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Yi Jiang Date

Design, Synthesis and Biological Evaluation of C4-C9 Bridged Epothilone Analogs

By

Yi Jiang

Doctor of Philosophy

Chemistry

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Date

Design, Synthesis and Biological Evaluation of C4-C9 Bridged Epothilone Analogs

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Yi Jiang

M.S. Fudan University, 2004
B.S. Anhui Unversity of Science and Technology, 2000

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An abstract of
a dissertation submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
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in Chemistry

2011

Abstract

C4-C9 bridged epothilone analogs were computationally designed to derive experimental evidence for the recently proposed EC binding model of epothilone A in the tubulin binding site. Two generations of synthetic routes toward the target molecule were devised and implemented. The first generation synthesis based on macrolactonization and ring-closing metathesis failed to deliver the desired target molecule presumably due to the difficulty of esterification of the C9-OH group. The second generation synthesis based on *B*-alkyl Suzuki coupling and macrolactonization provided the precursor to the desired C4-C9 bridged epthilone D analog. However, upon global deprotection, an unexpected Michael addition between the C-3 OH group and the unsaturated macrolactone bridge led to formation of additional THF ring in the resulting bridged epothilone D and B analogs. The biological evaluation of the two bridged epothilone analogs indicated that they are 150 and 300 times less active than Taxol®, respectively.

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Dedicated To My Family

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List of Schemes

Abbreviations

9-BBN	9-Borabicyclo[3.3.1]nonane
BORSM	Basis on Recycle Starting Material
calcd	Calculated
cat	Catalytic
compd	Compound
DCM	Dichloromethane
DIBAL-H	Diisobutylaluminum Hydride
DMAP	*N,N*-Dimethylaminopyridine
DMDO	3,3-Dimethyldioxirane
EC	Electron Crystallography
EC_{50}	Half maximal effective concentration
EDCI	1-Ethyl-3-((dimethylamino)propyl)carbodiimide hydrochloride
Epo	Epothilone
ESI	Electron Spray Ionization
EtOAc	Ethyl Acetate
equiv	Equivalents
GTP	Guanosine-5'-triphosphate
h	Hours
HMPA	Hexamethylphosphoramide
HRMS	High Resolution Mass Spectrometry
IC_{50}	Concentration that is required for 50% inhibition
INPHARMA	Interligand NOE for Pharmacophore Mapping
IR	Infrared Spectroscopy

i-Pr	*iso*-Propyl
kDa	kiloDalton
*m*CPBA	*meta*-Chloroperoxybenzoic Acid
MDR	Multidrug Resistance
Me	Methyl
mg	Milligram
min	Minutes
mL	Milliliter
mmol	Millimole
mp	Melting Point
NMO	*N*-Methylmorpholine Oxide
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
NOESY	Nuclear Overhauser Effect Spectroscopy
P-gp	Phosphoglycoprotein
Ph	Phenyl
PTX	Paclitaxel
SAR	Structure Activity Relationship
sat.	Saturated
TBAF	Tetra-*n*-Butylammonium Fluoride
TBSCl	*tert*-butyldimethylsilyl chloride
TFA	Trifluoroacetic Acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography

1.1. Introduction and Background

1.1.1 Microtubules: A Validated Target for Anti-Cancer Drugs

Microtubules, key components of the cytoskeleton, are long, hollow, cylindrical protein polymers composed of two polymerized α and β tubulin units (Figure 1). The two tubulin units are about 50% identical to each other with a molecular weight of about 55 kDa.[1a] The αβ tubulin units bind to one another to form a functional subunit, a heterodimer. An alternating head to tail assemble of the heterodimers under certain favorable intracellular conditions create the protofilaments. When thirteen of these protofilaments are arranged parallel to a cylindrical axis, they self-assemble to form microtubes with a diameter of 24 nm.[1] The polymerization of microtubules occurs by a nucleation-elongation mechanism with relatively slow formation of a short microtubule 'nucleus', followed by rapid elongation of the microtubule at its ends by the reversible, non-covalent addition of tubulin heterodimers (Figure 1).[2] The reversible association and disassociation of αβ-tubulin heterodimers are regulated via a unique GTP binding and hydrolysis property.[3] As a result, microtubules are intrinsically dynamic polymers and possess two unusual dynamic properties, dynamic instability and treadmilling. Dynamic instability is a process in which the individual microtubule ends switch between phases of growth and shortening,[2a] and treadmilling describes the net growth of a microtubule at one end and balanced net shortening at the opposite end.[4]

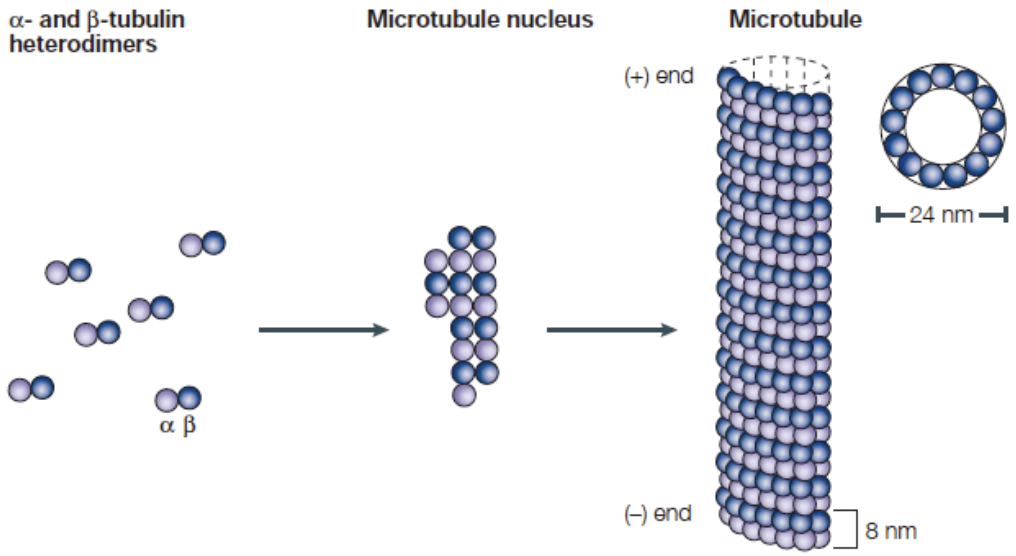
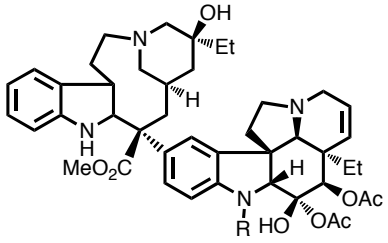


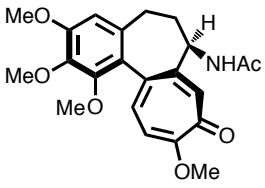
Figure 1. Polymerization of Microtubules (Adapted from ref. 6a)

Microtubule dynamics are involved in numerous cellular functions, including the maintenance of cell shape and polarity, intracellular transport, secretion, and neurotransmissions.[1c] Specifically, microtubules play a crucial role in mitosis. Mitosis is the process during cell replication in which a cell duplicates the chromosomes in its cell nucleus and generates two identical daughter cells. With the development of sophisticated techniques for observing microtubule dynamics in living cells, it has become clear that the microtubules in mitotic spindles have uniquely rapid dynamics that are crucial to successful mitosis.[5] Suppression of microtubule dynamics impairs successful chromosome attachment and movement, which subsequently blocks cell cycle progression with engaging the spindle checkpoint. This critical role that microtubules play in cell division makes them very suitable targets for the development of chemotherapeutic drugs against the rapidly dividing cancer cells.[6]

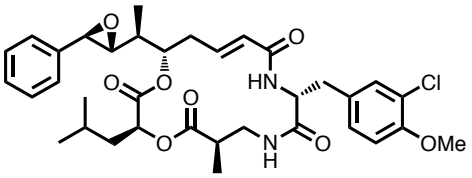
A large number of chemically diverse natural products have been identified to bind with soluble tubulin and/or directly to tubulin in the microtubules.[7] They exert their inhibitory effects on cell proliferation primarily by potently suppressing microtubule dynamics, which in turn blocks mitotic progression and induces apoptosis.[8] Based on different action mechanisms, microtubule-interacting agents usually can be classified into two distinct functional groups, namely microtubule-destabilizing agents (or tubulin polymerization inhibitors) and microt-



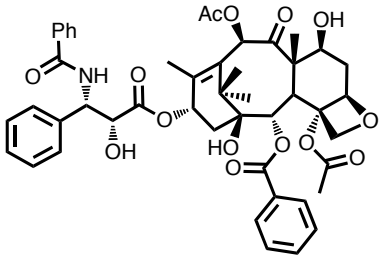
1: R=Me, Vinblastine
2: R=CHO, Vincristine



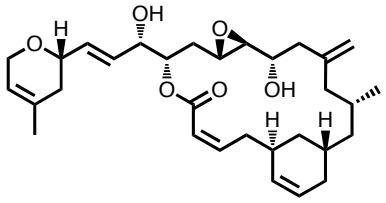
3: Colchicine



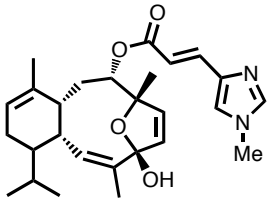
4: Cryptophycin A



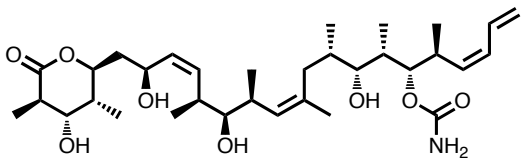
5: R_1=Ph, R_2=Ac, Paclitaxel
6: R_1=O-*t*Bu, R_2=H, Docetaxel



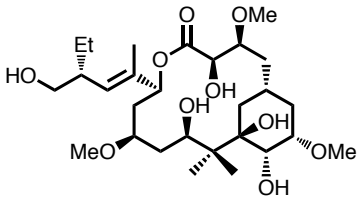
7: Laulimalide



8a: R=Me, Sacrodictyin A
8b: R=Et, Sacrodictyin B



9: Discodermolide



10: Peloruside A

Figure 2. Molecular structures of selected microtubule-interacting agents.

ubule-stabilizing agents.[9] Microtubule-destabilizing agents inhibit microtubule polymerization at high concentrations and include several compounds such as the Vinca alkaloids (vinblastine (**1**), vincristine (**2**), etc.), colchicine (**3**) and cryptophycin A (**4**). Microtubule-stabilizing agents stimulate microtubule polymerization and include compounds such as paclitaxel (**5**,Taxol®), docetaxel (**6**,Taxotere®), laulimalide (**7**), sarcodictyins (**8a** and **8b**), discodermolide (**9**) and peloruside (**10**) (Figure 2).

The interaction sites between microtubules and microtubule-interacting agents are variable. Currently, there are three well established drug binding sites on β-tubulin: vinca domain,[10] taxane site[11] and colchicine site[12] (Figure 3). The vinca domain is located at the microtubule plus end surface. Vinblastine and many other agents bind to tubulin at the vinca domain with very high affinity and tremendously reduce both treadmilling and dynamic instability of microtubules. The taxane site resides in a deep hydrophobic pocket at the lateral interface between adjacent protofilaments, within the lumen of the microtubule. Binding of paclitaxel to its site on the inside microtubule surface stabilizes the microtubule, and also increases microtubule polymerization and its affinity for neighboring tubulin molecules.[6a] Finally, the colchicine site is located at the intra-dimmer interface between α and β tubulin. Free colchicine itself probably does not bind directly to microtubule ends. Instead, it first binds to soluble tubulin to form a poorly reversible tubulin-colchicine complex, which then copolymerizes into the microtubule ends.[12] The tubulin-colchicine complexes might have a

conformation that disrupts the microtubule lattice in a way that slows, but does not prevent, new tubulin addition. In addition to these three well characterized binding domains, laulimalide [7] seems to occupy a different binding site which remains elusive.[6b]

Among the microtubule-interacting agent family, the significance of paclitaxel[5] and its semisynthetic analogue docetaxel[6] could never be overemphasized. They were among the most important new additions to the chemotherapeutic arsenal in the late twentieth century. Isolated originally from the bark of the Pacific yew tree, Taxus brevifolia in 1967 by Monroe E. Wall and Mansukh C. Wani,[13] paclitaxel[5] did not receive much attention until it was discovered to pos-

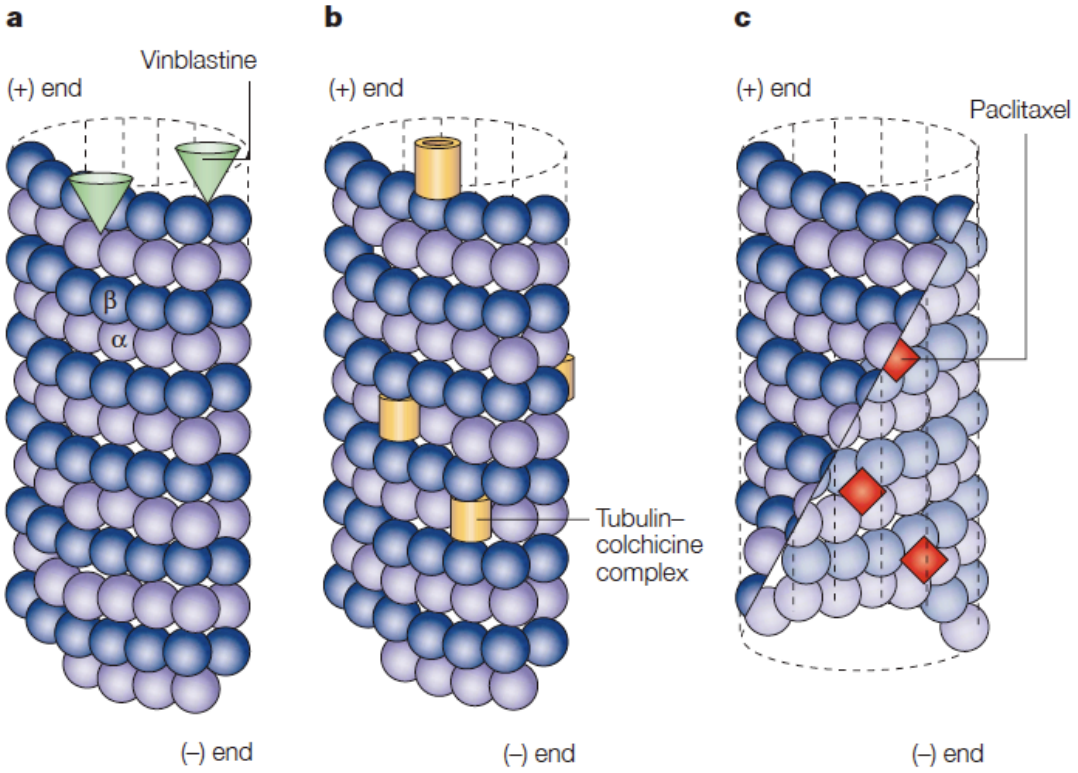


Figure 3. Antimitotic drugs bind to microtubules at diverse sites.

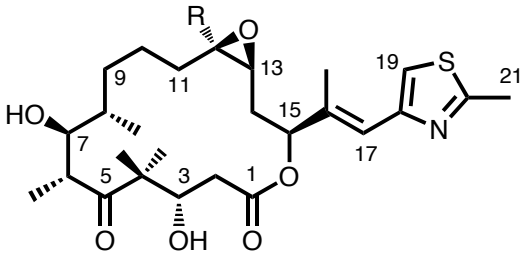
sess microtubule-stabilizing activity by Peter Schiff and Susan Band Horwitz in 1979.[14] Even then, its development for clinical use was impeded by limited supplies of the natural compound until procedures for its semi-synthesis made its production feasible from a precursor isolated from the needles of the European yew Taxus baccata.[15] By 1992, it was approved for clinical use and it is now widely used to treat breast, ovarian, prostate and non-small-cell lung cancer, as well as Kaposi's sarcoma. Docetaxel[6] is more water-soluble than paclitaxel, and is also more active than paclitaxel against cancer cell proliferation.[16] It is now used clinically for the treatment of breast, prostate and non-small-cell lung cancer. However, its clinical success has been accompanied by significant side effects and primary as well as acquired (secondary) resistance. The principal side effects include neurotoxicity and myelosuppression.[17] The mechanism of resistance to taxanes is not fully understood and, as with many other agents, is likely to be multifactional. It could include the presence of β-mutations, high microtubule-associated protein tau expression and their recognition of cellular efflux mechanism, such as the P-glycoprotein, which contributes to the loss of activity in cells overexpressing the multidrug-resistance (MDR) phenotype.[18]

1.1.2 Epothilones: New Age for Anti-Cancer Drugs Targeting Microtubules

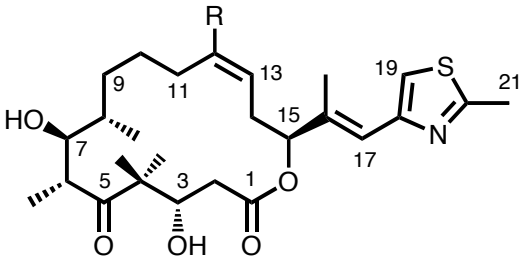
The successful development of the taxane class of antimicrotubule chemotherapy agents as effective anticancer drug arguably represents one of

the milestones in the history of cancer chemotherapy.[19] This success is strongly attributed to the assessment that tubulin is one of the best clinically validated targets in therapy. However, it took 16 years after the elucidation of taxol's mode of action in 1979[14] until other compounds acting through a similar mechanism were identified by Bollag et al. at Merck Research Laboratories.[20] This marks the commencement of the age of epothilones as potential anti-cancer microtubule targeting drugs.[21]

Epothilone A (EpoA, **11**) and B (EpoB, **12**) (Figure 4) were originally isolated and characterized by Höfle, Reichenbach and coworkers at the "Gesellschaft für Biotechnologische Forschung" (GBF) in Braunschweig, Germany from the cellulose-degrading myxobacterium strain Sorangium celluosum Soce 90 in a screen for new antifungal agents.[22] The compounds were named "epothilones" by Reichenbach and Höfle to reflect their basic structural features, including an epoxide moiety, a thiazole-containing side chain, and a single ketone function. Although EpoA and EpoB were the major products isolated from myxobacterium,



11: R=H, Epothilone A
12: R=Me, Epothilone B



13: R=H, Epothilone C
14: R=Me, Epothilone D

Figure 4. Molecular structures of epothilones A, B, C and D.

numerous other related structures of the epothilone class have been identified as minor components of the fermentation of myxobacteria, including, for example, epothilone C (EpoC, **13**) and D (EpoD, **14**).[23-26]

EpoA and EpoB were recognized shortly after their initial isolation to be potent inhibitors against breast and colon cancer cells.[21b] However, their mechanism of action had not been explored until their discovery by Bollag and his colleagues from Merck in 1995.[20] Further in-depth profiling by the Merck group as well as by Hamel and co-workers[27] confirmed that both EpoA and EpoB exhibit potent anticancer properties by inducing tubulin polymerization *in vitro* and stabilizing microtubules under normally destabilizing conditions which is similar to taxol. It is believed that the microtubule binding sites of paclitaxel and EpoA/B either largely overlap or are identical.[20, 27] For example, competitive experiments have indicated that epothilones are able to displace [^{3}H]-paclitaxel from microtubules with similar or superior efficiencies to that of unlabelled paclitaxel or docetaxel. In addition, kinetic experiments also demonstrated that inhibition of paclitaxel binding by epothilones occurs in a competitive fashion.

