/C (706 mg) and applied hydrogen gas through a balloon. The whole mixture was stirred for 12 hr. The reaction mixture was filtered through celite and concentrated *in vacuo*. The crude **87-1** was used to the next step without further purification.

ν_{max} (neat)/cm^{-1} 2952, 2857, 1736, 1472, 1428, 1377, 1232, 1168, 1103; $[\alpha]^{20}_D$ +32.9 (c = 2.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 7.65 (ddd, *J* = 23.7, 8.0, 1.5 Hz, 4H), 7.49 – 7.35 (m, 6H), 4.36 (dd, *J* = 11.5, 4.9 Hz, 1H), 3.63 (s, 3H), 3.60 (s, 3H), 3.51 (dd, *J* = 11.3, 4.9 Hz, 1H), 2.37 – 2.15 (m, 3H), 2.01 (ddd, *J* = 15.7, 10.3, 5.4 Hz, 1H), 1.94 (s, 3H), 1.95-1.86 (m, 1H), 1.87 – 1.76 (m, 2H), 1.71 – 1.58 (m, 3H), 1.50 (ddd, *J* = 14.0, 10.2, 5.8 Hz, 1H), 1.31 (s, 3H), 1.19 (s, 3H), 1.04 (s, 9H); δ_C (125 MHz,

$CDCl_3$) 174.5, 174.5, 169.8, 136.1, 135.9, 134.3, 132.7, 130.2, 129.9, 128.0, 127.7, 77.4, 76.6, 74.1, 72.8, 72.5, 51.6, 51.5, 36.5, 36.3, 30.8, 28.1, 27.1, 21.2, 21.1, 21.0, 19.4; Accurate mass (ES^+): Found 599.2953 (-4.8 ppm), $C_{33}H_{48}O_8Si$ ($M+H^+$) requires 599.3040.



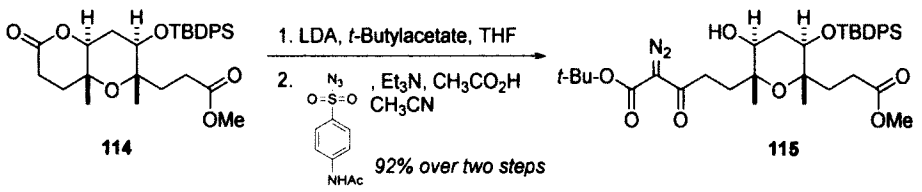
methyl 3-((2S,3R,4aS,8aR)-3-((tert-butyldiphenylsilyl)oxy)-2,8a-dimethyl-6-oxooctahydropyrano[3,2-b]pyran-2-yl)propanoate:

To a reaction solution of bis-methyl ester **87-1** (14.6 g, 24.38 mmol) in MeOH (100 ml) was added a solution of NaOMe (8.33 g, 219.44 mmol) in MeOH (140 ml) at 0 °C. The mixture was allowed to room temperature and stirred for 2 hr. The reaction was quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted with EtOAc (x3). The combined organic layer was washed with brine and dried over sodium sulfate. The crude mixture was filtered and concentrated *in vacuo*. The crude material was used to the next step without further purification.

To a reaction mixture of the crude alcohol in acetonitrile (480 ml) was added amberlyst 15 ion exchange resin (7 g) at room temperature. The reaction was stirred for 24 hr at 30 °C. The reaction was filtered through celite pad and concentrated *in vacuo*. The crude material **114** (9.72 g, 18.53 mmol, 76%) was pure enough to use to the next step without further purification.

ν_{max} (neat)/cm^{-1} 3063, 3018, 2952, 2891, 2856, 1736, 1472, 1428, 1203, 1110; $[\alpha]^{20}_D$ -168.9 (c = 2.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 7.66 (ddt, *J* = 20.8, 6.7, 1.4 Hz, 4H), 7.49 – 7.34 (m, 6H), 3.68-2.61 (m, 1H), 3.62 (s, 3H), 2.65 (ddd, *J* = 18.7, 10.8, 4.0 Hz, 1H), 2.52 (ddd, *J* = 18.6, 9.4, 6.6 Hz, 1H), 2.18

– 2.09 (m, 1H), 2.00 – 1.88 (m, 4H), 1.79 – 1.58 (m, 3H), 1.39 (s, 3H), 1.24 (s, 3H), 1.16 – 1.08 (m, 1H), 1.05 (s, 9H); δ_C (125 MHz, $CDCl_3$) 174.2, 171.2, 136.0, 135.8, 133.7, 132.5, 130.2, 129.9, 128.0, 127.7, 77.9, 77.7, 72.3, 70.8, 51.4, 36.0, 34.1, 30.4, 28.1, 27.5, 27.0, 21.9, 19.3, 19.2; Accurate mass (ES^+): Found 525.2656 (-3.0 ppm), $C_{30}H_{41}O_6$ ($M+H^+$) requires 525.2672.



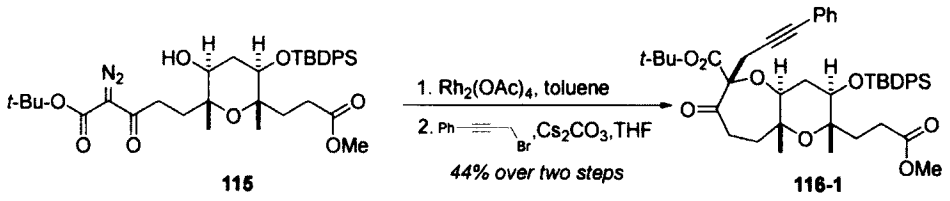
tert-butyl 5-((2R,3S,5R,6S)-5-((tert-butyldiphenylsilyl)oxy)-3-hydroxy-6-(3-methoxy-3-oxopropyl)-2,6-dimethyltetrahydro-2H-pyran-2-yl)-2-diazo-3-oxopentanoate:

A solution of *tert*-Butyl acetate (4.51 ml, 33.62 mmol) in THF (30 ml) was added dropwise to a solution of freshly prepared LDA (33.62 mmol) in THF (70 ml) and stirred for 1 hr at -78 °C. After 1 hr, the solution of lithiated *tert*-BuOAc in THF was added dropwise to a solution of lactone **114** (8.40 g, 16.01 mmol) in THF (60 ml) at -78 °C. The whole mixture was stirred for 3 hr at -78 °C. The reaction was quenched with 10% acetic acid in THF (20 ml) at -78 °C. The reaction was allowed to warm to 0 °C, water was added. The biphasic mixture was extracted with EtOAc (x3). The combined organic layer was washed with brine and filtered and concentrated *in vacuo*. The crude material was used to the next step without further purification.

To a solution of *β*-keto ester (10.3 g, 16.02 mmol) in acetonitrile (320 ml) was added Et_3N (7.54 ml, 54.07 mmol) and acetic acid (0.52 ml, 8.01 mmol) at room temperature. The reaction mixture was cooled to 0 °C and *p*-acetamidebenzenesulfonyl azide (5.47 g, 54.07 mmol). The reaction mixture was warm to room temperature. After stirring of 15 hr, the reaction was diluted with ethyl ether, filtered through a Celite pad, and rinsed with cold ether. The filtrate was concentrated

under reduced pressure. The crude material was purified by flash column chromatography to give pure diazo product **115** (9.82 g, 14.73 mmol, 92%)

ν_{max}(neat)/cm^{-1} 3512, 2979, 2933, 2858, 2131, 1712, 1732, 1651, 1473, 1428, 1370, 1310; $[\alpha]^{20}_D$ +19.6 (c = 2.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 7.72 – 7.62 (m, 4H), 7.44 – 7.32 (m, 6H), 3.61 (s, 3H), 3.45 (dd, *J* = 11.5, 4.5 Hz, 1H), 3.10 (dd, *J* = 11.2, 4.4 Hz, 1H), 2.83 (dt, *J* = 16.8, 7.2 Hz, 1H), 2.74 – 2.63 (m, 2H), 2.22 (ddd, *J* = 15.5, 10.9, 5.0 Hz, 1H), 1.98 (ddd, *J* = 15.6, 10.9, 4.8 Hz, 1H), 1.94 – 1.79 (m, 2H), 1.78 – 1.69 (m, 3H), 1.69 – 1.58 (m, 1H), 1.49 (s, 9H), 1.30 (s, 3H), 1.17 (s, 3H), 1.03 (s, 9H); δ_C (125 MHz, $CDCl_3$) 194.1, 174.5, 160.6, 136.0, 136.0, 135.9, 134.4, 133.0, 129.9, 129.6, 127.8, 127.7, 127.5, 127.5, 83.2, 76.2, 76.0, 73.2, 70.3, 51.3, 36.3, 35.1, 34.2, 33.4, 28.3, 28.3, 28.3, 27.9, 27.0, 21.5, 20.6, 19.3; Accurate mass (ES$^+$): Found 668.3488 (+0.7 ppm), $C_{36}H_{52}N_2O_8$ (M+H$^+$) requires 668.3493.

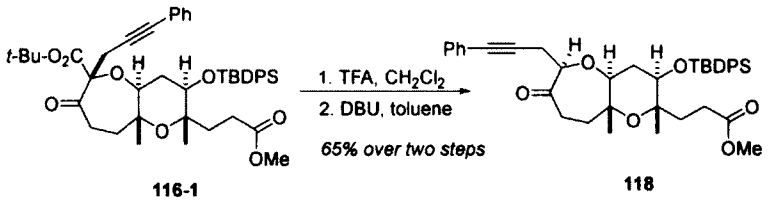


tert-butyl (2S,3R,4aS,6S,9aR)-3-((tert-butyldiphenylsilyl)oxy)-2-(3-methoxy-3-oxopropyl)-2,9a-dimethyl-7-oxo-6-(3-phenylprop-2-yn-1-yl)octahydro-2H-pyrano[3,2-b]oxepine-6-carboxylate:

Dirhodium tetraacetate (20 mg, 0.05 mmol) was added in one portion to a solution of the dizo compound **115** (3.3 g, 4.94 mmol) in toluene (247 ml) at 80 °C and the mixture stirred for 1 hr. This solution was cooled to room temperature and the residual material passed through a short silica pad. The resulting filtrate was concentrated *in vacuo*. The crude enol-keto mixture was used to the next step without further purification.

To a solution of keto-enol compound (2.04 g, 3.19 mmol) and phenylpropargyl bromide (690 mg, 3.51 mmol) in THF (20 ml) was added Cs_2CO_3 (1.56 g, 4.79 mmol). The reaction was stirred for 14 hr at room temperature and then filtered through a Celite pad. The resulting filtrate was concentrated *in vacuo*. The crude oil was purified by flash column chromatography to give alkylated product **116-1** (1.61 g, 2.17 mmol, 44% over two steps).

ν_{max} (neat)/cm^{-1} 2933, 2859, 1739, 1717, 1491, 1473, 1428, 1369, 1163, 1105; $[\alpha]^{20}_D$ +14.7 (c = 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 7.71 – 7.61 (m, 4H), 7.45 – 7.33 (m, 8H), 7.32 – 7.27 (m, 3H), 3.60 (s, 3H), 3.50 (ddd, *J* = 11.7, 6.9, 4.6 Hz, 2H), 3.12 (ddd, *J* = 14.4, 12.6, 3.4 Hz, 1H), 2.93 (q, *J* = 17.2 Hz, 2H), 2.98 (d, *J* = 17.2 Hz, 1H), 2.89 (d, *J* = 17.2 Hz, 1H), 2.15 – 1.93 (m, 3H), 1.89 – 1.75 (m, 2H), 1.69 (ddd, *J* = 13.8, 5.7, 3.4 Hz, 1H), 1.64 – 1.54 (m, 1H), 1.41 (s, 3H), 1.36 (s, 3H), 1.28 (s, 9H), 1.04 (s, 9H); δ_C (125 MHz, $CDCl_3$) 209.9, 174.5, 167.3, 136.2, 136.2, 136.1, 134.3, 132.8, 131.7, 130.1, 129.8, 128.4, 128.3, 128.0, 127.6, 123.2, 88.3, 84.3, 84.1, 82.9, 79.8, 76.6, 76.0, 72.6, 51.5, 39.8, 38.6, 35.9, 32.7, 28.1, 28.0, 27.9, 27.1, 22.1, 19.4, 18.8; Accurate mass (ES^+): Found 753.3848 (+3.3 ppm), $C_{45}H_{57}O_8Si$ ($M+H^+$) requires 753. 3823.



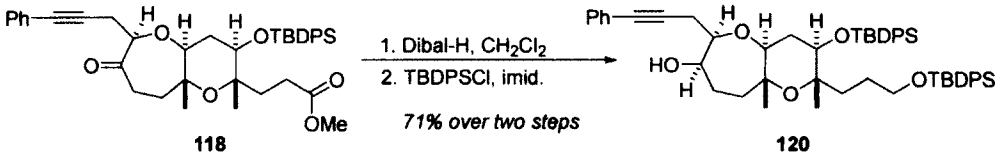
116-1 118

methyl 3-((2S,3R,4aS,6R,9aR)-3-((tert-butyldiphenylsilyl)oxy)-2,9a-dimethyl-7-oxo-6-(3-phenylprop-2-yn-1-yl)octahydro-2H-pyrano[3,2-b]oxepin-2-yl)propanoate:

t-Butyl ester **116-1** (3.51 g, 4.66 mmol) was dissolved in a mixture of CH_2Cl_2/TFA (16 ml, v:v =3:1) and stirred for 3 hr at room temperature. The resulting solution was concentrated *in vacuo*. The

crude material was re-dissolved in toluene (93.2 ml) and reflux for 3 hr. DBU (12.02 ml, 93.23 mmol) was added to the reaction mixture and reflux for additional 36 hr. The reaction mixture was concentrated *in vacuo*. The crude material was purified by flash column chromatography to give pure product **118** (1.98 g, 3.03 mmol, 65% over two steps).

ν_{max}(neat)/cm^{-1} 2954, 2859, 1738, 1714, 1490, 1428, 1101; $[\alpha]^{20}_{D}$ +2.8 (c = 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 7.74 – 7.65 (m, 4H), 7.52 – 7.44 (m, 2H), 7.41 (tt, *J* = 8.0, 1.0 Hz, 4H), 7.39 – 7.35 (m, 2H), 7.31 (dtd, *J* = 5.0, 2.5, 2.0, 1.2 Hz, 3H), 3.82 (t, *J* = 4.9 Hz, 1H), 3.64 (s, 3H), 3.44 (dd, *J* = 11.6, 4.4 Hz, 1H), 2.96 (ddd, *J* = 14.3, 12.6, 3.1 Hz, 1H), 2.77 (dd, *J* = 17.1, 5.1 Hz, 1H), 2.74 – 2.64 (m, 2H), 2.35 (ddd, *J* = 12.6, 6.1, 2.3 Hz, 1H), 2.15 (tt, *J* = 11.7, 9.6 Hz, 1H), 2.03 (q, *J* = 12.1 Hz, 1H), 1.99 – 1.89 (m, 2H), 1.86 – 1.68 (m, 3H), 1.44 – 1.43 (m, 3H), 1.40 (s, 3H), 1.06 (s, 9H); δ_C (125 MHz, $CDCl_3$) 215.3, 174.5, 136.1, 136.0, 134.4, 132.7, 131.7, 130.3, 129.9, 128.4, 128.2, 128.0, 127.7, 123.3, 84.6, 84.5, 83.4, 82.7, 77.4, 76.7, 75.7, 73.0, 51.5, 39.2, 38.4, 36.1, 32.7, 28.2, 27.1, 24.2, 22.2, 19.4, 19.0; Accurate mass (ES$^+$): Found 653.3239 (-9.0 ppm), $C_{40}H_{48}O_6Si$ (M+H$^+$) requires 653.3298.



118 **120**

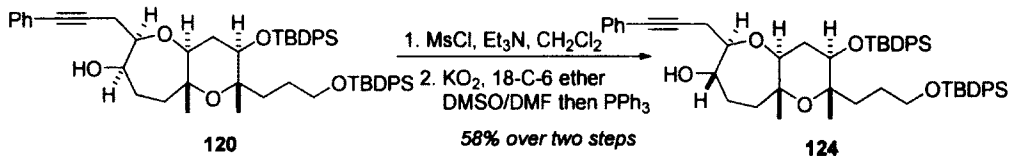
(2S,3R,4aS,6R,7R,9aR)-3-((tert-butyldiphenylsilyl)oxy)-2-(3-((tert-butyldiphenylsilyl)oxy)propyl)-2,9a-dimethyl-6-(3-phenylprop-2-yn-1-yl)octahydro-2H-pyrano[3,2-b]oxepin-7-ol:

To a solution of ketone **118** (1.33 g, 2.04 mmol) in CH_2Cl_2 (41 ml) was added Dibal-H (1.45 ml, 8.15 mmol) at -78 °C. The mixture was stirred for 2 hr at -40 °C. The reaction was quenched with addition of MeOH and Rochelle salt. The biphasic mixture was stirred for 6 hr. The clean biphasic

mixture was extracted with CH_2Cl_2, washed with brine, and dried over sodium sulfate. The resulting filtrate was concentrated *in vacuo*. The crude diol **119** was used to the next step without further purification.

To a solution of crude diol **119** (1.28 g, 2.04 mmol) in DMF (6.9 ml) were added imidazole (0.21 g, 3.09 mmol) and TBDPSCl (0.54 ml, 2.06 mmol) at 0 °C. The whole mixture was stirred for 1 hr at 0 °C. The reaction was diluted with EtOAc and washed with water (x3) and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude material was purified by flash column chromatography to give pure mono protected alcohol **120** (1.26 g, 1.45 mmol, 71% over two steps).

ν_{max} (neat)/cm^{-1} 3447, 3071, 2931, 2891, 2857, 1490, 1472, 1427, 1377; $[\alpha]^{20}_D$ -13.9 (c = 2.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 7.74 – 7.61 (m, 8H), 7.49 – 7.30 (m, 14H), 7.29 – 7.24 (m, 3H), 3.99 (m, 1H), 3.67 (td, *J* = 6.1, 3.6 Hz, 1H), 3.58 – 3.46 (m, 3H), 2.83 (dd, *J* = 12.2, 3.8 Hz, 1H), 2.64 (d, *J* = 6.1 Hz, 2H), 1.99 – 1.86 (m, 2H), 1.84 – 1.65 (m, 4H), 1.63-1.48 (m, 2H), 1.45 – 1.33 (m, 3H), 1.31 (s, 3H), 1.29 (s, 3H), 1.05 (s, 9H), 1.02 (s, 9H); δ_C (125 MHz, $CDCl_3$) 136.4, 136.3, 136.1, 136.0, 134.9, 134.7, 134.6, 133.4, 131.9, 130.3, 130.0, 129.9, 129.8, 128.6, 128.2, 128.2, 128.1, 128.0, 127.9, 127.9, 87.4, 82.6, 81.1, 80.9, 77.6, 77.1, 76.6, 74.2, 72.4, 65.3, 40.2, 38.4, 33.3, 30.2, 27.4, 27.3, 27.2, 26.7, 23.0, 22.9, 21.0, 19.7, 19.6; Accurate mass (ES^+): Found 865.4644 (-4.6 ppm), $C_{55}H_{69}O_5Si_2$ ($M+H^+$) requires 865.4684.



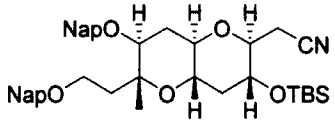
120 124

(2S,3R,4aS,6R,7S,9aR)-3-((tert-butyldiphenylsilyl)oxy)-2-(3-((tert-butyldiphenylsilyl)oxy)propyl)-2,9a-dimethyl-6-(3-phenylprop-2-yn-1-yl)octahydro-2H-pyrano[3,2-b]oxepin-7-ol:

A solution of *syn*-alcohol **120** (1.0 g, 1.16 mmol) in CH_2Cl_2 (12 ml) was cooled to 0 °C. Triethylamine (483 µL, 3.47 mmol) was added slowly followed by the addition of mesyl chloride (134 µL, 1.73 mmol) dropwise. The mixture was allowed to stir at room temperature for 4.5 hr. The mixture was diluted with CH_2Cl_2 and washed with 10 % aqueous solutions of ammonium chloride, sodium bicarbonate, and brine before drying over Na_2SO_4. The solvent was then removed under reduced pressure to afford the product as a pale yellow-brown oil. The crude was used to the next step without further purification.

To a solution of mesylated **120** in DMSO/DMF (6 ml, v:v = 1:1) were added KO_2 (500 mg, 6.93 mmol) and 18-crown-6 ether (1.83 g, 6.93 mmol) at 0 °C. The reaction mixture was stirred for 20 min at 0 °C. The reaction was diluted with EtOAc and washed with water (x3) and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude material was re-dissolved in ether and added PPh_3 (300 mg, 1.16 mmol) to the solution. After stirring of 1 hr at room temperature, the solution was concentrated *in vacuo*. The crude oil was purified by flash column chromatography to give pure *trans*-alcohol **124** (580 mg, 0.67 mmol, 58% over two steps).

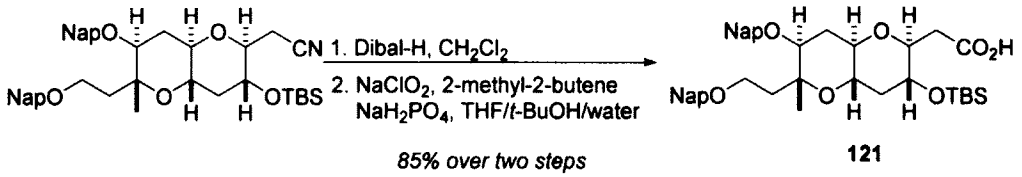
ν_{max}(neat)/cm^{-1} 3436, 3070, 2857, 1589, 1490, 1472, 1428, 1377, 1111, 1090; $[\alpha]^{20}_D$ -2.3 (c = 2.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 7.70-7.65 (m, 8H), 7.45 – 7.31 (m, 14H), 7.29-7.27 (m, 3H), 4.10 (dd, *J* = 6.4, 2.4 Hz, 1H), 3.61 (ddd, *J* = 7.2, 4.9, 2.1 Hz, 1H), 3.54 (ddt, *J* = 14.9, 7.7, 3.7 Hz, 3H), 3.16 (dd, *J* = 12.3, 4.1 Hz, 1H), 2.55 (dd, *J* = 16.8, 4.8 Hz, 1H), 2.46 (dd, *J* = 16.8, 7.6 Hz, 1H), 1.91 – 1.73 (m, 3H), 1.71-1.63 (m, 2H), 1.63 – 1.52 (m, 2H), 1.52 – 1.34 (m, 4H), 1.52 – 1.34 (m, 4H), 1.23 (s, 3H), 1.05 (s, 9H), 1.02 (s, 9H); δ_C (125 MHz, $CDCl_3$) 136.1, 136.0, 135.8, 134.8, 134.4, 134.4, 133.3, 131.7, 130.0, 129.7, 129.6, 129.6, 128.4, 128.0, 127.9, 127.7, 127.7, 127.6, 123.6, 123.6, 86.3, 83.3, 82.4, 78.7, 77.0, 76.7, 75.9, 73.8, 73.8, 65.0, 38.2, 35.8, 33.2, 27.2, 27.1, 26.9, 26.3, 25.6, 22.3, 20.2, 19.5, 19.4; Accurate mass (ES$^+$): 865.4601 (-9.6 ppm), $C_{55}H_{69}O_5Si_2$ ($M+H^+$) requires 865.4684.



2-((2S,3R,4aS,6R,7S,8aR)-3-((tert-butyldimethylsilyl)oxy)-6-methyl-7-(naphthalen-2-ylmethoxy)-6-(2-(naphthalen-2-ylmethoxy)ethyl)octahydropyrano[3,2-b]pyran-2-yl)acetonitrile:

ν_{max}(neat)/cm^{-1} 2954, 2858, 1517, 163, 1375, 1124, 1090, 1124, 1090; $[\alpha]^{20}_D$ +11.6 (c = 1.0 in $CHCl_3$); δ_H (600 MHz, $CDCl_3$) 7.86 – 7.75 (m, 6H), 7.73 (s, 1H), 7.69 (s, 1H), 7.51 – 7.44 (m, 4H), 7.42 (dd, *J* = 8.5, 1.7 Hz, 2H), 4.75 (d, *J* = 11.9 Hz, 1H), 4.63 – 4.49 (m, 3H), 3.94-3.92 (m, 1H), 3.67 – 3.57 (m, 3H), 3.57 – 3.51 (m, 1H), 3.47 (dt, *J* = 11.4, 3.3 Hz, 1H), 2.82 (ddd, *J* = 11.7, 9.3, 4.3 Hz, 1H), 2.64 – 2.56 (m, 1H), 2.51 (dd, *J* = 16.5, 7.3 Hz, 1H), 2.30 (dt, *J* = 11.8, 4.5 Hz, 1H), 2.05 – 1.96 (m, 3H), 1.62 (q, *J* = 11.6 Hz, 1H), 1.41 (ddd, *J* = 13.2, 11.4, 2.7 Hz, 1H), 1.25 (s, 3H), 0.91 (s, 7H), 0.10 (s, 3H), 0.09 (s, 3H); δ_C (150 MHz, $CDCl_3$) 136.2, 136.0, 133.4, 133.3, 133.1, 133.0, 128.3, 128.2, 128.0, 128.0, 127.8, 126.5, 126.5, 126.2, 126.2, 126.0, 126.0, 126.0, 125.9, 117.7, 77.6, 77.5, 76.4,

75.8, 73.1, 71.1, 68.0, 65.8, 65.4, 39.7, 37.3, 30.6, 25.9, 25.8, 20.4, 18.2, 17.0, -4.5, -4.9; Accurate mass (ES+): Found 666.3557 (-8.7 ppm), $C_{41}H_{52}NO_5Si$ ($M+H^+$) requires 666.3615.



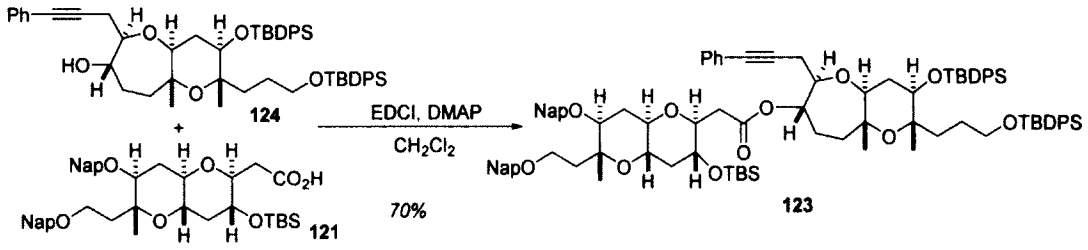
2-((2S,3R,4aS,6R,7S,8aR)-3-((tert-butyldimethylsilyl)oxy)-6-methyl-7-(naphthalen-2-ylmethoxy)-6-(2-(naphthalen-2-ylmethoxy)ethyl)octahydropyrano[3,2-b]pyran-2-yl)acetic acid:

To a solution of nitrile (46 mg, 0.07 mmol) in CH_2Cl_2 (2 ml) was added a solution of DIBAL-H (51 µL, 0.08 mmol, 1.5 M solution in toluene) at -78 °C. After 30min at -78 °C, the reaction was quenched with 1eq. of MeOH and saturated aq. sodium potassium tartrate solution. The whole mixture was stirred for additional 30 min at room temperature. The mixture was extracted with EtOAc(x3) and washed with brine. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude material was used to the next step without further purification.

To a reaction mixture of aldehyde in THF (1 ml) and *t*-BuOH (1 ml) was added 2-methyl-2-butene (0.9 ml, 2.0 M solution in THF) A solution of $NaClO_2$ (24.5 mg, 0.22 mmol) and NaH_2PO_4 (49.8 mg, 0.36 mmol) solution in water (0.3 ml) at 0 °C. The reaction was allowed to room temperature and stirred overnight. The reaction was diluted with additional water (5 ml). The mixture was extracted with EtOAc and washed with brine. The combined organic layer was filter and concentrated *in vacuo*. The crude was purified by flash column chromatography to give pure acid **121** (42 mg, 0.060 mmol, 85%).

ν_{max} (neat)/cm^{-1} 2951, 2933, 2845, 1703, 1257, 1095, 961; $[\alpha]^{20}_D$ +2.6 (c = 0.5 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.85 – 7.74 (m, 6H), 7.72 (s, 1H), 7.68 (s, 1H), 7.49 – 7.44 (m, 4H), 7.44 – 7.39

(m, 2H), 4.75 (d, *J* = 11.9 Hz, 1H), 4.68 – 4.54 (m, 3H), 3.89 (q, *J* = 2.5 Hz, 1H), 3.73 – 3.65 (m, 1H), 3.65 – 3.57 (m, 3H), 3.49 (dd, *J* = 11.5, 4.5 Hz, 1H), 2.90 (ddd, *J* = 11.7, 9.3, 4.3 Hz, 1H), 2.69 (dd, *J* = 16.5, 7.9 Hz, 1H), 2.50 (dd, *J* = 16.5, 5.0 Hz, 1H), 2.31 (dt, *J* = 11.6, 4.4 Hz, 1H), 2.11 – 1.91 (m, 3H), 1.67 (q, *J* = 11.7 Hz, 1H), 1.50 – 1.38 (m, 1H), 1.25 (s, 3H), 0.90 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); δ_C (150 MHz, $CDCl_3$) 173.7, 136.3, 136.0, 133.4, 133.3, 133.1, 133.1, 128.3, 128.2, 128.0, 128.0, 127.8, 127.8, 126.5, 126.4, 126.2, 126.2, 126.0, 126.0, 126.0, 125.9, 77.8, 77.7, 76.4, 76.4, 73.1, 71.2, 68.9, 65.9, 65.7, 39.8, 37.6, 36.6, 30.7, 25.9, 18.2, 17.1, -4.5, -4.8; Accurate mass (ES+): Found 685.3537 (-3.5 ppm), $C_{41}H_{53}O_7Si$ ($M+H^+$) requires 685.3561.

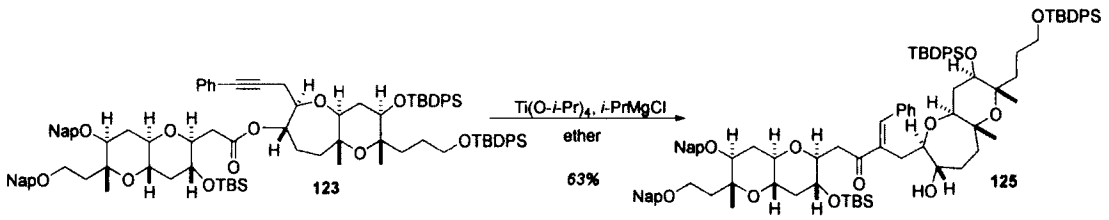


(2S,3R,4aS,6R,7S,9aR)-3-((tert-butyldiphenylsilyl)oxy)-2-(3-((tert-butyldiphenylsilyl)oxy)propyl)-2,9a-dimethyl-6-(3-phenylprop-2-yn-1-yl)octahydro-2H-pyrano[3,2-b]oxepin-7-yl 2-((2S,3R,4aS,6R,7S,8aR)-3-((tert-butyldimethylsilyl)oxy)-6-methyl-7-(naphthalen-2-ylmethoxy)-6-(2-(naphthalen-2-ylmethoxy)ethyl)octahydropyrano[3,2-b]pyran-2-yl)acetate:

To a reaction mixture of acid **121** (47 mg, 0.07 mmol) and alcohol **124** (59.4 mg, 0.07 mmol) in CH_2Cl_2 (2 ml) were added DMAP (25 mg, 0.21 mmol) and EDCI (26 mg, 0.14 mmol). The mixture was stirred for 14 hr at room temperature. The reaction mixture was diluted with EtOAc and washed with *aq.* 1N HCl, water, and brine. The organic layer was dried with sodium sulfate, filtered, and concentrated *in vacuo*. The crude oil was purified by flash column chromatography to give pure ester **123** (72 mg, 0.049 mmol, 70%).

ν_{max} (neat)/cm^{-1} 3046, 2954, 2930, 2857, 1734, 1472, 1427, 1113, 1089; $[\alpha]^{20}_D$ +4.5 (c = 5.0 in $CHCl_3$); δ_H (600 MHz, $CDCl_3$) 7.84 – 7.74 (m, 7H), 7.72 (s, 1H), 7.71 – 7.64 (m, 10H), 7.45 (dt, *J* = 6.0,

3.7 Hz, 4H), 7.43 – 7.29 (m, 17H), 5.15 (dt, *J* = 6.3, 1.9 Hz, 1H), 4.69 (d, *J* = 11.9 Hz, 1H), 4.59 – 4.49 (m, 3H), 3.91 (t, *J* = 3.0 Hz, 1H), 3.69 (td, *J* = 6.6, 1.4 Hz, 1H), 3.65 – 3.56 (m, 5H), 3.54-3.48 (m, 2H), 3.44 (dd, *J* = 11.6, 4.5 Hz, 1H), 2.98 (dd, *J* = 12.2, 4.2 Hz, 1H), 2.88 (ddd, *J* = 11.7, 9.4, 4.4 Hz, 1H), 2.61 – 2.47 (m, 4H), 2.25 (dt, *J* = 11.7, 4.4 Hz, 1H), 2.10 – 1.98 (m, 2H), 1.94 (ddd, *J* = 16.9, 10.3, 5.0 Hz, 1H), 1.91 – 1.76 (m, 3H), 1.76 – 1.64 (m, 2H), 1.64 – 1.58 (m, 1H), 1.58-1.51 (m, 1H), 1.51 – 1.39 (m, 4H), 1.33 (s, 3H), 1.24 (s, 6H), 1.05 (s, 9H), 1.03 (s, 9H), 0.86 (s, 9H), 0.00 (s, 3H), -0.07 (s, 3H); δ_C (150 MHz, $CDCl_3$) 170.5, 136.3, 136.1, 136.1, 136.0, 135.7, 134.8, 134.4, 134.3, 133.4, 133.3, 133.3, 133.1, 133.0, 131.8, 130.0, 129.7, 129.6, 128.3, 128.2, 128.2, 128.0, 128.0, 128.0, 127.8, 127.8, 127.8, 127.7, 127.6, 126.4, 126.3, 126.2, 126.1, 126.0, 125.9, 125.9, 125.9, 123.6, 85.7, 82.6, 81.0, 79.3, 78.1, 77.5, 76.7, 76.6, 76.4, 76.3, 75.7, 74.3, 73.1, 71.0, 68.5, 66.1, 65.9, 64.9, 39.9, 38.6, 37.7, 36.5, 33.1, 30.7, 27.2, 27.1, 26.2, 25.9, 25.6, 24.8, 24.2, 23.5, 22.1, 19.9, 19.5, 19.4, 18.2, 17.0, -4.7, -4.7; Accurate mass (ES+): Found: 1531.7931 (+7.9 ppm), $C_{96}H_{119}O_{11}Si_3$ ($M+H^+$) requires 1531.8060.