While epothilones exert their antiproliferative activity through the same action mechanism as taxol, the two classes of compounds are distinctly different in terms of their potency (Table 1) and ability to inhibit the growth of multidrug-resistant cancer cell lines (Table 2).[21, 27, 28] As illustrated by tubulin polymerizati-

Table 1. Induction of tubulin polymerization by epothilones and taxol.

	EpoA	EpoB	Taxol
Microbutule protein polymerization(% of control)	69	90	49
EC_{50} (microtubule protein) [μM]	1.1	0.7	1.9
EC_{50} (pure protein) [μM]	5.8	1.9	4.6

Table 2. IC_{50} values [nM] for net growth inhibition of human cancer cell lines by epothilone A and B in comparison to taxol (Adapted from ref.21b).

	EpoA	EpoB	Taxol
HCT-116 (colon)	2.51	0.32	2.79
PC3 (prostate)	4.27	0.52	4.77
A549 (lung)	2.67	0.23	3.19
MCF-7 (breast)	1.49	0.18	1.80
MCF-7/MDR[a]	27.5	2.92	9150
KB-31 (epidermoid)	2.1	0.19	2.31
KB-8511[b]	1.0	0.19	533

[a]Multiple resistance mechanism/MDR. [b]P-gp overexpression/MDR

on data shown in Table 1, the epothilones are more potent promoters than taxol with EpoB being the most active. Different from taxol, epothilones have been proven to be very poor substrates for the phosphoglycoprotein 170 (P-gp) efflux pump and thus retains almost full activity against P-gp-overexpressing, taxol-

resistant cell lines (e.g. KB-8511, Table 2). Furthermore, epothilones are also active against cells with tubulin mutations that induce the paclitaxel resistance.[28a] This suggests that epothilone-derived drugs might be useful in treating drug resistant tumors.

In addition to the superior biological properties in comparison to taxanes, epothilones also exhibit more favorable biopharmaceutical profiles. For example, epothilones posses much better water solubility than taxol.[22c] The increased water solubility facilitates the drug formulation, and enables their administration with less problematic clinical vehicles than Cremophor® EL. Due to poor water solubility, taxol is administered as a 6 mg/mL Cremophor® EL/ethanol mixture diluted with normal saline or 5% dextrose in water to the desired final concentration.[29] The large doses Taxol administrated to patients also expose them to large amounts of Cremophor® EL, which is believed to contribute to the drug's clinical side effects such as idiosyncratic histamine release, clinical acute hypersensitivity reactions characterized by dyspnoea, flushing, rash, chest pain, tachycardia, hypotension, angio-oedema, and generalized urticaria.[29, 30]

1.1.3 SAR Studies of Epothilones

These exceptional advantages, combined with the ease of synthesis by comparison with paclitaxel have evoked a vast research effort within academic and pharmaceutical research groups.[21] Numerous total and partial syntheses

have been published since the determination of their absolute stereochemistry in 1996.[31] Pioneering work in the area of epothilone total synthesis was performed by the research groups of Nicolaou,[32-34] Danishefsky,[35, 36] and Schinzer.[37] During the development of these syntheses, many methodologies have arisen that have enabled the development of libraries of synthetic analogs, which have contributed to mapping the extensive structure-activity relationship (SAR) profiles of epothilones and to elucidating the interactions between the ligand and microtubules.[38-40]

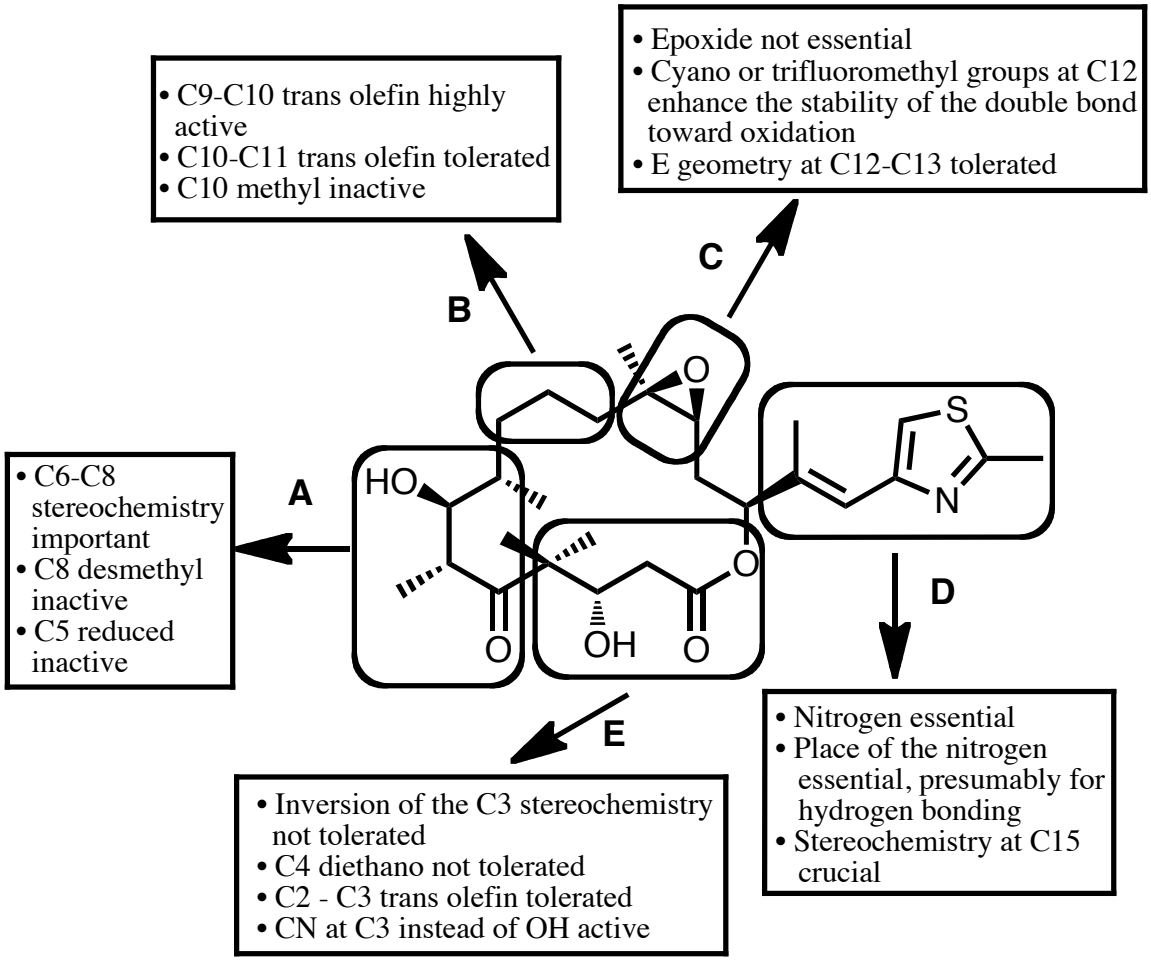


Figure 5. Structure-activity relationships in epothilone.

Region A (C5-C8) is highly sensitive to any modification: epimerization at C8[41] or addition/removal of the methyl group at C8[41] will considerably lower the cytotoxicity. Removal of C6 or C7 substituents or reduction of the ketone at C5 also lead to loss of biological activity. The sensitivity to change of region A suggests that it plays an important role in the binding to the active site.[42]

Region B (C9-C11). The C10-methyl analogue was found to be inactive[43], but hydroxyl[44] and fluoro[45] groups are tolerated at C11. Except in the case of the 18-membered ring analogue of epothilone A (which led to significant tubulin polymerization),[46] change in the ring size results in considerable loss of biological activity.[46] The C10-C11 olefin analogue, also known as epothilone 490 (**15**, Figure 6), gives very promising results in vitro but has disappointing results in vivo, due to the hydrolysis of the lactone.[47] Recently, Danishefsky reported a C9-C10 trans analogue of epothilone D, *trans*-9,10-didehydro-EpoD (**16**, Figure 7), which was nearly three times as active as the parent compound.[48] This can be rationalized by the impact of the trans double bond on the polypropionate region. Following the finding of *trans*-9,10-didehydro-EpoD (**16**, Figure 7), *trans*-9,10-didehydro-26-trifluoro-EpoD (**17**, Fludelone, Figure 6) was discovered by Danishefsky and co-workers,[49] and has shown an excellent pharmacological profile with super in vivo antitumor activity without obvious lethality or irreversible toxicity.

Region C (C12-C14). Both epoxide and olefin analogues are active as well as both epoxide isomers and both possible double bond geometries.[50, 41] However, epothilone A and B (C12-C13 epoxide) are about four to 20 times more active than the corresponding olefinic compounds (epothilone C and D). It was first proposed that an intramolecular hydrogen bond between C3 hydroxyl proton and the epoxide rigidifies the active conformation.[51] However, Nicolaou reported a variety of active cyclopropane (both cis and trans) and cyclobutane analogues (**18**, Figure 6),[52-54] proving rather than acting as a reactive electrophile or hydrogen bond acceptor, the epoxide moiety may simply have a conformational role and serve to stabilize the proper bioactive conformation of the macrolactone ring. This was further confirmed by Regueiro-Ren, who reported a series of active 12α, 13α-aziridinyl epothilone derivatives (**19a-d**, Figure 6).[55] Interestingly, the parent compound **19a** exhibits comparable activity with epothilone A. Substitution of the aziridine nitrogen is well tolerated for a number of diverse groups, several of which lead to significantly improved potency over the parent natural product.[55] Moreover, substituents at C12, particularly methyl, trifluoromethyl[56, 57] or cyano groups[58] significantly enhance the cytotoxicity. Larger substituents, such as ethyl, propyl or hydroxymethyl show reduced activity but the cytotoxicity is not lost.[59] Finally, the C12 cyano substituted analogs are more stable at lower pH, which is a great advantage for the oral dosage.

The side chain (Region D) is very sensitive to modifications. Removal, direct

attachment of the aromatic moiety at C15, or replacement of the methyl group at C20 with bulkier substituents, results in the loss of cytotoxicity. Furthermore, the replacement of the C16 methyl group with an ethyl group, and replacement of the thiazole ring turned out to have negative effects. However, 4- or 5-methylpyridine and related derivatives, where the nitrogen is on the same position as in the natural compound, give even better results than the original 2-methylthiazole analogues.[60] In particular, a methylsulfanyl replacement for the methyl group on the thiazole moiety (**20**, Figure 7) enhances the potency.[61, 53] Recently, Nicolaou[52] reported a 12, 13-*cis*-cyclopropane methylsulfanyl analogue of epothilone B (**21**, Figure 6), that is six times more active than epoB

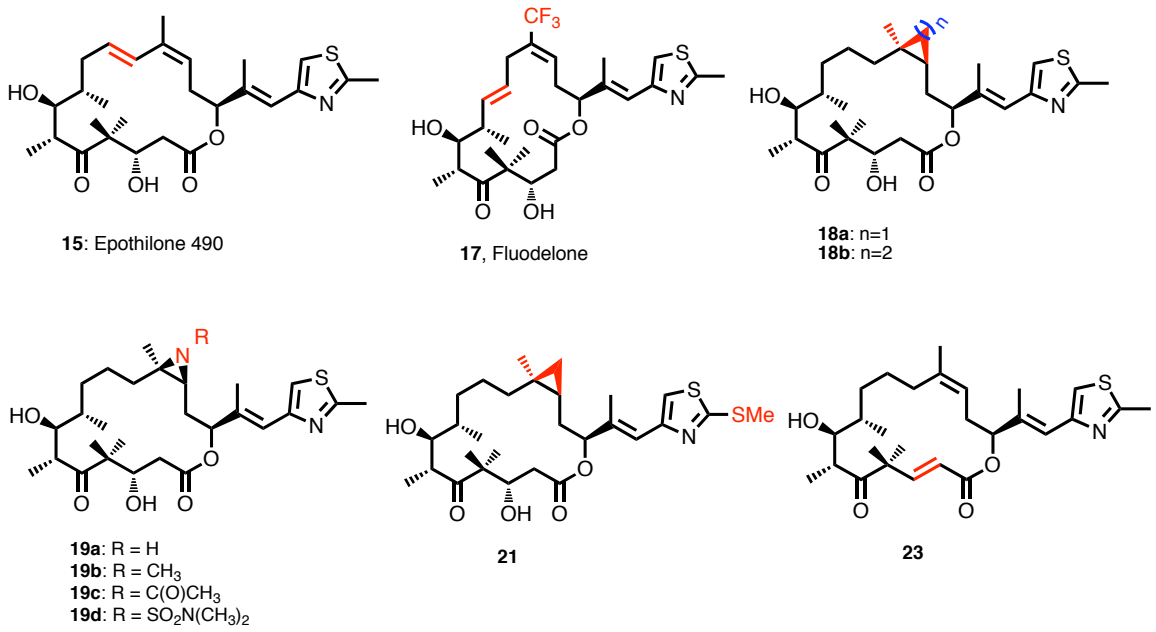


Figure 6. Molecular structures of selected epothilone analogs.

against the 1A9 ovarian carcinoma cells. The rigidification of the entire side chain scaffold has led to the discovery of compound ZK-Epo (**22**, Figure 7) from the Novartis research group which is currently being studied in advanced clinical trial.[62] Finally, change of the C15 stereochemistry leads to loss of the biological activity.[54]

Region E (O16-C4) hardly tolerates any changes. Indeed, inversion of the C3 stereochemistry[41] or substitution of the gem dimethyl group at C4 by a cyclopropane[63] both resulted in significant loss of activity. It has been proposed that a hydrogen bond between the C3 hydroxyl and C1 ketone plays an important role from a conformational point of view.[64] However, the presence of an *trans*-3-deoxy-2,3-dihehydro derivatives at C2-C3 (**23**, Figure 6), which is believed to rigidify the C1-C3 backbone, retain most of the activity of the parent natural products.[58] Moreover, when the C3 hydroxyl is replaced by a cyano group,[58] the analogue is active in both tubulin polymerization and cytotoxicity assays. Thus, the hydrogen bond, if present, is not crucial for cytotoxicity. Lactam analogues usually have clearly inferior tubulin polymerizing and cytotoxic potencies than the corresponding lactone. One of the most important achievements from the modifications around region E is the discovery of Ixabepilone® (**24**, **BMS-247550**, Figure 7) which not only maintains the high biological activity of EpoB, but also is reported to overcome the limited stability of EpoB in rodent plasma.[65] More recently, Ixabepilone® has been approved by the FDA for clinical use in treating

advanced breast cancer in humans.[21d]

The tremendous efforts involved in the SAR studies of epothilones have greatly aided in our understanding of the pharmacophore of the epothilones, and in developing natural/unnatural analogs with improved biological activity and reduced toxicity. However, more importantly, these efforts have delivered at least seven compounds in advanced clinical trials (Figure 7), one of which has recently been approved by FDA as anti-cancer drug (**24**, Ixabepilone®). Additionally, it is worth mentioning that ZK-Epo is reported to be the first fully synthetic epothilone analogue to have entered clinical studies, while others are produced by biosynthesis or partial synthesis.[62]

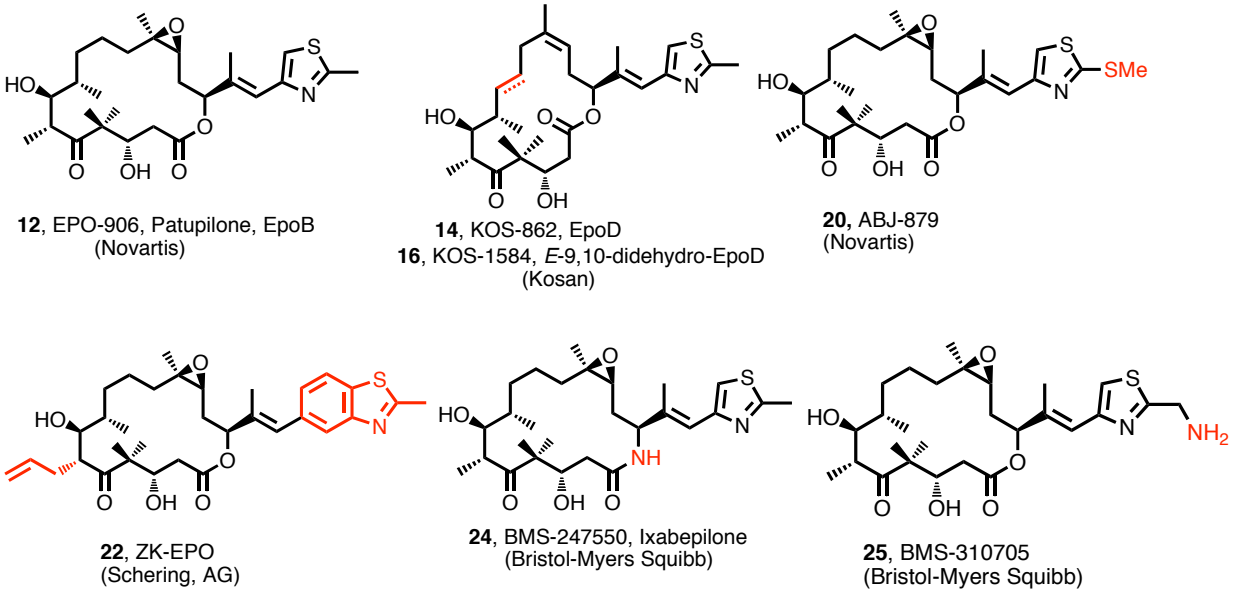


Figure 7. Molecular structures of epothilones in clinic trials.