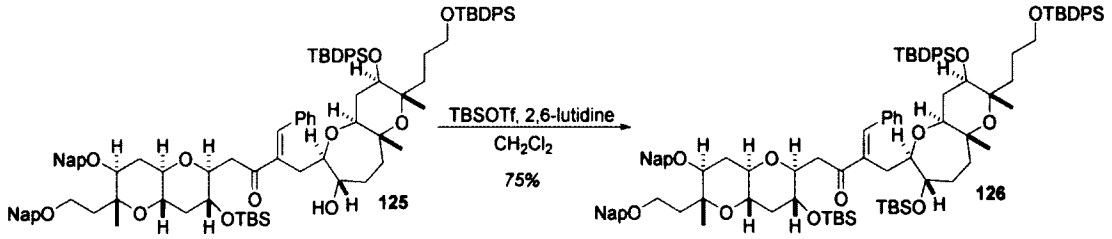


(E)-1-((2S,3R,4aS,6R,7S,8aR)-3-((tert-butyldimethylsilyl)oxy)-6-methyl-7-(naphthalen-2-ylmethoxy)-6-(2-(naphthalen-2-ylmethoxy)ethyl)octahydropyrano[3,2-b]pyran-2-yl)-3-(((2S,3R,4aS,6R,7S,9aR)-3-((tert-butyldiphenylsilyl)oxy)-2-(3-((tert-butyldiphenylsilyl)oxy)propyl)-7-hydroxy-2,9a-dimethyloctahydro-2H-pyrano[3,2-b]oxepin-6-yl)methyl)-4-phenylbut-3-en-2-one:

To a reaction mixture of Ti(O-*i*-Pr)$_4$ (0.13 ml, 0.43 mmol) in ether(3 ml) was added *i*-PrMgCl solution (0.85 ml, 1.0 M solution in THF) at -40 °C over 5 min. The mixture was stirred for 30min at -40 °C and warm to 0 °C. After 20 min, the mixture was re-cooled to -40 °C and the alkyne-ester **123** (65.5 mg, 0.04 mmol) in ether (1.3 ml) was added to the Ti(II) solution by cannular. The

reaction was warmed to -10 °C and stirred for 3 hr. The reaction was quenched by 1N HCl and extracted with EtOAc(x3). The combined organic layer was washed with brine and dried over Na_2SO_4. The organic layer was filtered and concentrated *in vacuo*. The crude was purified by flash column chromatography to give enone **125** (41 mg, 0.025 mmol, 63%).

ν_{max} (neat)/cm^{-1} 3465, 2056, 2937, 2928, 2856, 1723, 1663, 1454, 2472, 2428, 1099, 1087, 1978; $[\alpha]^{20}_D$ +7.6 (c = 0.5 in $CHCl_3$); δ_H (600 MHz, $CDCl_3$) 7.85-7.76 (m, 7H), 7.70-7.74 (m, 11H), 7.61 (s, 1H), 7.56 – 7.27 (m, 19H), 7.24 – 7.18 (m, 2H), 4.76 (d, *J* = 12.0 Hz, 1H), 4.64-4.56 (m, 4H), 4.06 (d, *J* = 3.1 Hz, 1H), 3.92 (dtd, *J* = 9.5, 5.1, 2.3 Hz, 1H), 3.71-3.62 (m, 5H), 3.59 – 3.48 (m, 4H), 3.43 (ddd, *J* = 9.7, 7.1, 4.2 Hz, 1H), 3.18 (dd, *J* = 17.5, 7.3 Hz, 1H), 3.09 – 2.92 (m, 3H), 2.71 (dd, *J* = 13.8, 5.7 Hz, 1H), 2.56 (dd, *J* = 13.8, 6.6 Hz, 1H), 2.34 (dt, *J* = 11.6, 4.4 Hz, 1H), 2.07-1.94 (m, 4H), 1.75 – 1.60 (m, 4H), 1.60 – 1.48 (m, 6H), 1.31 (s, 3H), 1.31 (s, 3H), 1.19 (s, 3H), 1.06 (s, 9H), 1.04 (s, 9H), 0.93 (s, 9H), 0.08 (s, 3H), -0.02 (s, 3H); δ_C (150 MHz, $CDCl_3$); 200.7, 142.3, 138.4, 136.4, 136.1, 136.1, 135.7, 135.3, 135.0, 134.4, 134.4, 133.4, 133.3, 133.3, 133.1, 133.1, 130.0, 123.0, 129.8, 129.7, 129.6, 129.2, 128.5, 128.2, 128.2, 128.0, 128.0, 127.9, 127.8, 127.8, 127.7, 127.5, 126.4, 126.4, 126.2, 126.2, 126.0, 125.9, 125.9, 84.8, 78.9, 78.1, 77.6, 76.7, 76.6, 76.4, 75.9, 74.5, 73.9, 73.1, 71.2, 68.6, 66.1, 66.1, 65.0, 39.9, 39.4, 38.3, 37.7, 36.5, 33.1, 32.1, 31.8, 31.2, 31.0, 29.9, 29.8, 27.6, 27.2, 27.1, 26.3, 26.0, 22.9, 22.4, 21.0, 19.4, 19.4, 18.2, 17.0, 14.3, -4.5, -4.7; Accurate mass (ES+): Found 1533.8283 (+4.3 ppm), $C_{96}H_{121}O_{11}Si_3$ ($M+H^+$) requires 1533.8217.

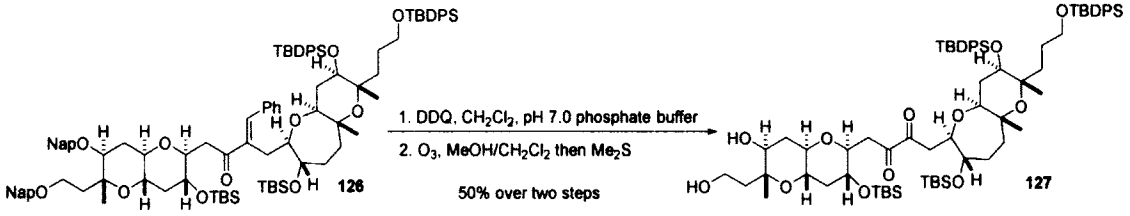


(E)-3-(((2S,3R,4aS,6R,7S,9aR)-7-((tert-butyldimethylsilyl)oxy)-3-((tert-butyldiphenylsilyl)oxy)-2-(3-((tert-butyldiphenylsilyl)oxy)propyl)-2,9a-dimethyloctahydro-2H-pyrano[3,2-b]oxepin-6-yl)methyl)-1-((2S,3R,4aS,6R,7S,8aR)-3-((tert-butyldimethylsilyl)oxy)-6-methyl-7-(naphthalen-2-ylmethoxy)-6-(2-(naphthalen-2-ylmethoxy)ethyl)octahydropyrano[3,2-b]pyran-2-yl)-4-phenylbut-3-en-2-one:

The alcohol **125** (81 mg, 0.05 mmol) was dissolved in CH_2Cl_2 (5 ml) and cooled to 0 °C. To this solution was added 2, 6-lutidine (12 μL, 0.11 mmol) followed by slow addition of *t*-butyldimethylsilyltrifluoromethane sulfonate (13 μL, 0.06 mmol). After 1 hr of stirring at 0 °C, the reaction mixture was quenched with saturated 10 % aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (x3). The combined organic layers were washed with brine, dried $MgSO_4$, filtered and concentrated *in vacuo*. The crude oil was purified by flash column chromatography to provide silyl ether **126** (65.5 mg, 0.038 mmol, 75%) as a clear oil.

ν_{max} (neat)/cm^{-1} 3060, 3048, 2953, 2928, 2856, 1722, 1554, 1471, 1458, 1471, 1458, 1428, 1105, 1087; $[\alpha]^{20}_D$ +8.3 (c = 0.5 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.84-7.74 (m, 7H), 7.72 – 7.60 (m, 9H), 7.56 (s, 1H), 7.52 – 7.30 (m, 21H), 7.25 – 7.22 (m, 2H), 4.75 (d, *J* = 12.0 Hz, 1H), 4.65 – 4.54 (m, 4H), 4.04-4.01 (m, 1H), 3.91 (dtd, *J* = 6.4, 5.0, 2.2 Hz, 1H), 3.91 (dtd, *J* = 6.4, 5.0, 2.2 Hz, 1H), 3.66-3.63 (m, 2H), 3.53-3.48 (m, 3H), 3.45 – 3.36 (m, 2H), 3.25 (dd, *J* = 12.3, 4.0 Hz, 1H), 3.17 – 3.03 (m, 1H), 3.03 – 2.90 (m, 2H), 2.67 (dd, *J* = 13.8, 8.0 Hz, 1H), 2.43 (dd, *J* = 13.7, 5.5 Hz, 1H), 2.33 (dt, *J* = 11.5, 4.4 Hz, 1H), 2.14 – 1.95 (m, 4H), 1.84 – 1.64 (m, 7H), 1.57 – 1.39 (m, 7H), 1.31 (s, 3H), 1.27 (s, 3H), 1.18 (s, 3H), 1.05 (s, 9H), 1.04 (s, 9H), 0.91 (s, 9H), 0.71 (s, 9H), 0.06 (s, 3H), -0.04 (s, 3H), -0.11 (s, 3H), -0.18 (s, 3H); δ_C (150 MHz, $CDCl_3$) 199.7, 141.6, 138.5, 136.4, 136.1, 136.0, 136.0, 135.7, 135.4, 135.1, 134.4, 133.4, 133.3, 133.1, 133.0, 133.0, 130.0, 129.7, 129.5, 129.5, 129.2, 128.6, 128.2,

128.2, 128.0, 128.0, 127.8, 127.8, 127.7, 127.5, 126.4, 126.4, 126.2, 126.2, 125.9, 125.9, 83.7, 78.2, 77.5, 76.6, 76.5, 76.3, 76.0, 76.0, 73.7, 73.1, 72.7, 71.2, 68.6, 66.1, 65.0, 39.9, 39.5, 37.7, 37.3, 35.2, 33.0, 32.1, 31.8, 31.0, 30.0, 29.9, 29.8, 27.2, 27.0, 26.0, 25.9, 25.9, 25.2, 22.9, 22.6, 20.3, 19.4, 19.4, 18.2, 17.9, 17.0, 14.3, -4.5, -4.7, -4.8, -4.8; Accurate mass (ES+): Found 1647.9001 (-4.9 ppm), $C_{102}H_{135}O_{11}Si_4$ (M+H+) requires 1647.9082.



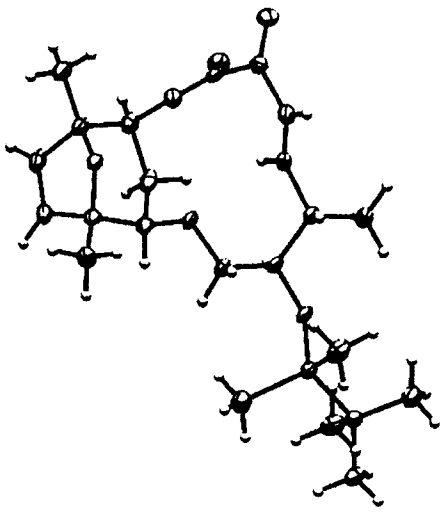
1-((2S,3R,4aS,6R,7S,9aR)-7-((tert-butyldimethylsilyl)oxy)-3-((tert-butyldiphenylsilyl)oxy)-2-(3-((tert-butyldiphenylsilyl)oxy)propyl)-2,9a-dimethyloctahydro-2H-pyrano[3,2-b]oxepin-6-yl)-4-((2S,3R,4aS,6R,7S,8aR)-3-((tert-butyldimethylsilyl)oxy)-7-hydroxy-6-(2-hydroxyethyl)-6-methyloctahydropyrano[3,2-b]pyran-2-yl)butane-2,3-dione:

The Nap protected substrate **126** (107 mg, 0.06 mmol) was dissolved in a mixture of CH_2Cl_2 (6 ml) and pH 7.0 phosphate buffer (1 ml). The mixture was cooled to 0 °C and DDQ (75.2 mg, 0.32 mmol) added. The reaction mixture stirred in the presence of the cooling bath for 3 hr. Saturated sodium bicarbonate was then added to the yellow reaction mixture followed by CH_2Cl_2 and water. The yellow / orange aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). Organics combined, dried with $MgSO_4$ and concentrated under reduced pressure to give a yellow oil. The crude was purified by flash column chromatography.

The enone was dissolved in CH_2Cl_2/MeOH (8 ml, v:v = 1:1) and cool to -78 °C. The reaction solution was bubbled with ozone until the solution changed into metallic blue color (ca. 5 min). After removing ozone source, the solution was stirred for additional 10 min at -78 °C. The reaction

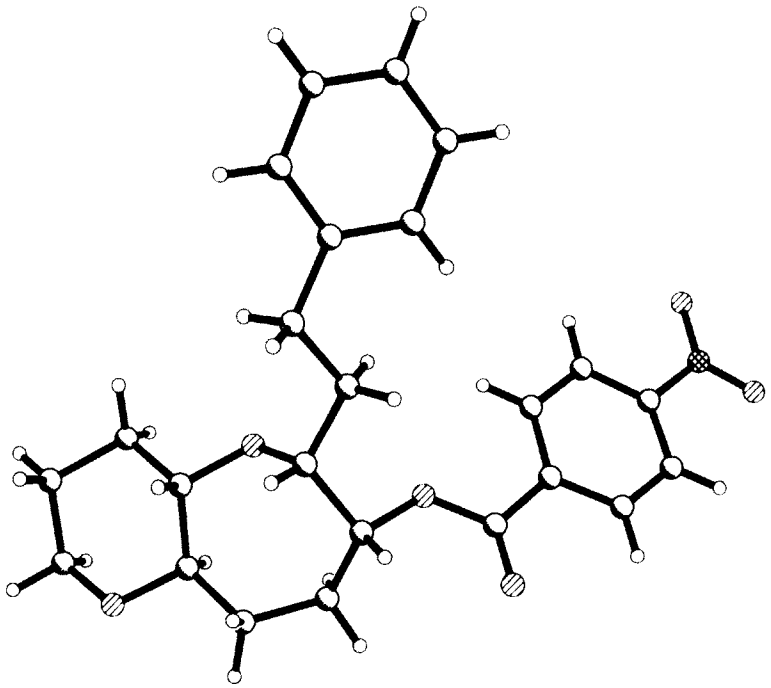
solution was bubbled with nitrogen until the blue color is disappear. The reaction was quenched with Me_2S (190 μL) and allowed to room temperature. The reaction was stirred overnight. The resulting solution was concentrated *in vacuo*. The crude was purified by flash column chromatography to give pure diketone **127** (42 mg, 0.03 mmol, 50%).

ν_{max} (neat)/cm^{-1} 3472, 3469, 3073, 2937, 2903, 2839, 1719, 1428, 1402, 1378, 1340, 1079, 1059; δ_H (400 MHz, $CDCl_3$) 7.73 – 7.61 (m, 4H), 7.48 – 7.30 (m, 6H), 3.93 – 3.88 (m, 2H), 3.87 – 3.75 (m, 4H), 3.72-3.58 (m, 4H), 2.50-3.41 (m, 6H), 3.37 (dd, *J* = 12.3, 4.1 Hz, 1H), 3.18 – 3.10 (m, 1H), 3.10 – 2.98 (m, 2H), 2.76 (dt, *J* = 17.0, 5.9 Hz, 2H), 2.66 – 2.56 (m, 1H), 2.34 (t, *J* = 7.5 Hz, 2H), 2.13 – 1.96 (m, 2H), 1.90-1.81 (m, 4H), 1.80 – 1.58 (m, 5H), 1.60 – 1.39 (m, 9H), 1.27 (s, 3H), 1.25 (s, 3H), 1.12 (s, 3H), 1.03 (s, 9H), 1.01 (s, 9H), 0.92 (s, 9H), 0.79 (s, 9H), 0.07 (s, 3H), 0.01 (s, 3H), -0.01 (s, 3H), -0.05 (s, 3H); δ_C (100 MHz, $CDCl_3$) 197.5, 196.7, 136.0, 135.7, 134.4, 130.2, 129.7, 129.5, 129.5, 127.9, 127.7, 127.6, 80.2, 79.2, 77.7, 76.5, 76.5, 76.4, 76.1, 75.9, 74.0, 72.8, 71.4, 68.8, 66.1, 65.0, 59.3, 42.5, 40.3, 38.4, 37.9, 37.4, 35.4, 34.2, 33.6, 32.1, 29.9, 27.2, 27.0, 26.0, 25.9, 24.9, 22.9, 22.6, 20.2, 19.4, 19.4, 18.2, 18.0, 15.0, 14.3, -4.5, -4.7, -4.7, -4.8; Accurate mass (ES+): Found (ppm), $C_{73}H_{113}O_{12}Si_4$ ($M+H^+$) requires 1293.7309.



Number	Label	Charge	SybylType	Xfrac + ESD	Yfrac + ESD	Zfrac + ESD	Symm. op.
1	C1	0	C.2	1.00000(17)	0.2094(2)	0.63437(14)	x,y,z
2	O1	0	O.2	1.10102(12)	0.22885(16)	0.60381(11)	x,y,z
3	C2	0	C.2	0.90935(17)	0.0831(2)	0.59929(14)	x,y,z
4	O2	0	O.2	0.93844(14)	-0.03480(14)	0.63600(11)	x,y,z
5	C3	0	C.2	0.79274(16)	0.1190(2)	0.52163(14)	x,y,z
6	H3A	0	H	0.7214	0.0556	0.5117	x,y,z
7	C4	0	C.2	0.78621(16)	0.24011(19)	0.46485(13)	x,y,z
8	H4A	0	H	0.859	0.3012	0.48	x,y,z
9	C5	0	C.3	0.67724(16)	0.29117(19)	0.37976(14)	x,y,z
10	H5A	0	H	0.5957	0.2446	0.3931	x,y,z
11	C6	0	C.3	0.66129(15)	0.45370(18)	0.38565(13)	x,y,z
12	H6A	0	H	0.7426	0.5013	0.373	x,y,z
13	C7	0	C.3	0.62581(17)	0.5057(2)	0.49359(14)	x,y,z
14	H7A	0	H	0.6146	0.6104	0.4902	x,y,z
15	H7B	0	H	0.5424	0.463	0.5033	x,y,z
16	O7	0	O.3	0.72076(11)	0.47066(13)	0.58623(9)	x,y,z
17	C8	0	C.3	0.80768(17)	0.58221(19)	0.63184(14)	x,y,z
18	H8A	0	H	0.7897	0.6706	0.5866	x,y,z
19	O9	0	O.3	0.81529(10)	0.48034(13)	0.81070(9)	x,y,z
20	C9	0	C.3	0.78479(17)	0.61147(18)	0.75040(13)	x,y,z
21	C10	0	C.2	0.88818(18)	0.7112(2)	0.80749(14)	x,y,z
22	H10A	0	H	0.8833	0.8122	0.8081	x,y,z
23	C11	0	C.2	0.98584(17)	0.6342(2)	0.85608(14)	x,y,z
24	H11A	0	H	1.0634	0.6703	0.8976	x,y,z
25	C12	0	C.3	0.95365(16)	0.47749(19)	0.83452(14)	x,y,z
26	C13	0	C.3	0.99999(17)	0.43439(19)	0.72764(14)	x,y,z
27	H13A	0	H	1.0964	0.4319	0.7386	x,y,z

28	O13	0	O.3	0.94690(11)	0.29191(13)	0.70180(10)	x,y,z
29	C14	0	C.3	0.94701(18)	0.5356(2)	0.63321(15)	x,y,z
30	H14A	0	H	1.0024	0.6214	0.6383	x,y,z
31	H14B	0	H	0.9529	0.4879	0.5626	x,y,z
32	C15	0	C.3	0.7038(2)	0.2465(2)	0.26590(15)	x,y,z
33	H15A	0	H	0.7137	0.1428	0.2637	x,y,z
34	H15B	0	H	0.7832	0.2923	0.2517	x,y,z
35	H15C	0	H	0.6315	0.2759	0.2096	x,y,z
36	C16	0	C.3	0.64764(18)	0.6522(2)	0.75776(16)	x,y,z
37	H16A	0	H	0.6399	0.6692	0.8348	x,y,z
38	H16B	0	H	0.5895	0.5748	0.7283	x,y,z
39	H16C	0	H	0.6245	0.7391	0.715	x,y,z
40	C17	0	C.3	0.99586(19)	0.3779(2)	0.92950(15)	x,y,z
41	H17A	0	H	0.9628	0.4123	0.9945	x,y,z
42	H17B	0	H	1.0903	0.3745	0.9453	x,y,z
43	H17C	0	H	0.962	0.2823	0.9104	x,y,z
44	O6	0	O.3	0.55761(11)	0.49445(14)	0.30095(9)	x,y,z
45	Si1	0	Si	0.55567(4)	0.63207(5)	0.21673(4)	x,y,z
46	C18	0	C.3	0.5723(2)	0.8020(2)	0.29466(18)	x,y,z
47	H18A	0	H	0.6576	0.806	0.3409	x,y,z
48	H18B	0	H	0.5054	0.8075	0.3411	x,y,z
49	H18C	0	H	0.5628	0.8822	0.2431	x,y,z
50	C19	0	C.3	0.69054(17)	0.6170(2)	0.13608(15)	x,y,z
51	H19A	0	H	0.7732	0.6241	0.1859	x,y,z
52	H19B	0	H	0.6839	0.6941	0.0819	x,y,z
53	H19C	0	H	0.6853	0.525	0.0981	x,y,z
54	C20	0	C.3	0.39269(15)	0.61943(19)	0.12624(13)	x,y,z
55	C21	0	C.3	0.38820(19)	0.4904(2)	0.04996(16)	x,y,z
56	H21A	0	H	0.3032	0.4849	0.0034	x,y,z
57	H21B	0	H	0.4037	0.4033	0.0941	x,y,z
58	H21C	0	H	0.4548	0.5001	0.0035	x,y,z
59	C22	0	C.3	0.28795(17)	0.6060(2)	0.19802(16)	x,y,z
60	H22A	0	H	0.2033	0.5995	0.151	x,y,z
61	H22B	0	H	0.2901	0.6899	0.2456	x,y,z
62	H22C	0	H	0.3033	0.5201	0.2435	x,y,z
63	C23	0	C.3	0.36759(18)	0.7541(2)	0.05493(15)	x,y,z
64	H23A	0	H	0.2829	0.747	0.0081	x,y,z
65	H23B	0	H	0.4345	0.7632	0.0087	x,y,z
66	H23C	0	H	0.3694	0.8379	0.1025	x,y,z



2.7 Reference.

1. Handbook of Marine Natural Products by Ernesto Fattorusso, William H. Gerwick and Orazio Taglialatela-Scafati, Springer, Berlin, 2012.
2. R. E. Gawley, K. S. Rein, G. Jeglitsch, D. J. Adams, E. A. Theodorakis, J. Tiebes, K. C. Nicolaou, D. G. Baden, *Chemistry & Biology*, **1995**, *2*, 533-541.
3. A. Gerssen, *Toxin*, **2010**, *2*, 878-904.
4. T. Nakata, *Chem. Rev.* **2005**, *105*, 4314-4347.
5. H. J. Dominguez, M. L. Souto, M. Norte, A. H. Daranas, J.J. Fernandez, *Toxicon*, **2010**, *55*, 1484-1490.
6. A) T. Yasumoto, M. Murata, *Chem. Rev.* **1993**, *93*, 1897; B) *Phycotoxin: Chemistry and Biochemistry*; Blackwell Publishing Ames, **2007**, p.345.
7. T. Aune, R. Sorby, T. Yasumoto, H. Ramstad, T. Landsverk, *Toxicon*, **2002**, *40*, 77-82
8. A) T. Mori, K. Nogami, H. Hayashi, R. Noyori, *J. Org. Chem.* **2003**, *68*, 9050-9060. B) Y. Mori, T. Takase, R. Noyori, *Tetraheron* **2003**, *44*, 2319-2322.
9. A) K. Torikai, K. Watanabe, H. Minato, T. Imaizumi, M. Murata, T. Oishi, *Synlett*, **2008**, *15*, 2368-2372. B) K. Watanabe, M. Suzuki, M. Murata, T. Oishi, *Tetrahedron Lett.* **2005**, *46*, 3991-3995.
10. T. Sakai, A. Sugimoto, H. Tatematsu, Y. Mori, *J. Org. Chem.* **2012**, *77*, 11177-11191.
11. A) I. Kadota, T. Abe, Y. Sato, C. Kabuto, Y. Yamaoto, *Tetrahedron Lett.* **2006**, *47*, 6545-6548. B) I. Kadota, H. Ueno, Y. Sato, Y. Yamamoto, *Tetrahedron Lett.* **2006**, *47*, 89-92.
12. A) N. Hiramatsu, Y. Mori, *Heterocycles*, **2006**, *69*, 437-446. B) I. Kadoko, H. Ueno, Y. Yamamoto, *Tetrahedron Lett.* **2003**, *44*, 8935-8938. C) Y. Mori, K. Nogami, H. Hayashi, R. Noyori, *J. Org. Chem.* **2003**, *23*, 9050-9060. D) K. Torikai, K. Watanabe, H. Minato, T.

Imaizumi, M. Murata, T. Oishi, *Synlett*, **2008**, *15*, 2368-2372. E) C. O. Akoto, J. Rainier, *Angew. Chem. Int. Ed.* **2008**, *47*, 8055-8058.

13. K. C. Nicolaou, K. P. Cole, M. O. Frederick, R. J. Aversa, R. M. Denton, *Angew. Chem. In. Ed.* **2007**, *46*, 8875-8879.
14. M. Sasaki, *Bull. Chem. Soc. Jpn.* **2007**, *80*, 856-871.
15. Y. Mori, S. Mitsuoka, H. Furukawa, *Tetrahedron Lett.* **2000**, *41*, 4161-4164.
16. M. Maruyama, M. Inoue, T. Oishi, H. Oguri, Y. Ogasawara, Y. Shindo, M. Hirama, *Tetrahedron* **2002**, *58*, 1835-1851.
17. A) K.C. Nicolaou, E. A. Theodorakis, F.P. Rutjes, J. Tiebes, M. Sato, E. Untersteller, X. Xiaou, J. *Am. Chem. Soc.* **1995**, *117*, 1171. B) K. C. Nicolaou, F. P. Rutjes, E. A.Theodrakis, J. Tiebes, M. Sato, Untersteller, E. *J. Am. Chem. Soc.* **1995**, *117*, 1173. C) K. C. Nicolaou, C. K. Hwang, M. E. Duggan, D. A. Nugiel, Y. Abe, K. Bal Reddy, S. A. DeFredds, D. R. Reddy, R. A. Awartani, S. R. Conley, F. J. T. Rutjes, E. A. Theodrakis, *J. Am. Chem. Soc.* **1995**, *117*, 10227. D) K. C. Nicolaou, E. A. Theodrakis, F. P. J. T. Rutjes, M. Sato, J. Tiebes, X. Xiao, C. K. Hwang, M. E. Duggan, E. A. Yang, Couladouros, F. Sato, Shin, *J. Am. Chem. Soc.* **1995**, *117*, 10239. E) K. C. Nicolaou, E. P. J. T. Rutjes, E. A. Theodrakis, J. Tiebes, M. Sato, *J. Am. Chem. Soc.* **1995**, *117*, 10252.
18. A) M. Inoue, N. Lee, K. Miyazaki, T. Usuki, S. Matsuoka, M. Hirama, *Angew. Chem. In. Ed.* **2008**, *47*, 1-5, B) M. Inoue, K. Miyazaka, H. Uehara, M. Maruyama, M. Hirama, *Proc Natl Acad Sci USA*, **2004**, *101, 12013-12018*, C) M. Masayuki, M. Inoue, T. Oishi, H. Oguri, Y. Ogasawara, Y. Shindo, M. Jirama, *Tetrahedron* **2002**, *58*, 1835-1851, D) M. Inoue, S. Yamashita, A. Tatami, K. Miyazaki, M. Hirama, *J. Org. Chem.* **2004**, *69*, 2797-2804.
19. K. C. Nicolaou, T. M. Baker, T. Nakamura, *J. Am. Chem. Soc.* **2011**, *133*, 220-226.
20. K. C. Nicolaou, J. H. Seo, T. Nakamura, R. J. Aversa, *J. Am. Chem. Soc.* **2011**, *133*, 214-219.

21. K. C. Nicolaou, T. Montagnon, P. S. Baran, *Angew. Chem. Int. Ed.* **2002**, *41*, 993-996.

22. A) F. Sato, S. Okamoto, *Adv. Synth. Catal.* **2001**, *343*, 759. B) F. Sato, H. Urabe, S. Okamoto, *Synlett*, **2000**, *6*, 753-775. C) O. G. Kulinkovich, *Eur. J. Org. Chem.* **2004**, 4517-4529. D) O. G. Kulinkovich, *Chem. Rev.* **2003**, *103*, 2597-2632. E) O. G. Kulinkovich, A. D. Meijere, *Chem. Rew.* **2000**, *100*, 2789-2834.

23. Y. Mori, K. Nogami, H. Hayashi, R. Noyori, *J. Org. Chem. Chem.* **2003**, *68*, 9050-9060.

24. D. F. Law, S. W. Tobey, *J. Am. Chem. Soc.* **1968**, *90*, 2796-2386.

25. R. S. Orugunty, D. L. Writ, M. A. Battiste, R. J. Helmich, K. Abboud, *J. Org. Chem.* **2004**, *69*, 406-416.

26. W. Yang, X. Lu, S. Kulkarni, S. Hung, *Tetrahedron Lett.* **2003**, *44*, 7837-7840.

27. A) M. J. Davies, J. C. Heslin, C. J. Moody, *J. Chem. Soc. Perkin Trans 1*, **1989**, *12*, 2473-2384. B) M. J. Martin, C. J. Moody, R. J. Talor, *Synlett*, **1990**, *2*, 93-94. C) C. J. Moody, R. J. Taylor, *J. Chem. Soc. Perkin Trans 1*, **1989**, *4*,721-731.

28. E. J. Corey, K. C. Nicolaou, M. Shibasaki, Y. Machida, C. S. Shiner, *Tetrahedron Lett.* **1975**, *37*, 3183-3186.

29. The conformation is calculated by Spartan 07 with MM2 and MMFF (Merck Molecular Force Field).

30. A) T. Nakata, *Chem. Rev.* **2005**, *105*, 4314-4347. B) M. Sasaki, *Bull. Chem. Soc. Jpn.* **2007**, *80*, 856-871.

Chapter 3. Total synthesis and structure assignment of Nosperin.

3.1 Introduction.

The mixed polyketide-peptide natural product nosperin (**1**) was isolated in 2013 by Piel and co-workers from a lichen-associated *Nostoc sp.* cyanobacterium (Figure 3-1). Although the overall outcome may parallel other stories that begin with environmental isolates of microorganisms, this story has significant differences and provides a glimpse of on the power of new methods in metagenomics, bioinformatics, and symbiont cultivation.[1] In contrast with most studies which begin with bioactivity-guided isolation of a compound and the subsequent tracing back to the proteins involved in biosynthesis and genomic DNA, the discovery of Nosperin begins with sequencing (Figure 3-2).

Figure 3-1. The foliose lichen Peltogera membranacea and Nostoc symbionts. (A) Lichen in situ. (B) Rhizines on lower surface and apothecia (Apo) protrunding from thallus edge. (C) Internal structure including photosynthetic cyanobiont layer. (D) Nostoc sp. in culture.[1]

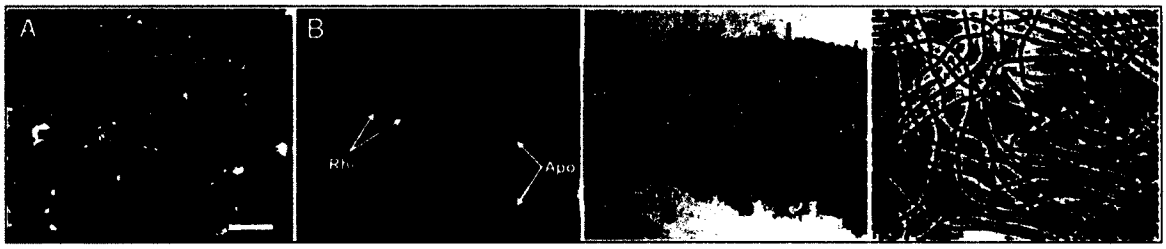
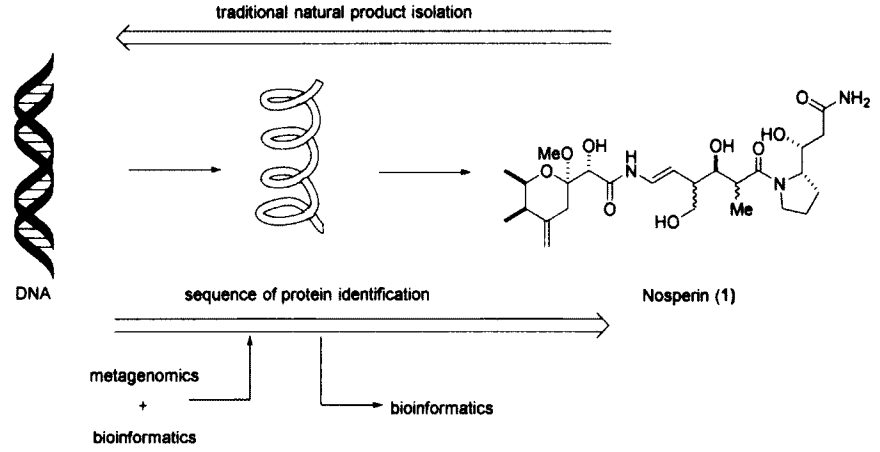
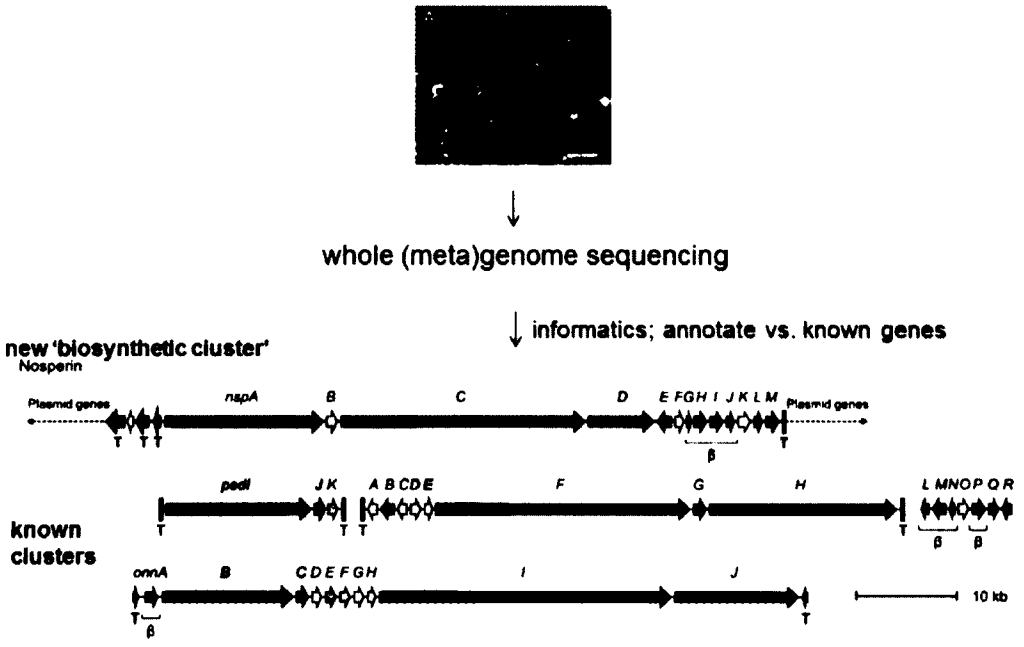


Figure 3-2. Isolation strategy based on metagenomics and bioinformatics.