1.1.4 Bioactive Conformation of Epothilones

A detailed understanding of the functional mechanism for the interaction of epothilones with αβ-tubulin would allow for the structural-based design of pharmacologically optimized compounds acting on the tubulin polymerization equilibrium. Whereas the crystal structure of free epothilone B is known,[22c] its bioactive conformation is still a topic of debate.[66] Since the discovery of the microtubule-stabilizing properties of epothilones in 1995, efforts have been exerted to describe a common pharmacophore for the structurally diverse taxanes and epothilones in order to facilitate the rational design of improved and perhaps structurally simplified analogs. [51, 64, 67, 68]

A variety of epothilone conformations and binding modes on tubulin have been proposed by pharmacophore mapping,[51, 64] solution NMR,[43, 69] and the superposition of epothilones on taxanes in the electron crystallographic tubulin complex.[67, 68] All these attempts for the binding mode are generally based on an assumption of a common tubulin binding site between epothilones and taxanes,[20, 27] and the macrocyclic epothilone ring occupies a common space with the baccatin core of Taxol, whereas the thiazole side chain superposes one of its three phenyl rings. For example, Giannakakou and co-workers[68] developed a model placing the epoxide oxygen atom of epothilones where the oxetane oxygen in taxol occupied in the binding pocket, while the epothilone side chain is located in the same region as either the C3'-phenyl group or the C2-benzoyloxyl

moiety of taxol. Wang[51] proposed the C3'-phenyl and Ojima[64] proposed the C3'-benzoyloxyl phenyl as coincident with the thiazole ring from epothilones.

The first experimental study of the bioactive conformation of epothilones was conducted by solution-state NMR for epothilone A (EpoA, which lacks the methyl group at C12) bound to nonpolymerized αβ-tubulin. [69] This bioactive conformation unraveled by Carlomagno et al. using transferred nuclear Overhauser enhancement (trNOE) [70] and transferred cross-correlated relaxation (trCCR) [71, 72] methods is consistent with some of the SAR data described in the

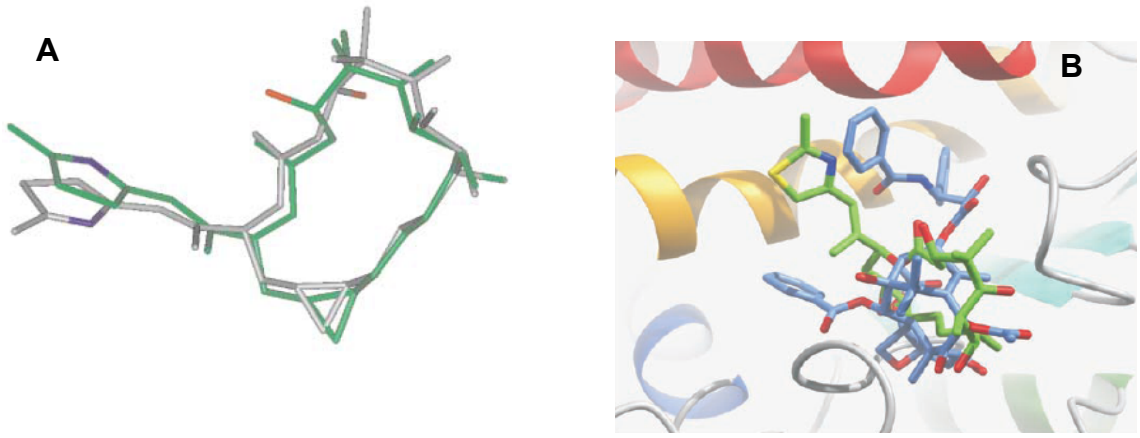


Figure 8. (A) Comparison of NMR-derived tubulin-bound conformation of EpoA (green) in aqueuous solution with X-ray crystal structure of EpoA (gray). (B) Superposition of NMR-derived EpoA (rods; C green, N blue, O red, S yellow) binding mode and EC-derived PTX (rods; C light blue, N blue, O red) binding mode to β-tubulin.

previous section. The binding mode of EpoA based on this NMR-determined bioactive conformation was derived using a combination of the interligand NOE for pharmacophore mapping (INPHARMA) methodology[73] and molecular modeling. Most importantly, the NMR-derived binding mode of EpoA to nonpolymerized αβ-tubulin partially resembles the EC-derived binding mode of PTX[74] to polymerized tubulin (Figure 8B), reviving the idea of a common pharmacophor for taxanes and epothilones.

Combining NMR spectroscopy, electron crystallography, and molecular modeling, an alternative model has been proposed by Nettles et al.[75] that contradicts the common pharmacophore models by referring to the tubulin binding cavity as promiscuous (Figure 9). According to the Nettles model,[75] epothilone and taxol occupy the same gross binding pocket, and the actual binding is mediated through different sets of hydrogen bonding and hydrophobic interactions for the two compounds. The obtained electron crystallographic structure of epothilone was superimposed with that of taxol bound to tubulin. The superimposition showed that the thiazole moiety of epothilone A and the benzoyloxyl phenyl of taxol did not reside in the same region of the tubulin pocket. Among the five oxygen-containing polar groups on epothilone, only C7-OH falls near the similar C7-OH moiety in taxol. This is the only common center between the two molecules. The EC binding complex accommodates both the broad-based epothilone structure-activity relationship and the known mutational

resistance profile. [75]

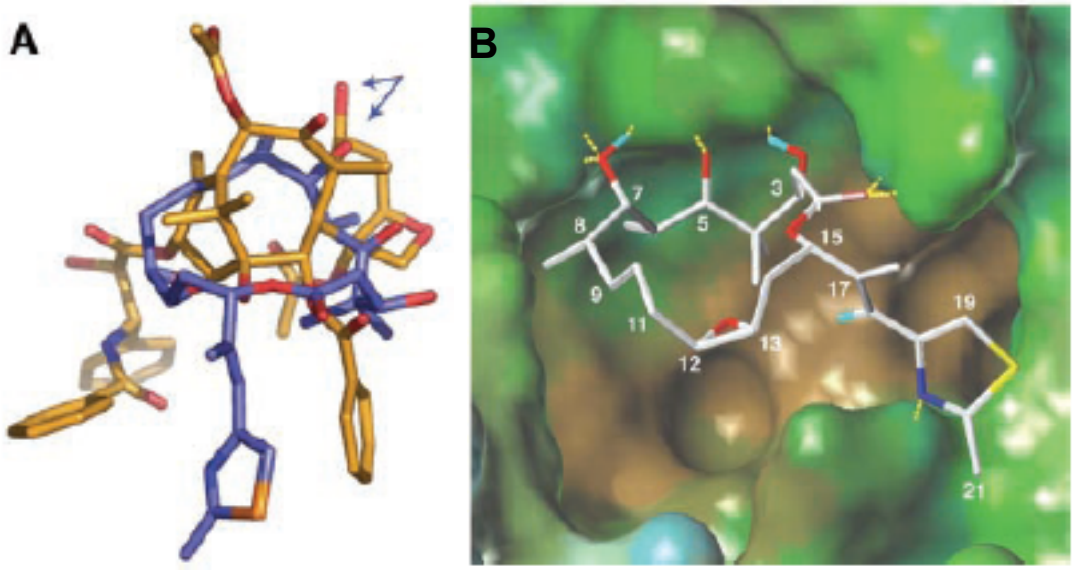


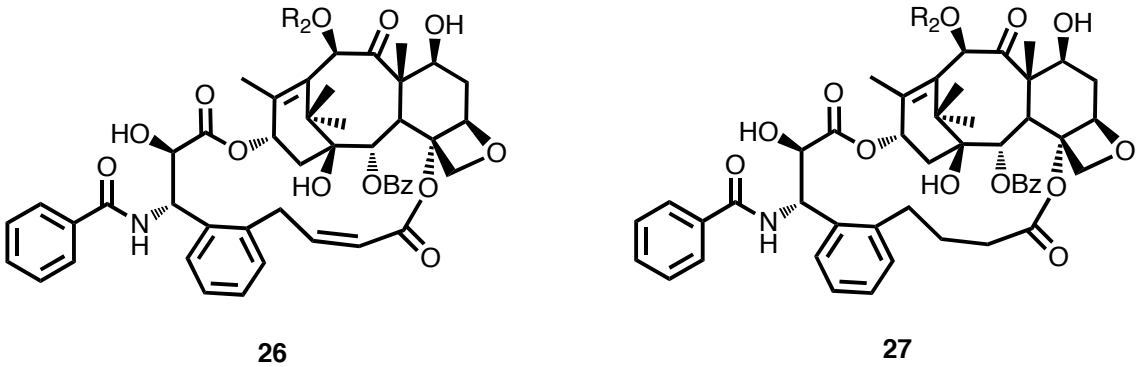
Figure 9. (A) Superposition of EpoA (blue) and T-Taxol (gold) in β-tubulin as determined by EC. (B) Hydrophobic to hydrophilic properties at binging site (white, EpoA). (Adapted from ref. 75)

1.2. Design and Synthesis of C4-C9 Bridged Epothilones

1.2.1 Design Rationale

Design and synthesis of conformationally constrained analogs has been very successful in deriving experimental evidence for the T-Taxol binding conformation of taxol in tubulin binding site.[76] Among these efforts, ortho-bridged compound **26** synthesized by ring-closing metathesis strategy and its bridge-saturated analog **27** turned out to be up to 20 fold more potent than taxol in both

A2780 ovarian cancer and PC-3 prostate cancer cell lines.[76b]



26 **27**

Figure 10. Molecular structures of two bridged taxol analogs.

Ever since the proposal of the EC binding mode of epothilone,[75] a handful of conformationally constrained epothilone analogs have been designed and synthesized to test the EC binding conformation. As shown in Figure 11, a variety of C4-C12 bridged EpoD analogs have been synthesized by Chen and Ganesh using ring-closing metathesis strategy.[77] Unfortunately, cell-based activities of these analogs were significantly less than that of EpoD.[77a] It is worth noting, however, that formation of a five-membered lactone between C3-OH and C4-allyl catalyzed by Grubbs' catalyst during the synthesis of these bridged analogs led to equipotent compounds compared to EpoD and EpoB.[77b]

A peculiar feature of the proposed EC binding conformation is the presence of a *syn*-pentane interaction between methyl groups at C-6 and C-8[75] that can be locked in place by incorporating the corresponding carbons in a 6-membered ring. To test these specific geometric details of the epothilone conformation in the

C6-C8 sector, a C6-C8 EpoA analog has been synthesized by Zhan.[78] Unfortunately, the target compound possessed a rather low potency compared to EpoA.[78]

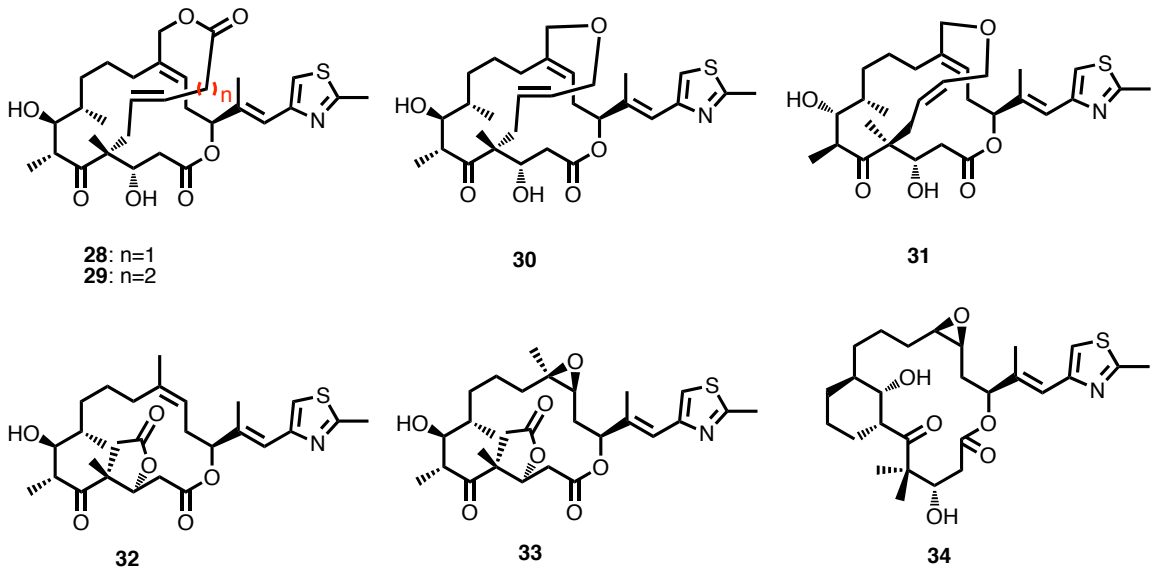


Figure 11. Molecular structures of selected synthesized bridged epothilone analogs.

As part of our continuous effort to delineate the binding conformation of epothilone, design and synthesis of bridged epothilone analogs remains of great interest. Careful examination of the EC binding model (Fig 12A) revealed that the 16-membered ring in the epothilone EC structure is suspended above the spacious hydrophobic basin while forming key hydrogen bonding interactions with residues Gln229, Arg282, Thr274, Arg276 and His227.[75] The hydrophobic cavity in the unliganded protein is most certainly filled with water molecules that are either displaced or reorganized upon binding of the ligands, but

unobservable at ~3 Å resolution. Therefore, building a bridge underneath the 16-membered ring would be not only possible but would likely result in a favorable entropy contribution to the binding of bridged analogs.

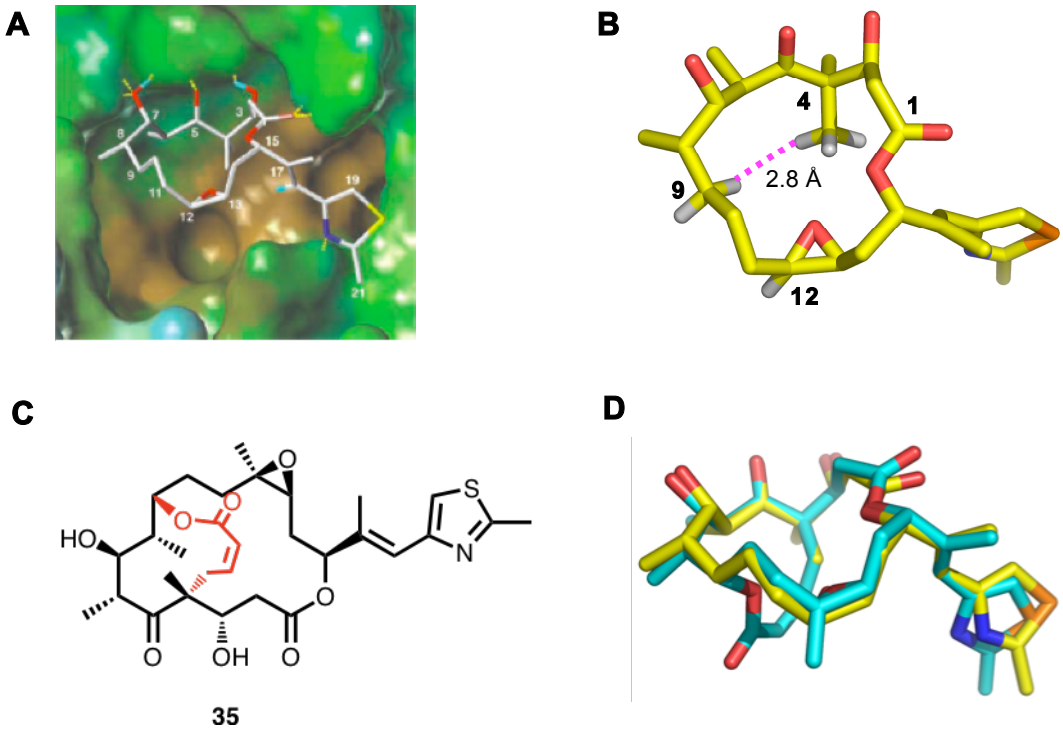


Figure 12. (A) Electron crystallographic binding model of EpoA in tubulin binding site. (B) EC binding pose of EpoA. (C) Molecular structure of bridged EpoB analog **35**. (D) Superimposition of EC binding pose of EpoA (yellow) and MMFF/GBSA/H_2O optimized bridged EpoB analog **35** (cyan).

A top view of the binding pose of EpoA as shown in Fig 12B disclosed that C-4 methyl group offers a nice opportunity to builde a bridge underneath the macrolactone ring in terms of both its inward orientation and close proximity to

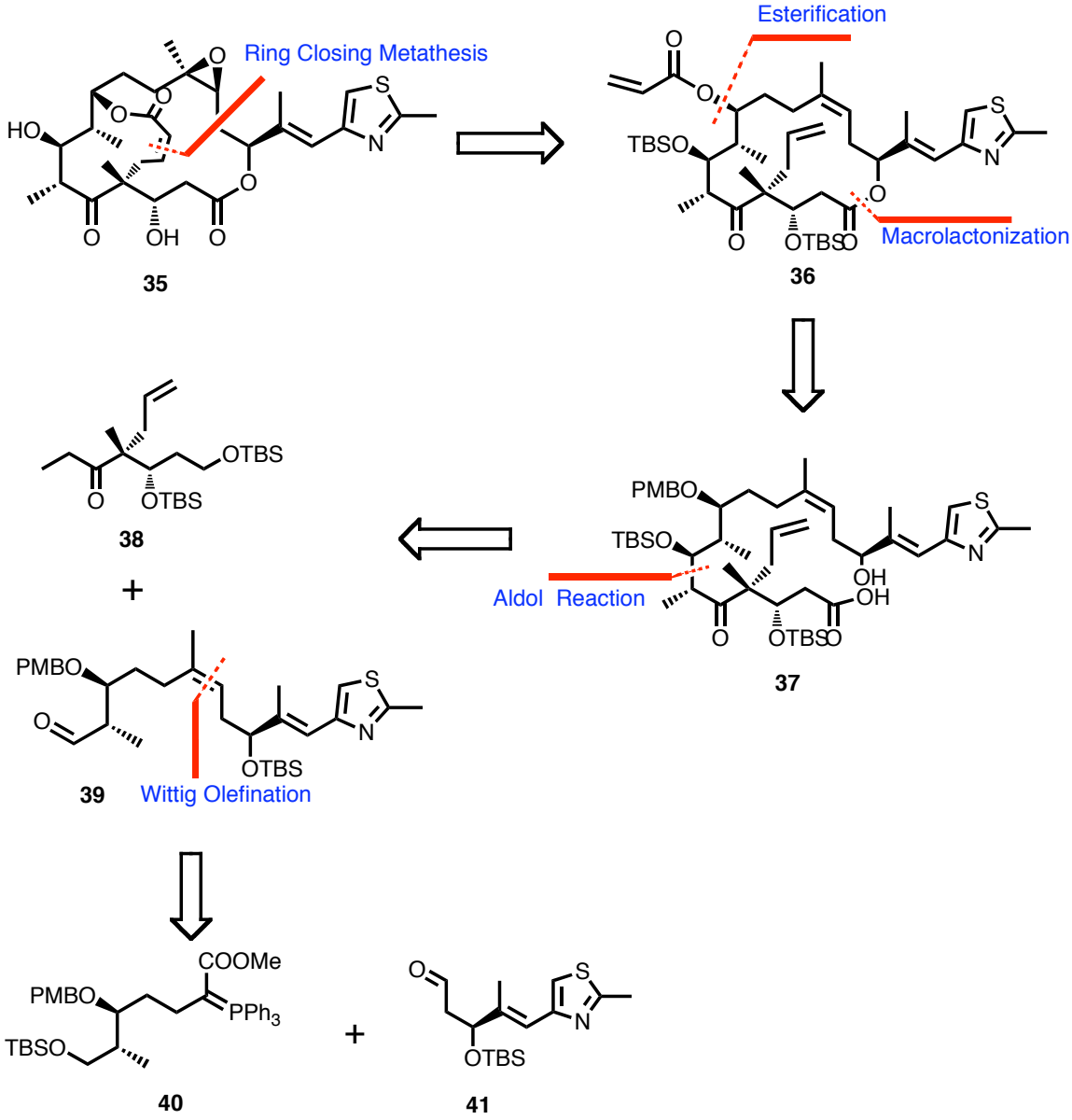
the other side of the ring. The distance between one hydrogen atom of C-4 methyl group and the hydrogen of C-9 methylene unit is 2.8 Å. Based on the above analysis, EpoB analog **35** (Fig 12C) with an α,β-unsaturated lactone bridge connecting C-9 and the C-4 methyl group was designed with the binding conformation of EpoA as a template. As shown in Fig 12D, optimization of bridged analog **35** with MMFF/GBSA/H_2O suggests that the C4-C9 bridged EpoB analog can adopt the proposed EC conformation as a local minimum.

1.2.2 First Generation Synthesis via Ring Closure Metathesis

Scheme 1 outlines the ring closing metathesis and macrolactonization based retrosynthetic analysis of bridged epothilone analog **35**. Thus, ring closing metathesis of diene **36** will furnish the final bridged epothilone analog **35**. The second major retrosynthetic step along the route is the disconnection of the macrocyclic ring at the lactone site, leading to hydroxy acid **37** as an advanced intermediate. Moving further along the retrosynthetic path, an aldol-type disconnection allows the generation of ketone **38** whose synthesis has been developed by Chen et al.[77a] for synthesis of bridged epothilone D analogs. The disconnection of the larger intermediate **39** involves a retro-Wittig type reaction, leading to a stabilized ylide **40** and aldehyde **41** whose synthesis has been reported by Nicolaou et al.[79]

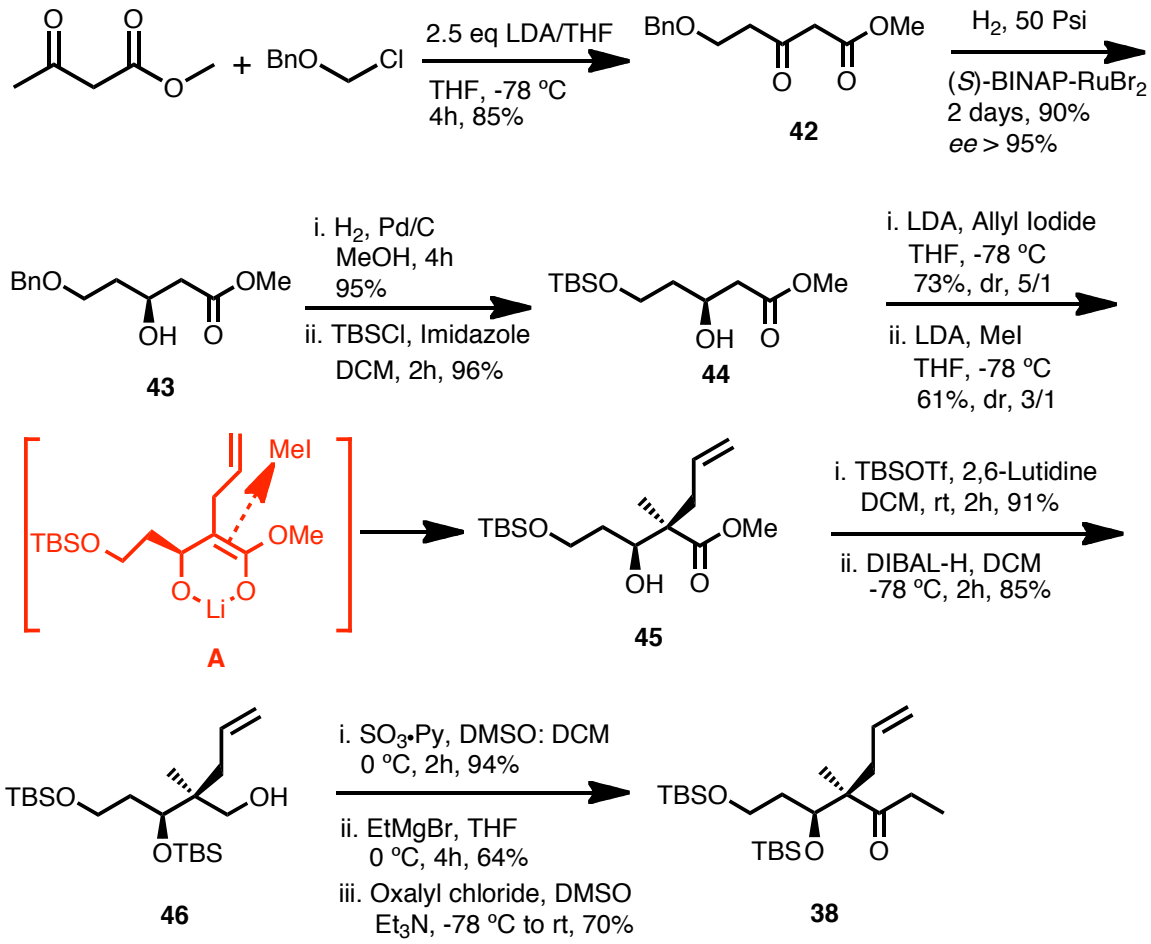
As shown in Scheme 2, the synthesis of **38** starts with commercially available methyl acetoacetate and benzyl chloromethyl ether. Treatment of methyl acetoacetate with LDA generated a dianion that reacted with benzyl chloromethyl ether to produce β-keto ester **42** which was subjected to Noyori asymmetric reduction[80] of the ketone to provide β-hydroxyl ester **43** in 80% yie-

Scheme 1. Initial Retrosynthetic Approach to Bridged Epothilone Analog **35**.



ld for the two steps. Removal of benzyl protecting group by hydrogenation provided a diol that was then treated with TBSCl and imidazole to selectively give the primary silyl ether **44** in 90% overall yield. Compound **44** was sequentially treated with LDA and allyl iodide to provide an allyl derivative in moderate yield and excellent diastereoselectivity, which was subjected to LDA and iodomethane to provide **45** as the major diastereomer in 61% yield (*dr.* 3:1). The above transformation presumably proceeded via transition state A depicted in scheme 2. Protection of the secondary alcohol in **45** as silyl ether followed by reduction

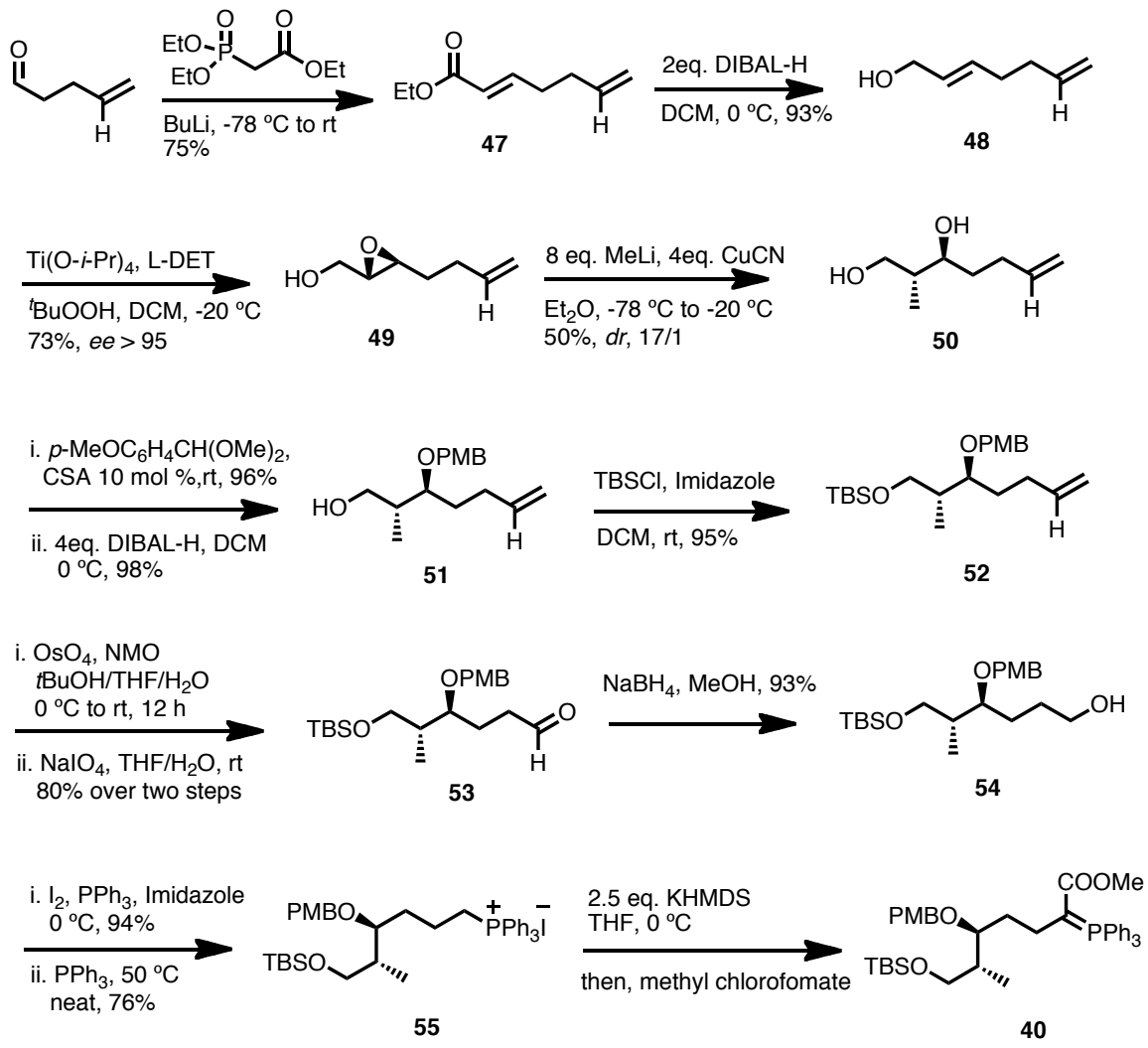
Scheme 2. Synthesis of ketone **38**.



of the methyl ester with DIBAL-H afforded a primary alchol **46** in 77% yield for the two steps. Subsequent Parick-Doring oxidation of the primary alcohol produced an aldehyde that was subjected to Grignard addition to afford a mixture of two diastereomeric secondary alcohols (*dr.* 9:1). Finally, without separation, the two diastereomers were subjected to Swern oxidation to deliver the desired ketone **38** in *ca.* 40% overall yield for the last three steps.

As shown in Scheme 3, synthesis of ylide **40** commenced with the commercially available 4-pentenal. Horner-Wadsworth-Emmons reaction[81] of the volatile 4-pentenal generated the α,β-unsaturated ester **47** that was subsequently reduced to the allylic alcohol **48** using DIBAL-H in 83% overall yield. Exposure of allylic alcohol to the Sharpless asymmetric epoxidation[82] condition produced the epoxy alcohol **49** in 73% yield with excellent enantioselectivity (*ee* > 95%) as determined by Mosher ester analysis. Opening of the epoxide with *in situ* generated Me_2CuLi gave rise to a mixture of the desired 1,3-diol and its regioisomer, the 1,2-diol in ca 3:2 ratio as determined by ^1H NMR of the crude mixture. Exposure of the crude mixture of diols with aqueous $NaIO_4$ in THF followed by chromatography delivered the desired 1,3- diol **50** in 50% overall yield and excellent diastereoselectivity. Treatment of diol **50** with *p*-anisaldehyde dimethyl acetal catalyzed by CSA gave rise to a PMP ketal that was cleaved by excessive DIBAL-H to selectively afford the primary alcohol **51** in excellent yield.

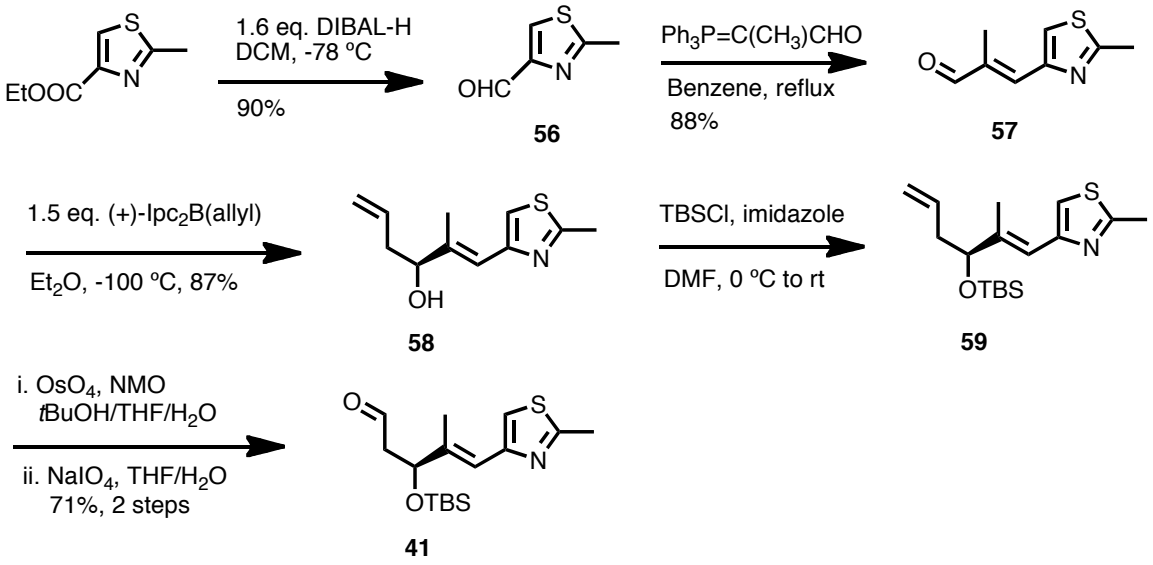
Scheme 3. Synthesis of ylide **40**.