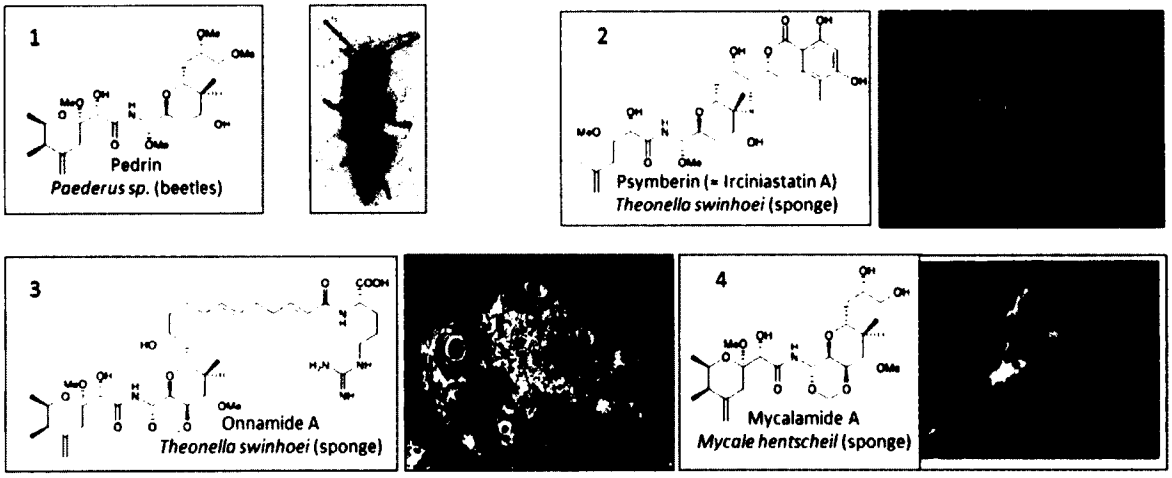
Whole genome sequencing was conducted on total DNA extracted from a lichen collected in Iceland (Figure 3-3). This metagenomic effort provided large amounts of sequence data that supported the identification by bioinformatics of 18 candidate gene clusters that seemed likely to code for proteins involved in classic bacterial polyketide and NRPS synthesis pathways (Figure 3-3).

Figure 3-3. Nosperin biosynthetic gene cluster nsp.[1]



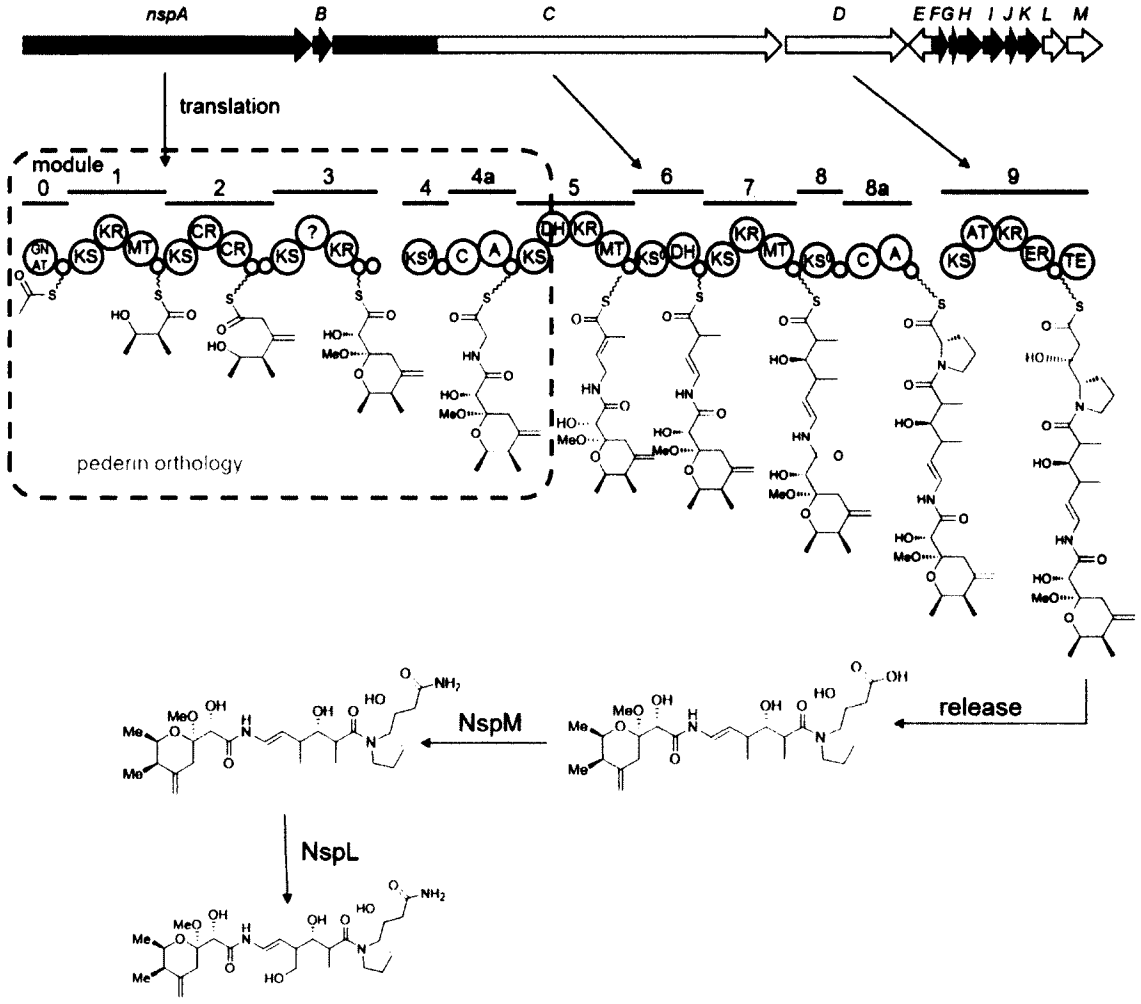
Among these putative bacterial gene clusters, two gene clusters were identified that had high homology to *trans*-acyltransferase (AT) polyketide synthase proteins – biosynthetic machinery that is found almost exclusively in symbiotic bacteria.[2] Detailed comparisons of these gene clusters provided hints that the genes might code for proteins that produce molecules of the pederin and onnamide family of compounds (e.g. mycalamide and onnamide, Figure 3-4).

Figure 3-4 Pedrin family compounds and symbioses. 1) Image of Paederus fuscipes courtesy of Christoph Benisch (www.kerbtier.de). 2) Image of Psammocinia aff. Bulbosa (www.springerimages.com). 3) Image of Theonella swinhoei courtesy of Yoichi Nakao. 4) Image of Mycale hentscheli courtesy of Mike page.



Careful analysis of the sequence data and use of homology models provided a model for protein domain functions and this ultimately led to a prediction of a structure for Nosperin (Figure 3-3).

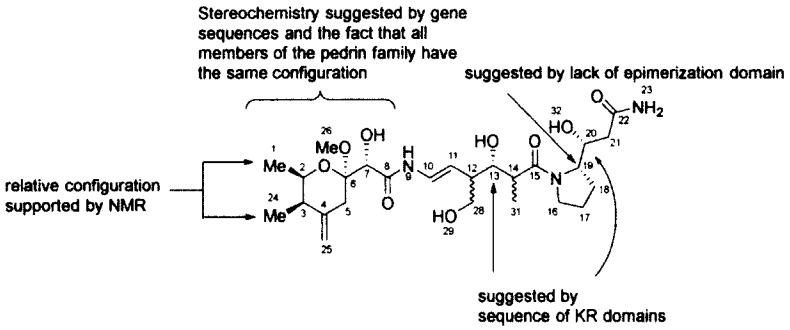
Figure 3-5. The nsp gene cluster and proposed biosynthetic pathway.[1]



With ideas of the chemical structure in hand, it was possible to focus compound identification on areas of the chromatogram that were most likely to contain candidates. A small amount of material (30 μg) allowed for structure elucidation, and partial assignment of sterochemistry, although it was not possible to unequivocally assign stereochemistry. Some resolution to these questions were possible from careful analysis of homology models, which are reasonable predictors for stereochemical features of the ketoreductase domains in PKS. Further bioinformatics analysis of the stereoselectivity controlling features of keto reductase (KR) domains KR1, KR7 and KR9 suggested absolute configurations at C2, C13 and C20, respectively, to be shown in Figure. 3-6. The t*rans*-olefin (C_{10}-C_{11}) streochemistry was determined to be *trans* by

the large $^3J_{HH}$ coupling (J = 14.5 Hz). The configuration at C19 was deduced from the absence of an epimerization domain in NRPS module, leading to the incorporation of L-proline at this position. This resulted in stereochemistry for all positions except C12 and C14. The C12 stereochemistry, derived from a double bond migration, and C14 stereochemistry which is installed by a C-methylation with a methyl transfer (MT) domain were resistant to bioinformatics-driven predictions due to limited analogy to known enzymatic functions.

Figure 3-6. Stereochemistry prediction of Nosperin.



C_2: analysis of the stereoselectivity of KR domain / NMR coupling constant.
C_3: the overall domain organization in comparison with other pedrin-type biosynthetic gene clusters / NMR coupling constant.
C_6: the overall domain organization in comparison with other pedrin-type biosynthetic gene clusters / NMR coupling constant.
C_7: the overall domain organization in comparison with other pedrin-type biosynthetic gene clusters / NMR coupling constant.
trans C_{10}-C_{11}: NMR coupling constant.
C_{13}: analysis of the stereoselectivity of KR domain.
C_{19}: the NRPS domain structure.
C_{20}: analysis of the stereoselectivity of KR domain.

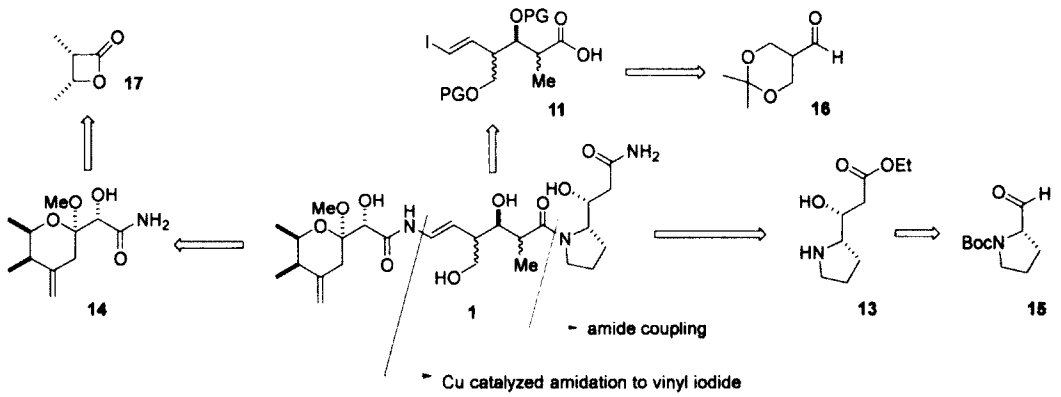
3.2. Results

3.2.1 Stereodivergent synthesis of Nosperin and diastereomers

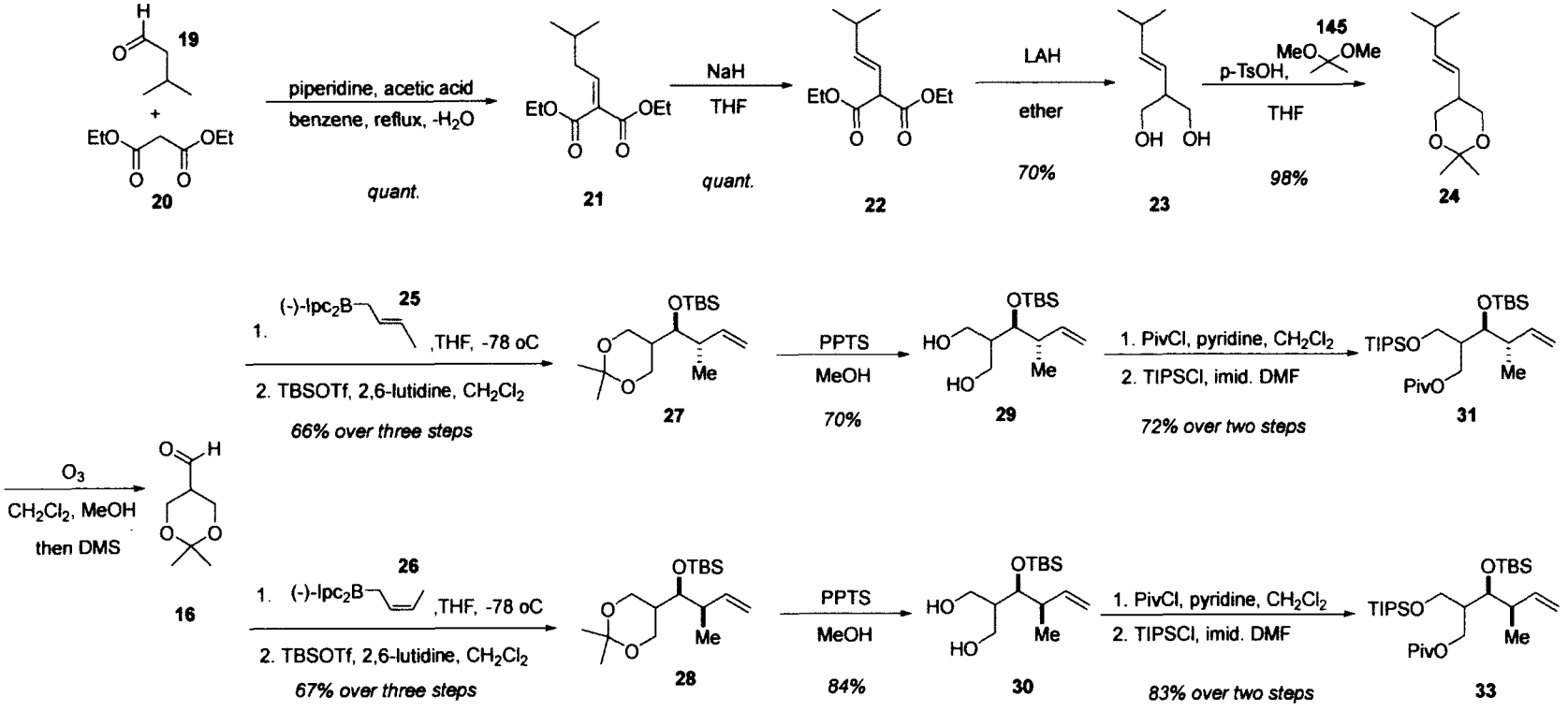
We were interested in developing a synthesis of nosperin to assign the remaining elements of stereochemistry not assigned by bioinformatics – thus also providing an orthogonal measure of structure elucidation to bioinfomatics – as well as producing material for biological evaluation. The overall strategy and key building blocks are shown in Scheme 3-1. We envisioned constructing nosperin **1** from three subunit amine **11**, amide **13**, and acid **14** via amide coupling and subsequent

Cu-catalyzed enamide coupling. We planned to synthesize **13** by an aldol reaction with proline aldehyde **15**, amide **14** by a known synthetic route from β-lactone **17**, and acid **11** by a newly developed stereodivergent sequence commencing with Brown crotylation of aldehyde **16**.

Scheme 3-1 Retrosynthetic analysis



Our synthesis was commenced with building four diastereomers **11** to be coupled with amide **14** and amine **13**. Knoevenagel condensation between isoamyl aldehyde **19** and ethyl malonate **20** yielded enone **21** in a quantitative yield.[3] Enone **21** was isomerized to de-conjugated malonate **22** with NaH and the resulting diester **22** reduced to diol **23** with LAH.[3] A two steps sequence including diol protection with acetonide, followed by ozonolysis produced aldehyde **16**. The aldehyde **16** was then split into two reaction batches. The sequence here is described for one arm of the sequence for reasons of clarity. Crotylation of **16** with Brown's (*E*)-Ipc$_2$Bcrotyl reagent and TBS protection produced **27**. A sequence of acetonide deprotection (**27** → **29**), mono-protection as the Piv ester, and TBDPS protection gave **31** as a mixture of diastereomers. A directly analagous route from **16** using Brown's (*Z*)-Ipc$_2$Bcrotyl reagent in the first step ultimately provided **33**.



Scheme 3-2 Synthesis of the polyketide domain.[4]

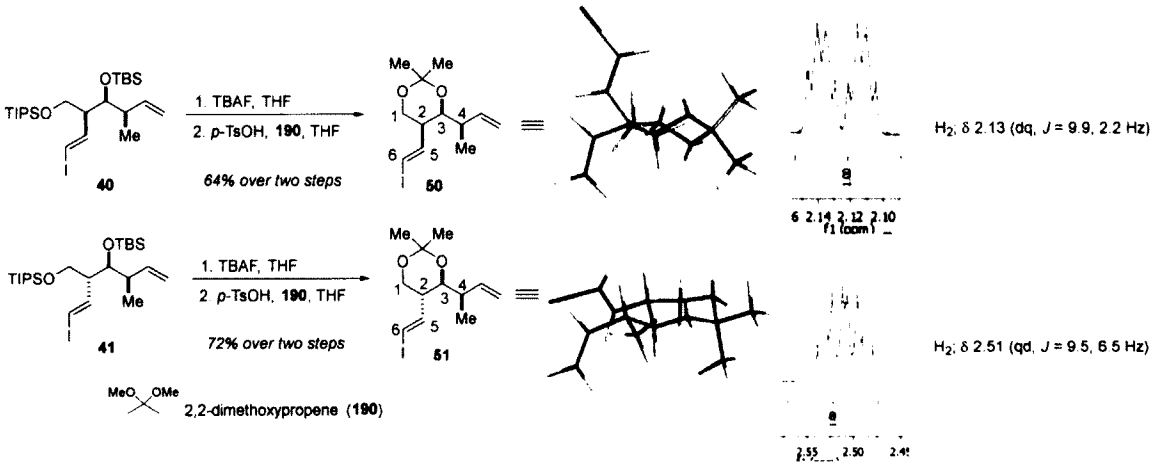
After Piv deprotection of a diastereomeric mixture **31** with Dibal-H, separation of the desired compounds was readily acheivable to give each pure diastereomeric alcohol **34** and **35** by FCC (Scheme 3-3). Each diastereomer was oxidized to aldehyde and treated to Takai olefination condition to produce vinyl iodide **38** and **39**, respectively. Chemoselective dihydroxylation of vinyl iodide **38** and **39** with AD-mix-β yielded diol **42** and **43**. Each acid **46** and **47** which are coupling substrates corresponding to the polyketide domains of nosperin, was complete with a two steps sequence of oxidative cleavage with $NaIO_4$, followed by Lindgren-Pinnick oxidation.

The other two diastereomers **48** and **49** were synthesized with the same route from the diastereomeric mixture **33**.

Scheme 3-3 Synthesis of four diastereomers of the polyketide subunit.[4]

The stereochemistry of these central polyketide fragments (**46**, **47**, **48**, and **49**) was confirmed by an analysis of $^{3}J_{HH}$ values for acetonides **50** and **51** (Scheme 3-4). H2 in acetonide **50** showed one large coupling constant (H2-H5, $^{3}J_{HH}$ = 9.9 Hz) and three small equivalent couplings (H2-H1, H2-H1', and H2-H3, $^{3}J_{HH}$ = 2.2 Hz). This set of J-couplings is expected to produce a doublet of quartest and is also expected to be found for a proton that is the equatorial or pseudo equatorial position in the 1, 3-dioxane. On the other hand, H2 in acetonide **51** had three large equivalent couplings (H2-H5, H2-H1, and H2-H3, $^{3}J_{HH}$ = 9.5 Hz) and one small coupling constant (H2-H1', $^{3}J_{HH}$ = 6.5 Hz). This pattern corresponding to a quartet of doublets, and is reasonable for a proton in an axial position in the six membered cyclic system that has 4 protons adjacent. The stereochemistry of the other two diastereomers, **38** and **39,** was also confirmed by the same method.

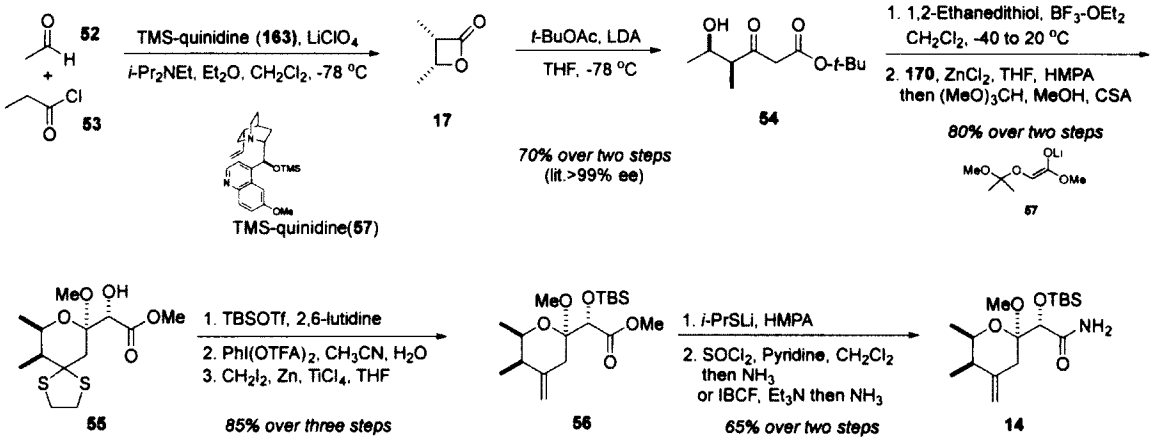
Scheme 3-4 Confirmation of stereochemistry.



Many novel approaches to common pyran ester fragment of the pederins e.g. **56** have been reported to date.[5, 6] In light of the overall goals of the synthesis we chose to combine elements of Nakata and Floreancig's novel approachs (outlined in Scheme 3-5).[6] β-lactone **17** was prepared from acetaldehyde **52** and propionyl chloride **53** in the presence of Et_3N, TMS-quinidine **57**, and

$LiClO_4$ and the volatile β-lactone **17** was treated to the lithium enolate of *tert*-butyl acetate to provide β-keto ester **54** in 70% yield over two steps. In accord with Nakata's route, β-keto ester **54** was transformed to thioketal-pyran **55** through two steps sequence including ketone protection with thioacetal/lactone cyclization and stereoselective Claisen condensation with enolate **57** in the present of $ZnCl_2$, followed by ketal formation under acidic methanol condition. TBS protection, thioacetal deprotection, and exocyclic olefination with Nozaki-Takai reagent produced methyl ester **56**. Thiolate-mediated hydrolysis of methyl ester **56** yielded free carboxylic acid and the acid converted to amide **14** through a mixed anhydride or acid chloride formation, followed by an addition of *aq.* NH_4OH. Based on this scalable and efficient route, 3-4 g of amide **14** was prepared from each batch and overall yield over 9 steps was 31%.

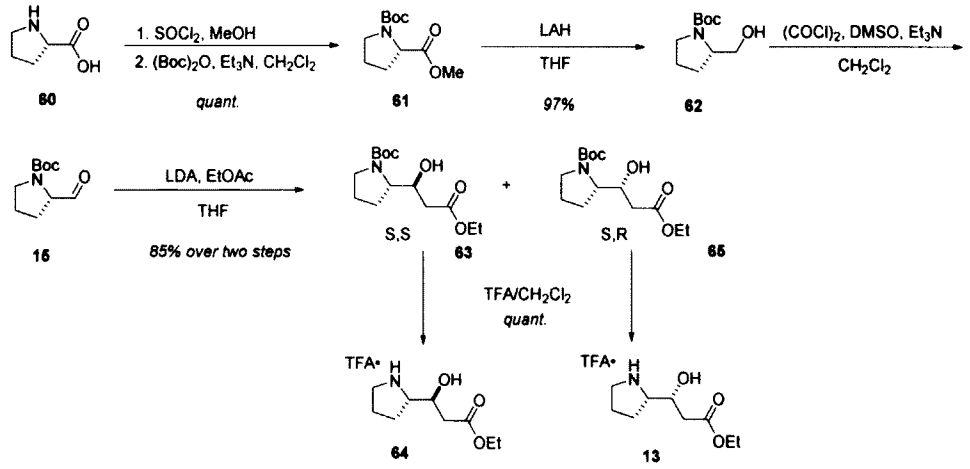
*Scheme 3-5 Synthesis of amide **14***



The synthesis of the proline derivative **13** is shown in Scheme 3-6. L-proline **60** was converted to Boc-methyl ester proline **61** via two steps sequence. Methyl ester **61** was reduced to alcohol **62** with $LiAlH_4$. Oxidation and aldol reaction with enolate of ethyl acetate yielded separable two diastereomers **63** and **65** and the ratio determined by crude NMR was **63**:**65** = 1:3. The mixture of the two diastereomers was separated by preparative HPLC (Waters Sunfire SiO_2 column, 10X250

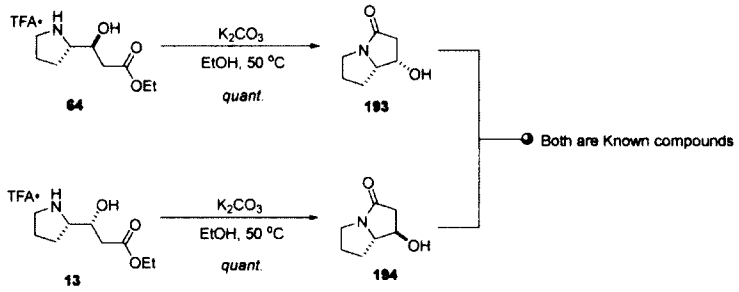
mm, 5 μm particle size, continuous gradient 1:10 to 1:1 = Hex:EtOAc, flow rate = 1 ml/min, elution time of **63** = 34 min, **65** = 33 min). Each Boc protected proline **63** and **65** were treated to a 1:1 mixture of TFA and CH_2Cl_2 to remove Boc group. Each amine –TFA salt **64** and **13** were used to amide coupling with the middle fragment **46**, **47**, **48**, and **49**.

*Scheme 3-6 Synthesis of proline subunit **135** and **175**.*



The stereochemistry in amine-TFA salts **13** and **64** was confirmed by a comparison with reported NMR data of lactam **193** and **194**. The amine-TFA salt **64** and **13** were cyclized under K_2CO_3 and thermal condition to produce lactam **193** and **194**, respectively. NMR data of those were well matched to the reported NMR data of the two lactams prepared by other methods.[7]

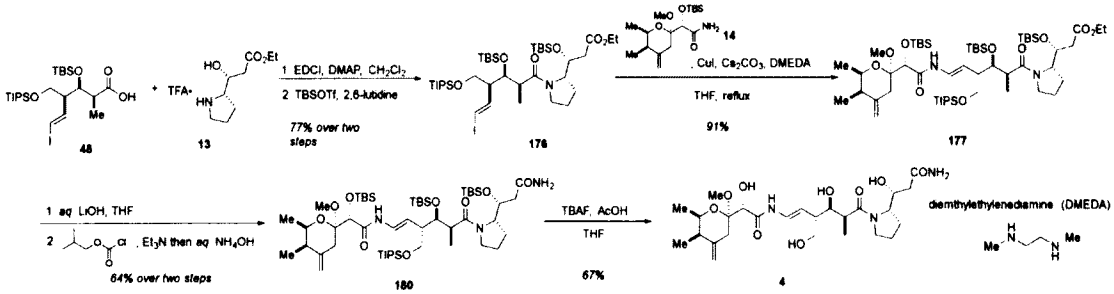
Scheme 3-7 Confirmation of stereochemistry.



With each of the needed fragments: amine **64**, **13** (two diastereomers), amide **14**, acid **46**, **47**, **48**, and **49** (four diastereomers) in hand it was possible to examine strategies for connection of

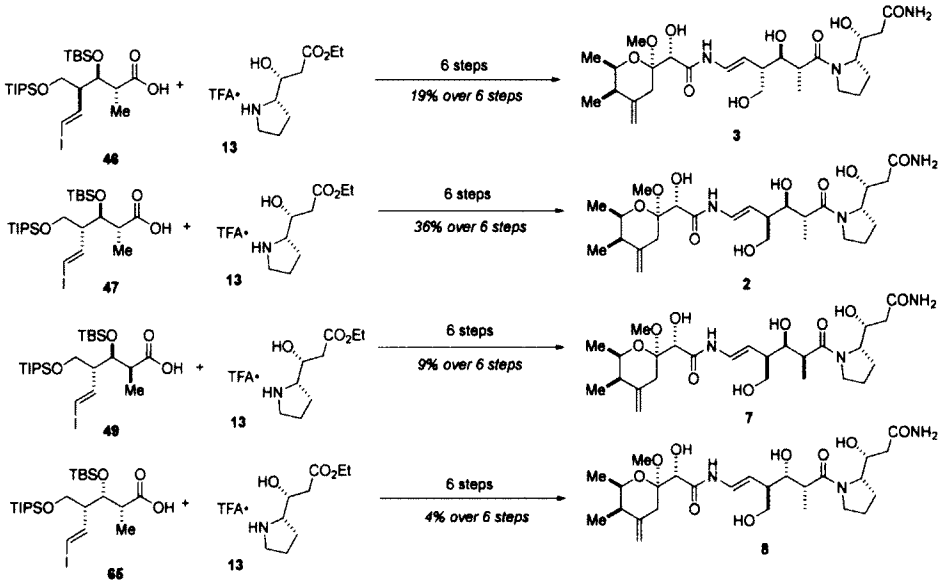
the three fragments to produce nosperin (Scheme 3-8). Amide coupling of acid **48** and amine-TFA salt **13**, followed by TBS protection gave amide **176** in 77% yield over two steps. Vinyl iodide **176** was coupled with amide **14** with Buchwald's condition using CuI, Cs_2CO_3, and DMEDA in 91% yield.[8] Fully connected ethyl ester **177** was then converted to terminal amide **180** using a two steps sequence of hydrolysis with *aq.* LiOH and mixed anhydride formation, followed by quenching with *aq.* NH_4OH. The fully protected amide **180** was subjected to global deprotection with TBAF buffered with AcOH to give a first diasteromer corresponding to nosperin.

Scheme 3-8 Coupling fragments



Three other diastereomers (**3**, **2**, and **7**) were readily prepared by the same overall process as in Scheme 3-8 and are shown in Scheme 3-9. In addition, a minor diastereomer (**65**) was also isolated from the sequence leading to diastereomer **4** by spearation and presumably stems from a poor *ee* of the E-crotylation reaction earlier in the sequence.

Scheme 3-9 Synthesis of diastereomers of nosperin

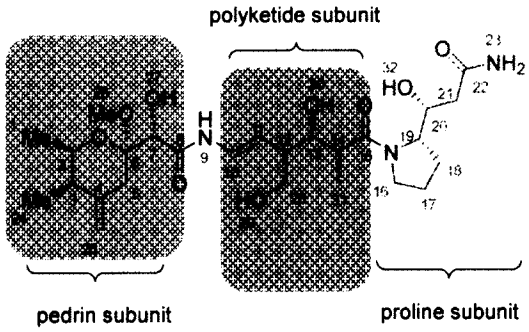


Unfortunately, none of these five diastereomers matched reported ^{1}H and ^{13}C NMR data for nosperin, clearly bringing into question the informatics-based assignment of stereochemisty. At this juncture significant effort was invested into a careful analysis of the trends in the NMR data for synthesized compounds *vs* what could be modeled.

3.2.2 NMR data analysis and conformational study for structure elucidation

Although the initial five compounds did not provide the desired outcome, the ^{1}H and ^{13}C NMR data of the initial set of compounds were very instructive and provided important clues in our efforts to deduce the stereochemistry of nosperin. On the basis of an expectation that nosperin could be considered as three non-coupled stereochemical units, we divided nosperin into three parts (pedrin, polyketide, and proline subunits) so as to facilitate the analysis of NMR data (Figure 3-7).