Protection of the primary alcohol with TBSCl provided the silyl ether **52** in 95% yield. Dihydroxylation of the terminal alkene mediated by OsO_4/NMO system followed by oxidative cleavage of the resulting 1,2-diol by aqueous $NaIO_4$ in THF generated the aldehyde **53** in 80% overall yield. Reduction of the aldehyde using sodium borohydride led to the primary alcohol **54** in 93% yield. Iodination of **54** under Mitsunobu condition provide an iodide that upon heating with triphenylphosphine in neat at 50 ºC gave rise to the phosphonium salt **55** in 71%

yield for two steps. Treatment of the phosphonium salt **55** with KHMDS followed by subsequent addition of methyl chloroformate at 0 ºC, after workup, furnished the desire ylide **40** without chromatography.

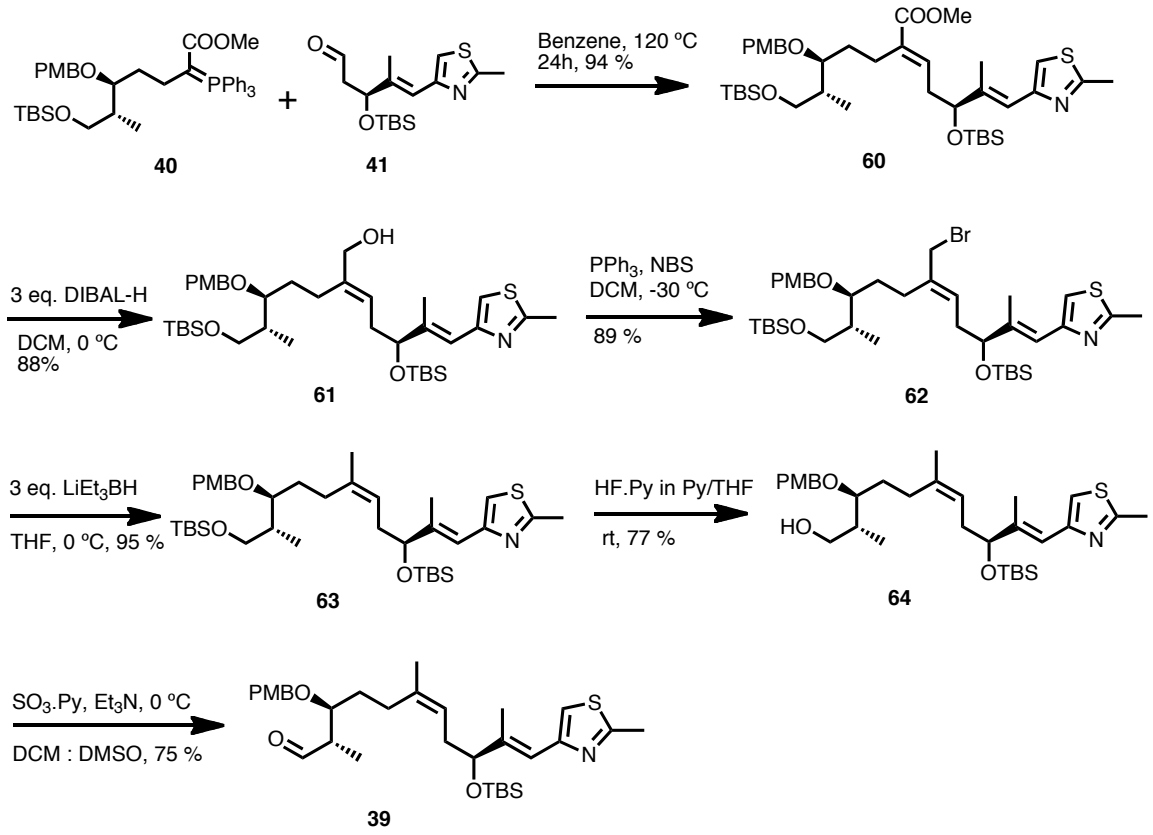
Scheme 4. Synthesis of aldehyde **41**.



The synthesis of thiazole-containing aldehyde **41** was accomplished as shown in Scheme 4. Reduction of the commercially available thiazole ester with DIBAL-H at -78°C provide the aldehyde **56**. Aldehyde **56** was then subjected to Wittig olefination with the stabilized ylide [Ph_3P=C(Me)CHO] in refluxing benzene to afford the required (E)-α,β-unsaturated aldehyde **57**. Addition of (+)-Ipc_2B(allyl) prepared from (-)-Ipc_2BCl and allylmagnesium bromide [83] to **57** at -100°C gave allylic alcohol **58** in 83% yield and excellent enantioselectively. Protection of the resulting second alcohol in **58** led to a silyl ether **59** that was converted to the desired aldehyde **41** through a two-step sequence involving chemoselective

dihydroxylation mediated by OsO_4/NMO followed by oxidative cleavage of the resulting diol with aqueous $NaIO_4$.

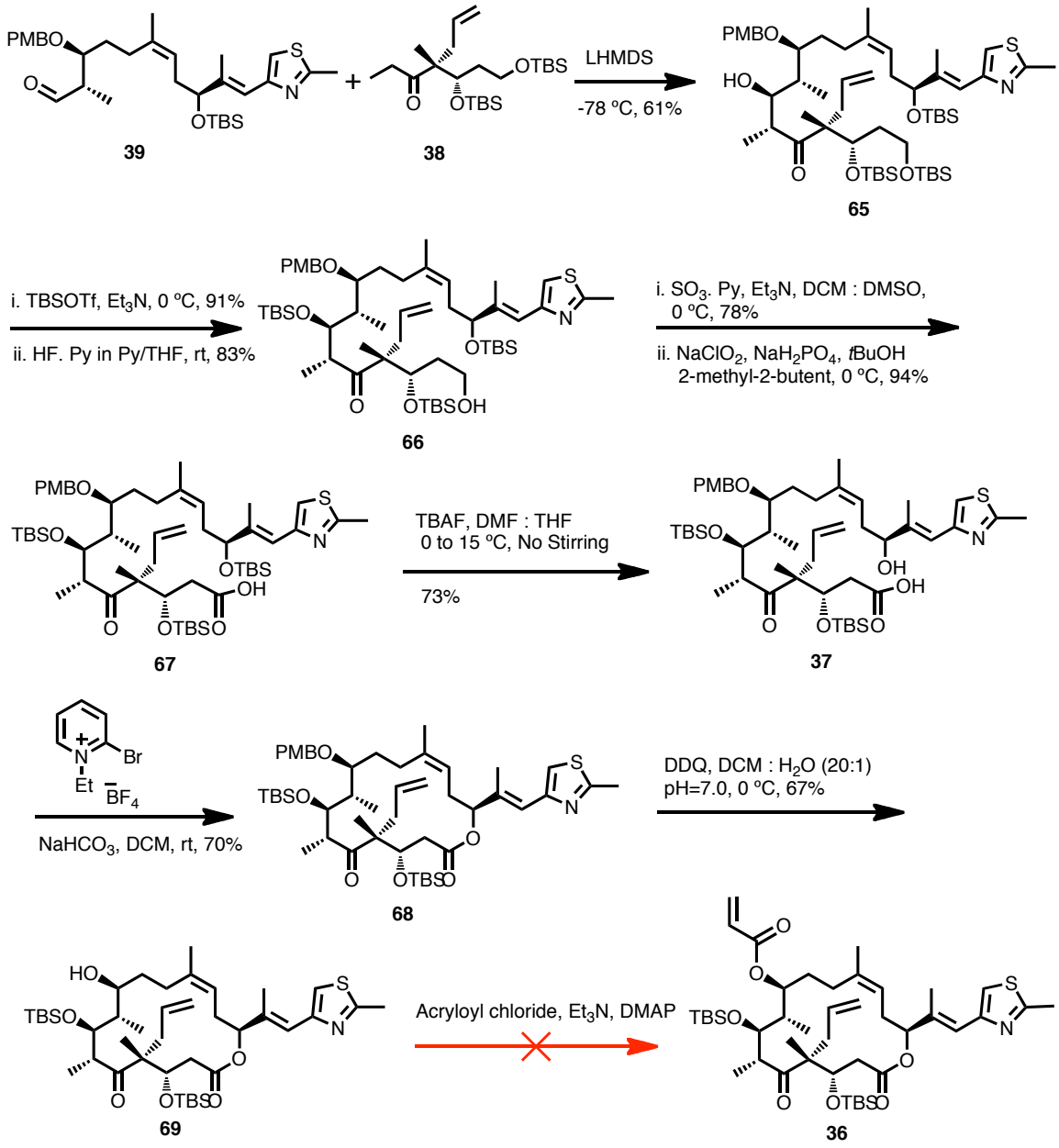
Scheme 5. Synthesis of aldehyde **39**.



With stabilized ylide **40** and aldehyde **41** in hands, Wittig olefination of **40** and **41** proceeded smoothly to give the α,β-unsaturated methyl ester **60** in 94% yield (Scheme 5). Reduction of the α,β-unsaturated methyl ester **60** provided an allylic alcohol **61** which was subjected to PPh_3/NBS condition to generate a bromide **62** in 76% yield for the two steps. Reductive removal of bromine with super hydride (lithium triethylborohydride) afforded **63** in 95% yield. Selective desilylation[84] of **63** with hydrogen fluoride pyridine complex buffered with

pyridine produced a primary alcohol **64** that was oxidized to the desired aldehyde **39** using Parick-Doring oxidation[85] condition in 57% yield for the last two steps.

Scheme 6. Synthesis towards the designed target molecule.



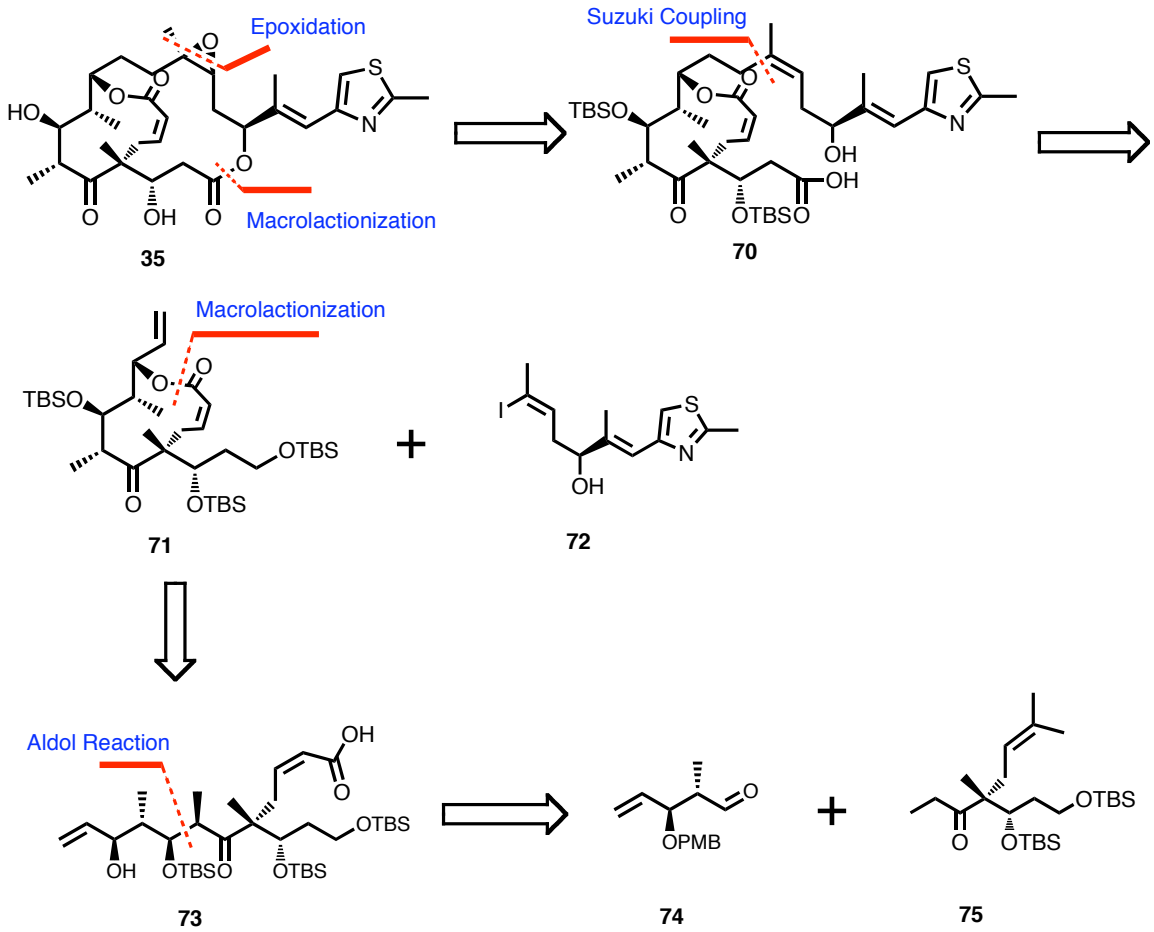
With aldehyde **39** and ketone **38** in hands, we embarked on elaboration towards the designed target as shown in Scheme 6. Treatment of ketone **38** with LHMDS generated an enolate that underwent aldol reaction with the aldehyde partner **39** very rapidly (within 5 min) to provide the aldol adduct **65** as a single diastereomer, albeit in moderate yield (61%). Prolonged reaction time led to very poor yield presumably due to the retro-aldol reaction. The diastereoselectively of this double stereodifferentiating *syn* aldol reaction will be discussed in a later chapter. The resulting aldol adduct was immediately protected as a tetrakis-TBS ether in 90% yield. Selective desilylation of the tetrakis-TBS ether[84] gave rise to the primary alcohol **66** in 83% yield. Subsequent Parick-Doring oxidation[85] of the primary alcohol afforded an aldehyde that was further oxidized up to acid using Pinnick oxidation[86] condition to provide the acid **67** in 73% yield over the two steps. Exposure of **67** to TBAF in THF or DMF selectively deprotected the allylic TBS ether and led to the hydroxy acid **37**, setting the stage for the macrolactonization. Initial attempt to cyclize the 16-membered macrolatone ring using Yamaguchi condition[87] proceeded in only 30-40% yield. Gratifyingly, treatment of **37** with the modified Mukaiyama salt[88] and $NaHCO_3$ in dichloromethane provided the desired macrolatone **68** in 70% yield. Deprotection of the PMB ether with DDQ provided the secondary alcohol **69** in 67% yield. Exposure of **69** to acryloyl chloride and triethylamine in the presence of a catalytic amount of DMAP, however, didn't lead to formation of any of the desired acrylate. Esterification of the C-9 OH using acrylic acid/DCC/DMAP and other

esterifcation conditions failed to give the desired acrylate. The steric congestion of the C-9 OH might be responsible for the infeasibility of the esterification step.

1.2.3 Second Generation Synthesis via Suzuki coupling

In light of the failure of the first generation synthesis, the second-generation synthesis was devised with the idea of reversing the order of the two ring-closure events, that is, furnishing the α,β-unsaturated marcolactone bridge prior

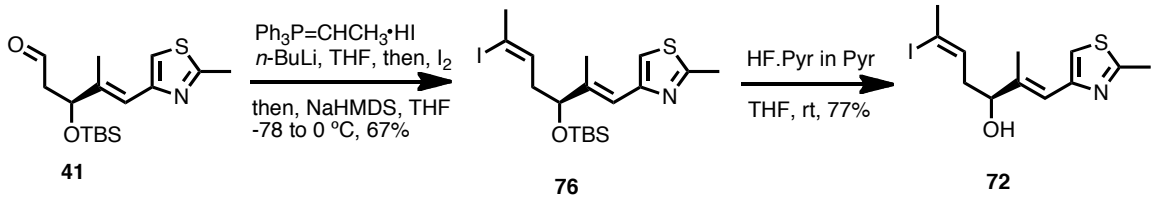
Scheme 7. Revised Retrosynthetic Approach to Bridged Epothilone Analog **35**.



to the cyclization of the 16-membered macrolactone ring. In doing so, Suzuki coupling and double marcolactonization strategy were employed as key steps in the second-generation synthesis.

The second-generation retrosynthetic approach is summarized in Scheme 7. Disconnection of the epoxide and 16-membered macrolactone leads to the hydroxy acid intermediate **70** which is envisioned to arise from *B*-alkyl Suzuki coupling[89] of the alkenyl macrolactone **71** and the vinyl iodide **72** followed by adjustment of oxidation state. The alkenyl macrolactone **71** is conceived to derive from the acyclic alkenyl hydroxy acid intermediate **73** via macrolactonization. Finally, retro-aldol type disconnection of **73** produces the aldehyde **74** and the ketone **75**.

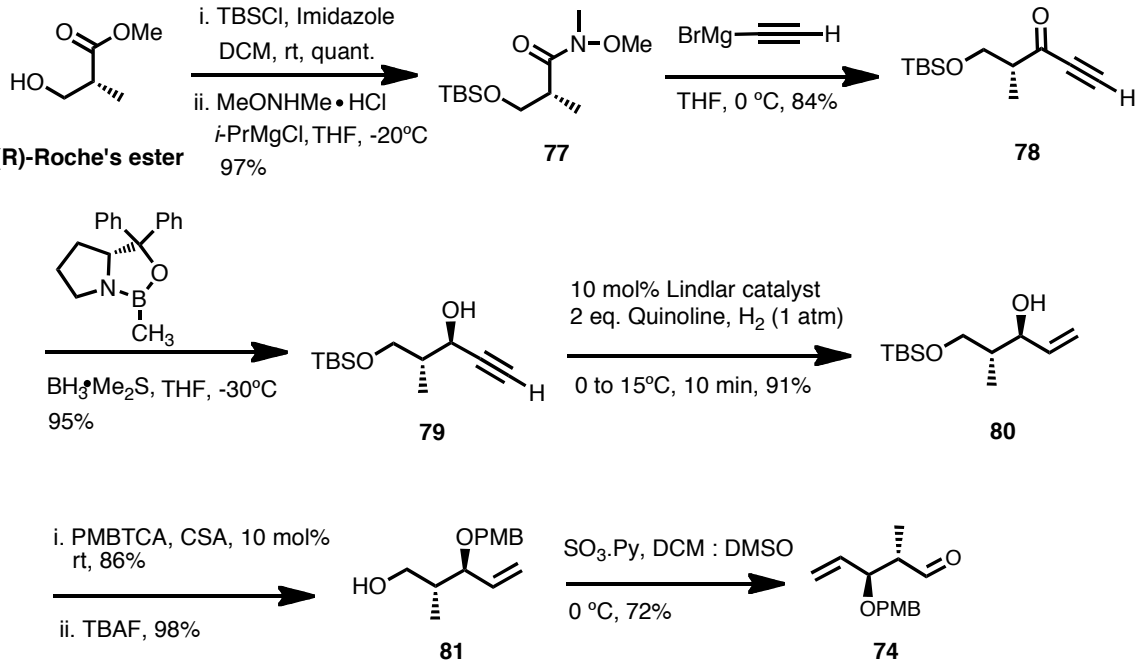
Scheme 8. Synthesis of the vinyl iodide **72**.



As shown in Scheme 8, the known vinyl iodide **76** has been reported in literature to be generated from the aldehyde **40** via the one-step Stork-Zhao olefination.[90] Thus, following the procedure described in literature, the vinyl iodide **76** was obtained in 67% yield. Deprotection of the TBS ether in **76** with hydrogen fluoride pyridine complex produced the desired vinyl iodide **72**.

As shown in Scheme 9, synthesis of the aldehyde **74** commenced with commercially available (*R*)-Roche's ester. Protection of the (*R*)-Roche's ester as its *tert*-butyldimethylsilyl ether followed by formation of Weinreb amide using a procedure developed by Merck (*i*PrMgCl, THF, -20 °C) gave the desired amide **77**.[91] Formation of propargyl ketone **78** occurred smoothly by treatment of the Weinreb amide **77** with ethynylmagnesium bromide at 0 °C in 84 % yield. Asym-

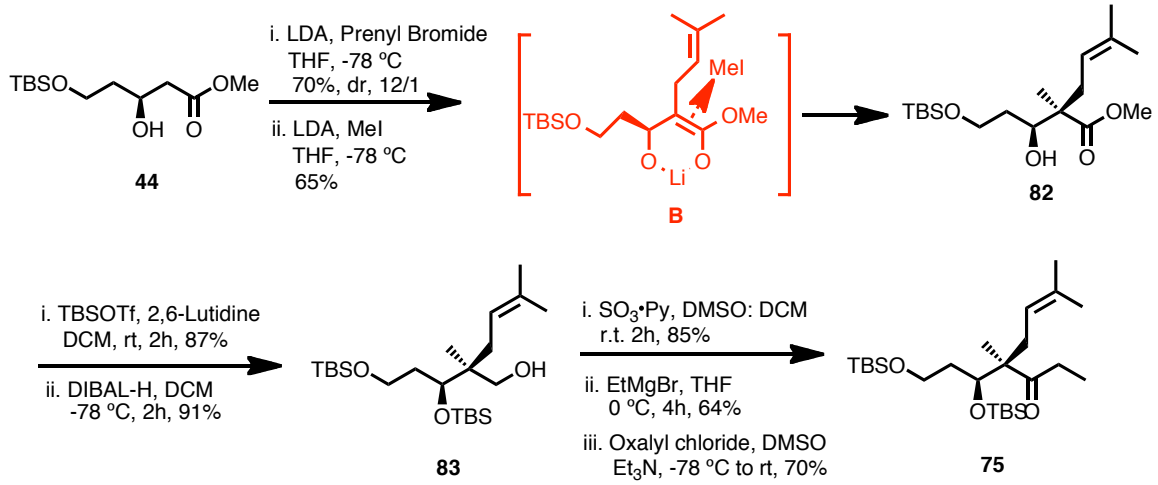
Scheme 9. Synthesis of the aldehyde **74**.



metric reduction of the ketone in **78** was furnished by CBS reduction, which was nearly quantatively along with a 12/1 ratio diastereoselectivity using 2 equiv. of 2-methyl-(*S*)-CBS-oxazaborolidine at -30 °C, but the selectivity eroded to 5/1 when catalytic amount were employed.[92] Reduction of the alkyne to alkene

proceeded very rapidly (10 min) by partial hydrogenation of **79** using the Lindlar catalyst in conjunction with 2 equiv of quinoline at 0 -10 °C, providing the desired alkene **80** in 91% yield. Protection of the secondary alcohol in **80** as its *p*-methoxybenzyl ether using *p*-methoxybenzyl trichloroacetimidate under acidic condition (CSA) followed by desilylation using TBAF generated the primary alcohol **81** in excellent yield. Subsequent Parick-Doring oxidation[85] of the primary alcohol completed the synthesis of the aldehyde **74** in 72% yield.

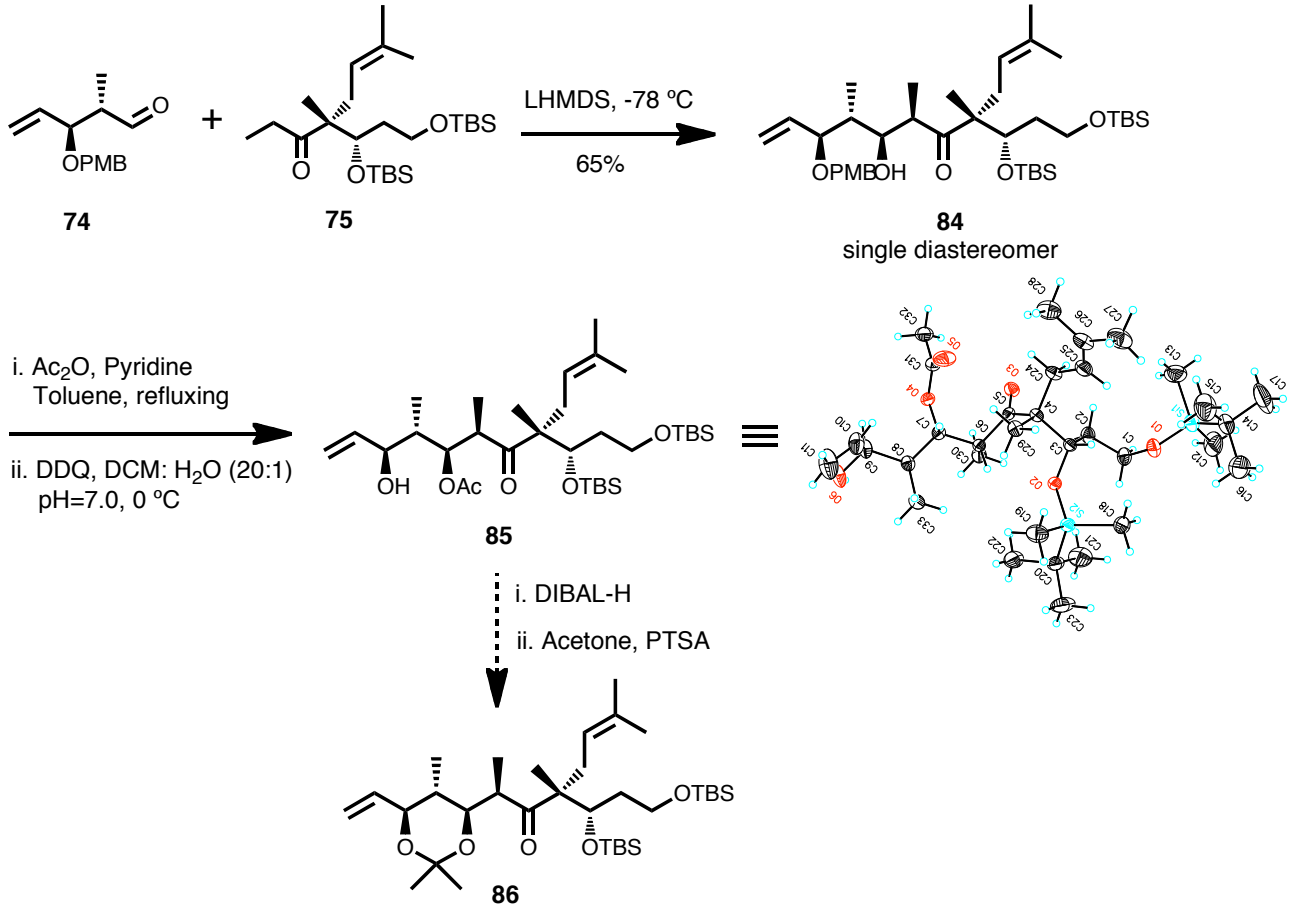
Scheme 10. Synthesis of the ketone **75**.



Synthesis of ketone **75** was adapted from synthesis of ketone **38** in the first generation syntheis, as shown in Scheme 10. Starting from β-hydroxy methyl ester **44**, two successive Frater-Seebach alkylation[93] using prenyl bromide and iodomethane gave rise to the β-hydroxy methyl ester **82** in good yield along with excellent diastereselectivity. Protection of **82** as its *tert*-butyldimethylsilyl ether

followed by reduction of methyl ester into alcohol using DIBAL-H provided the primary alcohol **83**. Subsequent Parick-Doring oxidation[85] of **83** gave rise to an aldehyde that upon addition of ethylmagnesium bromide afforded a mixture of two diastereomeric secondary alcohol in *ca.* 10/1 ratio. Without chromatographic separation, the two diastereomers were subjected to Swern oxidation, furnishing the synthesis of ketone **75** in 70% yield.

Scheme 11. Double stereodifferentiating *syn* aldol reaction and confirmation of stereochemistry.



With aldehyde **74** and ketone **75** in hands, we embarked on the double stereodifferentiating *syn* aldol reaction,[94] as shown in Scheme 11. Treatment of **75** with LHMDS at -78 °C generated an enolate that reacted with the aldehyde **74** very rapidly (5 min) to afford the aldol adduct **84** as a single diastereomer in 65% yield.

It is well known that β stereoinduction can play a significant role in dictating facial bias of aldehydes that have β alkoxy substituent in aldol reactions.[94, 95] Evans et al. has systematically investigated the stereo outcome of aldol reactions of aldehydes having both α and β stereoinductions, known as the double stereodifferentiating aldol reaction.[94] Illustrated in Figure 13 is a summary of stereo outcome of a set of double stereodifferentiating *syn* aldol rea-

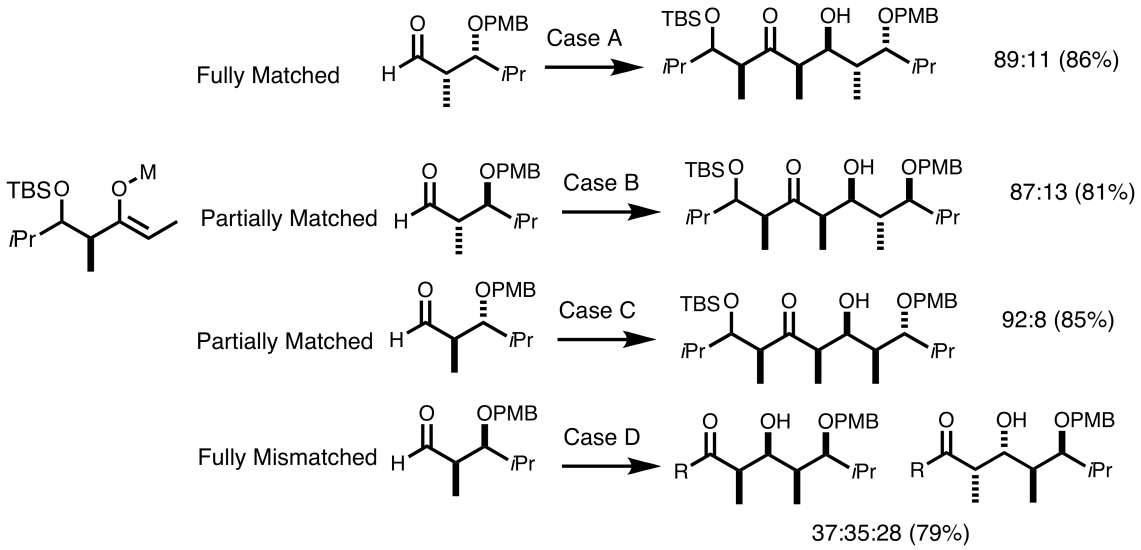


Figure 13. Double stereodifferentiating *syn* aldol reactions between chiral reaction partners.

ctions of chiral (*Z*) enolate and aldehydes having PMB ether at β position. [94] Among the four cases given in Figure 13, the stereochemistry of both α and β positions in case B matches that of the aldehyde **74**, however, the substitution pattern at the α position of the (*Z*) enolate given in Figure 13 is different from that of **75** (tertiary *vs* quaternary). Therefore, the stereo outcome of case B is not transferable to aldol reaction of **74** and **75**.

Recently, White et al. reported in their epothilone synthesis a double stereodifferentiating *syn* aldol reaction of an aldehyde bearing a primary *p*-methoxybenzyl ether substituent and a (Z) enolate having a gem-dimethyl group at the α position.[96] The transition state **C** proposed for this reaction by White et al. (Figure 14A) showed that a double metal chelation involving both lone pairs of the aldehyde oxygen is invoked in the chairlike transition state.[96] In addition, it would be the secondary chelation between the primary PMB ether and aldehyde carbonyl which directs the addition of the (Z) enolate of the ketone generated by lithium base toward the *re* face of the aldehyde, leading to the anti-Felkin aldol adduct as the sole stereoisomer.[96] With this literature precedent, it is reasonable to envision that the double stereodifferentiating *syn* aldol reaction of **74** and **75** would go through the transition state **D** depicted in Figure 14B, leading to the formation of the aldol adduct **84** as the single diastereomer. By placing the allyl group in the equatorial position and the hydrogen in axial position, the

stereochemistry of the β center of the aldehyde in the transition state **D** matches that of the substrate, the aldehyde **74**.