Figure 3-7 Three subunits of Nosperin

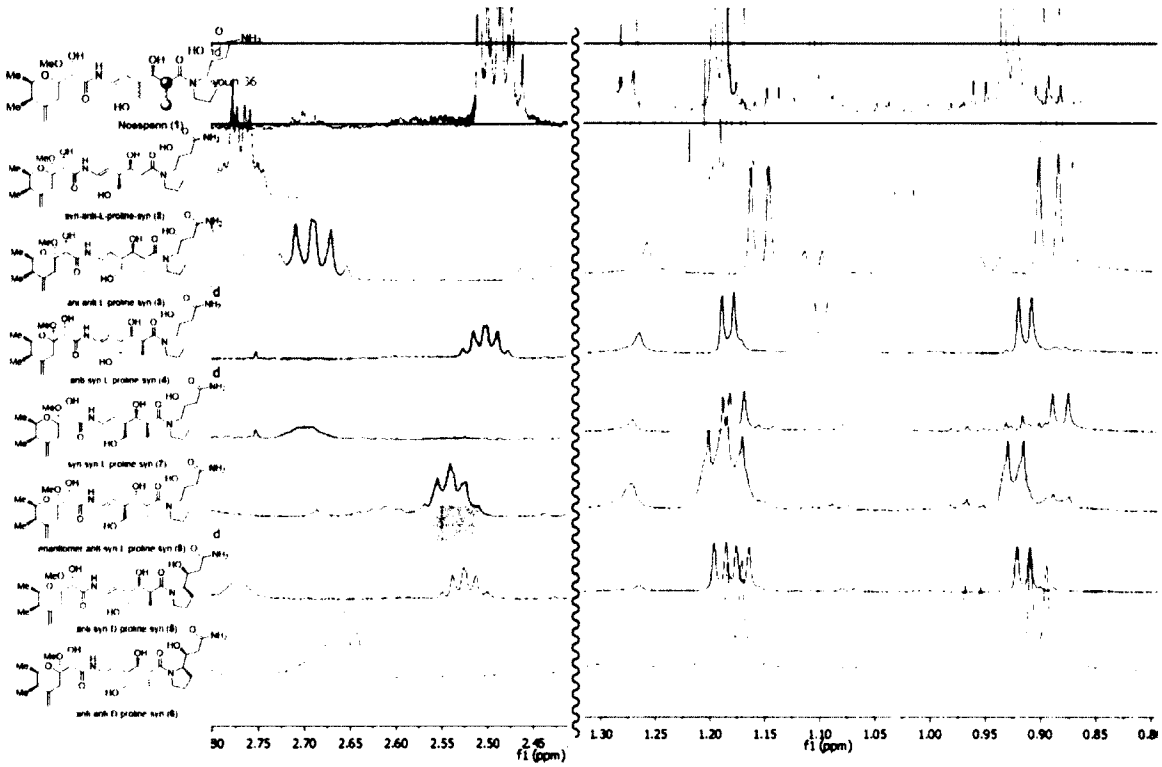


For all five of the initially prepared diastereomers, the ^{1}H and ^{13}C NMR resonances for the pedrin subunit were well matched to the authentic NMR data of nosperin. This data implied the relative stereochemistry of the pedrin domain suggested by bioinformatics and NMR analysis was reliable. It is worth noting that the absolute configuration of the pedrin domain was predicted by bioinformatics on the basis of stereoselectivity features of the initial KR1. In addition to the bioinformatics suggestion, most pedrin domains in the same natural product family have the same absolute stereochemistry. Based on these data, and encouraged by the match in NMR data for a series of diasteromers, we were confident that the proposed absolute stereochemistry for nosperin was most likely correct. It is worth noting that much of this confidence is based on negative evidence and as such there is a reasonable element of uncertainty

There are three continuous stereogenic centers with an adjacent allylic system in the polyketide subunit. This densely functionalized polyketide has no homologs in the literature to data and the delicate balance of minimization of *syn*-pentane interactions and possible hydrogen bonding was borne out in apparent, and significant, changes in ^{1}H and ^{13}C NMR data. The resonances for H14 and H31 were especially diagnostic: for example a *syn* relationship between H13 and H14 resulted in diagnostic chemical shifts for H14 of ~2.50 ppm; when *anti* this proton

was more commonly found downfield of 2.65 ppm (Scheme 3-8). The chemical shift for the H31 methyl group was very variable, and when coupled to the chemical shift of H14 (in nosperin, this proton comes at 2.50ppm), was diagnostic for sterochemical changes in the region immediately adjacent the proline amide. Patterns in our data strongly suggested that the relative stereochemistry in polyketide domain was *anti* between H12 and H13 and *syn* between H13 and H14. The chemical shifts for H14 and H31 in the other diastereomers that didi not have the *anti-syn* stereochemistry were signfiicantly different from the authentic NMR data of nosperin. In addition to the chemical shift observations for H14 and H31, $^{3}J_{H}$ constants and peak multiplicities for H13 and H14 also supported these observations.

Figure 3-8 H13 and H31 in seven diastereomers of nosperin



In order to more fully understand the conformational underpinnings of the observed patterns, we employed computational studies and computed peak multiplicities based on observed $^3J_{HH}$ coupling values to predict the relative configuration of nosperin. Summary figures of the computational studies are shown in Figures 3-9, 3-10, 3-11, and 3-12. In a typical example, the conformational space of a hypothetical diasteromer was calculated by molecular mechanics (Monte-Carlo conformer search, MM94 force field, minimum 1000 conformer starting points, implemented in Spartan 2013, WaveFunction Inc.) and was calibrated to molecules playing a significant role in the overall picture of ±5 kcal/mol as defined by a Boltzmann-type distribution. In the case of the *syn, anti*-L-Pro model shown in Figure 3-9 it is clear that the conformer space is populated by three major families: an extended, or E-shape, a U shape, and a V shape that shares similarities to the U shape molecules. This analysis underpinned the calculation (simulation) of conformer-averaged coupling constants that could be used to generate hypothetical peaks. Based on an analysis of the overall data set, the *anti-syn* diastereomer shown in Figure 3-11 was most similar to the coupling patterns of nosperin. H14 and H13 in ^{1}H NMR of nosperin are δ 2.48 (dq, J = 9.3, 6.8 Hz) and δ 3.87 (dd, J = 9.3, 3.1 Hz), respectively, therefore $^3J_{H13\text{-}H14}$ is 9.3 Hz and $^3J_{H12\text{-}H13}$ is 3.1 Hz. These coupling constants were well matched to the dihedral angels of H12-H13-H14 (θ (H12, H13) = 60 °, 3.3 Hz; θ (H13, H14) = 176 °, 9.7 Hz) in the calculated conformation of the *anti-syn* diastereomer (Figure 3-11). Based on this analysis, we cautiously predicted that the relative stereochemistry of the polyketide domain is *anti-syn*.

Figure 3-9. Conformation and $^3J_{HH}$ coupling of syn-anti-L-Proline.

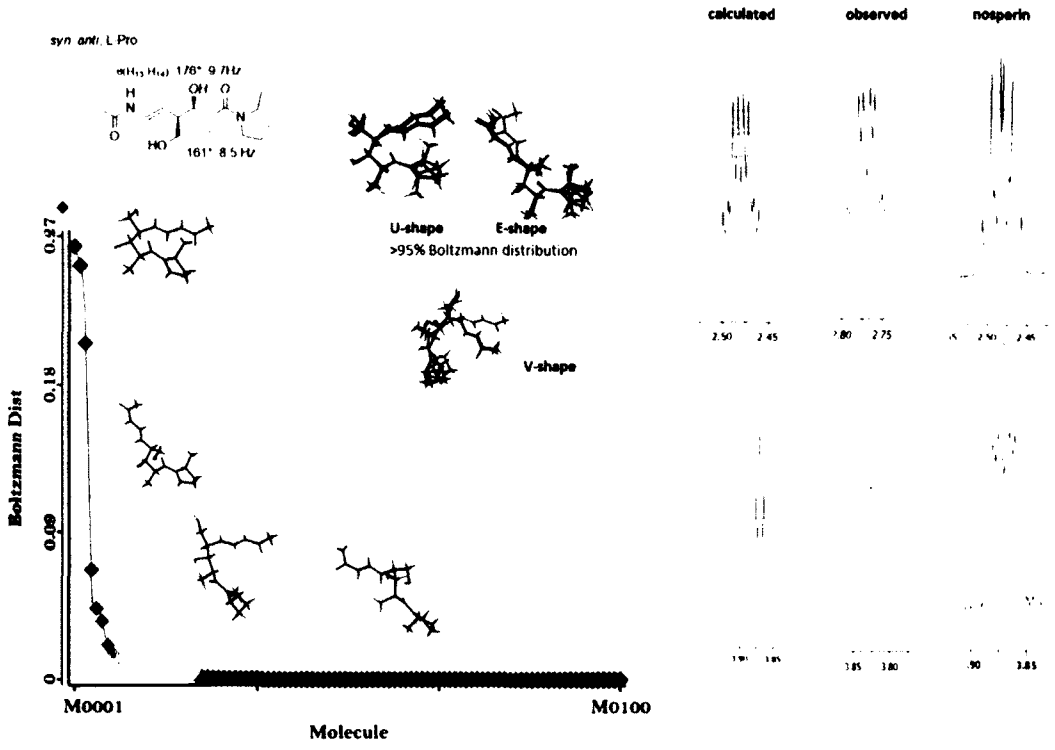


Figure 3-10. Conformation and $^3J_{HH}$ coupling of syn-syn-L-Proline.

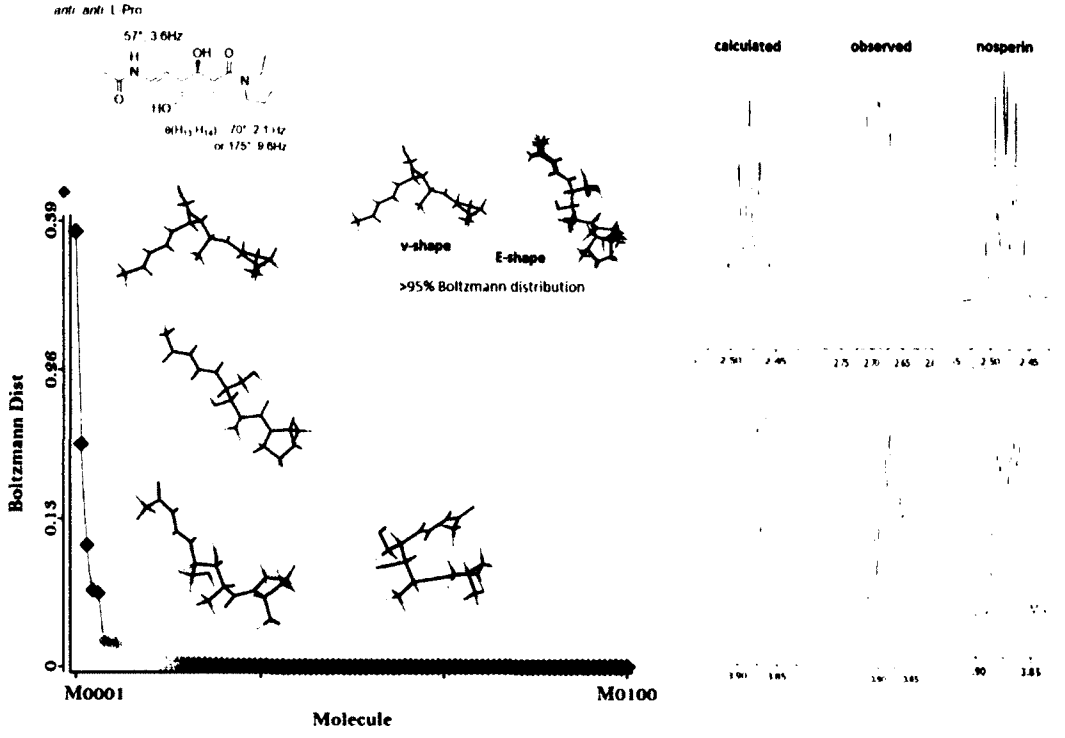


Figure 3-11. Conformation and $^3J_{HH}$ coupling of anti-syn-L-Proline.

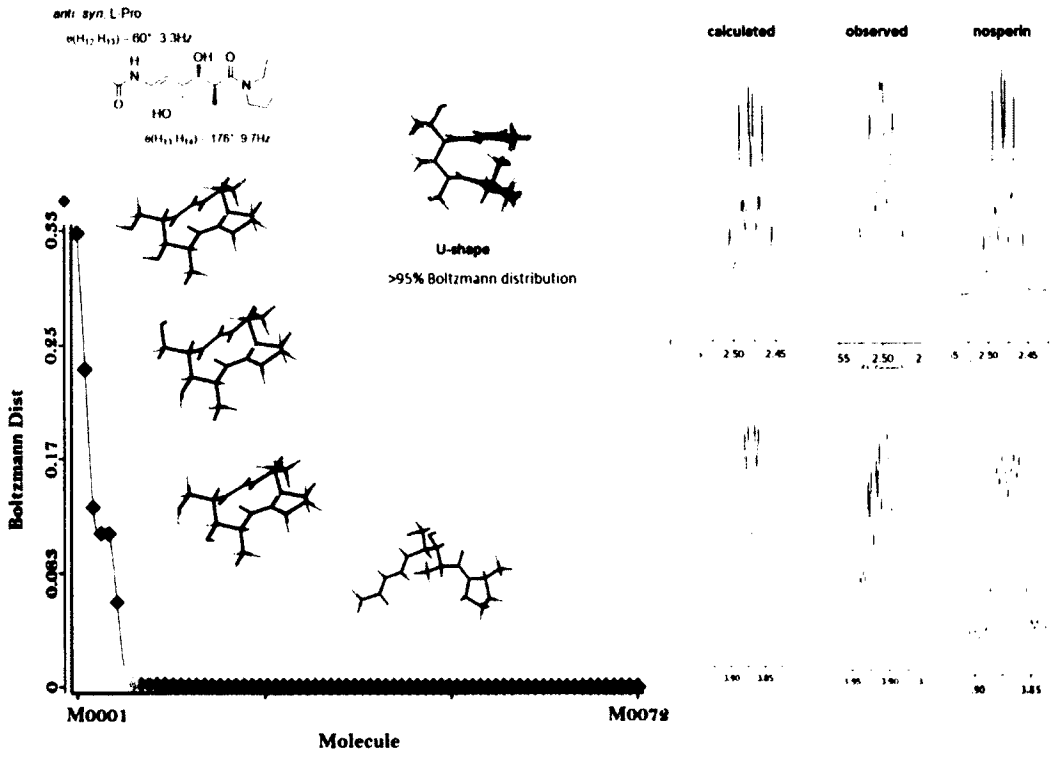
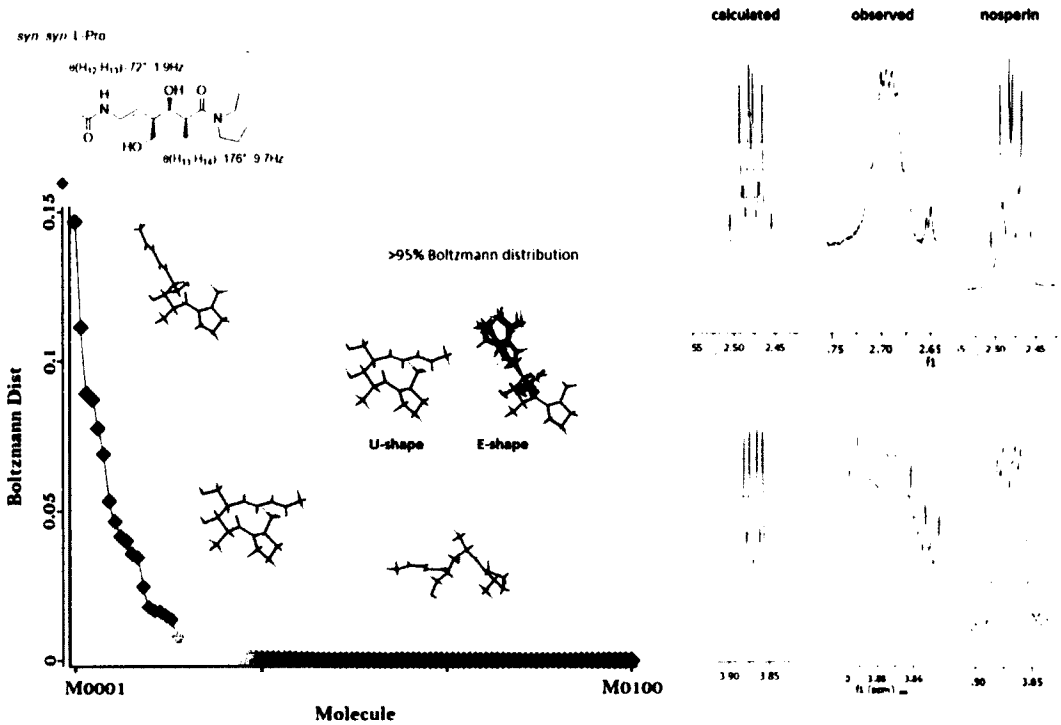


Figure 3-12. Conformation and $^3J_{HH}$ coupling of syn-syn-L-Proline.



We also considered the prospects of an error in stereochemisty in the proline domain. An analysis of the ^{13}C NMR of nosperin vs. the synthesized compounds was very revealing. In all diastereomers we synthesized, most carbons in the pedrin domain were well matched or very small deviations (compound **2**, **3**, **4**, **7**, and **8** in Figure 3-13 and 3-14). However, chemical shifts of the carbons in the polyketide domain varied sizeable amounts as a function of stereochemistry. In addition, carbons in the proline domain of the all cases gave big deviations. For example *anti-anti*-L-pro-*syn* (**3**), *anti-syn*-L-*syn* (**4**), *syn-syn*-L-pro-*syn* (**7**) and ent.-*anti-syn*-L-pro-*syn* (**8**) in Figure 3-13 and 3-14, the $\Delta^{13}C$ values over the pedrin and polyketide domains are 0 to ±1 ppm, but carbons in the proline domain have $\Delta^{13}C$ values that range much higher (±2-6 ppm). Gratifyingly, the *anti-syn* diastereomer (**4**) was well matched to the data reported for nosperin, and suggested a need for correction of the stereocenter(s) on proline domain. Although the lack of an epimerase domain in the PKS at this position supports the idea of (L)-proline as a building block, it is not an unequivocal proof that rules out a role for (D)-proline. We set out to prepare *anti-syn*-D-proline-*syn* (**5**) and *anti-anti*-D-proline-*syn* (**6**) using the same chemistry described in the previous section.

Figure 3-13. $\Delta^{13}C$ NMR of nosperin diastereomers

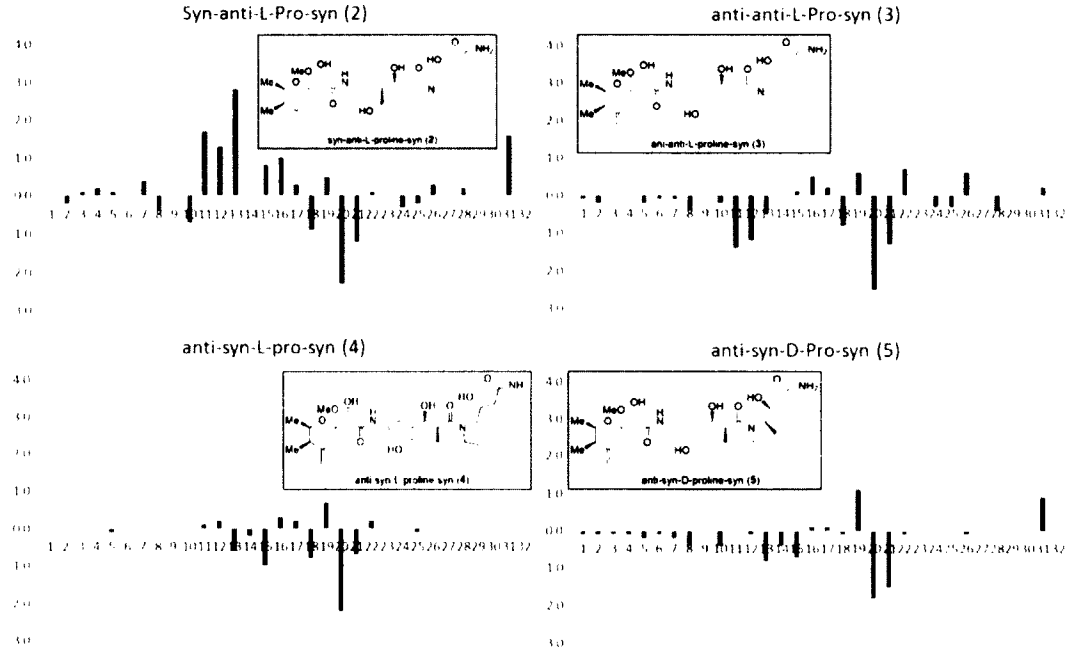
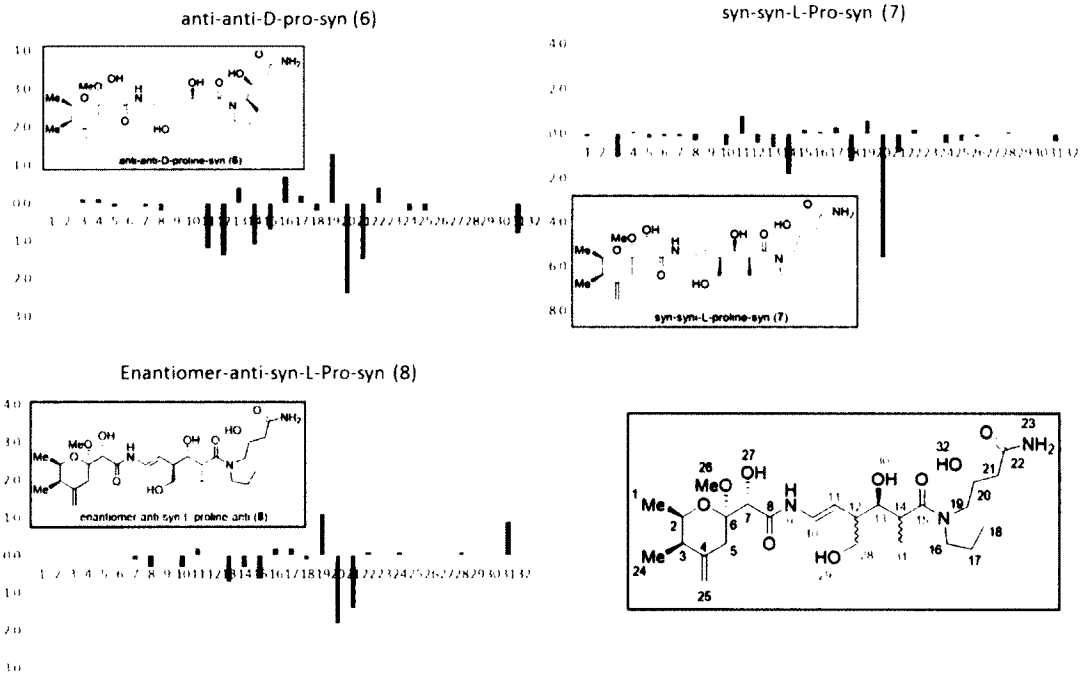


Figure 3-14. Δ value in ^{13}C NMR.

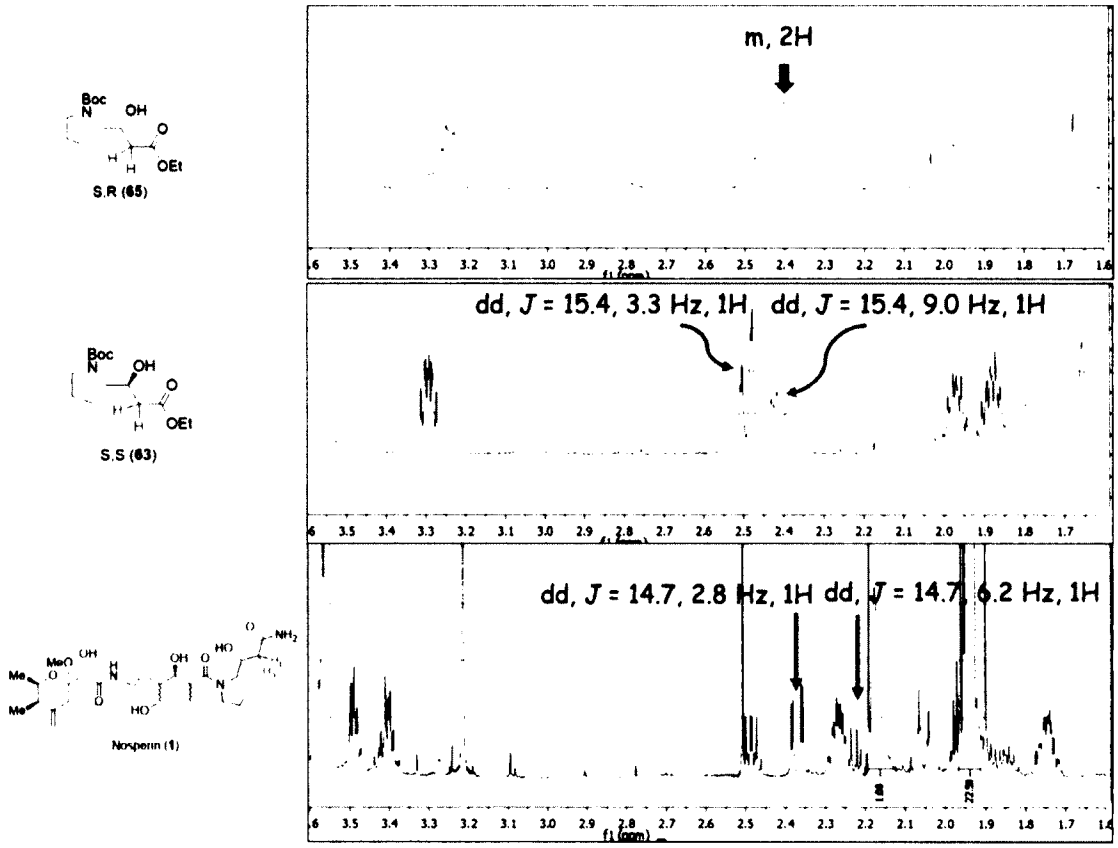


Frustratingly, the introduction of D-Pro derived compounds failed to produce the desired changes in NMR data. Both C19 and C20 in the modified compounds **5** and **6** resulted in sizable

deviations from authentic chemical shift values for nosperin. In addition to this ^{13}C NMR data, δ H31 (α-methyl) of the compound **5** in ^{1}H NMR was more down field (δ_H 1.17) in comparison with the authentic peak of nosperin (δ_H 1.10, Figure 3-8). From this overall analysis, we concluded that *anti-syn* polyketide domain combined with an L-proline domain would be an optimal series to pursue.

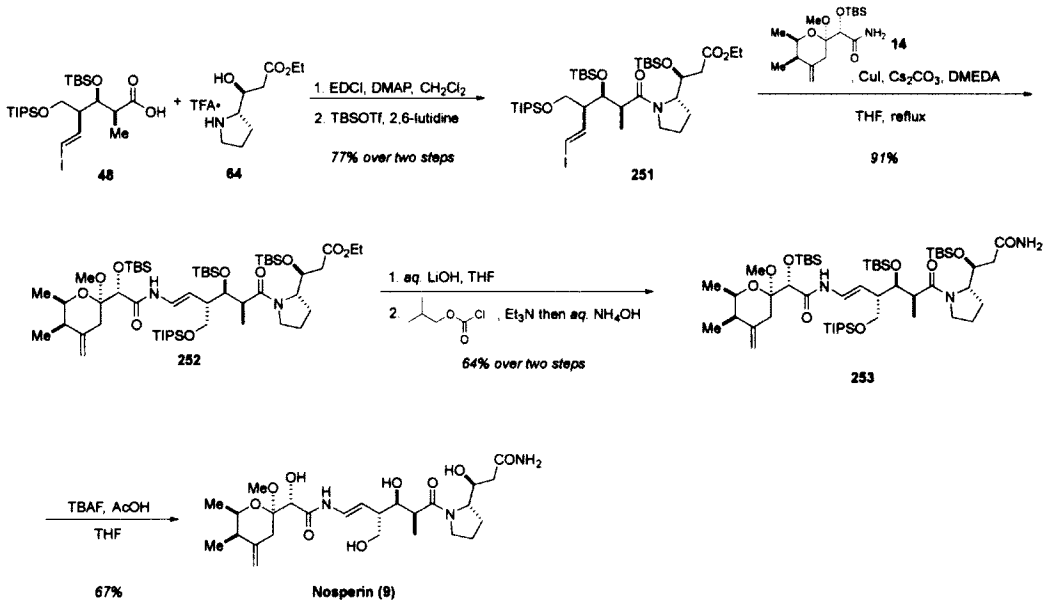
Important guidance also appeared at this stage in an analysis of the ^{1}H NMR of aldol adducts **63** and **65** (Figure 3-15). Aldol reaction between aldehyde **15** and ethyl acetate gave a mixture of *syn* aldol adduct **65** and *anti* aldol adduct **63** and the mixture was separated by preparative HPLC. Notwithstanding the limits of using Boc protected secondary amines as models, it is very clear that the methylene peaks adjacent the terminal amide for *syn* aldol adduct **65** were a broad multiplet (δ_H 2.45-2.36, m, 2H). The peaks in *anti* aldol adduct **63** were two sets of doublet of doublets (δ_H 2.49, dd, J = 15.4, 3.3 Hz, 1H; 2.41, dd, J = 15.4, 9.0 Hz, 1H). This data is represented pictorially in Figure 3-15. These studies resulted in defining a*nti* aldol adduct **63** as a key target for synthesis.

Figure 3-15 Coupling patterns of proline subunits



The final assembly of the key building blocks identified as most likley to represent the stereochemistry of nosperin is shown below in Scheme 3-10 and begins with *anti*-L-Pro derivative **64**. Synthesis of the amide **251** and protection was followed almost immediately by Cu-catalyzed enamide formation. Hydrolysis of the terminal ester, activation with IBCF and aminolysis of the intermediate anhydride gave **253**. Deprotection gave the *anti-syn*-L-proline-*anti* compound, **9**, which was identical to nosperin as measured by ^{1}H and ^{13}C NMR. In addition, a co-sampling NMR experiment with natural material provided by Professor Joern Piel confirmed that natural nosperin and compound **9** were identical by NMR. The absolute stereochemistry was also established by comparisons of optical rotations: natural nosperin $[\alpha]^{25}_{D}$ +24.7 (c = 0.14 in CH_3OH); synthetic nosperin $[\alpha]^{20}_{D}$ +20.2 (c = 0.5 in CH_3OH)).

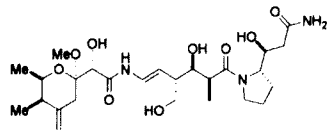
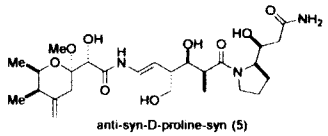
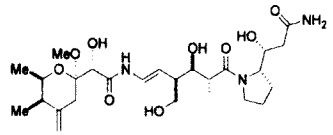
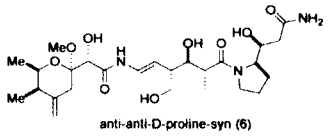
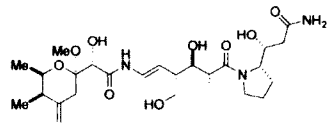
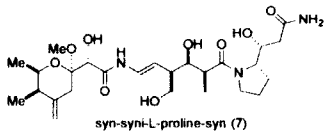
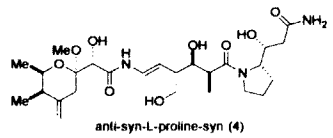
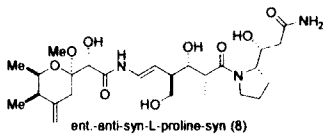
Scheme 3-10. Synthesis of Nosperin (9).



3.2.3 – Biological evaluation and SAR

Previous studies have established a role for the pederin class of molecules as cytotoxins that act by inhibition of protein biosynthesis, most likley by binding to the ribosome. [1, 2, 6] An initial evaluation of nosperin and seven analogs were tested for their cytotoxic effects against the HeLa cell line by Dr. Ueoka in Professor Joern Piel's groups at the ETH Zürich (Table 3-1). The SAR data points to an important role for overall conformation of the molecule in controlling the levels of cytotoxicity.

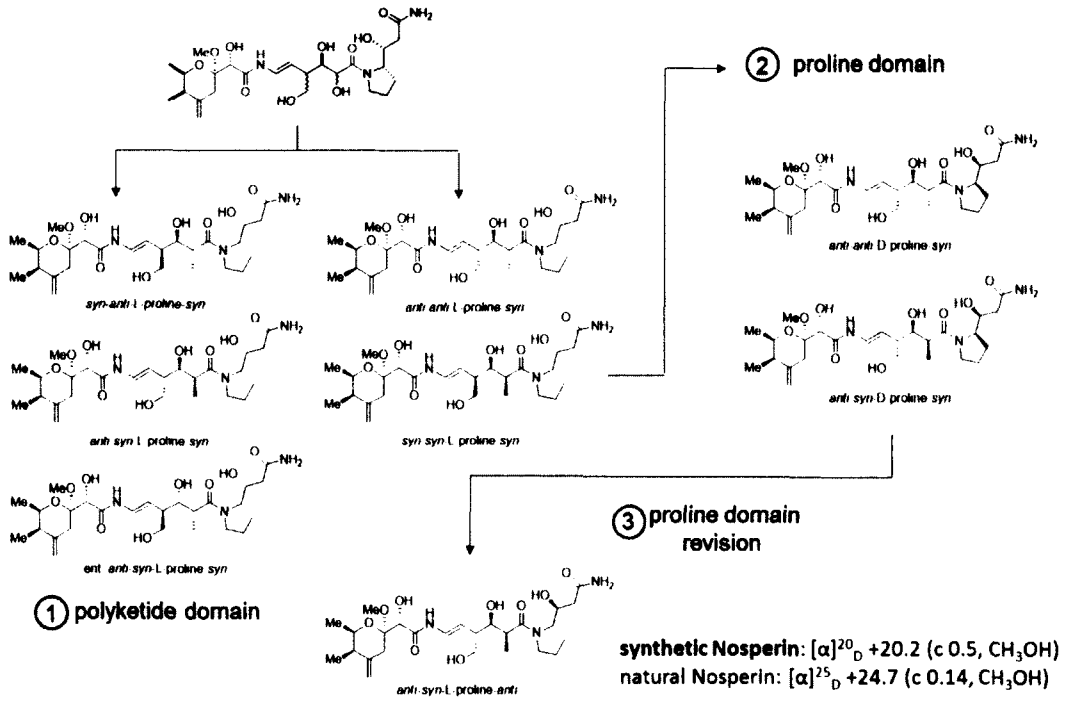
Table 3-1. SAR study of nosperin and its diastereomers

structure	IC_{50}	structure	IC_{50}
 Noesperin (1)	2.0 μg/mL	 anti-syn-D-proline-syn (5)	> 50 μg/mL
 syn-anti-L-proline-syn (2)	No activity at 50 μg/mL	 anti-anti-D-proline-syn (6)	> 50 μg/mL
 ani-anti-L-proline-syn (3)	No activity at 50 μg/mL	 syn-syni-L-proline-syn (7)	No activity at 50 μg/mL
 anti-syn-L-proline-syn (4)	4.5 μg/mL	 ent.-anti-syn-L-proline-syn (8)	> 50 μg/mL

3.3. Conclusion.

Nosperin was initially reported in 2013 from a metagenomics-based isolation from the lichen *Peltigera membranaces* and its rich collection of symbiotic microorganisms e.g. *Nostoc sp.* cyanobacterium. The initial structure elucidation left a number of stereochemical questions unanswered and here a highly convergent synthetic route to Nosperin and a number of diastereomers has been developed. A combination of synthetic chemistry, NMR, and computational chemistry was required to establish the stereochemistry and the overall approach is summarized in Figure 3-16. We note the the synthesis has defined a revision of the previously published relative stereochemistry in the proline domain.

Figure 3-16. Confirmation of relative and absolute stereochemistry



3.4. Experimental Procedures and Data.

^{1}H NMR and ^{13}C NMR spectra were recorded using the following spectrometers: Bruker Avance 500 (500/125 MHz), Bruker Avance 400 (400/100 MHz), or an Agilent DD2 400 (400/100 MHz). Chemical shifts are quoted in ppm relative residual solvent as an internal reference[3]. The following abbreviations are used to describe signal multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), dt (doublet of triplets) etc. COSY, HMQC, and DEPT experiments were used when appropriate to aid structure assignment. Diastereotopic protons are labeled as H'-X and H''-X and imply no particular stereochemistry. Compounds were numbered according to their names as indicated in their structures.

Accurate mass spectra were recorded on a Waters Synapt G1 qTOF spectrometer equipped with a Waters Acquity UPLC (fitted with a BEH C18 Column, 130 Å, 1.7 μm, 2.1× 50 mm). Positive and negative electrospray was used for ionization unless otherwise indictaed.

Infrared spectra were obtained using a Thermo Nicolet 6700 FTIR spectrometer fitted with a diamond ATR. The spectra of solids were recorded using a thin film of the neat product whereas the spectra of oils were recorded using a thin liquid film of the product indicated by the bracketed solvent.

Optical rotations were measured in a 100 mm length cell using a Perkin Elmer 341 Polarimeter fitted with a sodium source lamp and a Glan-Taylor polarizer.

---

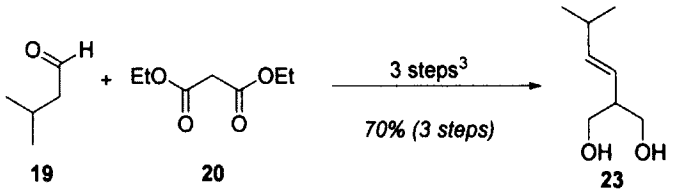
[3] The following values were used as internal locks ($^{1}H/^{13}C$ NMR spectra, respectively): 7.26/77.16 ppm in $CDCl_3$, 7.16/128.06 ppm in C_6D_6, 1.94/118.26 ppm in CD_3CN, and 4.87/49.0 ppm in CD_3OD.

Melting points were recorded using a digital Stanford Research Systems OptiMelt automated melting point system. The reported values are an average of duplicate measurements which were takes by slowly increasing the temperature from 25 °C at a rate of 2.5 °C per min.

Analytical thin-layer chromatography was carried out on SiliCycle glass-backed extra hard layer 60Å plates (20×20 cm particle, 250μm thickness), using either aqueous potassium permanganate or aqueous cerium ammonium molybdate stains to aid visualization.

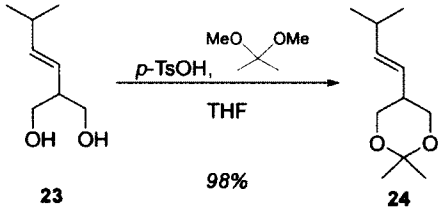
Flash column chromatography was carried out following the general principles of Still (W.C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.using SiliaFlash P60 silica (40-63 μm particle size, 230-400 mesh, SiliCycle). Preparative HPLC was performed on a Gilson HPLC consisting of a 215 liquid handler, 305/305 pump modules, and a 155 UV/VIS detector, all operating under control of Gilson's Trilution software. A Waters Sunfire silica column (10×250 mm, 5μm particle size) was used for purifications described herein

Non-aqueous reactions were carried out under an atmosphere of nitrogen, in flame-dried glassware, using solvents dried by passage though activated alumina as described by Bergman and Grubbs (P. J. Alaimo, D.W. Peters, J. Arnold and R.G. Bergman, *J. Chem. Educ.*, **2001**, *78*, 64; A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R.K. Rosen and F. J. Timmers, *Organometallics*, **1996**, *15*, 151) or obtained by distillation when more appropriate. Bases such as triethylamine, pyridine, and diisopropylamine (Hünig's base) were freshly distilled from CaH_2 prior to use. Brine refers to a saturated solution of sodium chloride and pH 2 sulfate buffer refers to an aqueous solution made of 1 M sodium bisulfate and 1 M sodium sulfate mixed in 1:1 v/v ratio.



(E)-2-(3-methylbut-1-en-1-yl)propane-1,3-diol:

ν_{max} (neat)/cm^{-1} 3327, 2957, 2870, 1708, 1465, 1383; δ_H (600 MHz, $CDCl_3$) 5.59 (ddd, *J* = 15.6, 6.6, 1.0 Hz, 1H), 5.20 (ddd, *J* = 15.6, 8.2, 1.4 Hz, 1H), 3.75 – 3.66 (m, 4H), 2.51 – 2.42 (m, 1H), 2.28 (dqd, J = 13.4, 6.7, 1.4 Hz, 1H), 2.15 (bs, 2H), 0.98 (d, J = 6.7 Hz, 6H); δ_C (151 MHz, $CDCl_3$) 142.1, 123.7, 65.4, 46.8, 31.4, 22.6; Accurate mass (ES$^+$): Found 145.1205 (-16.5 ppm), $C_8H_{17}O_2$ ($M+H^+$) requires 145.1229.

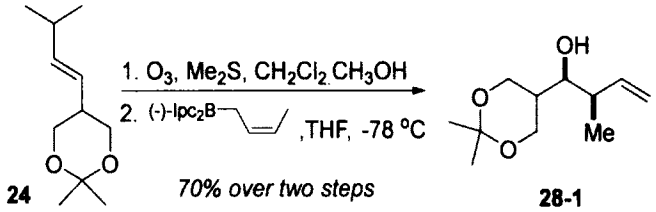


(E)-2,2-dimethyl-5-(3-methylbut-1-en-1-yl)-1,3-dioxane:

To a solution of diol **23** (19.61 g, 135.98 mmol) in THF (453 ml) were added 2,2-dimethoxypropane (24.99 ml, 203.97 mmol) and *p*-TsOH (1.29 g, 6.80 mmol). The reaction mixture was stirred for 1hr at room temperature. After reaction complete, Et_3N (few drops) was added and then stirred for additional 10 min. The reaction mixture was concentrated *in vacuo*. The crude material was purified by flash column chromatography to give pure acetonide product **24** (24.60 g, 133.26 mmol, 98%).

ν_{max} (neat)/cm^{-1} 2993, 2960, 2866, 1771, 1455, 1380, 1369; δ_H (400 MHz, $CDCl_3$) 5.56 – 5.46 (m, 1H), 5.11 (ddd, *J* = 15.6, 7.8, 1.4 Hz, 1H), 3.85 – 3.74 (m, 2H), 3.67 (td, *J* = 10.5, 1.3 Hz, 2H), 2.56 – 2.43 (m, 1H), 2.30 – 2.15 (m, 1H), 1.45 (s, 3H), 1.40 (s, 3H), 0.96 (d, *J* = 6.8 Hz, 6H); δ_C (100 MHz,

$CDCl_3$) 141.0, 123.0, 97.5, 64.8, 38.1, 31.3, 28.6, 22.5, 19.7; Accurate mass (ES-): Found 183.1379 (-3.3 ppm), $C_{11}H_{19}O_2$ ($M\text{-}H^+$) requires 183.1385.



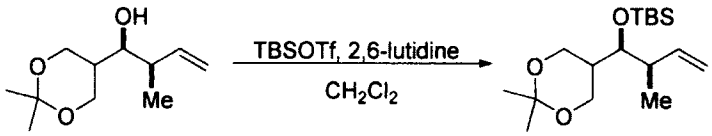
(1S,2R)-1-(2,2-dimethyl-1,3-dioxan-5-yl)-2-methylbut-3-en-1-ol:

The alkene **24** (8 g, 43.4 mmol) was dissolved in CH_3OH-CH_2Cl_2 (v:v = 1:1, 200 ml) and cooled to -78 °C. O_3/O_2 was bubbled through the solution for 15 minutes, at which point a steel blue color persisted. Stirring was continued 20 minutes at -78 °C, then N_2 gas was bubbled through the solution until the steel blue color dissipated. Dimethyl sulfide (31.9 ml, 434.1 mmol, 10 eq) was added and the reaction mixture was warm to room temperature, and stirring was continued for 12 hrs. The solution was concentrated *in vacuo*, and the crude residue was used to the next step without further purification.

To a stirred mixture of freshly sublimated potassium *tert*-butoxide (7.78 g, 69.36 mmol) in THF (200 ml) a solution of *cis*-2-butene (11.68 g, 208.09 mmol) in THF (50 ml) and *n*-butyllithium (27.75 ml, 69.36 mmol, 2.5 M solution in hexane) were added at -78 °C. After complete addition of *n*-butyllithium, the mixture was stirred at -45 °C for 10 min. The resulting solution was re-cooled to -78 °C, and a solution of (-)-B-methoxydiisopinocampheylborane (23.04 g, 72.83 mmol) in THF (75 ml) was added to the reaction mixture. After the reaction mixture was stirred for 30 min at -78 °C, boron trifluoride etherate (9.84 ml, 79.77 mmol) was added dropwise. Then a solution of aldehyde (5 g, 34.68 mmol) in THF (100 ml) was added dropwise. The reaction mixture was stirred at -78 °C

for 3 hr and then treated with 3 N NaOH (57.8 ml) and 30% H_2O_2 solution (15.59 ml). The resulting slurry was stirred overnight at room temperature. The bi-phasic mixture was extracted with EtOAc (x3), washed with brine, and dried over sodium sulfate. The residue, after removal of the solvent *in vacuo*, was purified by flash column chromatography to give pure alcohol **28-1** (4.89 g, 24.41 mmol, 70%)

ν_{max}(neat)/cm^{-1} 2450, 3070, 2956, 2927, 1724, 1688, 1456; $[\alpha]^{20}_D$ +23.1 (c = 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 5.80 (dddd, *J* = 16.4, 11.3, 6.9, 1.8 Hz, 1H), 5.19 – 5.07 (m, 2H), 4.06 – 4.00 (m, 1H), 3.96 (ddd, *J* = 11.9, 7.3, 1.8 Hz, 1H), 3.92 – 3.86 (m, 1H), 3.78 (ddd, *J* = 11.8, 7.6, 1.8 Hz, 1H), 3.62 – 3.56 (m, 1H), 2.38 – 2.26 (m, 1H), 1.96-1.90 (m, 1H), 1.78 (d, *J* = 4.4 Hz, 1H), 1.42 (s, 6H), 1.04 (d, *J* = 6.9 Hz, 3H); δ_C (125 MHz, $CDCl_3$) 140.9, 115.9, 98.2, 73.6, 62.3, 61.3, 40.4, 36.6, 25.4, 22.8, 12.9; Accurate mass (ES-): Found 199.1334 (0 ppm), $C_{11}H_{19}O_3$ ($M-H^+$) requires 199.1334.

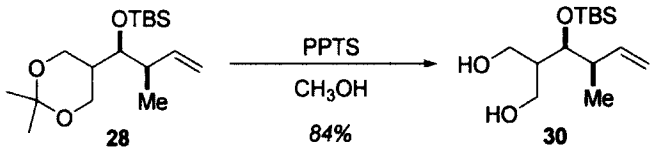


28-1 *96%* **28**

tert-butyl(((1S,2R)-1-(2,2-dimethyl-1,3-dioxan-5-yl)-2-methylbut-3-en-1-yl)oxy)dimethylsilane:

The alcohol **28-1** (4.89 g, 24.42 mmol, 1 eq) was dissolved in CH_2Cl_2 (48 ml) and cooled to 0 °C. To this solution was added 2, 6-lutidine (5.69 ml, 48.83 mmol, 2 eq) followed by the slow addition of *t*-butyldimethylsilyltrifluoromethane sulfonate (6.73 ml, 29.30 mmol, 1.2 eq). After 1hr of stirring at 0 °C, the reaction mixture was quenched with 10% aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (x3). The combined organic layers were washed with brine, dried $MgSO_4$, filtered and concentrated *in vacuo*. The crude was purified by flash column chromatography to provide silyl ether **28** (7.37 g, 23.44 mmol, 96%) as a clear oil.

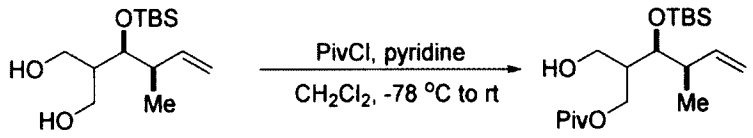
ν_{max}(neat)/cm^{-1} 2956, 2930, 2885, 2858, 1473, 1369, 1254; $[\alpha]^{20}_D$ +20.3 (c = 0.5 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 5.87 (dddd, *J* = 16.5, 11.0, 6.7, 1.0 Hz, 1H), 5.06 – 4.97 (m, 2H), 3.90 (ddt, *J* = 11.6, 5.1, 1.4 Hz, 1H), 3.87 – 3.84 (m, 1H), 3.84 – 3.77 (m, 1H), 3.66 (ddt, *J* = 11.4, 5.0, 1.4 Hz, 1H), 3.43 (t, *J* = 5.0 Hz, 1H), 2.31 – 2.22 (m, 1H), 2.05 (dddd, *J* = 14.9, 8.9, 5.5, 4.5 Hz, 1H), 1.41 (s, 3H), 1.36 (s, 3H), 0.99 (d, J = 6.9 Hz, 3H), 1.90 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); δ_C (125 MHz, $CDCl_3$) 140.9, 114.6, 97.6, 74.9, 63.0, 61.7, 42.0, 37.5, 28.4, 26.1, 19.9, 18.4, 14.6, -3.5, -4.1; Accurate mass (ES-): Found 313.2205 (+1.9 ppm), $C_{17}H_{33}O_3Si$ ($M-H^+$) requires 313.2199.



2-((1S,2R)-1-((tert-butyldimethylsilyl)oxy)-2-methylbut-3-en-1-yl)propane-1,3-diol:

To a solution of acetonide **28** (7.96 g, 25.31 mmol) in CH_3OH (253 ml) was added pyridium *p*-toluenesulfonate (PPTS, 640 mg, 2.55 mmol) at room temperature. The reaction mixture was stirred for 6 hr. After reaction complete, the reaction was quenched with Et_3N (few drops) and concentrated *in vacuo*. The residue was purified by flash column chromatography to give diol **30** (6.69 g, 21.26 mmol, 84%) as a clear oil.

ν_{max}(neat)/cm^{-1} 2285, 2956, 2930, 2888, 2858, 1472, 1361, 1255; $[\alpha]^{20}_D$ +11.3 (c = 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 5.97 – 5.79 (m, 1H), 5.11 – 5.00 (m, 2H), 3.94 (dd, *J* = 11.3, 4.9 Hz, 1H), 3.84 (dd, *J* = 10.5, 7.5 Hz, 1H), 3.81 – 3.72 (m, 3H), 2.54-2.45 (m, 1H), 2.08 (bs, 2H), 1.95 – 1.87 (m, 1H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.91 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H); δ_C (100 MHz, $CDCl_3$) 140.66, 115.0, 76.6, 64.4, 62.6, 44.6, 43.0, 26.2, 18.3, 16.5, -3.8, -4.2; Accurate mass (ES+): Found 275.2009 (-12.0 ppm), $C_{14}H_{31}O_3Si$ ($M+H^+$) requires 275.2042.

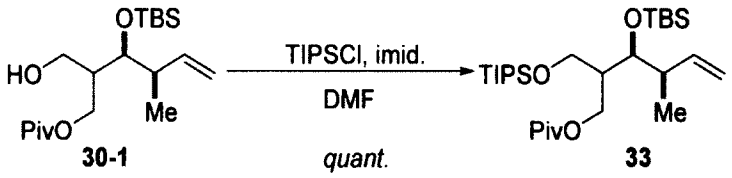


30 *83%* (a mixture of two diastereomer) **30-1**

(3S,4R)-3-((tert-butyldimethylsilyl)oxy)-2-(hydroxymethyl)-4-methylhex-5-en-1-yl pivalate:

The diol **30** (3 g, 10.93 mmol) was dissolved in pyridine (4.42 ml, 54.65 mmol) and CH_2Cl_2 (40 ml). The reaction mixture was cool to -78 °C and pivaloyl chloride (1.37 ml, 10.93 mmol) was added dropwise over 5min. The reaction mixture was allowed to slowly warm to room temperature over 3hrs. The reaction was concentrated *in vacuo* and purified by flash column chromatography to give mono-pivalate **30-1** (3.26 g, 9.07 mmol, 83%, ca. 1:7 mixture of two diastereomer).

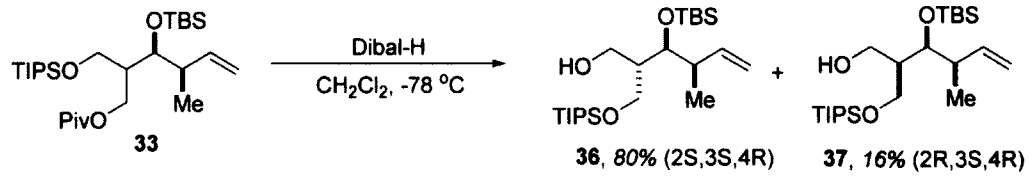
ν_{max} (neat)/cm^{-1} 3449, 2958, 2931, 2858, 1730, 1480, 1473, 1462, 1398, 1362; δ_H (600 MHz, $CDCl_3$, major diastereomer) 5.82 (ddd, *J* = 14.8, 10.4, 7.5 Hz, 1H), 5.10 – 5.01 (m, 2H), 4.31 (dd, *J* = 11.5, 4.7 Hz, 1H), 4.05 – 3.97 (m, 1H), 3.79 (dd, *J* = 5.9, 3.9 Hz, 1H), 3.66 (dd, *J* = 10.9, 6.8 Hz, 1H), 3.61 (dd, *J* = 10.9, 5.9 Hz, 1H), 2.43 (q, *J* = 6.9 Hz, 1H), 2.29 (bs, 1H), 2.14 – 2.07 (m, 1H), 1.20 (s, 9H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.90 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); δ_C (125 MHz, $CDCl_3$) 179.1, 141.3, 115.0, 74.8, 62.9, 61.9, 44.8, 42.2, 39.0, 27.4, 26.2, 18.4, 16.0, -3.8, -4.2; Accurate mass (ES+): Found 359.2618 (0.0 ppm), $C_{19}H_{39}O_4Si$ ($M+H^+$) requires 359.2618.



(3S,4R)-3-((tert-butyldimethylsilyl)oxy)-4-methyl-2-(((triisopropylsilyl)oxy)methyl)hex-5-en-1-yl pivalate:

To a solution of alcohol **30-1** (3.26 g, 9.09 mmol) in DMF (9 ml) imidazole (1.24 g, 18.18 mmol) and TIPSCl (2.41 ml, 10.91 mmol) were added at room temperature. After stirring fro 6hr at room temperature, the reaction mixture was diluted with EtOAc and washed with aqueous 1 N HCl, water (x2), and brine. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude oil was purified by flash column chromatography to give an inseparable mixture **33** of two diastereomers (4.7 g, 9.09 mmol, *quant.*).

ν_{max}(neat)/cm^{-1} 2958, 2866, 1732 1463, 1283, 1254; δ_H (500 MHz, $CDCl_3$, major diastereomer) 5.86 (ddd, *J* = 17.5, 10.4, 7.4 Hz, 1H), 5.11 – 4.95 (m, 2H), 4.36 (dd, *J* = 11.4, 4.2 Hz, 1H), 3.94 (dd, *J* = 5.8, 3.0 Hz, 1H), 3.83 (dd, *J* = 11.4, 8.8 Hz, 1H), 3.74 (dd, *J* = 9.9, 5.2 Hz, 1H), 3.67 (dd, *J* = 9.9, 8.3 Hz, 1H), 2.47-2.40 (m, 1H), 2.06 (tq, *J* = 8.5, 4.3 Hz, 1H), 1.18 (s, 9H), 1.10-1.05 (m, 3H), 1.06 (s, 18H), 1.02 (d, J = 6.8 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); δ_C (125 MHz, $CDCl_3$) 178.6, 141.7, 114.5, 73.5, 62.8, 61.7, 44.3, 42.7, 38.9, 27.4, 26.2, 18.5, 18.2, 16.1, 12.1, -3.8, -4.1; Accurate mass (ES+): Found 525.3970 (+3.5 ppm), $C_{28}H_{59}O_4Si_2$ ($M+H^+$) requires 515.3952.



36, *80%* (2S,3S,4R) **37**, *16%* (2R,3S,4R)

(2S,3S,4R)-3-((tert-butyldimethylsilyl)oxy)-4-methyl-2-(((triisopropylsilyl)oxy)methyl)hex-5-en-1-ol and (2R,3S,4R)-3-((tert-butyldimethylsilyl)oxy)-4-methyl-2-(((triisopropylsilyl)oxy)methyl)hex-5-en-1-ol:

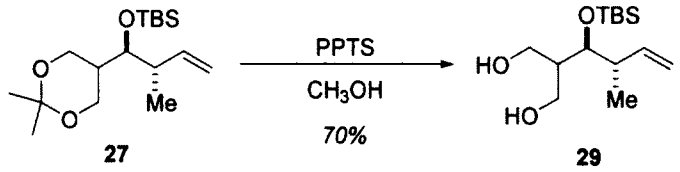
Pivalate **33** (4.7 g, 9.13 mmol) was dissolved in CH_2Cl_2 (91 ml) and cooled to -78 °C. Dibal-H (6.51 ml, 36.51 mmol) was added to the reaction mixture dropwise. The reaction mixture was stirred for 3hrs at -78 °C and quenched with addition of CH_3OH at -78 °C. The reaction mixture was allowed to warm up to room temperature and a saturated aqueous solution of Rochell's salt was added to the reaction mixture. The biphasic mixture was stirred for 6 hr at room temperature. The clear biphasic mixture was then extracted with CH_2Cl_2 (x3), washed with brine, dried over $MgSO_4$, and filtered. The resulting organic layer was concentrated *in vacuo*. The crude oil was purified by flash column chromatography (1:10 = Et_2O:Hex) to give pure 2S,3S,4R-alcohol (3.13 g, 7.30 mmol, 80%) and 2R,3S,4R-alcohol (0.64 g, 1.46 mmol, 16%) respectively.

(2S,3S,4R)-3-((tert-butyldimethylsilyl)oxy)-4-methyl-2-(((triisopropylsilyl)oxy)methyl)hex-5-en-1-ol:

ν_{max}(neat)/cm^{-1} 3429, 2940, 2874, 2835, 1471, 1380, 1243; $[\alpha]^{20}_D$ +22.4 (c = 0.5 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 5.87 (ddd, J = 17.2, 10.6, 7.3 Hz, 1H), 5.09 – 5.00 (m, 2H), 3.88 (dd, J = 11.3, 5.2 Hz, 1H), 3.85 – 3.79 (m, 3H), 3.74 (dd, J = 11.3, 4.0 Hz, 1H), 3.01 (bs, 1H), 2.52 – 2.38 (m, 1H), 1.95 – 1.86 (m, 1H), 1.13-1.08 (m, 4H), 1.07 (s, 11H), 1.05 (s, 7H), 1.03 (d, J = 6.9 Hz, 3H), 0.91 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); δ_C (125 MHz, $CDCl_3$) 141.0, 114.8, 76.1, 65.0, 63.1, 45.2, 43.2, 26.2, 18.4, 18.2, 16.3, 12.0, -3.9, -4.1; Accurate mass (ES+): Found 431.3310 (-15.5 ppm), $C_{23}H_{51}O_3Si_2$ ($M+H^+$) requires 431.3377.

(2R,3S,4R)-3-((tert-butyldimethylsilyl)oxy)-4-methyl-2-(((triisopropylsilyl)oxy)methyl)hex-5-en-1-ol:

ν_{max}(neat)/cm^{-1} 3426, 2942, 2890, 2866, 1463, 1389, 1255; $[\alpha]^{20}_D$ +11.9 (c = 2.0 in $CHCl_3$); δ_H (600 MHz, $CDCl_3$) 5.83 (ddd, *J* = 17.5, 10.4, 7.3 Hz, 1H), 5.09 – 4.98 (m, 2H), 4.00 (ddd, *J* = 10.0, 4.9, 1.3 Hz, 1H), 3.87 (dd, *J* = 10.5, 8.3 Hz, 1H), 3.78 (t, *J* = 9.9 Hz, 1H), 3.72 – 3.64 (m, 1H), 3.58 (dd, *J* = 6.2, 3.1 Hz, 1H), 3.28 (bs, 1H), 2.35 (tdt, *J* = 7.3, 6.2, 1.3 Hz, 1H), 2.12 (ddtd, *J* = 9.6, 8.0, 4.7, 3.1 Hz, 1H), 1.15 – 1.08 (m, 3H), 1.06 (s, 12H), 1.06 (s, 6H), 1.02 (d, J = 6.8 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); δ_C (150 MHz, $CDCl_3$) 141.2, 114.5, 75.9, 66.9, 65.2, 46.1, 42.8, 26.1, 18.4, 18.1, 16.4, 11.9, -3.8, -4.1; Accurate mass (ES+): Found 431.3306 (-16.7 ppm), $C_{23}H_{51}O_3Si_2$ ($M+H^+$) requires 431.3377.

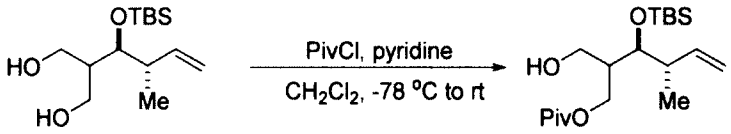


2-((1S,2S)-1-((tert-butyldimethylsilyl)oxy)-2-methylbut-3-en-1-yl)propane-1,3-diol:

To a solution of acetonide **27** (8.70 g, 27.66 mmol) in CH_3OH (277 ml) was added pyridium *p*-toluenesulfonate (PPTS, 700 mg, 2.79 mmol) at room temperature. The reaction mixture was stirred for 6 hr. After reaction complete, the reaction was quenched with Et_3N and concentrated *in vacuo*. The residue was purified by flash column chromatography to give diol **29** (7.59 g, 19.36 mmol, 70%) as a clear oil.

ν_{max}(neat)/cm^{-1} 2284, 2959, 2930, 2882, 2865, 1472, 1362, 1255; $[\alpha]^{20}_D$ +11.3 (c = 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 5.83 (ddd, *J* = 17.7, 10.4, 7.5 Hz, 1H), 5.13 – 4.99 (m, 2H), 3.91 (dd, *J* = 11.1, 5.2 Hz, 1H), 3.86 – 3.77 (m, 3H), 3.74 (dd, *J* = 10.7, 5.2 Hz, 1H), 2.49 – 2.40 (m, 3H), 1.88 (dt, *J* =

6.9, 4.7 Hz, 1H), 1.06 (d, J = 7.0 Hz, 3H), 0.90 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); δ_C (125 MHz, $CDCl_3$) 140.7, 115.3, 75.8, 64.2, 63.3, 45.0, 43.3, 26.1, 18.3, 16.3, -3.9, -4.2; Accurate mass (ES+): Found 275.2022 (-7.3 ppm), $C_{14}H_{31}O_3Si$ ($M+H^+$) requires 275.2042.

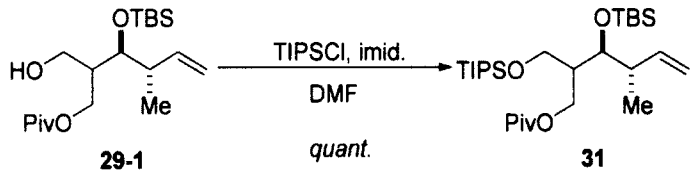


29 *72%* (a mixture of two diastereomer) **29-1**

(3S,4S)-3-((tert-butyldimethylsilyl)oxy)-2-(hydroxymethyl)-4-methylhex-5-en-1-yl pivalate:

The diol **29** (5.34 g, 19.46 mmol) was dissolved in pyridine (7.87 ml, 97.28 mmol) and CH_2Cl_2 (65 ml). The reaction mixture was cool to -78 °C and pivaloyl chloride (2.44 ml, 19.46 mmol) was added dropwise over 5 min. The reaction mixture was slowly allowed to warm up to room temperature over 3 hrs. The reaction was concentrated *in vacuo* and purified by flash column chromatography to give mono-pivalate **29-1** (5.00 g, 14.01 mmol, 72%, ca. 1:2.7 mixture of two diastereomer).

ν_{max} (neat)/cm^{-1} 3449, 2958, 2931, 2858, 1730, 1480, 1473, 1462, 1398, 1362; δ_H (600 MHz, $CDCl_3$, *minor diastereomer) 5.93 – 5.85 (ddd, J = 17.8, 10.4, 7.6 Hz, 1H), 5.81* (ddd, J = 17.8, 10.4, 7.6 Hz, 1H), 5.13 – 5.00 (m, 2H+2H*), 4.34 (dd, J = 11.4, 4.8 Hz, 1H), 4.23 – 4.12* (m, 2H), 4.12 – 4.06 (m, 1H), 3.87 – 3.78 (m, 1H+2H*), 3.73* (dd, J = 11.7, 4.9 Hz, 1H), 3.65 (dd, J = 11.5, 5.8 Hz, 1H), 3.54 (dd, J = 11.4, 6.0 Hz, 1H), 2.66* (bs, 1H), 2.54 – 2.46* (m, 1H), 2.46 – 2.37 (m, 1H), 2.20 (bs, 1H), 2.12 – 1.98 (m, 1H+1H*), 1.21 (s, 9H), 1.21* (s, 9H), 1.07 (d, J = 7.0 Hz, 3H), 1.06* (d, J = 7.0 Hz, 3H), 0.91 (s, 9H+9H*), 0.12* (s, 3H), 0.10* (s, 3H), 0.09 (s, 3H), 0.09 (s, 3H); δ_C (150 MHz, $CDCl_3$) 179.13, 178.53*, 140.37, 140.28*, 115.40*, 115.08, 76.06*, 74.37, 63.81*, 62.79, 61.65*, 60.99, 44.79, 43.24*, 42.35*, 42.24, 38.86, 38.81*, 27.24, 27.21*, 26.00, 25.98*, 18.27, 18.16*, 17.21, 15.86*, -4.02*, -4.08, -4.27, -4.36*; Accurate mass (ES+): Found 359.2618 (0.0 ppm), $C_{19}H_{39}O_4Si$ ($M+H^+$) requires 359.2618.

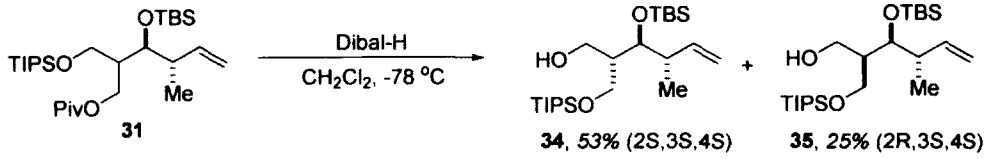


29-1 31

(3S,4R)-3-((tert-butyldimethylsilyl)oxy)-4-methyl-2-(((triisopropylsilyl)oxy)methyl)hex-5-en-1-yl pivalate:

To a solution of alcohol **29-1** (5.00 g, 13.94 mmol) in DMF (14 ml) imidazole (1.90 g, 27.89 mmol) and TIPSCl (3.69 ml, 16.73 mmol) were added at room temperature. After stirring at room temperature for 6 hrs, the reaction mixture was diluted with EtOAc and washed with aqueous 1 N HCl, water (x2), and brine. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude oil was purified by flash column chromatography to give pure product **31** (7.18 g, 13.94 mmol, *quant.* a mixture of two diastereomer).

ν_{max}(neat)/cm^{-1} 2959, 2863, 1730 1469, 1283, 1254; δ_H (500 MHz, $CDCl_3$, *minor diastereomer) 5.93 – 5.79 (m, 1H+1H*), 5.08 – 4.96 (m, 2H+2H*), 4.36 (dd, *J* = 11.2, 4.5 Hz, 1H), 4.18 – 4.08* (m, 2H), 3.96 – 3.86 (m, 2H+1H*), 3.83* (dd, *J* = 5.0, 3.6 Hz, 1H), 3.70 (d, *J* = 6.3 Hz, 2H), 3.64* (dd, *J* = 10.0, 8.1 Hz, 1H), 2.50 – 2.37 (m, 1H+1H*), 2.16 – 2.07* (m, 1H), 2.01 (dtt, *J* = 8.5, 6.3, 4.4 Hz, 1H), 1.19 (s, 9H+9H*), 1.09 – 1.01 (m, 24H+24H*), 0.90 (s, 9H+9H*), 0.07 (s, 3H), 0.06 (s, 3H), 0.05* (s, 3H), 0.04* (s, 3H); δ_C (125 MHz, $CDCl_3$) 178.6, 178.5*, 141.2, 141.0*, 114.8*, 114.7, 74.2*, 73.5, 62.9, 62.6*, 61.6*, 61.3, 45.7*, 44.7, 42.9, 42.2*, 38.9*, 27.4, 26.2, 26.1*, 18.5, 18.4*, 18.3*, 18.2, 18.2, 18.2*, 18.0, 17.1*, 12.1, 12.0*, -3.8, -3.9*, -4.1, -4.1*; Accurate mass (ES+): Found 515.3193 (-7.6 ppm), $C_{28}H_{59}O_4Si_2$ ($M+H^+$) requires 515.3952.



(2S,3S,4R)-3-((tert-butyldimethylsilyl)oxy)-4-methyl-2-(((triisopropylsilyl)oxy)methyl)hex-5-en-1-ol and (2R,3S,4R)-3-((tert-butyldimethylsilyl)oxy)-4-methyl-2-(((triisopropylsilyl)oxy)methyl)hex-5-en-1-ol:

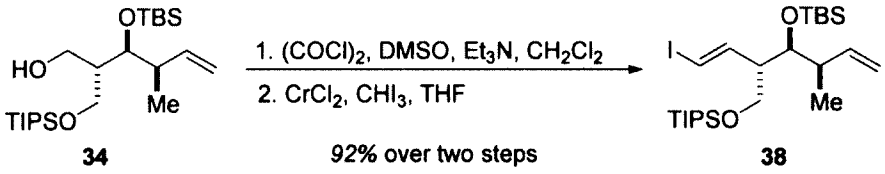
The pivalate **31** (7.26 g, 14.10 mmol) was dissolved in CH_2Cl_2 (94 ml) and cooled to -78 °C. Dibal-H (5.78 ml, 32.43 mmol) was added to the reaction mixture dropwise. The reaction mixture was stirred for 3 hrs at -78 °C and quenched with an addition of CH_3OH at -78 °C. The reaction mixture was then slowly allowed to warm up to room temperature and saturated aqueous Rochell's salt solution was added to the reaction mixture. The biphasic mixture was stirred for 6hr at room temperature. The clear biphasic mixture was extracted with CH_2Cl_2 (x3), washed with brine, dried over $MgSO_4$, and filtered. The resulting organic layer was concentrated *in vacuo*. The crude oil was purified by flash column chromatography (1:10 = Et_2O:Hex) to give pure 2S,3S,4S-alcohol **34** (3.20 g, 7.47 mmol, 53%) and 2R,3S,4S-alcohol **35** (1.50 g, 3.53 mmol, 25%), respectively.