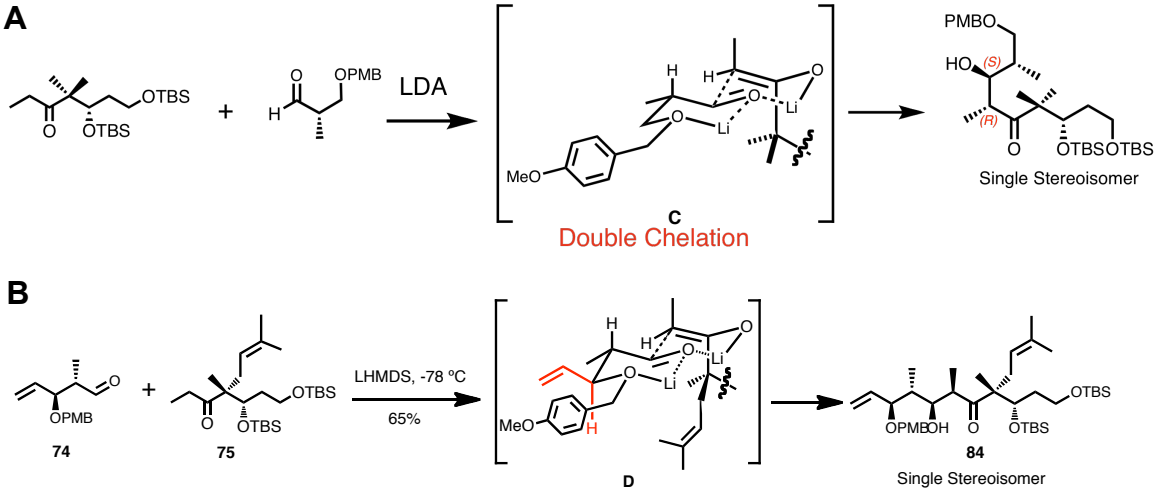


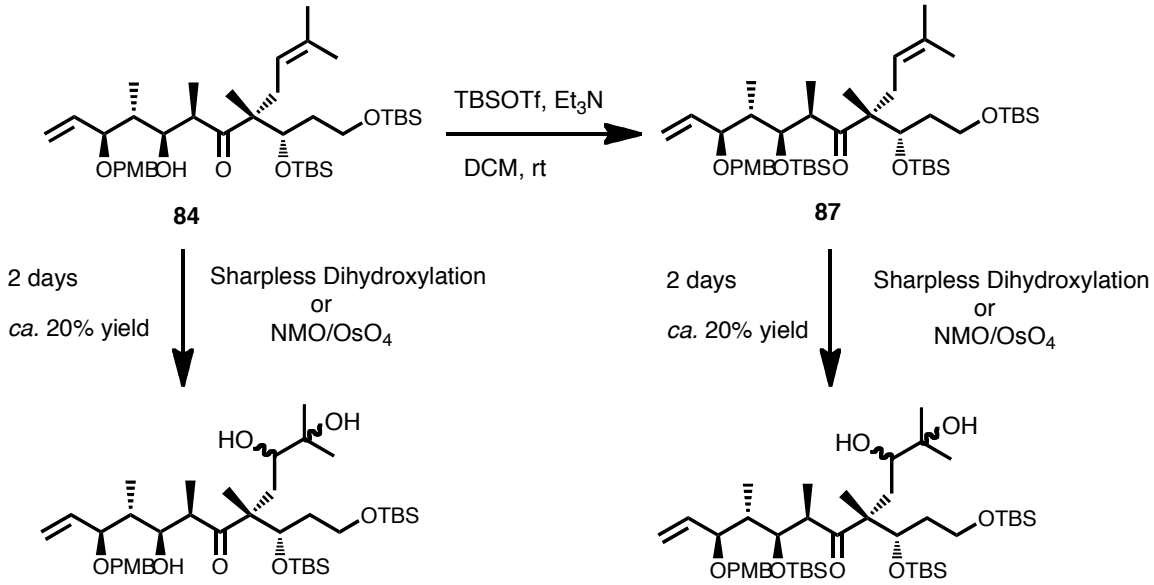
Figure 14. (A) Double chelation chairlike transition state proposed for White's double stereodiefferentiating *syn* aldol reaction. (B) Possible transition state of the double stereodifferentiating *syn* aldol reaction between **74** and **75**.

To confirmation the stereochemistry of **84**, we initially attempted to form Mosher's esters from the aldol adduct **84**. Unfortunately, treatment of **84** with either (*S*)- or (*R*)-Mosher's acid chloride in the presence of pyridine and DMAP failed to give any of the desired Mosher's ester even under refluxing conditions. Alternative effort to access the stereochemical information of **84** was to form the Rychnovsky acetonide **86** (Scheme 11).[97] In doing so, the secondary alcohol of **84** resulted from aldol reaction was first protected as an acetate to give, after deprotection of the secondary PMB ether by treatment with DDQ, the allylic

alcohol **85**. Gratifyingly, **85** turned out to be crystalline after slow evaporation of the solvent, ethyl acetate. Crystallographic structure of **85** (Scheme 11) unambiguously confirmed all the stereochemistry that had been set. It also confirmed that the stereochemistry of aldol adduct **65** resulted from the *syn* aldol reaction of **38** and **39** in the first generation synthesis which was dictated by similar double-chelation transition state.

Having confirmed the stereochemistry of the aldol adduct, we embarked on conversion of the prenyl group into the α,β-unsaturated ester. Initial attempt involved a three-step sequence: chemoselective dihydroxylation, oxidative cleavage of the resulting diol into aldehyde and Still-Genari olefination. [98] The aldol adduct was first protected as its *tert*-butyldimethylsilyl ether **87** which was then subjected to Sharpless asymmetric dihydroxylation condition. [82] However, as shown in Scheme 12, the dihydroxylation reaction of **87** turned out to be very

Scheme 12. Dihydroxylation of **84** and **87**.

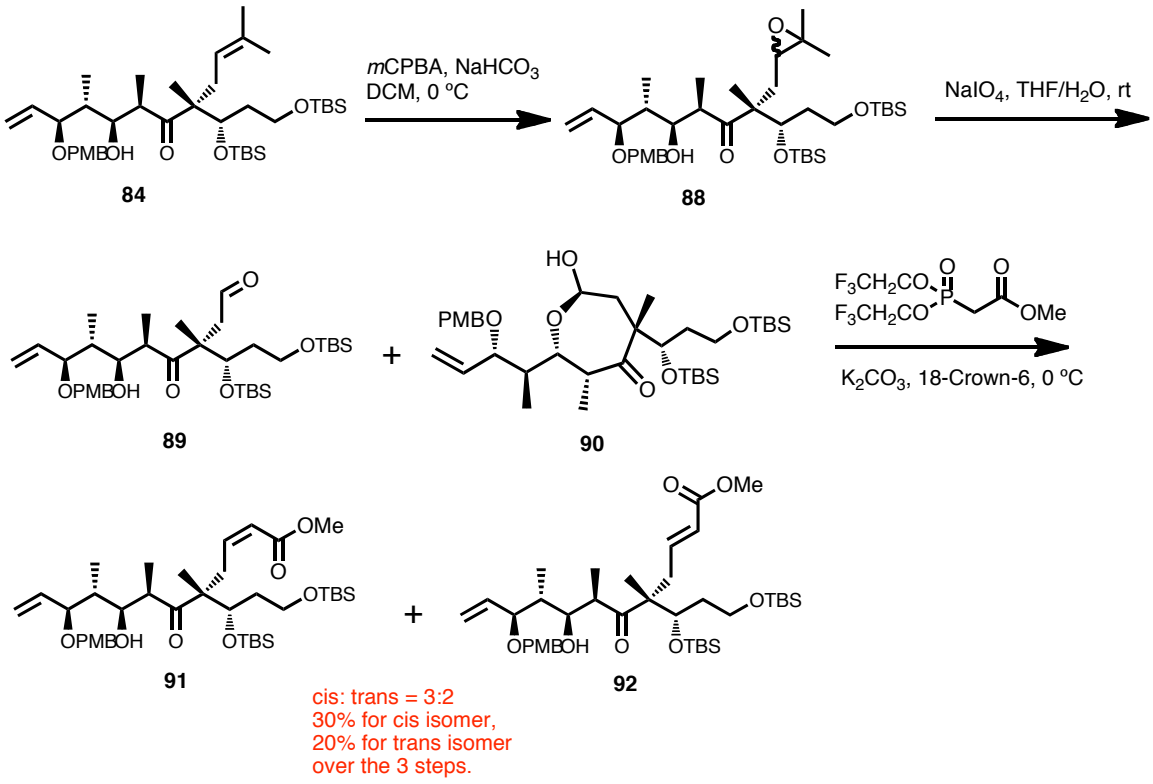


sluggish and low yielding, providing only *ca.* 20% yield after 2 days along with significant decomposition. The reaction profile remained the same when the NMO/OsO_4 conditions waere employed. The yield of the dihydroxylation reaction did not improve when the aldol adduct **84** was used as the substrate.

Alternative strategy to convert the prenyl group into a precursor that can be oxidized into an aldehyde was selective epoxidation of the prenyl group in the presence of the terminal olefin. As shown in Scheme 13, epoxidation of fully protected **87** by using *m*CPBA only gave a complex mixture of uncharacterized products. Fortunately, exposure of the aldol adduct **84** to *m*CPBA in the presence of $NaHCO_3$ provided a product whose mass matched that of the desired epoxide **88**. However, the epoxide turned out to be very unstable on silica gel. Therefore, without chromatographic separation, **88** was carried forward to next step which is formation of the aldehyde. Treatment of **88** with

aqueous $NaIO_4$ in THF cleaved the epoxide smoothly to provide the hydroxy aldehyde **89** and its corresponding seven-membered lactol **90** which underwent rapid equilibrium upon chromatography. Mass spectrometry of the mixture of **89** and **90** gave the expected m/z, confirming the hypothesis that epoxidation of **84** with *m*CPBA would chemoselectively occur on the electron-rich prenyl group instead of the terminal olefin. After chromatographic separation, the *ca.* 1:1 mixture of aldehyde **89** and lactol **90** was subjected to Still-Genari olefination [98] providing a mixture of desired *cis* α,β-unsaturated methyl ester **91** along with its *trans* isomer **92** in *ca.* 3:2 ration in 50% overall yield for the three-step sequence. The structures of **91** and **92** were explicitly confirmed by ^{1}H and ^{13}C NMR.

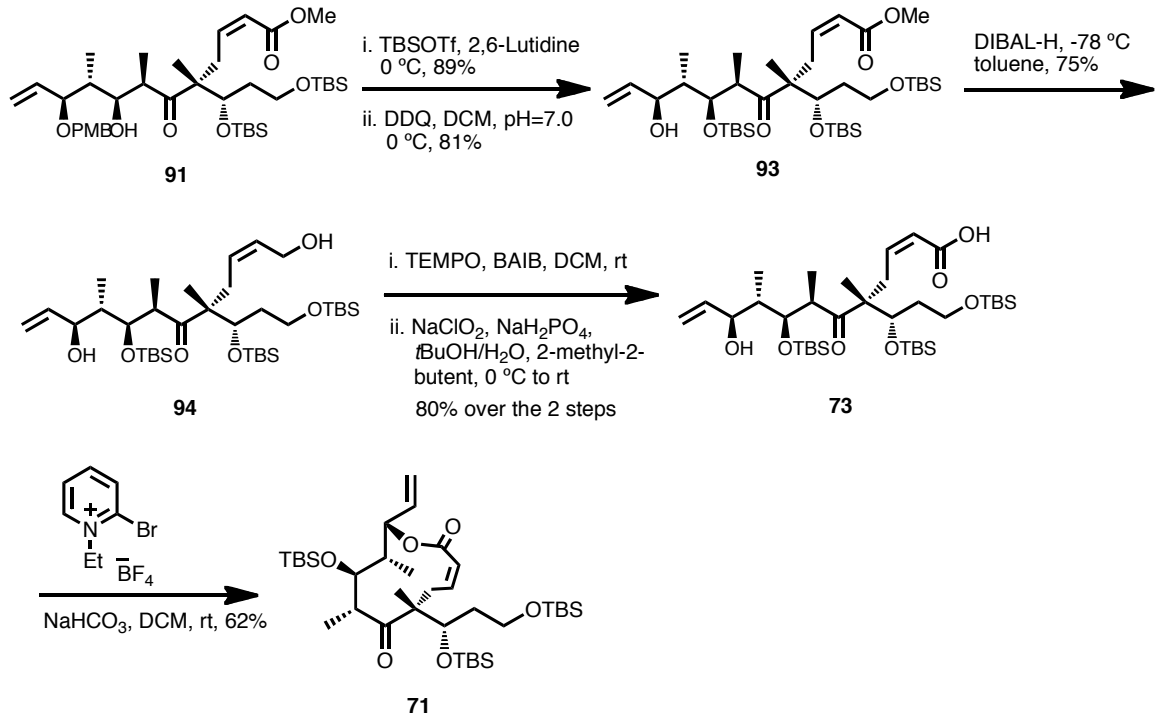
Scheme 13. Elaboration toward the α,β-unsaturated methyl ester **91**.



Having accessed the *cis* α,β-unsaturated methyl ester **91**, we moved ahead to furnish the first ring-closure event as depicted in Scheme 14. Protection of **91** as its *tert*-butyldimethylsilyl ether provided, after deprotection of the secondary PMB ether with DDQ, the allylic alcohol **93**. A variety of saponification conditions such as basic hydrolysis and demethylation methods were screened to convert the methyl ester moiety into corresponding acid. However, only trace amount of the desired product was observed along with severe decomposition of starting material under these conditions. Having understood that steric hinderance of the ketone imposed by the α quaternary center compared to the *cis* α,β-unsaturated methyl ester, a three-step redox sequence was devised to achieve the desired hydroxy acid **73**. First, the *cis* α,β-unsaturated methyl ester was carefully

reduced by treatment with DIBAL-H in toluene at -78 °C with the ketone moiety intact to provide the allylic diol **94** in 75% yield along with *ca.* 10% the corresponding partially reduced α,β-unsaturated aldehyde. Exposure of **94** to [bis(acetoxy)iodo]benzene (BAIB) and catalytic amount of tetramethylpiperidine-1-oxyl (TEMPO) selectively oxidize the primary allylic alcohol in **94** up to α,β-unsaturated aldehyde[99] which was subjected to Pinnick oxidation[86] to afford the

Scheme 14. Synthesis of alkenyl macrolactone **71**.

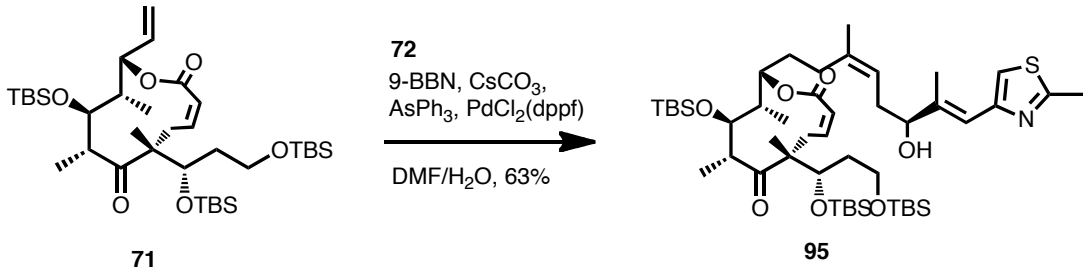


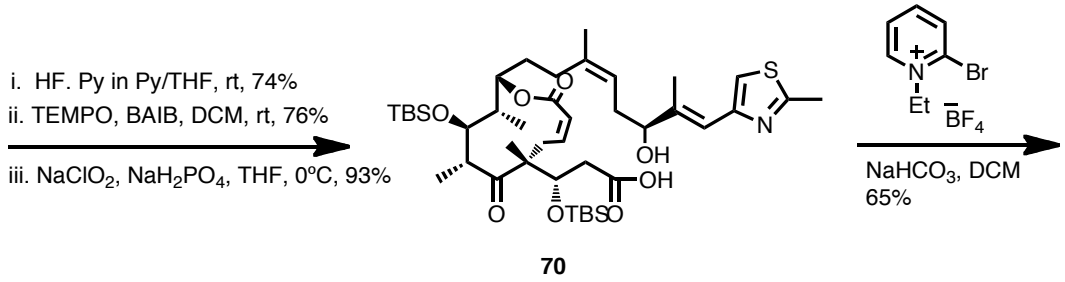
desired hydroxy acid **73** in 80% yield over the 2 steps. To minimize potential isomerization of the *cis* α,β-unsaturated methyl ester into its *trans* isomer *via* reversible Michael addition during the macrolactonization process, the modified Mukaiyama salt with non-nuclephilic counter-ion, tetrafluoborate, was the choice

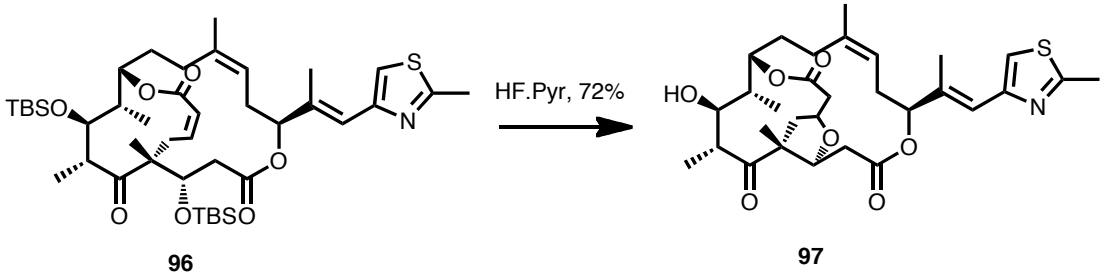
of reagent,[88, 100] furnishing the alkenyl macrolactone **71** in 62% yield without formation of detectable isomerized *trans* product.

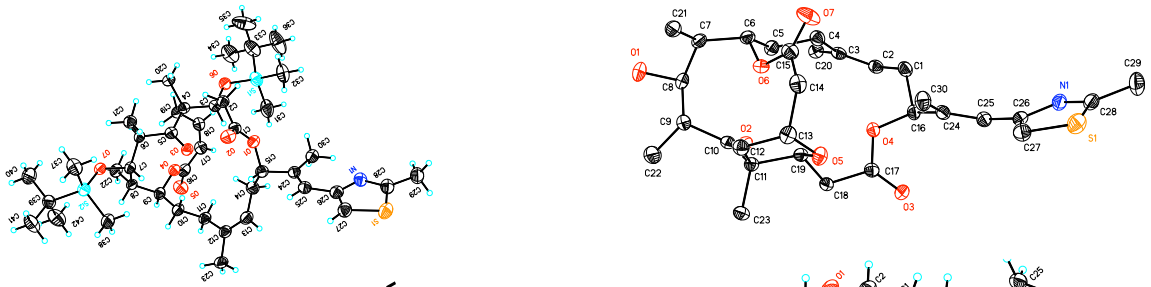
With required building blocks in hand, final steps toward the designed target are illustrated in Scheme 14. Treatment of alkenyl macrolactone **71** with 9-BBN at room temperature generated an alkyl borate that, without purification, rapidly coupled with the vinyl iodide partner **72** in the presence of $CsCO_3$, $AsPh_3$, $PdCl_2$(dppf) and H_2O to provide the desired *cis*-olefin **95** in modest yield.[89] Selective desilylation[84] of the primary TBS ether in **95** gave rise to a diol of which the primary alcohol was regioselectively oxidized to an aldehyde by using TEMPO/BAIB condition.[99] Subsequent Pinnick oxidation[86] of the aldehyde furnished the hydroxy acid **70** in excellent yield.