(2R,3S,4S)-3-((tert-butyldimethylsilyl)oxy)-4-methyl-2-(((triisopropylsilyl)oxy)methyl)hex-5-en-1-ol:

ν_{max}(neat)/cm^{-1} 3429, 2940, 2874, 2835, 1471, 1380, 1243; $[\alpha]^{20}_D$ -20.0 (c = 0.1 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 5.87 (ddd, *J* = 17.2, 10.3, 7.9 Hz, 1H), 5.14 – 4.96 (m, 2H), 3.98 (ddd, *J* = 9.9, 5.0, 1.1 Hz, 1H), 3.85 – 3.75 (m, 2H), 3.71 (dd, *J* = 10.8, 4.4 Hz, 1H), 3.63 (t, *J* = 4.1 Hz, 1H), 3.14 (bs, 1H), 2.41 – 2.30 (m, 1H), 2.08 (dh, *J* = 7.9, 4.6 Hz, 1H), 1.17 – 1.00 (m, 24H), 0.90 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); δ_C (125 MHz, $CDCl_3$) 140.8, 115.0, 75.5, 65.8, 65.5, 46.7, 43.1, 26.1, 18.3, 18.1, 17.6, 11.9, -4.0, -4.0; Accurate mass (ES+): Found 431.3311 (-15.3 ppm), $C_{23}H_{51}O_3Si_2$ ($M+H^+$) requires 431.3377.

(2S,3S,4S)-3-((tert-butyldimethylsilyl)oxy)-4-methyl-2-(((triisopropylsilyl)oxy)methyl)hex-5-en-1-ol:

ν_{max}(neat)/cm^{-1} 3426, 2942, 2890, 2866, 1463, 1389, 1255; $[\alpha]^{20}_{D}$ -10.0 (c = 0.5 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 5.82 (ddd, *J* = 17.6, 10.4, 7.6 Hz, 1H), 5.10 – 4.97 (m, 2H), 3.92 – 3.73 (m, 5H), 3.09 (bs, 1H), 2.43-2.35 (m, 1H), 1.99 – 1.87 (m, 1H), 1.17 – 1.00 (m, 24H), 0.90 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H); δ_C (150 MHz, $CDCl_3$) 140.9, 115.0, 75.6, 65.3, 63.9, 45.6, 43.4, 26.2, 18.4, 18.1, 16.5, 12.0, -4.0, -4.1; Accurate mass (ES+): Found 431.3328 (-11.4 ppm), $C_{23}H_{51}O_3Si_2$ ($M+H^+$) requires 431.3377.



34 **38**

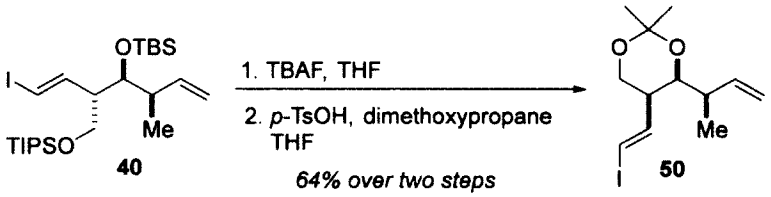
(5S,6S)-5-((R)-but-3-en-2-yl)-6-((E)-2-iodovinyl)-9,9-diisopropyl-2,2,3,3,10-pentamethyl-4,8-dioxa-3,9-disilaundecane:

To a solution of oxalyl chloride (1.11 ml, 12.80 mmol) in CH_2Cl_2 (64 ml) was added DMSO (1.36 ml, 19.20 mmol) dropwise at -78 °C. The mixture was stirred for 10 min at -78 °C, and then a solution of alcohol **34** (2.75 g, 6.38 mmol) in CH_2Cl_2 (10 ml) was added slowly. After reaction temperature maintained at -78 °C for 30 min, Et_3N (5.36 ml, 38.34 mmol) was added over 10 min at -78 °C, and the mixture warmed up to 0 °C over 30 minute. The reaction was diluted with CH_2Cl_2 and washed with water (x2) and brine. The organic layer was dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The crude oil was used to the next step without further purification.

To a solution of $CrCl_2$ (4.64 g, 37.53 mmol) in THF (100 ml) at 0 °C was added a co-solution of aldehyde (2.74 g, 6.39 mmol) and CHI_3 (2.73 g, 6.94 mmol) in THF (26 ml) dropwise. The reaction stirred for 5 hr with slowly warming up to room temperature. After reaction complete monitored

by TLC (*ca.* 3-5 hr), the resulting solution was filtered through a short silica pad. The solution was diluted with EtOAC and washed with 10% aqueous sodium thiosulfate and brine. The organic layer was dried over Na_2SO_4 and filtered. The resulting solution was concentrated *in vacuo*. The crude oil was purified by flash column chromatography (1:10 = Et_2O:Hex) to give pure vinyl iodide **38** (3.24 g, 5.87 mmol).

ν_{max}(neat)/cm^{-1} 2955, 2937, 2867, 1464, 1254, 1097; $[\alpha]^{20}_D$ +7.1 (c = 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 6.51 (dd, *J* = 14.6, 9.5 Hz, 1H), 6.00 (dd, *J* = 14.5, 0.6 Hz, 1H), 5.71 (ddd, *J* = 17.1, 10.5, 7.8 Hz, 1H), 5.02 – 4.91 (m, 2H), 3.75 (dd, *J* = 7.0, 2.2 Hz, 1H), 3.64 (dd, *J* = 9.9, 8.0 Hz, 1H), 3.53 (dd, J = 9.8, 6.4 Hz, 1H), 2.48 (dddd, *J* = 9.9, 8.3, 6.4, 2.3 Hz, 1H), 2.39 – 2.28 (m, 1H), 1.12 – 1.06 (m, 3H), 1.05 (s, 12H), 1.04 (s, 6H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.92 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); δ_C (125 MHz, $CDCl_3$) 144.4, 141.5, 114.5, 77.5, 73.7, 63.8, 52.8, 43.2, 26.3, 18.5, 18.2, 16.9, 12.1, -3.6, -4.0; Accurate mass (ES-): Found 551.2238 (0 ppm), $C_{24}H_{48}IO_2Si_2$ ($M-H^+$) requires 551.2238.

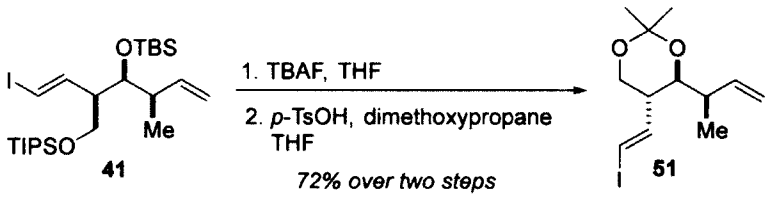


(4S,5S)-4-((R)-but-3-en-2-yl)-5-((E)-2-iodovinyl)-2,2-dimethyl-1,3-dioxane:

To a reaction mixture of vinyl iodide **40** (170 mg, 0.31 mmol) in THF (3.1 ml) were added TBAF (0.92 ml, 0.92 mmol, 1 M solution in THF). The whole mixture was stirred for 2 hr at room temperature. The reaction was diluted with EtOAc and the organic layer was washed with water and brine. The organic layer was dried with sodium sulfate and filtered. The resulting filtrate was concentrated *in vacuo*. The crude oil was purified by flash column chromatography to give pure diol (62 mg, 0.22 mmol, 71%)

To a solution of diol (62 mg, 0.22 mmol) in THF (11 ml) were added 2,2-dimethoxypropane (34 μL, 0.33 mmol) and a catalytic amount of *p*-TsOH (2 mg, 0.011 mmol). The reaction mixture was stirred for 1 hr at room temperature. After reaction complete, Et_3N (0.1 ml) was added and then stirred additional 5 min. The volatile solvent was removed under reduced pressure, and the residue was purified by flash column chromatography to give pure acetonide **50** (64 mg, 0.20 mmol, 90%).

ν_{max}(neat)/cm^{-1} 2991, 2926, 2863, 1603, 1381, 1370, 1238, 1082; $[\alpha]^{20}_D$ +93.3 (c = 1.0 in $CHCl_3$); δ_H (600 MHz, $CDCl_3$) 6.93 (dd, *J* = 14.6, 9.9 Hz, 1H), 6.12 (d, *J* = 14.6 Hz, 1H), 5.53 (ddd, *J* = 17.1, 10.3, 8.6 Hz, 1H), 5.12 – 4.97 (m, 2H), 4.04 (dd, *J* = 11.6, 2.8 Hz, 1H), 3.70 (dd, *J* = 11.6, 1.7 Hz, 1H), 3.51 (dd, *J* = 10.1, 2.3 Hz, 1H), 2.21 (ddt, *J* = 15.9, 9.4, 6.7 Hz, 1H), 2.14 (dq, *J* = 9.9, 2.2 Hz, 1H), 1.43 (s, 3H), 1.42 (s, 3H), 0.99 (d, *J* = 6.6 Hz, 3H); δ_C (150 MHz, $CDCl_3$) 143.6, 139.0, 116.3, 99.2, 77.6, 74.3, 65.2, 44.0, 40.9, 29.8, 19.0, 16.9; Accurate mass (ES-): Found 321.0369 (+5.3 ppm), $C_{12}H_{18}IO_2$ (M-H$^+$) requires 321.0352.

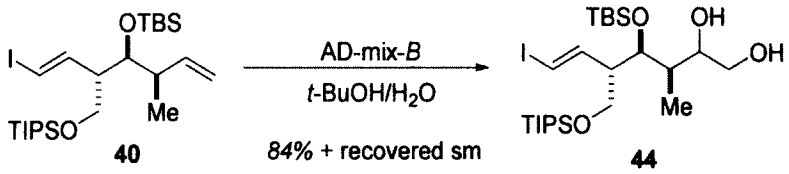


(4S,5R)-4-((R)-but-3-en-2-yl)-5-((E)-2-iodovinyl)-2,2-dimethyl-1,3-dioxane:

Same reaction procedure with the previous reaction.

ν_{max}(neat)/cm^{-1} 3070, 2991, 2937, 2859, 1639, 1606, 1458; $[\alpha]^{20}_D$ -81.4 (c = 0.5 in $CHCl_3$); δ_H (600 MHz, $CDCl_3$) 6.26 (dd, *J* = 14.5, 9.2 Hz, 1H), 6.20 (d, *J* = 14.5 Hz, 1H), 5.85 (ddd, *J* = 17.5, 10.4, 7.3 Hz, 1H), 5.09 – 4.96 (m, 2H), 3.74 – 3.64 (m, 3H), 2.51 (qd, *J* = 9.5, 6.5 Hz, 1H), 2.30 (tdd,

J = 10.1, 5.2, 2.5 Hz, 1H), 1.41 (s, 3H), 1.37 (s, 3H), 0.99 (d, J = 6.9 Hz, 3H); δ_C (150 MHz, $CDCl_3$) 143.0, 141.7, 114.1, 98.4, 78.5, 74.6, 63.3, 45.2, 39.8, 29.4, 19.2, 13.2; Accurate mass (ES-): Found 321.0356 (+1.2 ppm), $C_{12}H_{18}IO_2$ ($M\text{-}H^+$) requires 321.0352.



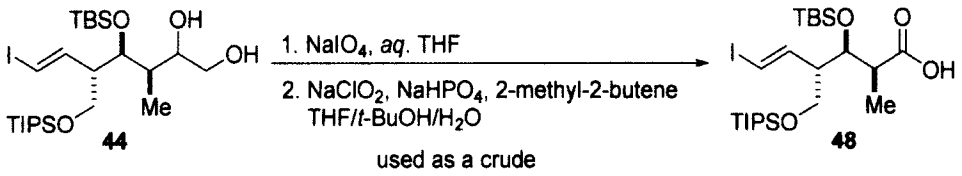
40 **44**

(3R,4R,5S,E)-4-((tert-butyldimethylsilyl)oxy)-7-iodo-3-methyl-5-(((triisopropylsilyl)oxy)methyl)hept-6-ene-1,2-diol:

To a solution of alkene **40** (4.00 g, 7.24 mmol) in t-BuOH/H_2O (120 ml, v:v = 1:1) were added AD-mix-β (10.86 g), methanesulfonamide (1.38 g, 14.47 mmol), and $NaHCO_3$ (3.65 g, 43.42 mmol) as solids at 0 °C. The reaction stirred for 48 hr at 0 °C. Upon completion by TLC, 10% *aq.* $Na_2S_2O_3$ solution was added and allowed to stir for 10 min at 0 °C then the reaction was warmed to room temperature and diluted with EtOAc and H_2O. The resulting mixture was stirred for additional 1 hr. The organic layer was decanted off and washed with brine. After concentration *in vacuo*, the residue was purified by flash column chromatography to give diol **44** (3.57 g, 6.08 mmol, a mixture of two diastereomers) and starting material (400 mg, 0.72 mmol) as a clear oil, respectively.

ν_{max} (neat)/cm^{-1} 3307, 2955, 2939, 2879, 1456, 1373; δ_H (500 MHz, $CDCl_3$, * minor diastereomer) 6.69* (dd, J = 14.6, 9.5 Hz, 1H), 6.65 (dd, J = 14.6, 9.5 Hz, 1H), 6.19* (d, J = 14.6 Hz, 1H), 6.17 (d, J = 14.6 Hz, 1H), 4.20 (t, J = 3.0 Hz, 1H), 4.20* (dd, J = 3.0 Hz, 1H), 3.95 (dd, J = 4.7, 2.5 Hz, 1H), 3.87 – 3.49 (m, 5H+4H*), 3.44* (dd, J = 11.3, 4.8 Hz, 1H), 2.51 (dtd, J = 10.3, 7.2, 6.7, 2.7 Hz, 1H), 2.02* (ddd, J = 10.3, 6.9, 3.3 Hz, 1H), 1.88 – 1.81* (m, 1H), 1.68 (dq, J = 9.9, 3.7, 2.9 Hz, 1H), 1.11-1.02 (m, 24H+24H*), 0.93* (s, 9H), 0.91 (s, 9H), 0.15* (s, 3H), 0.13* (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H);

δ_C (125 MHz, $CDCl_3$) 144.9, 144.0*, 78.1*, 78.0, 74.4*, 74.0*, 72.7, 71.4, 66.0, 65.0*, 64.2, 64.0*, 52.2, 51.0*, 40.7, 39.5*, 26.2, 26.1*, 26.0, 26.0*, 18.2*, 18.2, 13.2, 12.1*, 12.1, 11.0*, -3.8, -4.0*, -4.1, -4.6*; Accurate mass (ES+): Found 587.2469 (+3.4 ppm), $C_{24}H_{52}IO_4Si_2$ ($M+H^+$) requires 587.2449.

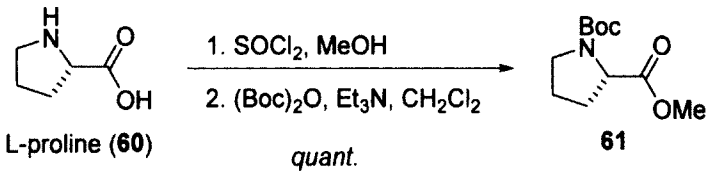


(2S,3R,4S,E)-3-((tert-butyldimethylsilyl)oxy)-6-iodo-2-methyl-4-(((triisopropylsilyl)oxy)methyl)hex-5-enoic acid:

To a solution of diol **44** (255 mg, 0.43 mmol) in H_2O/THF (v:v = 1:10, 11 ml) was added $NaIO_4$ (191.67 mg, 0.87 mmol). The reaction mixture was stirred for 3 hr at room temperature. After reaction complete, the reaction was diluted with Et_2O and washed with saturated aqueous NH_4Cl. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude aldehyde was used to the next step without further purification.

To a reaction mixture of aldehyde (240.0 mg) in THF/*t*-BuOH (v:v = 1:1, 10 ml) were added 2-methyl-2-butene solution (3.24 ml, 2 M solution in THF) and a solution of NaH_2PO_4 (89.6 mg, 0.65 mmol) and $NaClO_2$ (68.5 mg, 0.61 mmol) in H_2O (2 ml) at room temperature. The reaction mixture was stirred for 3 hr. The reaction was diluted with EtOAc and H_2O. The mixture was extracted with EtOAc and washed with brine. The organic layer was dried with Na_2SO_4, filter and concentrated *in vacuo*. The crude acid **48** (245 mg, 0.43 mmol) was used to the next amide coupling step without further purification.

ν_{max}(neat)/cm^{-1} 2928, 2891, 2865, 1707, 1463, 1254; $[\alpha]^{20}_{D}$ +14.0 (c = 0.1 in $CHCl_3$); δ_H (600 MHz, $CDCl_3$) 9.35 (bs, 1H), 6.44 (dd, *J* = 14.6, 9.8 Hz, 1H), 6.19 (dd, *J* = 14.6, 0.5 Hz, 1H), 4.25 (dd, *J* = 5.6, 2.9 Hz, 1H), 3.68 (dd, *J* = 10.1, 8.0 Hz, 1H), 3.60 (dd, *J* = 10.1, 5.8 Hz, 1H), 2.68 (qd, *J* = 7.1, 5.6 Hz, 1H), 2.46 – 2.38 (m, 1H), 1.17 (d, *J* = 7.1 Hz, 3H), 1.13 – 1.02 (m, 21H), 0.93 (s, 9H), 0.16 (s, 3H), 0.12 (s, 3H); δ_C (150 MHz, $CDCl_3$) 176.0, 142.4, 79.74, 71.7, 63.2, 53.0, 43.8, 29.9, 26.1, 18.1, 12.8, 12.1, -4.2, -4.3..; Accurate mass (ES+): Found 571.2084 (-9.1 ppm), $C_{23}H_{48}IO_4Si_2$ ($M+H^+$) requires 571.2136.

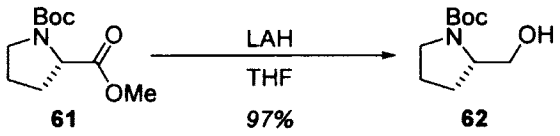


L-proline (**60**) *quant.* **61**

1-(tert-butyl) 2-methyl pyrrolidine-1,2-dicarboxylate:

A solution of L-proline **60** (5 g, 43.43 mmol) in MeOH (30 ml) was cooled to 0 °C under nitrogen and thionyl chloride (3.47 ml, 47.77 mmol) was added dropwise over 10 min. After refluxing 1 hr, the solvent was removed *in vacuo* to afford yellow oil which was then dissolved in CH_2Cl_2 (70 ml). Et_3N (15.74 ml, 112.92 mmol) was added to the solution at room temperature and the resulting solution was stirred for 10 min. A solution of $(Boc)_2O$ (10.97 g, 47.77 mmol) in CH_2Cl_2 (30 ml) was added dropwise over 20 min. After stirring for 18hr, the white precipitate was filtered and the bulk of the solvent was evaporated. The crude oil was dissolved in 100 ml of ether and washed with 1 N HCl (x2), sat. sodium bicarbonate, and brine. The ether layer was dried over sodium sulfate and concentrated *in vacuo*. Further drying on a vaccum gave the pure product **61** (9.96 g, 43.43 mmol, *quant.*) as a colorless oil.

ν_{max}(neat)/cm^{-1} 2976, 2934, 2876, 1748, 1697, 1393, 1365; $[\alpha]^{20}_D$ -107.2 (c = 1.0 in $CHCl_3$); δ_H (600 MHz, $CDCl_3$,*minor rotamer) 4.32* (dd, *J* = 8.6, 3.4 Hz, 1H), 4.25 – 4.18 (m, 1H), 3.72* (s, 3H), 3.72 (s, 3H), 3.57-3.49 (m, 1H, 1H*), 3.45 (dt, *J* = 10.6, 6.9 Hz, 1H), 3.37* (dt, *J* = 10.7, 7.0 Hz, 1H), 2.26-2.22 (m, 1H), 2.21-2.13* (m, 1H), 1.99-1.91 (m, 3H), 1.89-1.81* (m, 3H), 1.46* (s, 9H), 1.40 (s, 9H); δ_C (150 MHz, $CDCl_3$) 173.9, 173.7*, 154.6*, 153.9, 80.0, 79.9*, 59.2, 58.8*, 52.3*, 52.1, 46.7*, 46.4, 31.0, 30.1*, 28.6*, 28.4, 24.5*, 23.8; Accurate mass (ES+): Found 230.1397 (+2.2 ppm), $C_{11}H_{20}NO_4$ ($M+H^+$) requires 230.1392.

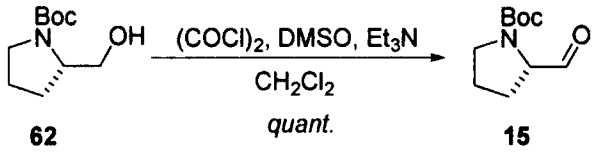


61 **62**

tert-butyl (S)-2-(hydroxymethyl)pyrrolidine-1-carboxylate:

To a reaction mixture of LAH (6.62 g, 0.17 mol) in THF (200 ml) was added a solution of metylester **61** (20 g, 87.23 mmol) in THF (90 ml) dropwise at 0 °C. The whole mixture was stirred for 40 min at 0 °C. The reaction mixture was quenched with a sequential addition of 6.6 ml of water, 6.6 ml of 15% aq. NaOH solution, and 19.8 ml of water. The mixture was stirred for 30 min and $MgSO_4$ was added to the mixture. The mixture was filtered through Celite and concentrated *in vacuo*. The crude alcohol **62** (17 g, 84.5 mmol, 97%) was used to the next step without further purification.

ν_{max}(neat)/cm^{-1} 3435, 2974, 2878, 1693, 1669, 1394, 1366; $[\alpha]^{20}_D$ -182 (c = 1.0 in $CHCl_3$); δ_H (600 MHz, $CDCl_3$) 4.81 (bs, 1H), 3.90 (dq, *J* = 10.8, 4.2, 3.4 Hz, 1H), 3.55 (h, *J* = 11.0, 9.7 Hz, 2H), 3.39 (dt, *J* = 10.9, 6.9 Hz, 1H), 3.25 (dt, *J* = 11.0, 6.9 Hz, 1H), 1.95 (dp, *J* = 16.8, 9.4, 8.3 Hz, 1H), 1.79-1.70 (m, 2H), 1.56 – 1.47 (m, 1H), 1.41 (s, 9H); δ_C (150 MHz, $CDCl_3$) 157.1, 80.2, 67.5, 60.1, 47.6, 28.7, 28.5, 24.1; Accurate mass (ES+): Found 202.1453 (+4.9 ppm), $C_{10}H_{20}NO_3$ ($M+H^+$) requires 202.1443.

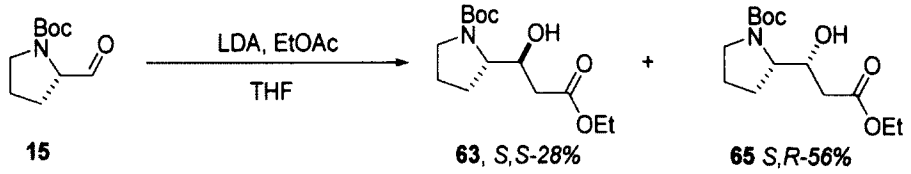


62 15

***tert*-Butyl (S)-2-formylpyrrolidine-1-carboxylate:**

To $(COCl)_2$ (4.76 ml, 54.65 mmol) in CH_2Cl_2 (60 ml) was added DMSO (4.06 ml, 57.14 mmol) in CH_2Cl_2 (10 ml) over 30 minutes at -78 °C. The mixture was stirred for 10 min at -78 °C, and then alcohol **62** (5 g, 24.84 mmol) in CH_2Cl_2 (13 ml) was added over 30 minutes. After reaction temperature maintained at -78 °C for 30 min, Et_3N (20.86 ml, 149.06 mmol) was added at -78 °C (over 15 minutes), and the mixture warmed up to 0 °C. The reaction solution was stirred for 30 minutes. The reaction was quenched with water (just until solids dissolved), washed with aqueous 10% ammonium chloride, sodium bicarbonate, and brine. The organic layer was dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The crude aldehyde **15** (4.95 g, 24.84 mmol, *quant.*) was used to the next step without further purification.

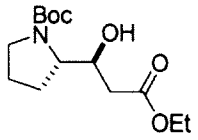
ν_{max}(neat)/cm^{-1} 2976, 2933, 2874, 1736, 1690, 1392, 1367; $[\alpha]^{20}_D$ -463.2 (c = 1.0 in $CHCl_3$); δ_H (600 MHz, $CDCl_3$, * minor isomer) 9.55-9.53* (m, 1H), 9.45-9.43 (m, 1H), 4.20-4.12 (m, 1H), 4.05-4.01* (1H), 3.56-3.51 (m, 1H), 3.50 (m, 1H, 2H*), 2.14-2.08 (m, 1H), 2.06-2.00* (m, 1H), 1.99-1.91 (m, 1H),1.90-1.81 (m, 2H, 3H*), 1.50 – 1.44* (m, 9H), 1.44 – 1.38 (m, 9H) ; δ_C (150 MHz, $CDCl_3$) 200.9*, 200.7, 155.0*, 154.1, 80.8, 80.3, 65.1, 65.0*, 47.0*, 46.8*, 28.5*, 28.4, 28.1, 26.9.*, 24.8*, 24.10; Accurate mass (ES+): Found 288.1793 (-6.2 ppm), $C_{10}H_{18}NO_3$ ($M+H^+$) requires 288.1811.



15 **63**, *S,S-28%* **65** *S,R-56%*

tert-butyl (S)-2-((S)-3-ethoxy-1-hydroxy-3-oxopropyl)pyrrolidine-1-carboxylate and tert-butyl (S)-2-((R)-3-ethoxy-1-hydroxy-3-oxopropyl)pyrrolidine-1-carboxylate:

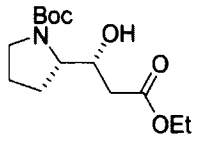
To a mixture of ethyl acetate (0.44 ml, 5.02 mmol, dried with 4Å MS) in THF (24 ml) was added freshly prepared LDA (5 ml, 1 M solution in THF) at -78 °C. The reaction mixture was stirred for 30 min at -78 °C. This enolate solution was added dropwise to a solution of aldehyde **15** (1 g, 5.02 mmol) in THF (12 ml) at -78 °C. The reaction mixture was stirred for 1hr at -78 °C. The reaction was quenched with sat. ammonium chloride and then extracted with EtOAc. The combined organic layer was dried with sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by preparative HPLC (Waters Sunfire silica column, 10x250 mm, 5 *u*m particle size, continuous gradient 1:10 to 1:1 = Hex:EtOAc).



tert-butyl (S)-2-((S)-3-ethoxy-1-hydroxy-3-oxopropyl)pyrrolidine-1-carboxylate (63):

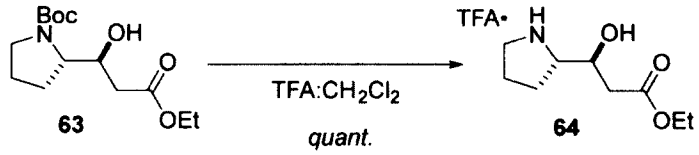
28% yield; ν_{max} (neat)/cm^{-1} 3436, 2977, 2913, 1736, 1693, 1395, 1367; $[\alpha]^{20}_{D}$ -58.6 (c = 0.5 in $CHCl_3$); δ_H (600 MHz, $CDCl_3$) 5.00 (s, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 4.06 – 3.96 (m, 1H), 3.92 (dt, *J* = 7.7, 3.9 Hz, 1H), 3.47 (dd, *J* = 12.7, 5.9 Hz, 1H), 3.29 (ddd, *J* = 11.0, 7.5, 5.4 Hz, 1H), 2.49 (dd, *J* = 15.4, 3.3 Hz, 1H), 2.41 (dd, *J* = 15.4, 9.0 Hz, 1H), 1.97 (dt, *J* = 12.8, 7.6 Hz, 1H), 1.92-1.81 (m, 1H), 1.82-1.75 (m, 1H), 1.67-1.63 (m, 1H), 1.45 (s, 9H), 1.26 (t, *J* = 7.1 Hz, 3H); δ_C (150 MHz, $CDCl_3$) 172.1, 157.8,

80.6, 72.8, 62.1, 60.8, 47.6, 40.4, 28.6, 28.5, 24.3, 14.3; Accurate mass (ES+): Found 288.1768 (-14.9 ppm), $C_{14}H_{26}NO_5$ ($M+H^+$) requires 288.1811.



tert-butyl (S)-2-((R)-3-ethoxy-1-hydroxy-3-oxopropyl)pyrrolidine-1-carboxylate (65):

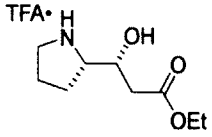
56% yield; ν_{max} (neat)/cm^{-1} 3436, 2976, 2917, 1735, 1693, 1671, 1394, 1167; $[\alpha]^{20}_D$ -24.0 (c = 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 4.91 (bs, 1H), 4.51 – 4.36 (m, 1H), 4.17 (t, *J* = 7.3 Hz, 2H), 3.97 – 3.88 (m, 1H), 3.52-3.43 (m, 1H), 3.25 (dt, *J* = 11.7, 6.3 Hz, 1H), 2.45-2.36 (m, 2H), 1.99-1.94 (m, 1H), 1.91-1.84 (m, 1H), 1.80-1.73 (m, 2H), 1.46 (s, 9H), 1.26 (t, *J* = 7.2 Hz, 3H); δ_C (125 MHz, $CDCl_3$) 172.7, 156.4, 80.2, 70.4, 62.4, 60.8, 48.0, 38.1, 28.6, 27.7, 24.2, 14.3; Accurate mass (ES+): Accurate mass (ES+): Found 288.1793 (-6.2 ppm), $C_{14}H_{26}NO_5$ ($M+H^+$) requires 288.1811.



ethyl (S)-3-hydroxy-3-((S)-1l4-pyrrolidin-2-yl)propanoate, 2,2,2-trifluoroacetate salt:

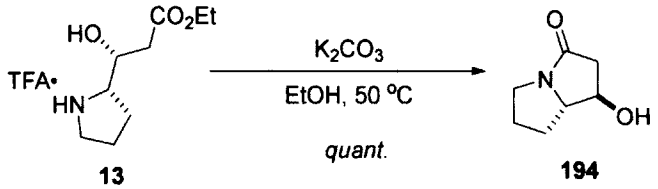
The S, S-aldol adduct **63** (600 mg, 2.09 mmol) was dissolved in CH_2Cl_2 (9 ml). TFA (9 ml) was added to the reaction solution. The reaction mixture was stirred for 1 hr and concentrated *in vacuo*. The crude semi-solid **64** (630 mg, 2.09 mmol, *quant.*) was used to the next step without further purification.

ν_{max} (neat)/cm^{-1} 2986, 1733, 1675, 1425, 1202, 1134; $[\alpha]^{20}_D$ +11.6 (c = 0.5 in $CHCl_3$); δ_H (600 MHz, $CDCl_3$) 9.49 (bs, 1H), 8.68 (bs, 1H), 8.29 (bs, 1H), 4.18-4.13 (m ,1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.70-3.63 (m, 1H), 3.38-3.33 (m, 2H), 2.69 – 2.55 (m, 2H), 2.24 – 1.98 (m, 3H), 1.82 – 1.68 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 3H); δ_C (150 MHz, $CDCl_3$) 171.2, 162.2, 131.1, 68.7, 64.5, 61.4, 45.4, 39.5, 27.5, 24.4, 14.1; Accurate mass (ES+): Found 188.1265 (-11.7 ppm), $C_9H_{18}NO_3$ ($M+H^+$) requires 188.1287.



ethyl (R)-3-hydroxy-3-((S)-1l4-pyrrolidin-2-yl)propanoate 2,2,2-trifluoroacetate (13):

ν_{max} (neat)/cm^{-1} 2985, 1733, 1674, 1428, 1203, 1178, 1136; $[\alpha]^{20}_D$ -11.1 (c = 1.0 in $CHCl_3$); δ_H (600 MHz, $CDCl_3$) 9.66 (bs, 1H), 8.17 (bs, 1H), 8.13 (bs, 1H), 4.60-4.55 (m, 1H), 4.15 (q, J = 7.1 Hz, 2H), 3.79-3.73 (m, 1H), 3.40-3.29 (m, 2H), 2.56 (dd, J = 16.3, 7.6 Hz, 1H), 2.52 – 2.44 (m, 1H), 2.27 – 2.04 (m, 2H), 2.04-1.97 (m, 2H), 1.25 (t, J = 7.1 Hz, 2H); δ_C (150 MHz, $CDCl_3$) 171.2, 161.9, 116.0, 64.9, 63.1, 61.2, 46.1, 38.6, 24.4, 23.2, 14.0; Accurate mass (ES+): Found 188.1306 (+10.1 ppm), $C_9H_{18}NO_3$ ($M+H^+$) requires 188.1287.



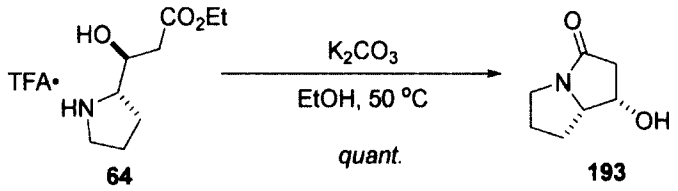
13 **194**

(1R,7aS)-1-hydroxyhexahydro-3H-pyrrolizin-3-one:

The amine salt **13** (97.5 mg, 0.32 mmol) was dissolved in EtOH (6.4 ml) and K_2CO_3 (302.6 mg, 2.16 mmol) was added in one portion. The mixture was stirred at 50 °C for 16 hr. The solvent was removed under reduced pressure and the crude was dissolved in EtOAc. The mixture was filtered

through Celite and concentrated *in vacuo*. The crude **194** (46 mg, 0.32 mmol, *quant.)* was pure enough for NMR analysis.

ν_{max} (neat)/cm^{-1} 3384, 2974, 2926, 2888, 1672, 1436, 1202; $[\alpha]^{20}_D$ +26.0 (c = 0.5 in $CHCl_3$); δ_H (600 MHz, $CDCl_3$) 4.26 (td, *J* = 8.3, 5.8 Hz, 1H), 3.76 (dt, *J* = 8.7, 6.0 Hz, 1H), 3.58 (dt, *J* = 11.6, 7.8 Hz, 1H), 3.09 – 3.02 (m, 1H), 2.82 – 2.72 (m, 2H), 2.16 (dtd, *J* = 12.5, 6.6, 3.3 Hz, 1H), 2.12 – 1.96 (m, 2H), 1.52 – 1.41 (m, 1H); δ_C (150 MHz, $CDCl_3$) 172.2, 73.4, 69.2, 44.4, 41.6, 29.8, 26.6; Accurate mass (ES+): Found 142.0856 (-8.4 ppm), $C_7H_{12}NO_2$ ($M+H^+$) requires 142.0868.

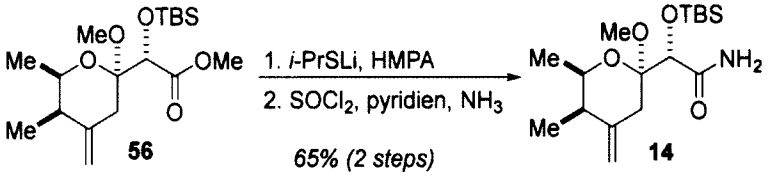


64 **193**

(1S,7aS)-1-hydroxyhexahydro-3H-pyrrolizin-3-one:

The amine salt **64** (46.0 mg, 0.15 mmol) was dissolved in EtOH (3 ml) and K_2CO_3 (128.5 mg, 0.92 mmol) was added in one portion. The mixture was stirred at 50 °C for 16 hr. The solvent was removed under reduced pressure and the crude was dissolved in EtOAc. The mixture was filtered through Celite and concentrated *in vacuo*. The crude **193** (21.2 mg, 0.15 mmol, *quant.*) was pure enough for NMR analysis.

ν_{max} (neat)/cm^{-1} 3086, 2968, 2933, 2877, 1667, 1439, 1404, 1190; $[\alpha]^{20}_D$ -16.2 (c = 0.5 in $CHCl_3$); δ_H (600 MHz, $CDCl_3$) 4.41 (t, *J* = 4.5 Hz, 1H), 3.99 (td, *J* = 7.4, 4.1 Hz, 1H), 3.57 (dt, *J* = 11.4, 7.2 Hz, 1H), 3.12 – 3.02 (m, 1H), 2.98 (ddt, *J* = 16.7, 4.7, 1.2 Hz, 1H), 2.40 (d, *J* = 16.8 Hz, 1H), 2.16 – 1.96 (m, 3H), 1.84 – 1.70 (m, 1H); δ_C (150 MHz, $CDCl_3$) 173.0, 68.3, 66.8, 45.7, 41.5, 27.2, 23.1; Accurate mass (ES+): Found 142.0853 (-10,6 ppm), $C_7H_{12}NO_2$ ($M+H^+$) requires 142.0868.



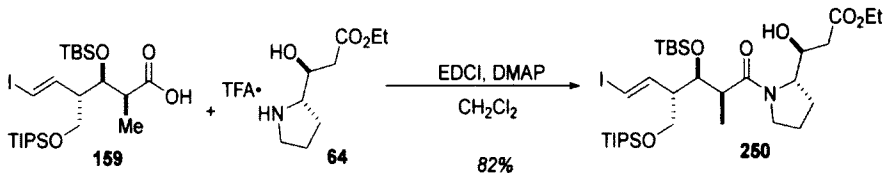
(S)-2-((tert-butyldimethylsilyl)oxy)-2-((2R,5R,6R)-2-methoxy-5,6-dimethyl-4-methylenetetrahydro-2H-pyran-2-yl)acetamide:

To a solution of methylester **56** (1.87 g, 5.22 mmol) in HMPA (13 ml) at 0 °C was added *i*-PrSLi solution in HMPA (5 ml). After stirring for 1hr at rt, the reaction was diluted with CH_2Cl_2, poured into ice-cold 0.5 M $NaHSO_4$. After separating the organic layer, the aqueous layer was extracted with CH_2Cl_2 (x3). The combined organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude was purified by flash column chromatography to give carboxylic acid.

To a solution of carboxylic acid in CH_2Cl_2 (17.5 ml) and pyridine (0.84 ml, 10.46 mmol) was added thionyl chloride (1.52 ml, 20.90 mmol) dropwise at 0 °C. The reaction was stirred for 30 min and concentrated under reduced pressure. The crude material was re-dissolved in CH_2Cl_2 and bubbled ammonia gas for 1 min at 0 °C. The solvent was removed under reduce pressure and purified by flash column chromatography to give pure amide **14** (1.20 g, 3.39 mmol, 65% over two steps).

ν_{max}(neat)/cm^{-1} 3482, 2929, 2859, 1745, 1692, 1618, 1464, 1252, 1168; $[\alpha]^{20}_D$ _18.1 (c = 5.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 6.47 (bs, 1H), 6.10 (bs, 1H), 4.79 (t, *J* = 1.7 Hz, 1H), 4.70 (t, *J* = 1.7 Hz, 1H), 4.18 (s, 1H), 3.84 (qt, *J* = 6.5, 3.3 Hz, 1H), 3.31 (s, 3H), 2.50 – 2.35 (m, 1H), 2.18 (qd, *J* = 6.9, 2.6 Hz, 1H), 1.15 (d, *J* = 6.5 Hz, 3H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.91 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H); δ_C (100 MHz, $CDCl_3$) 173.7, 146.9, 109.8, 99.4, 77.7, 69.6, 50.1, 41.5, 35.2, 25.9, 18.4, 17.9, 11.9, -

4.8, -5.1; Accurate mass (ES+): Found 366.2101 (6.6 ppm), $C_{17}H_{33}NO_4SiNa$ ($M+Na^+$) requires 366.2077.

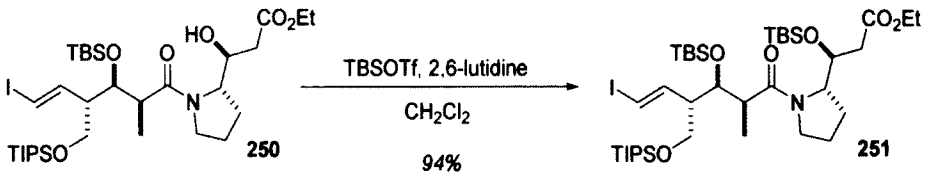


ethyl (S)-3-((S)-1-((2S,3R,4S,E)-3-((tert-butyldimethylsilyl)oxy)-6-iodo-2-methyl-4-(((triisopropylsilyl)oxy)methyl)hex-5-enoyl)pyrrolidin-2-yl)-3-hydroxypropanoate:

The carboxylic acid **159** (62.7 mg, 0.11 mmol) and amine salt **64** (49.65 mg, 0.16 mmol) were dissolved in dry CH_2Cl_2 (3.3 ml). DMAP (40.27 mg, 0.33 mmol) and EDCI (58.56 mg, 0.33 mmol) were added to the reaction mixture at one potion. The reaction mixture was stirred for 14 hr. The reaction was diluted with EtOAc and washed with aqueous 1 N HCl, water, and brine. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude oil was purified by flash column chromatography to give amide product **250** (69.9 mg, 0.095 mmol, 82%).

ν_{max}(neat)/cm^{-1} 3482, 2955, 2937, 2867, 1734, 1620, 1461, 1254; $[\alpha]^{20}_D$ -9.0 (c = 0.5 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 6.52 (dd, *J* = 14.4, 10.2 Hz, 1H), 6.23 (d, *J* = 14.4 Hz, 1H), 4.21 (dd, *J* = 8.2, 3.7 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.09 (dd, *J* = 9.2, 1.7 Hz, 1H), 3.91 (td, *J* = 8.3, 3.7 Hz, 1H), 3.65 (dd, *J* = 9.8, 7.4 Hz, 1H), 3.60 (ddd, *J* = 10.2, 7.7, 4.8 Hz, 1H), 3.53 (dd, *J* = 9.8, 7.7 Hz, 1H), 3.45 (dt, *J* = 10.2, 7.4 Hz, 1H), 2.59 (dtd, *J* = 10.0, 5.4, 4.6, 2.1 Hz, 2H), 2.54 (dd, *J* = 15.1, 3.6 Hz, 1H), 2.45 (dd, *J* = 15.1, 8.1 Hz, 1H), 2.09 – 2.01 (m, 1H), 1.99 – 1.93 (m, 1H), 1.91 – 1.84 (m, 1H), 1.70 (ddt, *J* = 10.3, 6.3, 3.9 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.13 (d, *J* = 6.9 Hz, 3H), 1.07-1.01 (m, 21H), 0.92 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H); δ_C (150 MHz, $CDCl_3$) 177.1, 171.9, 143.7, 78.8, 73.5, 72.9, 63.6, 62.1,

60.8, 53.9, 48.2, 44.3, 41.1, 28.3, 26.4, 24.3, 18.6, 18.2, 18.1, 15.6, 14.4, 12.1, -3.5, -3.6.; Accurate mass (ES+): Found 740.3306 (+9.1 ppm), $C_{32}H_{63}INO_6Si_2$ ($M+H^+$) requires 740.3239.

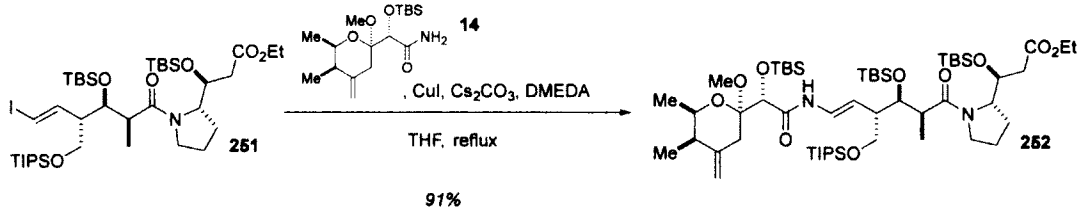


ethyl (S)-3-((tert-butyldimethylsilyl)oxy)-3-((S)-1-((2S,3R,4S,E)-3-((tert-butyldimethylsilyl)oxy)-6-iodo-2-methyl-4-(((triisopropylsilyl)oxy)methyl)hex-5-enoyl)pyrrolidin-2-yl)propanoate:

The alcohol **250** (51.50 mg, 0.07 mmol) was dissolved in CH_2Cl_2 (3 ml) and cooled to 0 °C. To this solution was added 2, 6-lutidine (20.3 µL, 0.17 mmol) followed by slow addition of *t*-butyldimethylsilyltrifluoromethane sulfonate (19.2 µL, 0.08 mmol). After 1 hr of stirring at 0 °C, the reaction mixture was quenched with saturated 10 % aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (x3). The combined organic layers were washed with brine, dried $MgSO_4$, filtered and concentrated *in vacuo*. The crude oil was purified by flash column chromatography to provide silyl ether **251** (56.2 mg, 0.066mmol, a mixture of rotamers, 94%) as a clear oil.

ν_{max} (neat)/cm^{-1} 2955, 2933, 2863, 1735, 1646, 1463, 1463, 1254; $[\alpha]^{20}_D$ +3.2 (c = 0.5 in $CHCl_3$); δ_H (600 MHz, $CDCl_3$, * minor rotamer) 6.61* (dd, *J* = 14.5, 9.8 Hz, 1H), 6.56 (dd, *J* = 14.5, 10.0 Hz, 1H), 6.07 (d, *J* = 14.5 Hz, 1H), 5.95* (d, *J* = 14.5 Hz, 1H), 4.58 (ddd, *J* = 10.1, 4.0, 2.7 Hz, 1H), 4.35* (ddd, *J* = 10.0, 5.1, 2.2 Hz, 1H), 4.23 (dt, *J* = 7.5, 3.5 Hz, 1H), 4.19 – 4.07 (m, 2H+3H*), 4.04* (ddd, *J* = 8.3, 5.0, 2.8 Hz, 1H), 3.99* (dd, *J* = 8.8, 1.5 Hz, 1H) 3.68 (dd, *J* = 9.7, 6.8 Hz, 1H), 3.65 – 3.58 (m, 1H), 3.57 – 3.49 (m, 1H+1H*), 3.49 – 3.42 (m, 1H+2H*), 3.36* (ddd, *J* = 12.9, 8.1, 5.3 Hz, 1H), 2.57-2.52 (m, 2H+1H*), 2.42 (td, *J* = 10.0, 9.3, 5.7 Hz, 1H), 2.35-2.30 (m, 2H+1H*), 2.23-2.19 (m, 1H+1H*), 2.18 – 2.11* (m, 1H), 2.08 – 1.98 (m, 1H+1H*), 1.97 – 1.78 (m, 2H+2H*), 1.32* (d, *J* = 6.7

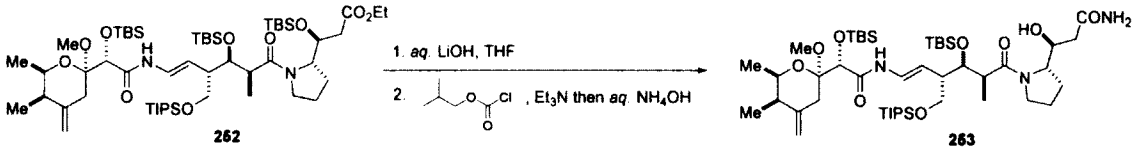
Hz, 3H), 1.27-1.23 (m, 3H+3H*), 1.13 (d, J = 6.9 Hz, 3H), 1.10 – 1.00 (m, 21H+21H*), 0.93* (s, 9H), 0.92 (s, 9H), 0.89* (s, 9H), 0.86 (s, 9H), 0.18* (s, 3H), 0.15 (s, 3H), 0.13* (s, 3H), 0.11 (s, 3H), 0.09 (s, 3H+3H*), 0.05 (s, 3H), 0.03* (s, 3H); δ_C (150 MHz, $CDCl_3$) 174.4, 174.4*, 171.7*, 171.6, 144.2, 143.9*, 78.0, 77.7*, 75.3*, 73.6, 70.7*, 69.5, 64.5*, 64.0, 61.4*, 60.9*, 60.7, 60.6, 54.0, 53.9*, 47.8, 46.7*, 44.4*, 44.2, 38.5, 37.6*, 26.4, 26.3*, 26.0*, 25.9, 25.7*, 24.6, 24.5, 22.9*, 18.6, 18.6*, 18.2, 18.2*, 18.2, 18.1*, 18.1*, 18.0, 17.9*, 15.6, 14.4, 14.3*, 12.1, 12.1*, -3.3*, -3.4, -3.5, -4.1*, -4.3, -4.9*, -4.9.; Accurate mass (ES+): Found 854.4077 (-3.2 ppm), $C_{38}H_{77}INO_6Si_3$ ($M+H^+$) requires 854.4104.



ethyl (S)-3-((tert-butyldimethylsilyl)oxy)-3-((S)-1-((2S,3R,4S,E)-3-((tert-butyldimethylsilyl)oxy)-6-((S)-2-((tert-butyldimethylsilyl)oxy)-2-((2R,5R,6R)-2-methoxy-5,6-dimethyl-4-methylenetetrahydro-2H-pyran-2-yl)acetamido)-2-methyl-4-(((triisopropylsilyl)oxy)methyl)hex-5-enoyl)pyrrolidin-2-yl)propanoate:

To a mixture of vinyl iodide **251** (89.5 mg, 0.105 mmol) and amide **14** (53.99 mg, 0.157 mmol) in THF (5 ml), CuI (79.82 mg, 0.42 mmol), Cs_2CO_3 (550 mg, 1.68 mmol) and *N*, *N'*-Dimethylethylenediamine (DMEDA, 90.2 µL, 0.84 mmol) were added. The reaction mixture was heated to 70 °C and stirred for 3 hr. After the reaction complete, the resulting solution was diluted with EtOAc and filtered through a short silica pad. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography to give a pure vinyl amide **252** (102.0 mg, 0.091 mmol, 91%).

ν_{max}(neat)/cm^{-1} 2928, 2888, 2857, 1738, 1700, 1645, 1463, 1274, 1252; $[\alpha]^{20}_D$ -15.0 (c = 0.5 in $CHCl_3$); δ_H (600 MHz, $CDCl_3$, major rotamer) 8.10 (d, *J* = 10.8 Hz, 1H), 6.67 (dd, *J* = 14.4, 10.8 Hz, 1H), 5.11 (dd, *J* = 14.4, 10.0 Hz, 1H), 4.81 (t, *J* = 1.9 Hz, 1H), 4.70 (t, *J* = 1.9 Hz, 1H), 4.69 – 4.64 (m, 1H), 4.26 (dd, *J* = 8.7, 1.3 Hz, 1H), 4.20 – 4.16 (m, 1H), 4.16 – 4.02 (m, 3H), 3.86 (qd, *J* = 6.6, 2.6 Hz, 1H), 3.67 (dd, *J* = 9.1, 6.9 Hz, 1H), 3.52 (dd, *J* = 9.8, 7.2 Hz, 1H), 3.45 (ddd, *J* = 9.9, 8.2, 4.0 Hz, 1H), 3.38 – 3.30 (m, 1H), 3.27 (s, 3H), 2.58 – 2.51 (m, 1H), 2.48 (dd, *J* = 14.1, 2.1 Hz, 1H), 2.40 – 2.31 (m, 3H), 2.22-2.18 (m, 2H), 2.09-2.03 (m, 1H), 1.96 – 1.87 (m, 1H), 1.86 – 1.75 (m, 2H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.16 (d, *J* = 6.5 Hz, 3H), 1.09 (d, *J* = 7.0 Hz, 3H), 1.08 – 1.04 (m, 21H), 0.95 (d, *J* = 7.2 Hz, 3H), 0.92 (s, 9H), 0.91 (s, 9H), 0.85 (s, 9H), 0.16 (s, 3H), 0.12 (s, 3H), 0.12 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H), 0.05 (s, 3H); δ_C (150 MHz, $CDCl_3$) 174.77, 171.87, 167.56, 146.67, 124.46, 110.76, 109.99, 99.69, 76.56, 73.26, 69.70, 69.01, 64.73, 61.05, 60.26, 49.86, 48.56, 47.55, 43.86, 41.49, 38.15, 34.68, 29.86, 26.37, 26.35, 25.92, 25.89, 24.59, 24.11, 18.24, 18.22, 18.21, 15.03, 14.43, 12.16, 11.93, -3.45, -3.74, -4.30, -4.77, -4.92, -5.0; Accurate mass (ES+): Found 1069.7301 (+13.3 ppm), $C_{55}H_{109}N_2O_{10}Si_4$ ($M+H^+$) requires 1069.7159.



(S)-3-((tert-butyldimethylsilyl)oxy)-3-((S)-1-((2S,3R,4S,E)-3-((tert-butyldimethylsilyl)oxy)-6-((S)-2-((tert-butyldimethylsilyl)oxy)-2-((2R,5R,6R)-2-methoxy-5,6-dimethyl-4-methylenetetrahydro-2H-pyran-2-yl)acetamido)-2-methyl-4-(((triisopropylsilyl)oxy)methyl)hex-5-enoyl)pyrrolidin-2-yl)propanamide:

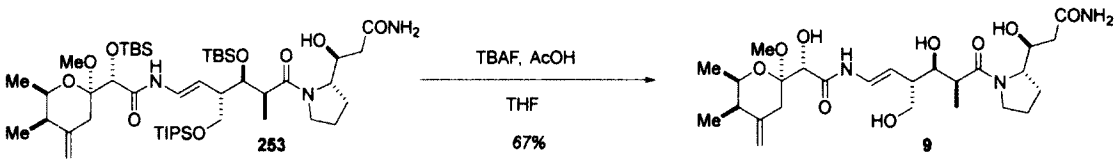
To a reaction mixture of ethyl ester **252** (32.7 mg, 0.03 mmol) in THF (2.5 ml) and CH_3OH (0.35 ml) was added a solution of LiOH in H_2O (1 ml) at room temperature. The mixture was stirred for 72 hr at room temperature. The reaction was quenched by an addition of pH 2 sulfate buffer refers to an aqueous solution made of 1 M sodium bisulfate and 1 M sodium sulfate mixed in 1:1 v/v

ratio. The aqueous layer was extracted with EtOAc(x3). The organic layer was washed with brine and dried over sodium sulfate. The crude mixture was filtered and concentrated *in vacuo*. The crude was used to the next step without further purification.

Crude carboxylic acid from the previous step was dissolved in CH_2Cl_2 and cooled to -10 °C. To this solution were added Et_3N (17 μL, 0.12 mmol) and isobutyl chloroformate (10.4 μL, 0.08 mmol), and the reaction was maintained at -10 °C for 2 hr. Aqueous ammonium hydroxide was added to the reaction mixture at -10 °C. The reaction was maintained at 0 °C for 20 min. The reaction mixture was diluted with EtOAc, washed with water and brine, then dried over $MgSO_4$ and concentrated *in vacuo*. The crude was purified by flash column chromatography to give pure amide **253** (20.5 mg, 0.019 mmol, 64%).

ν_{max} (neat)/cm^{-1} 2951, 2928, 2895, 2863, 1689, 1667, 1462, 1409, 1253, 1086; $[\alpha]^{20}_D$ +8.6 (c = 0.5 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$, major rotamer) 8.47 (d, *J* = 10.7 Hz, 1H), 6.94 (bs, 1H), 6.79 (dd, *J* = 14.4, 10.7 Hz, 1H), 5.25 (dd, *J* = 14.4, 9.8 Hz, 1H), 5.24 (bs, 1H), 4.87 (s, 1H), 4.76 (s, 1H), 4.42 (td, *J* = 6.3, 3.1 Hz, 1H), 4.28 (dd, *J* = 9.0, 4.6 Hz, 2H), 4.25 – 4.21 (m, 1H), 4.07 (qd, *J* = 6.5, 2.6 Hz, 1H), 3.95 (d, *J* = 6.7 Hz, 1H), 3.89 (d, *J* = 3.6 Hz, 1H), 3.66 (dd, *J* = 10.0, 8.1 Hz, 1H), 3.52 (dd, *J* = 9.9, 7.1 Hz, 1H), 3.46-3.37 (m, 2H), 3.33 (s, 3H), 2.64 – 2.57 (m, 1H), 2.47 (dd, *J* = 13.6, 5.8 Hz, 1H), 2.36 – 2.22 (m, 3H), 2.06 – 1.93 (m, 3H), 1.90 (td, *J* = 8.4, 4.1 Hz, 1H), 1.77 (ddt, *J* = 11.0, 8.5, 4.2 Hz, 1H), 1.22 (d, *J* = 6.5 Hz, 3H), 1.08 (d, *J* = 6.8 Hz, 3H), 1.07-1.03 (m, 21H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.92 (s, 9H), 0.89 (s, 9H), 0.17 (s, 3H), 0.16 (s, 3H), 0.14 (s, 3H), 0.11 (s, 3H); δ_C (150 MHz, $CDCl_3$) 175.1, 173.1, 168.5, 145.0, 124.5, 112.2, 111.3, 100.2, 73.2, 71.5, 70.2, 70.1, 69.8, 64.8, 60.3, 48.6, 48.4,

48.1, 43.8, 41.4, 40.7, 32.9, 26.4, 26.1, 24.4, 19.0, 18.6, 18.2, 18.1, 15.3, 12.2, 12.1, -3.4, -3.7, -4.5, -4.5.; Accurate mass (ES+): Found 926.6009 (-14.2 ppm) $C_{47}H_{92}N_3O_9Si_3$ ($M+H^+$) requires 926.6141.

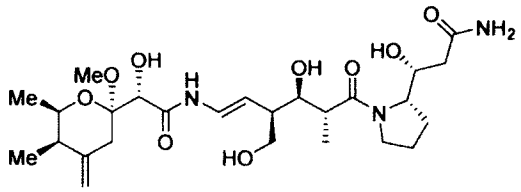


(S)-3-hydroxy-3-((S)-1-((2S,3R,4S,E)-3-hydroxy-6-((S)-2-hydroxy-2-((2R,5R,6R)-2-methoxy-5,6-dimethyl-4-methylenetetrahydro-2H-pyran-2-yl)acetamido)-4-(hydroxymethyl)-2-methylhex-5-enoyl)pyrrolidin-2-yl)propanamide, Nosperin:

Silyl-protected amide **253** (20.5 mg, 0.02 mmol) was dissolved in THF (3 ml). To the stirring solution was added TBAF (0.18 ml of a 1M solution in THF that has been neutralized with 5 µL of AcOH to *ca.* pH 7). The resulting solution was stirred for 16 hr at room temperature. After reaction complete, the resulting solution was concentrated *in vacuo*. The residue was purified by flash column chromatography (CH_2Cl_2:MeOH = 10:1 to 5:1) to give Nosperin **9** (8 mg, 0.015 mmol, 67%) as a white solid; ν_{max}(neat)/cm^{-1} 3352, 2972, 2932, 2888, 1714, 1661, 1613, 1529, 1464, 1433; $[\alpha]^{20}_D$ +20.2 (c = 0.5 in CH_3OH); Accurate mass (ES+): Found 542.3102 (+4.4 ppm) $C_{26}H_{44}N_3O_9$ ($M+H^+$) requires 542.3078.

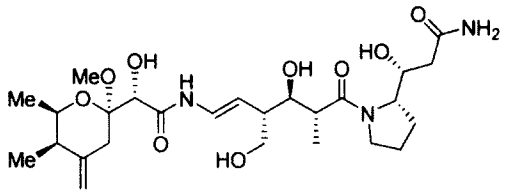
	Natural nosperin (1)		**Synthetic Anti-syn-L-Pro-anti (9)**	
#	δ_H	δ_C	δ_H	δ_C
1	1.19 (d, *J* = 6.5 Hz)	18.2	1.19 (d, *J* = 6.6 Hz, 1H)	18.2
2	3.93 (dq, *J* = 6.5, 2.6 Hz)	70.2	3.93 (qd, *J* = 6.6, 2.7 Hz, 1H)	70.2
3	2.26	42.1	2.26	42.1
4	-	147.5	-	147.5
5a	2.05	33.7	2.05 (dt, *J* = 14.3, 2.2 Hz, 1H)	33.7
5b	2.2	-	2.20 (d, J = 14.3 Hz, 1H)	-
6	-	100.8	-	100.8
7	4.23 (d, *J* = 4.2 Hz)	71.7	4.24 (d, J = 3.6 Hz, 1H)	71.7
8	-	170.0	-	170
9	8.57 (d, *J* = 10.3 Hz)	NH	8.59 (d, *J* = 10.7 Hz, 1H)	NH
10	6.75 (dd, *J* = 14.5, 10.6 Hz)	125.4	6.76 (dd, *J* = 14.4, 10.6 Hz, 1H)	125.5

11	5.31 (dd, *J* = 14.4, 10.4 Hz)	111.8	5.30 (dd, *J* = 14.4, 10.3 Hz, 1H)	111.8
12	2.27	47.3	2.27 (m, 1H)	47.3
13	3.87 (m)	74.5	3.90 – 3.83 (m, 1H)	74.5
14	2.48 (dq, *J* = 9.3, 6.8 Hz)	43.9	2.48 (dq, *J* = 9.4, 6.8 Hz, 1H)	43.9
15	-	177.5	-	177.5
16a	3.4 (m)	48.7	3.44 – 3.38 (m, 1H)	48.7
16b	3.4(m)	-	3.44 – 3.38 (m, 1H)	-
17a	1.74 (m)	24.6	1.78 – 1.69 (m, 1H)	24.6
17b	1.85 (m)	-	1.92 – 1.81 (m, 1H)	-
18a	1.75 (m)	27.7	1.78 – 1.69 (m, 1H)	27.8
18b	1.9 (m)	-	1.92 – 1.81 (m, 1H)	-
19	4.11 (ddd, *J* = 7.4, 7.4, 3.5 Hz)	62.6	4.12 (ddd, *J* = 7.5, 7.5, 3.5 Hz, 1H)	62.6
20	4.06	72.6	4.07 (ddd, *J* = 8.0, 6.4, 2.2 Hz, 1H)	72.6
21a	2.22	40.9	2.23	40.9
21b	2.37 (dd, *J* = 14.6, 2.9 Hz)	-	2.38 (dd, *J* = 14.7, 2.2 Hz, 1H)	-
22	-	174.7	-	174.9
23	-	NH_2	5.80 (bs, 1H), 6.68 (bs, 1H)	NH_2
24	0.93 (d, *J* = 7.0 Hz)	12.6	0.93 (d, *J* = 7.0 Hz, 1H)	12.7
25a	4.67 (dd, *J* = 2.1, 2.1 Hz)	110.5	4.67 (dd, *J* = 2.1, 2.1 Hz, 1H)	110.5
25b	4.82 (dd, *J* = 2.1, 2.1 Hz)	-	4.82 (dd, *J* = 2.1, 2.1 Hz, 1H)	-
26	3.21 (s)	48.5	3.21 (s, 3H)	48.5
27	3.79 (d, J = 4.6 Hz)	OH	-	OH
28a	3.56 (m)	65.2	3.56-3.59 (m, 1H)	65.3
28b	3.49 (m)	-	3.52 – 3.46 (m, 1H)	-
29	OH	OH	-	OH
30	3.23 (d, *J* = 5.2 Hz)	OH	-	OH
31	1.10 (d, *J* = 6.8 Hz)	14.3	1.10 (d, *J* = 6.8 Hz, 1H)	14.4
32	5.12 (d, *J* = 3.9 Hz)	OH	5.17 (bs, 1H)	OH
	δ_H (600 MHz, CD_3CN), δ_C (150 MHz, CD_3CN)			



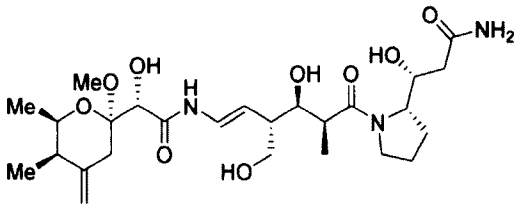
syn-anti-L-proline-syn (**2**)

ν_{max} (neat)/cm^{-1} 3350, 2970, 2929, 2886, 1717, 1667, 1611, 1532, 1460, 1429; $[\alpha]^{20}_D$ +8.8 (c = 1.2 in CH_3OH); Accurate mass (ES+): Found 542.3126 (+8.9 ppm) $C_{26}H_{44}N_3O_9$ ($M+H^+$) requires 542.3078.



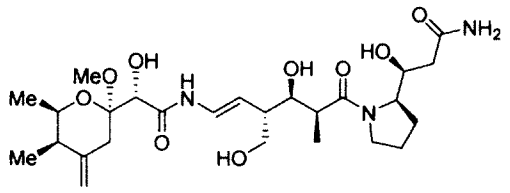
ani-anti-L-proline-syn (**3**)

ν_{max} (neat)/cm^{-1} 3352, 2974, 2927, 2884, 1719, 1660, 1604, 1538, 1464, 1438; $[\alpha]^{20}_{D}$ -20.6 (c = 0.5 in CH_3OH); Accurate mass (ES+): Found 542.3069 (-1.7 ppm) $C_{26}H_{44}N_3O_9$ ($M+H^+$) requires 542.3078.



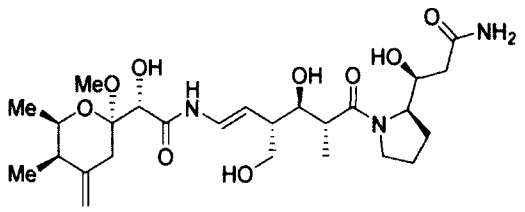
anti-syn-L-proline-syn (**4**)

ν_{max} (neat)/cm^{-1} 3354, 2979, 2929, 2882, 1719, 1663, 1611, 1539, 1469, 1439; $[\alpha]^{20}_{D}$ +17.1 (c = 0.7 in CH_3OH); Accurate mass (ES+): Found 542.3081 (+0.6 ppm) $C_{26}H_{44}N_3O_9$ ($M+H^+$) requires 542.3078.



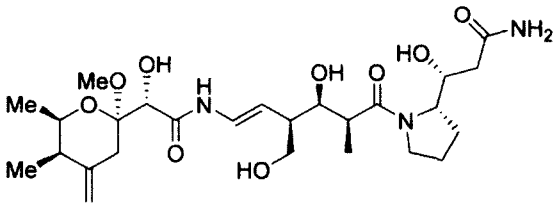
anti-syn-D-proline-syn (**5**)

ν_{max} (neat)/cm^{-1} 3356, 2969, 2932, 2880, 1714, 1660, 1608, 1542, 1470, 1443; $[\alpha]^{20}_{D}$ +64.6 (c = 1.5 in CH_3OH); Accurate mass (ES+): Found 542.3077 (-0.3 ppm) $C_{26}H_{44}N_3O_9$ ($M+H^+$) requires 542.3078.



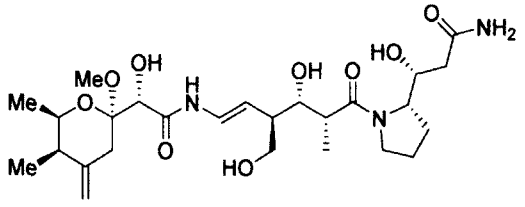
anti-anti-D-proline-syn (**6**)

ν_{max} (neat)/cm^{-1} 3352, 2974, 2929, 2882, 1717, 1662, 1603, 1540, 1461, 1439; $[\alpha]^{20}_{D}$ -10.4 (c = 1.3 in CH_3OH); Accurate mass (ES+): Found 542.3054 (-4.4 ppm) $C_{26}H_{44}N_3O_9$ ($M+H^+$) requires 542.3078.



syn-syn-L-proline-syn (**7**)

ν_{max} (neat)/cm^{-1} 3359, 2975, 2932, 2880, 1715, 1660, 1619, 1545, 1475, 1446; $[\alpha]^{20}_{D}$ +11.9 (c = 0.4 in CH_3OH); Accurate mass (ES+): Found 542.3096 (+3.3 ppm) $C_{26}H_{44}N_3O_9$ ($M+H^+$) requires 542.3078.



enantiomer-anti-syn-L-proline-syn (**8**)

ν_{max} (neat)/cm^{-1} 3356, 2974, 2925, 2886, 1715, 1668, 1613, 1538, 1469, 1442; $[\alpha]^{20}_{D}$ +48.6 (c = 0.8 in CH_3OH); Accurate mass (ES+): Found 542.2999 (-14.6 ppm) $C_{26}H_{44}N_3O_9$ ($M+H^+$) requires 542.3078.

	Syn-anti-L-Pro-syn (2)		Anti-anti-L-Pro-syn (3)	
#	δ_H	δ_C	δ_H	δ_C
1	1.18 (d, *J* = 6.6 Hz, 3H)	18.2	1.15 (d, *J* = 6.5 Hz, 3H)	18.1
2	3.91 (dq, *J* = 6.6, 2.7 Hz, 1H)	70	3.89 (dq, *J* = 6.6, 2.6 Hz, 1H)	70.0
3	2.25 (m, 1H)	42.2	2.25 (m, 1H)	42.1
4	-	147.7	-	147.5
5a	2.1	33.8	2.09	33.5
5b	2.19	-	2.2	-
6	-	100.8	-	100.7
7	4.19 (s, 1H)	72.1	4.21 (s, 1H)	71.6
8	-	169.6	-	169.6
9	8.48 (d, *J* = 10.6 Hz, 1H)	NH	9.38 (d, *J* = 10.5 Hz, 1H)	NH
10	6.67 (dd, *J* = 14.3, 10.6 Hz, 1H)	124.7	6.80 (dd, *J* = 14.5, 10.5 Hz, 1H)	125.2
11	5.13 (dd, *J* = 14.3, 10.2 Hz, 1H)	113.5	5.29 (dd, *J* = 14.5, 10.0 Hz, 1H)	110.4
12	2.22	48.6	2.32	46.1
13	3.41-3.48 (m, 1H)	77.3	3.81-3.88 (m, 1H)	74.0
14	2.77 (dq, *J* = 7.2, 2.9 Hz, 1H)	40	2.69 (dq, *J* = 8.8, 6.9 Hz, 1H)	42.7
15	-	178.3	-	177.6
16a	3.48-3.53 (m, 1H)	49.7	3.66-3.74 (m, 1H)	49.2
16b	3.32-3.38 (m, 1H)	-	3.30-3.37 (m, 1H)	-
17a	1.77-1.72 (m, 1H)	24.9	1.83-1.73 (m, 1H)	24.8
17b	1.89-1.83 (m, 1H)	-	1.93-1.88 (m, 1H)	-
18a	1.71-1.79 (m, 1H)	26.8	1.83-1.73 (m, 1H)	26.9
18b	1.82-1.89 (m,1H)	-	1.93-1.88 (m, 1H)	-
19	4.14 – 4.05 (m, 1H)	63.1	4.08 (ddd, *J* = 9.1, 3.2, 3.2 Hz, 1H)	63.2
20	4.14 – 4.05 (m, 1H)	70.3	3.99-4.05 (m, 1H)	70.1
21a	2.25-2.22 (m, 1H)	39.7	2.36-2.30 (m, 1H)	39.6
21b	2.25-2.22 (m, 1H)	-	2.36-2.30 (m, 1H)	-
22	-	174.8	-	175.4
23	6.41 (bs), 5.72 (bs)	NH_2	6.76 (bs), 6.02 (bs)	NH_2
24	0.89 (d, *J* = 7.0 Hz, 3H)	12.3	0.89 (d, *J* = 7.0 Hz, 3H)	12.3
25a	4.65 (dd, *J* = 2.1 Hz, 1H)	110.3	4.65 (dd, *J* = 2.1 Hz, 1H)	110.2
25b	4.81 (dd, *J* = 2.1 Hz, 1H)	-	4.80 (dd, *J* = 2.1 Hz, 1H)	-
26	3.21 (s)	48.8	3.20 (s, 3H)	49.1
27	3.85 – 3.77 (m, 1H)	OH		OH
28a	3.68 (dd, *J* = 10.6, 5.2 Hz, 1H)	65.4	3.58 (dd, *J* = 10.7, 7.3 Hz, 1H)	64.8
28b	3.56 (dd, *J* = 10.6, 5.3 Hz, 1H)	-	3.48 (dd, *J* = 10.7, 6.1 Hz, 1H)	-
29	OH	OH		OH

30		OH		OH
31	1.27 (d, *J* = 7.1 Hz, 3H)	15.9	1.02 (d, *J* = 6.8 Hz, 3H)	14.5
32	4.93 (d, *J* = 9.5 Hz, 1H)	OH		OH
	not assigned OH; 4.52 (bs, 1H), 3.81 (bs, 1H), 2.97 (bs, 1H)		4.93(bs, 1H),	

	Anti-syn-L-Pro-syn (4)		**Anti-syn-D-Pro-syn (5)**	
#	δ_H	δ_C	δ_H	δ_C
1	1.18 (d, *J* = 6.5 Hz, 3H)	18.2	1.19 (d, *J* = 6.6 Hz, 3H)	18.1
2	3.92 (dq, *J* = 6.5, 2.7 Hz, 1H))	70.2	3.93 (dq, *J* = 6.5, 2.7 Hz, 1H))	70.1
3	2.25 (m, 1H)	42.1	2.26 (m, 1H)	42.0
4	-	147.5	-	147.4
5a	2.06 (d, *J* = 14.2 Hz, 1H)	33.6	2.06	33.5
5b	2.2	-	2.2	-
6	-	100.8	-	100.7
7	4.23 (s, 1H)	71.7	4.21 (d, *J* = 4.5 Hz, 1H)	71.5
8	-	170	-	169.6
9	8.59 (d, *J* = 10.6 Hz, 1H)	NH	8.50 (d, *J* = 10.7 Hz, 1H)	NH
10	6.74 (dd, *J* = 14.5, 10.6 Hz, 1H)	125.4	6.67 (dd, *J* = 14.5, 10.7 Hz, 1H)	125.0
11	5.32 (dd, *J* = 14.5, 10.2 Hz, 1H)	111.9	5.31 (dd, *J* = 14.5, 10.3 Hz, 1H)	111.8
12	2.22	47.5	2.22	47.2
13	3.87 – 3.91 (m, 1H)	73.9	3.88 – 3.92 (m, 2H)	73.7
14	2.50 (dq, *J* = 8.1, 6.9 Hz, 1H)	43.7	2.52 (dq, *J* = 7.9, 7.0 Hz, 1H)	43.5
15	-	176.5	-	176.8
16a	3.45 (dt, *J* = 13.0, 6.8 Hz, 1H)	49	3.25 – 3.31 (m, 1H)	48.8
16b	3.34 (dt, *J* = 10.4, 6.8 Hz, 1H)	-	3.25 – 3.31 (m, 1H)	-
17a	1.84-1.79 (m, 1H)	24.8	1.81 – 1.70 (m, 1H)	24.7
17b	1.91-1.86 (m, 1H)	-	1.88 – 1.82 (m, 1H)	-
18a	1.68 – 1.77 (m, 1H)	26.9	2.05-1.99 (m, 1H)	27.6
18b	1.78 – 1.85 (m, 1H)	-	1.81 – 1.70 (m, 1H)	-
19	4.12-4.19 (m, 1H)	63.3	4.10 (ddd, *J* = 8.3, 5.3, 3.4 Hz, 1H)	63.7
20	4.04 (ddd, *J* = 8.2, 5.3, 2.8 Hz, 1H)	70.4	3.98 (ddd, *J* = 6.9, 6.9, 3.4 Hz, 1H)	70.8
21a	2.30-2.24 (m, 1H)	40.2	2.2 (m, 1H)	39.4
21b	2.30-2.24 (m, 1H)	-	2.2 (m, 1H)	-
22	-	174.9	-	174.6
23	6.72 (bs), 5.81 (bs)	NH_2	6.45 (bs, 1H), 5.65 (bs, 1H)	NH_2

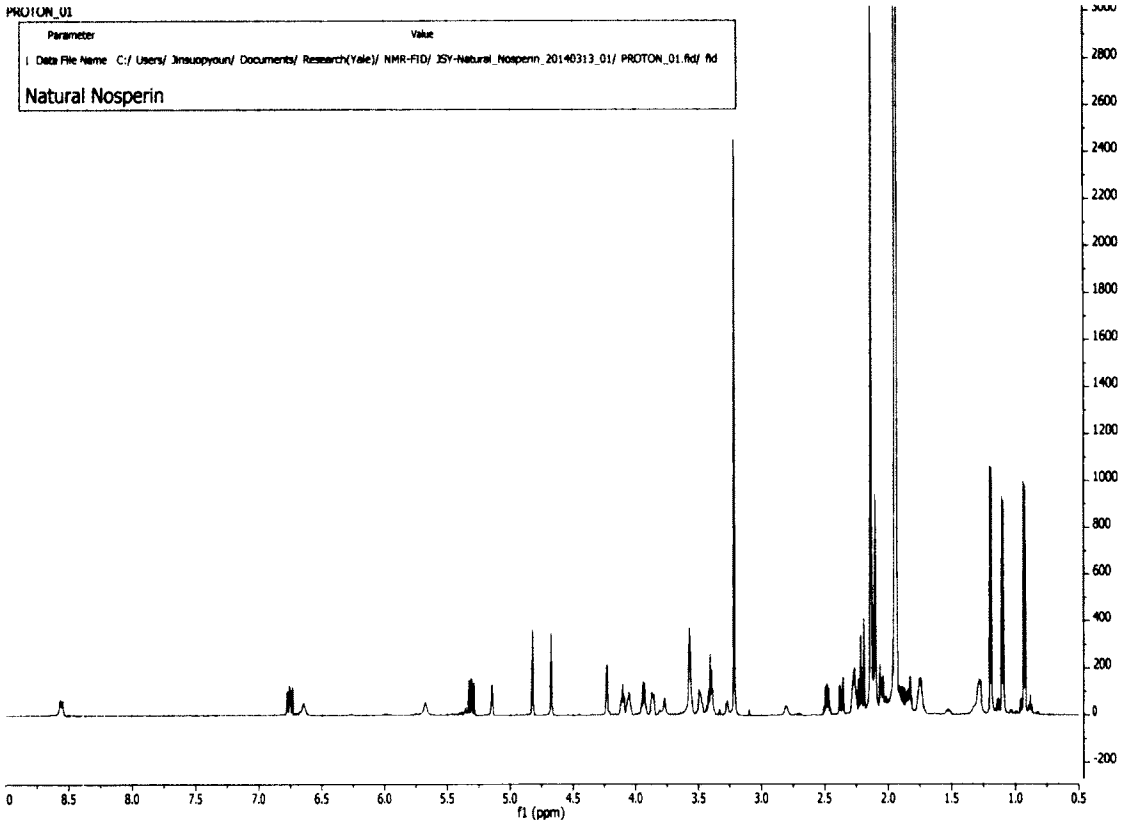
24	0.91 (d, *J* = 6.9 Hz, 3H)	12.6	0.92 (d, *J* = 7.0 Hz, 3H)	12.6
25a	4.66 (dd, *J* = 2.2 Hz, 1H)	110.4	4.67 (dd, *J* = 2.2 Hz, 1H)	110.5
25b	4.81 (dd, *J* = 2.2 Hz, 1H)	-	4.82 (dd, *J* = 2.2 Hz, 1H)	-
26	3.21 (s, 3H)	48.5	3.21 (s, 3H)	48.4
27	3.84 (m, 1H)	OH	3.78 (d, *J* = 4.5 Hz, 1H)	OH
28a	3.59 (dd, *J* = 10.6, 6.7 Hz, 1H)	65.2	3.51-3.57 (m, 1H)	65.2
28b	3.49 (dd, *J* = 10.6, 6.1 Hz, 1H)	-	3.45-3.49 (m, 1H)	-
29	OH	OH	OH	OH
30		OH		OH
31	1.10 (d, *J* = 6.8 Hz, 3H)	14.3	1.17 (d, *J* = 6.9 Hz, 3H)	15.2
32	4.95 (bs, 1H)	OH	5.10 (d, *J* = 7.0 Hz, 1H)	OH
			not assigned OH; 3.56 (m, 1H), 2.77 (bs, 1H)	

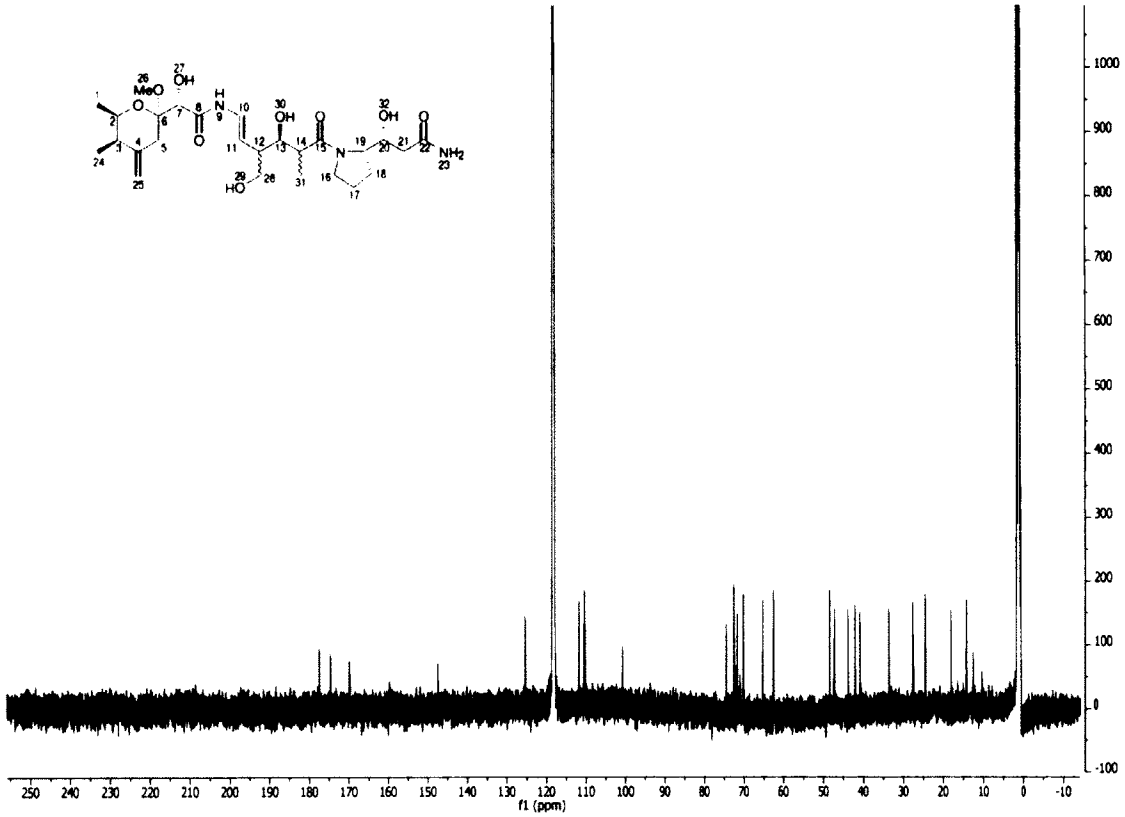
	Anti-anti-D-Pro-syn (6)		**Syn-syn-D-Pro-syn (7)**	
#	δ_H	δ_C	δ_H	δ_C
1	1.18 (d, *J* = 6.5 Hz, 3H)	18.2	1.17 (d, *J* = 6.6 Hz, 3H)	18.1
2	3.92 (dq, *J* = 6.5, 2.7 Hz, 1H))	70.2	3.91 (dq, *J* = 6.5, 2.7 Hz, 1H))	70.2
3	2.25 (m 1H)	42.2	2.24 (m, 1H)	41.1
4	-	147.6	-	147.6
5a	2.12	33.6	2.11	33.5
5b	2.2	-	2.2	-
6	-	100.8	-	100.7
7	4.22 (s, 1H)	71.6	4.21 (s, 1H)	71.6
8	-	169.8	-	169.7
9	8.52 (d, *J* = 10.5 Hz, 1H)	NH	8.52 (d, *J* = 10.6 Hz, 1H)	NH
10	6.82 (dd, *J* = 14.5, 10.5 Hz, 1H)	125.4	6.79 (dd, *J* = 14.4, 10.6 Hz, 1H)	124.9
11	5.33 (dd, *J* = 14.5, 9.7 Hz, 1H)	110.6	5.33 (dd, *J* = 14.4, 10.3 Hz, 1H)	112.6
12	2.35	45.9	2.18	46.9
13	3.89-3.91 (m, 1H)	74.9	3.87 (m, 1H))	73.9
14	2.66 (dq, *J* = 8.4, 7.0 Hz, 1H)	42.8	2.67-2.73 (m, 1H)	42.1
15	-	176.8	-	177.7
16a	3.50-3.56 (m, 1H)	49.4	3.48-3.51 (m, 1H)	48.8
16b	3.40 -3.46 (m, 1H)	-	3.35-3.42 (m, 1H)	-
17a	1.72-1.84 (m, 1H)	24.8	1.82-1.72 (m, 1H)	24.9
17b	1.99-1.89 (m, 1H)	-	1.92-1.86 (m, 1H)	-
18a	1.72-1.84 (m, 1H)	27.5	1.82-1.72 (m, 1H)	26.5

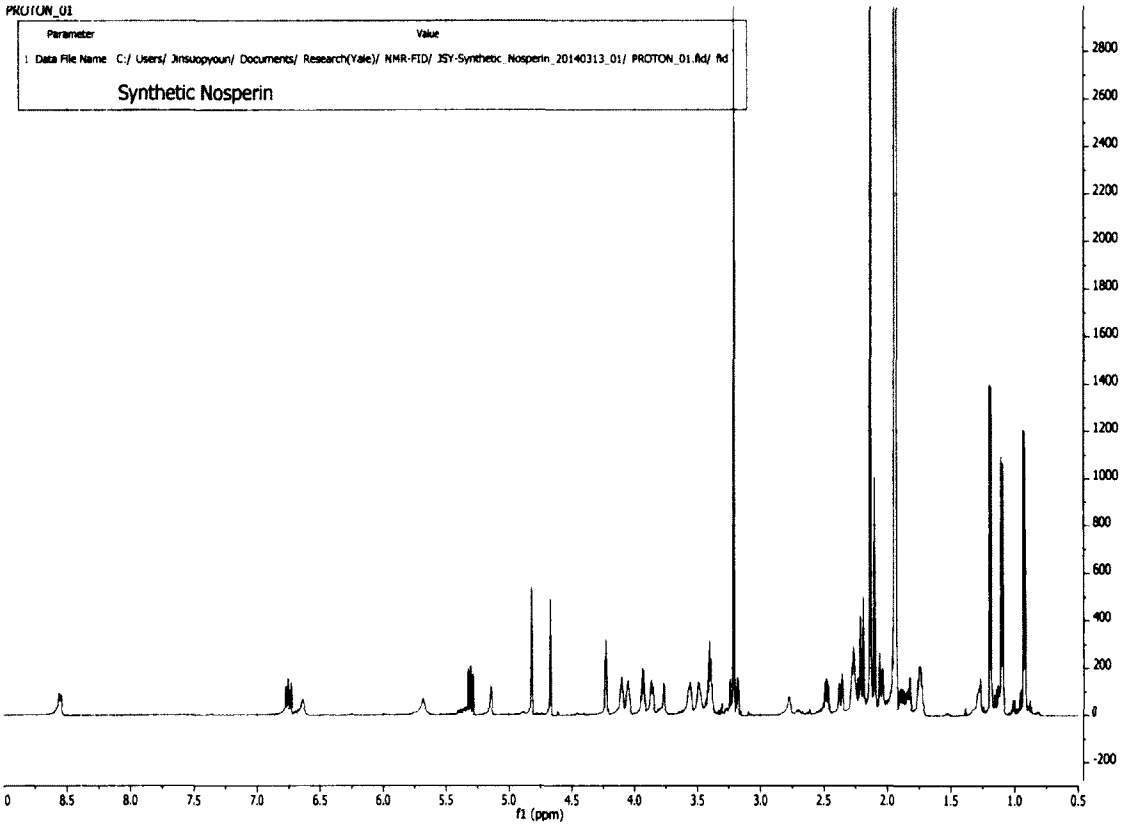
18b	1.99-1.89 (m, 1H)	-	1.92-1.86 (m, 1H)	-
19	4.11-4.16 (m, 1H)	63.9	3.95-4.02 (m, 1H)	63.2
20	3.99-4.04 (m, 1H)	70.2	3.85-3.90 (m, 1H)	67.0
21a	2.23 (m, 1H)	39.4	2.17 (m, 1H)	40.1
21b	2.23 (m, 1H)	-	2.17 (m, 1H)	-
22	-	175.1	-	174.9
23	6.61 (bs, 1H), 5.75 (s, 1H)	NH_2	6.47 (bs, 1H), 5.75 (s, 1H)	NH_2
24	0.90 (d, *J* = 7.1 Hz, 3H)	12.4	0.88 (d, *J* = 7.0 Hz, 3H)	12.2
25a	4.66 (dd, *J* = 2.1 Hz, 1H)	110.3	4.66 (dd, *J* = 2.2 Hz, 1H)	110.2
25b	4.81 (dd, *J* = 2.1 Hz, 1H)	-	4.81 (dd, *J* = 2.2 Hz, 1H)	-
26	3.22 (s, 3H)	48.5	3.27 (s, 3H)	48.4
27	5.11 (bs, 1H)	OH		OH
28a	3.61 (dd, *J* = 10.6, 7.2 Hz, 1H)	65.2	3.66 (dd, *J* = 10.8, 5.8 Hz, 1H)	65.3
28b	3.50-3.56 (m, 1H)	-	3.54-3.60 (m, 1H)	-
29	OH	OH	OH	OH
30		OH		OH
31	0.96 (d, *J* = 6.9 Hz, 3H)	13.5	1.06 (d, *J* = 7.0 Hz, 3H)	14.0
32	5.11 (bs, 1H)	OH		OH
	not assigned OH; 3.83 (m, 1H)		not assigned OH; 4.59 (bs, 1H)	

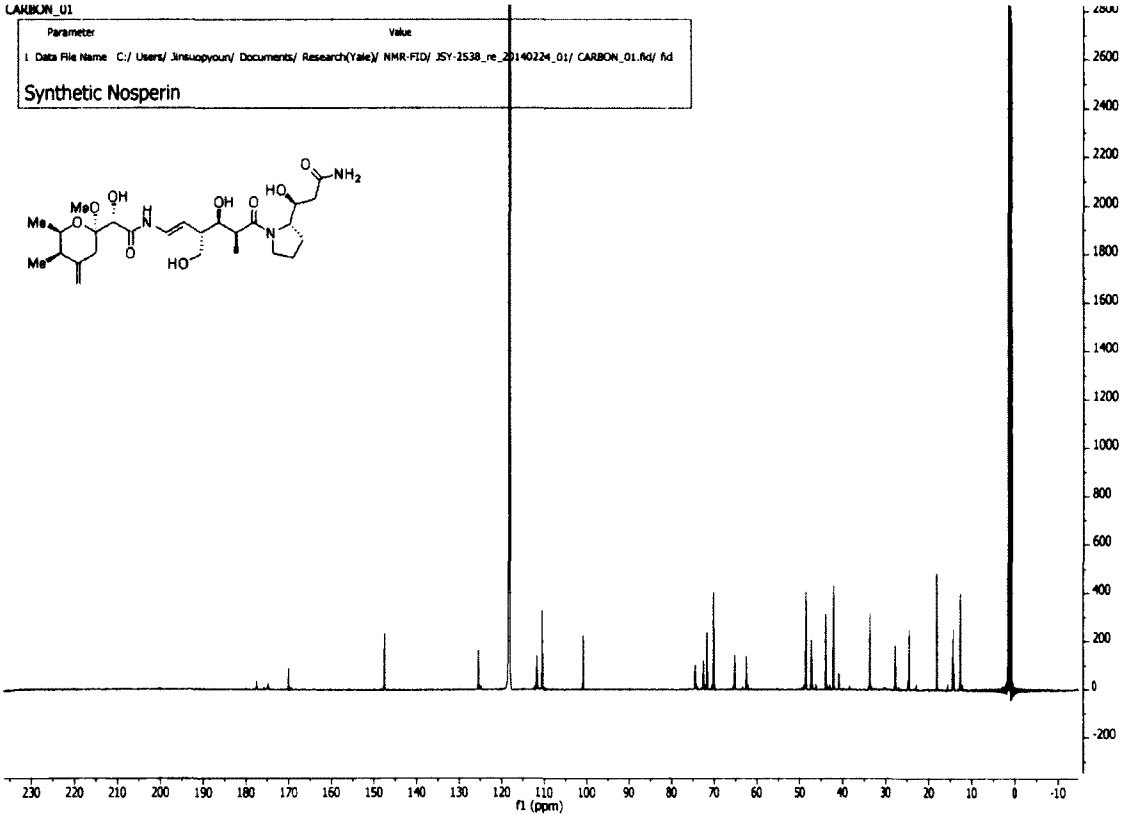
	Enantiomer-anti-syn-L-Pro-anti (8)	
#	δ_H	δ_C
1	1.19 (d, *J* = 6.6 Hz, 3H)	18.2
2	3.93 (dq, *J* = 6.5, 2.7 Hz, 1H))	70.2
3	2.25 (m, 1H)	42.1
4	-	147.5
5a	2.02	33.7
5b	2.2	-
6	-	100.8
7	4.22 (s, 1H)	71.6
8	-	169.7
9	8.50 (d, *J* = 10.7 Hz, 1H)	NH
10	6.67 (d, *J* = 14.4, 10.7 Hz, 1H)	125.1
11	5.32 (d, *J* = 14.4, 10.2 Hz, 1H)	112
12	2.22 (m, 1H)	47.3
13	3.90-3.93 (m, 1H)	73.8
14	2.58 – 2.50 (m, 1H)	43.6

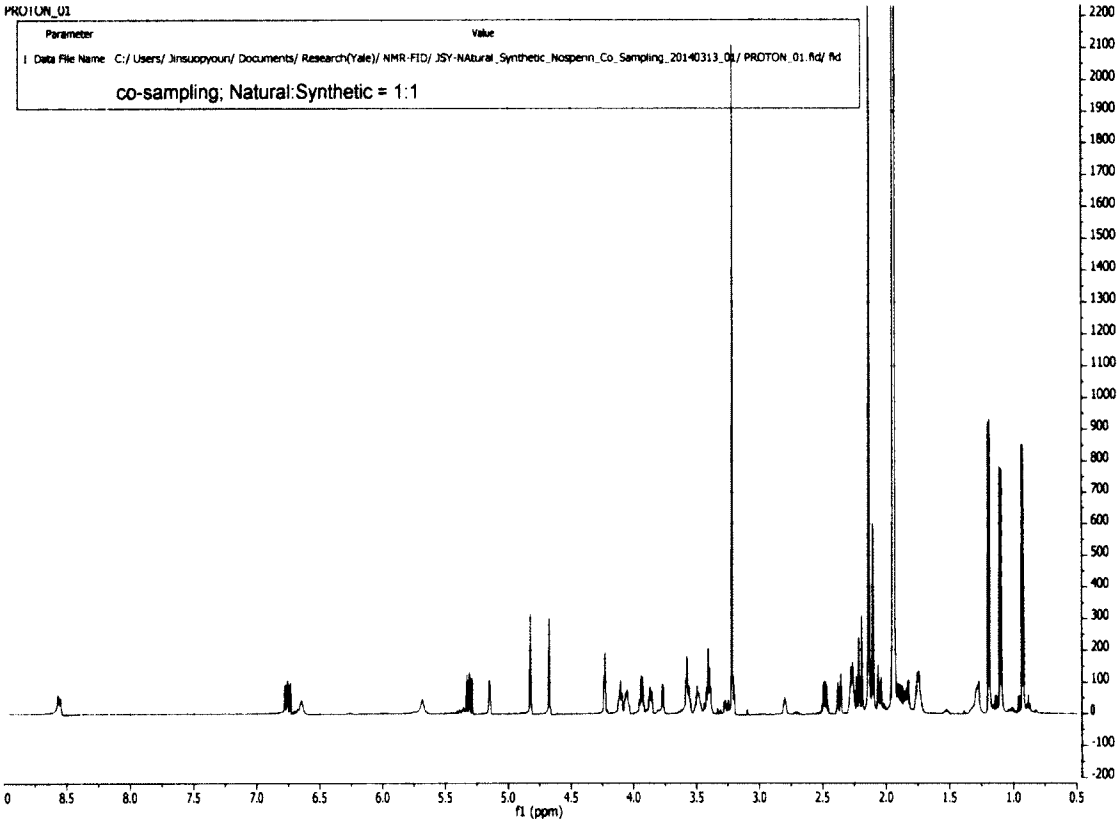
15	-	176.9
16a	3.28-3.38 (m, 1H)	48.9
16b	3.28-3.38 (m, 1H)	-
17a	1.71-1.83 (m, 1H)	24.8
17b	1.71-1.83 (m, 1H)	-
18a	1.71-1.83 (m, 1H)	27.6
18b	1.90-1.83 (m, 1H)	-
19	4.08-4.13 (m, 1H)	63.7
20	3.98-4.03 (m, 1H)	70.8
21a	2.18 (m, 1H)	39.5
21b	2.18 (m, 1H)	-
22	-	174.8
23	6.48 (bs, 1H), 5.70 (bs, 1H)	NH_2
24	0.92 (d, *J* = 7.1 Hz, 1H)	12.7
25a	4.67 (dd, *J* = 2.2 Hz, 1H)	110.5
25b	4.82 (dd, *J* = 2.2 Hz, 1H)	-
26	3.21 (s, 3H)	48.5
27		OH
28a	3.53-3.58 (m, 1H)	65.3
28b	3.46-3.50 (m, 1H)	-
29	OH	OH
30		OH
31	1.18 (d, *J* = 7.0 Hz, 3H)	15.2
32	5.06 (bs, 1H)	OH
	not assigned OH; 3.82 (m, 1H)	

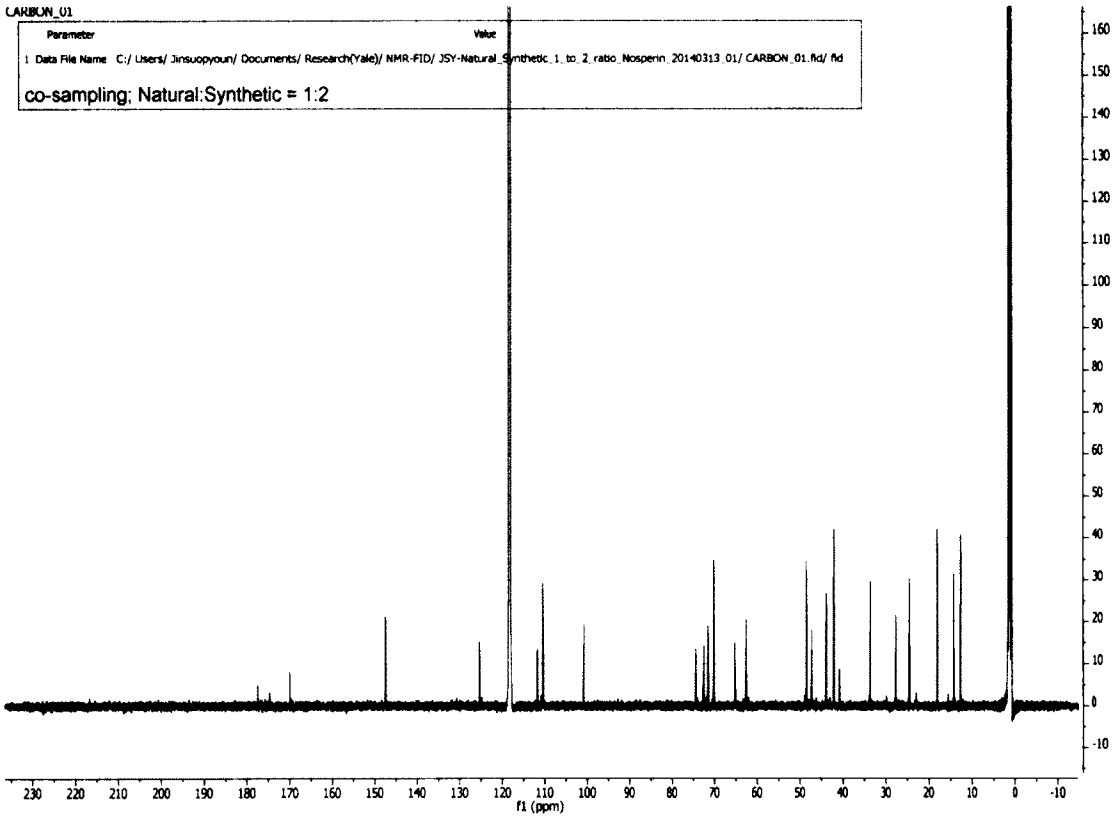

PROTON_01
Parameter
Value
1 Data File Name C:/ Users/ Jinsuopyoun/ Documents/ Research(Yale)/ NMR-FID/ JSY-Natural_Nosperin_20140313_01/ PROTON_01.fid/ fid
Natural Nosperin
f1 (ppm)


f1 (ppm)


PROTON_01
Parameter
Value
1 Data File Name C:/ Users/ Jinsuopyoun/ Documents/ Research(Yale)/ NMR-FID/ JSY-Synthetic_Nosperin_20140313_01/ PROTON_01.fid/ fid
Synthetic Nosperin
f1 (ppm)


CARBON_01
Parameter
Value
1 Data File Name C:/ Users/ Jinsuopyoun/ Documents/ Research(Yale)/ NMR-FID/ JSY-2538_re_20140224_01/ CARBON_01.fid/ fid
Synthetic Nosperin
f1 (ppm)


PROTON_01
Parameter
Value
1 Data File Name C:/ Users/ Jinsuopyoun/ Documents/ Research(Yale)/ NMR-FID/ JSY-NAtural_Synthetic_Nosperin_Co_Sampling_20140313_01/ PROTON_01.fid/ fid
co-sampling; Natural:Synthetic = 1:1
f1 (ppm)


CARBON_01
Parameter
Value
1 Data File Name C:/ Users/ Jinsuopyoun/ Documents/ Research(Yale)/ NMR-FID/ JSY-Natural_Synthetic_1_to_2_ratio_Nosperin_20140313_01/ CARBON_01.fid/ fid
co-sampling; Natural:Synthetic = 1:2
f1 (ppm)

3.5 References

1. A. Kampa, A. N. Gagunashvili, T. A. M. Gulder, B. I. Morinaka, C. Daolio, M. Godejohann, V. P. W. Miao, J. Piel, Ó. S. Andréson, *Proc Natl Acad Sci USA* 110(33):E3129-E3137.
2. A) J. Piel, Nat. Prod. Rep., 2010, 27, 996-1047, B) T. Nguyen, K. Ishida, H. Jenke-kodama, E. Dittmann, C. Gurgui, T. Hochmuth, S. Taudien, M. Platzer, C. Hertweck, J. Piel, *Nature Biotechnology* **2008**, *26*, 225-233.
3. G. Guanti, L. Banfi, E. Narisano, *J. Org. Chem.* **1992**, *57*, 1540-1554.
4. The synthesis were carried out with Dr. Kang suk-youn, Katelyn Billings, and Shannon Carpenter.
5. A) K. Tsuzuki, T. Watanabe, M. Yanagiya, T. Matsumoto, *Tetrahesron Lett.* **1976**, 4745, B) F. Matsuda, N. Tomiyoshi, M. Yanagiya, T. Matsumoto, *Tetrahedron* **1984**, *40*, 2337, C) T. Nakata, S. Nagao, T. Oishi, *Tetrahesron Lett.* **1985**, *26*, 6465, D) T. M. Willson, P. Kocienski, K. Jarowicki, K. Isaac, A. Faller, S. F. Campbell, J. Bordner, *Tetrahedron*, **1990**, *46*, 1757, E) P. Kocienski, K. Jarowicki, S. F. Campbell, *Synthesis* **1991**, 1191.
6. A) N. S. Trotter, S. Takahashi, T. Nakata, *Org. Lett.* **1999**, *1*, 957-959. B) S. Wan, F. Wu, J. C. Rech, M. E. Green, R. Balachandran, W. S. Horne, B. W. Day, P. E. Floreancig, *J. Am. Chem. Soc.* **2011**, *133*, 16668-16679.
7. A) M. Ocejo, L. Carrillo, J. L. Vicario, D. Badia, E. Reyes, *J. Org. Chem.* **2011**, *76*, 460-470, B) R. P. Beckett, S. G. Davies, *J. Chem. Soc., Chem Commun*, **1988**, 160-161.
8. L. Jiang, G. E. Job, A. Klapars, S. L. Buchwald, *Org. Lett.* **2003**, *5*, 3667-3669.