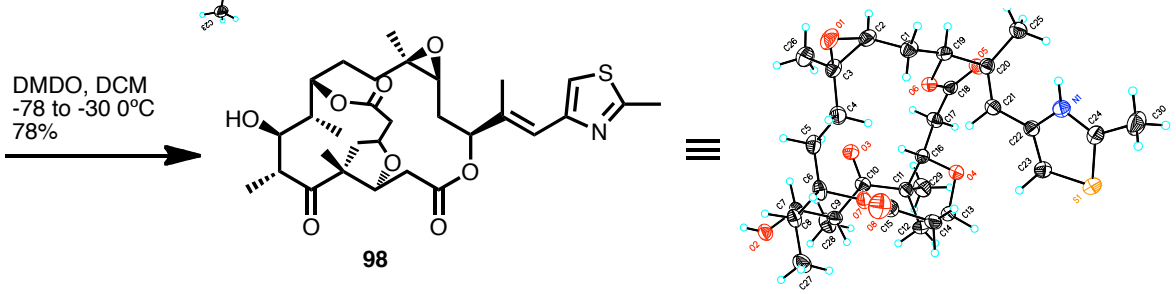
Scheme 15. Elaboration toward the target.


TBSO
OTBS
OTBS
O
O
O
71
72
9-BBN, CsCO3,
AsPh3, PdCl2(dppf)
DMF/H2O, 63%
TBSO
OH
OTBSOTBS
S
N
95


i. HF. Py in Py/THF, rt, 74%
ii. TEMPO, BAIB, DCM, rt, 76%
iii. NaClO2, NaH2PO4, THF, 0ºC, 93%
TBSO
OH
OH
OTBSO
70
Br
Et
BF4
NaHCO3, DCM
65%


TBSO
OTBSO
96
HF.Pyr, 72%
HO
97




DMDO, DCM
-78 to -30 0ºC
78%
HO
98

It is noteworthy that ^{1}H NMR of all intermediate after the fist macrolactonization (**71**, **70**, **95** and the three intermediates between **95** and **70**) were significantly broadened and most ^{13}C NMR peaks of these compounds had extremely low intensity even though the NMR experiments were performed with samples at very high concentrations. Neither high temperature nor low temperature NMR experiment improved the quality of the spectra. This is presumably due to multiple conformations that existed in solution for these compounds with medium-sized ring. With these in mind, we expected to observe normal NMR spectra after the second ring closure that would rigidify the structure and therefore significantly reduce the conformation distribution in solution.

The second macrolactonization proceeded smoothly by treatment of hydroxy acid **70** with the modified Mukaiyama salt in the presence of excessive $NaHCO_3$ to give the fully cyclized product **96** which turned out to be crystalline. As shown in Scheme 15, x-ray crystallographic study of **96** explicitly confirmed both the structure and stereochemistry. Furthermore, as we expected, peaks of both ^{1}H and ^{13}C NMR sharpened. However, ^{1}H NMR of **96** revealed that this compound is a mixture of two atropisomers in *ca.* 2:1 ratio in solution even though only one conformation existed in its crystal structure. ^{1}H NMR at higher temperature (60 °C) did not witness convergence of the two atropisomers. To complete the synthesis, compound **96** was initially subjected to global desilylation with TFA in dichloromethane. Surprisingly, no producted was formed by using this condition.

Treatment of **96** with hydrogen fluoride pyridine complex at room temperature, however, provided a compound with expected mass for the global desilylated product. A closer examination of the ^{13}C NMR revealed that the olefin moiety of the *cis* α,β-unsaturated macrolactone was reduced during the desilylation process. X-ray crystallographic study of this product, **97** as depicted in Scheme 15, showed that a five-membered tetrahydrofuran ring was formed *via* an intramolecular Michael addition of the C3-OH onto the *cis* α,β-unsaturated macrolactone presumably facilitated by the acidic reaction condition. The formation of the designed bridged epothilone D analog was so transient that the intramolecular Michael adduct was the exclusive product. Finally epoxidation of the intramolecular Michael adduct **97** with dimethyldioxriane in dichloromethane at -30 °C afforded the epoxide **98** with correct stereochemistry as confirmed by x-ray crystal structure.

1.3. Biological Evaluation of Analogs

All the C4-C9 bridged epothilone analogs (Figure 11) were subjected to the preliminary cytotoxicity studies using an assay against A2780 human ovarian cancer cell line,[101, 102] and Taxol® (**5**) was used as a control instead of natural epothilones because of their commercial availability and similar toxicity. As shown in Table 3, compound **97** is about 150 times less active than Taxol® and compound **98** is around 300 times less active than Taxol®.

Table 3. Cytotoxicities of Taxol and C4-C9 bridged epothilone analogs against A2780 cell lines.

Compd.	IC_{50} (μM)
5 (Taxol®)	0.028
97	4
98	8

1.4. Conclusion

C4-C9 bridged EpoB analog **35** was designed using molecular modeling to mimic the recently proposed EC binding model of epothilone in the tubulin binding site. The first generation synthesis toward **35** based on macrolactionization/RCM stragetegy failed to provide the desired target since the difficulity in esterification of the C-9 OH group. In light of the lesson learnt from the first generation synthesis, a second generation synthesis based on *B*-alkyl Suzuki coupling/macrolactionization strategy was devised and carried out. Unfortunately, upon global deprotection, an unexpected Michael addition reaction between C-3 OH and the α,β-unsaturated lactone formed an additional THF ring in the final products **97** and **98**. Selective reduction of the double bond in the α,β-unsaturated lactone bridge could have avoided the side reaction. Biological assay of **97** and **98** indicate both of them are *ca.* 150 and 300 times less active

than Taxol®.

1.5. Experimental Section

1.5.1 Chemistry

General Techniques. Unless otherwise noted, all reactions were carried out in oven-dried or flame-dried glassware under a positive pressure of argon using standard syringe/septa techniques. All reactions were stirred with Teflon® coated stir bars and a magnetic stir plate. Air- and moisture-sensitive liquids and solution were transferred *via* syringe or stainless cannula. Concentration under reduced pressure was performed using a Büchi rotary evaporator. Flash column chromatography was performed by employing either Sorbent Technologies 200-400 mesh or Waterman 230-400 mesh silica gel 60. Analytical thin-layer chromatography (TLC) was performed on pre-coated with silica gel 60 F254 (0.25mm thick) from EM Science. TLC plates were visualized by exposure to ultraviolet light (UV) and/or exposure to phosphomolybdic acid or potassium permanganate TLC stains followed by brief heating on a hot plate. Preparative TLC separation was performed on Analtech preparative plates pre-coated with silica gel 60 UV254 (0.5, 1.0 or 1.5 mm thick).

Commercial reagents and solvents were used as received unless otherwise noted. Dehydrated dichloromethane, *N*,*N*-dimethylformamide (DMF), tetrahydrofuran (THF), toluene, and Hexamethylphosphoramide (HMPA) were dried over 4Å molecular sieves. Trace water content was tested with 756 KF Coulometer from Brinkmann Instruments.

Melting points (mp), determined on a MEL-TEMP Melting Point Apparatus from Laboratory Devices, were uncorrected. Optical rotations were measured on a Perkin Elmer Model 341 digital polarimeter with a sodium lamp at room temperature. Infrared (IR) spectra were recorded on a Nicolet 370 with a diamond probe or ASI ReactIR 1000 FI-IR Spectrophotometer with a silicone probe and are reported in wavenumbers (cm^{-1}). Where noted “neat”, the sample was loaded as a thin film. Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were determined on an INOVA400 (^{1}H NMR: 400 MHz, and ^{13}C NMR: 100 MHz) or INOVA600 (^{1}H NMR: 600 MHz, and ^{13}C NMR: 150 MHz) instrument. Chemical shifts for ^{1}H NMR were reported in parts per million (δ scale) with deuterated chloroform (CDCl3) as the internal standard (7.26 ppm) and coupling constants were in hertz (Hz). The following abbreviations were used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet. Chemical shifts for ^{13}C NMR were reported in parts per million (δ scale) relative to the central line of the triplet at 77.0 ppm for deuterated chloroform (CDCl3). NMR data was analyzed by MestReNova (version 6.2.0). High resolution mass spectra (HRMS) were obtained on a JEOL JMS-SX102/SX102A/E or Thermo Finnigan LTQ-FTMS instrument.

Preparation of β-keto ester 42. To a solution of methyl acetoacetate (1.08 mL, 1.16g, 10 mmol) in THF was added freshly prepared LDA (2.5 equiv, 2.7 mmol)

dropwise over 15 min at 0 °C. The resulting solution was allowed to stir for additional 30 min to form brown solution which is then cooled down to -78 °C. The benzyl chloromethyl ether (1.67 mL, ca. 10 mmol) in 2 mL THF was then added dropwise over 10 min to the above brown suspension at -78 °C. The resulting mixture was allowed to stir at -78 °C for 1h and the warmed up to -25 °C and continue to react for 2 h. Following addition of cooled 40 mL 1N HCl, the two layers were separated. The aqueous layer was reextracted by ethyl ether (30 mL × 3), and the combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (5/1, hexane/ethyl acetate) to provide the product **42** (2 g, 85%) as a yellow oil. IR (thin film) *vmax* 2953, 2927, 2867, 1744, 1714, 1495, 1452, 1405, 1365, 1311,1260, 1150, 1099, 1000, 847, 739, 656 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.16 (m, 5H), 4.49 (s, 2H), 3.73 (t, J = 6.2 Hz, 2H), 3.70 (s, 3H), 3.48 (d, J = 3.2 Hz, 2H), 2.80 (t, J = 6.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.4, 167.5, 137.9, 128.7, 127.6, 126.9, 73.2, 64.9, 52.3, 49.4, 43.1. ^{13}C NMR (101 MHz, CDCl3) δ 201.4, 167.5, 137.9, 128.4, 127.7, 126.9, 73.2, 64.9, 52.3, 49.4, 43.1. HRMS (ESI) calcd for $C_{13}H_{16}O_4Na$ $[M+Na]^+$: 259.09408, found 259.09387.

Preparation of β-hydroxy ester 43. A degassed solution of acetone (8 mL) was added to an equimolar amounts of (*S*)-BINAP (32 mg) and bis-(methylallyl)-1,5-cyclooctadiene ruthenium (II) (16 mg). To the resulting suspension, a

solution of HBr in methanol (0.29 M, 0.44 mL, 2.5 equiv) was added and the resulting reaction mixture was stirred for 1 h. The volatiles were concentrated in vacuum to provide the catalyst as a light brown solid, which was used directly for the reduction. (*S*)-BINAP-$RuBr_2$ catalyst was added to a solution of β-keto ester **42** (3.38 g, 14 mmol) in CH_3OH (30 mL) and the resulting solution was hydrogenated (Parr hydrogenator) at 50 psi for 2 days. The reaction mixture was then filtered through a Celite pad, and the filtrate was concentrated to give crude product. The crude residue was subjected to chromatography over silica gel (5/1, hexane/ethyl acetate) to provide **43** (3 g, 90%) as a light yellow oil. $[\alpha]_D^{20}$ = + 11 (c = 2.2, $CHCl_3$). IR (thin film) *vmax* 3463, 2950, 2930, 2862, 1731, 1495, 1438, 1259, 1203, 1166, 1089, 1025, 988, 848, 738, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.14 (m, 5H), 4.49 (s, 2H), 4.23 (br s, J = 7.4 Hz, 1H), 3.67 (s, 3H), 3.69 – 3.58 (m, 2H), 3.50 (br s, 1H), 2.49 (d, J = 6.3 Hz, 2H), 1.84 – 1.72 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7, 137.9, 128.4, 127.6, 127.6, 73.2, 67.8, 66.8, 51.6, 41.4, 36.0. HRMS (APCI) calcd for $C_{13}H_{19}O_4$ $[M+H]^+$: 239.12779, found: 239.12769.

Preparation of silyl ether 44. Pd-C (10%, 0.6 g) was added to the solution of benzyl ether **43** (3.4 g, 14.2 mmol) in CH_3OH (20 mL), and the resulting solution was hydrogenated in a sealed tube at 35 psi for 4 h. The reaction mixture was then filtered off through a silica gel pad. The filtrate was concentrated to give residue, which was subjected to silica gel chromatography with 50% ethyl acetate in hexane to provide a diol (2.0 g, 95%). $[\alpha]_D^{20}$ = + 19.5 (c 2.0, $CHCl_3$).

IR (thin film) *vmax* 3368, 2955, 2924, 1710, 1401, 1264, 1164, 1053, 981, 875 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.20 (m, 1H), 3.90 (bs, 1H), 3.75 (m, 1H), 3.65 (s, 3H), 3.40 (bs, 1H), 2.46(dd, J = 5.8, 1.2 Hz, 1H) 1.65 (q, J = 5.6Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.2, 67.4, 60.5, 51.9, 41.7, 38.1. HRMS (APCI) calcd for $C_6H_{13}O_4$ $[M+H]^+$: 149.08084, found 149.08058.

To the solution of the diol (0.56 g, 3.78 mmol) obtained from the above reaction, in CH_2Cl_2 (8 mL) was sequentially added imidazole (0.38 g, 5.67 mmol, 1.5eq) and TBSCl (0.578 g, 3.78 mmol, 1eq), and the resulting solution was stirred for 30 min. A saturated solution of methanolic $NaHCO_3$ was added to quench the reaction and the solution was extracted with EtOAc (20 mL x 3). The combined organics were dried and concentrated to give crude product, which was subjected to silica gel chromatography with 5% EtOAc in hexane to provide **44** (0.95 g, 96%) as a colorless oil. $[\alpha]_D^{20}$ = +9.6 (c = 0.74, $CHCl_3$). IR (thin film) *vmax* 3411, 2953, 2930, 2886, 2857, 1724, 1439, 1253, 1202, 1167, 1089, 833, 774, 665 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.25 (ddd, *J* = 12.4, 7.9, 4.6 Hz, 1H), 3.91 – 3.77 (m, 2H), 3.70 (s, 3H), 2.51 (t, *J* = 6.1 Hz, 2H), 1.78 – 1.64 (m, 2H), 0.85 (s, 9H), 0.03 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 67.9, 61.8, 51.8, 41.8, 38.2, 26.0, 18.3, -5.4, -5.4. HRMS (APCI) calcd for $C_{12}H_{27}O_4Si$ $[M+H]^+$: 263.16731, found: 263.16715.

Preparation of 45. A solution of freshly prepared LDA (2 M, 3.16 mL, 6.32 mmol, 2.6 eq) in THF was added to a solution of **44** (0.638 g, 2.43 mmol) in THF (20 mL) at -78 ^{o}C, and the resulting solution was stirred brought to -20 ^{o}C and

stirred for 30 min. Allyl iodide (0.33 mL, 3.6 mmol, 1.5 eq) in HMPA (1.21 mL, 6.79 mmol, 1.08 eq to LDA) was added to the above reaction at -78 ^{o}C and the reaction mixture was brought to -20 ^{o}C and stirred for 1 h. Sat NH_4Cl (50 mL) was added to quench the above reaction. The two layers were separated and aqueous phase was extracted with ether (20 x 3). The combined organics were washed with water, brine, dried and concentrated to give the crude mass, which was subjected to silica gel chromatography, with 5% ethyl acetate in hexane, to provide the allyl derivative (0.54 g, 73%) as a pale yellow oil. $[\alpha]_D^{20}$ = +5.4 (c = 1.0, $CHCl_3$). IR (thin film) *vmax* 3505, 3080, 2952, 2930, 2885, 2857, 1735, 1438, 1361, 1253, 1194, 1168, 1089, 994, 915, 834, 776, 731, 662 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (ddt, *J* = 17.1, 10.1, 7.0 Hz, 1H), 5.12 – 4.98 (m, 2H), 4.02 – 3.93 (m, 1H), 3.91 – 3.83 (m, 1H), 3.79 (ddd, *J* = 10.2, 7.8, 4.5 Hz, 1H), 3.69 (s, 3H), 3.47 (d, *J* = 4.7 Hz, 1H), 2.63 – 2.53 (m, 1H), 2.46 – 2.28 (m, 2H), 1.79 – 1.59 (m, 2H), 0.86 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.8, 135.1, 117.1, 71.6, 61.9, 51.7, 51.4, 36.5, 33.1, 25.9, 18.3, -5.4, -5.4. HRMS (APCI) calcd for $C_{15}H_{31}O_4Si$ $[M+H]^+$: 303.19134, found 303.19841.

To a freshly prepared solution of LDA (0.6 M, 15.73 mmol, 2.6 eq) in THF (24 mL), a solution of the allyl derivative, obtained from the above reaction, (1.83 g, 6 mmol) in THF (15 mL) was added at -78 ^{o}C, and the resulting solution was brought to -20 ^{o}C and stirred for 4 h. Then a solution of methyl iodide (0.6 mL, 9.68 mmol, 1.6 eq) in HMPA (17 mmol, 1.08 eq to LDA) was added to the above reaction at -78 ^{o}C, then, the reaction mixture was brought to -20 ^{o}C and stirred

for 48 h. Saturated NH_4Cl (50 mL) was added to quench the above reaction. The two layers were separated and aqueous phase was extracted with ether (20 x 3). The combined organic phases were washed with water, brine, dried, and concentrated to give the crude mass, which was subjected to silica gel chromatography, with 5% ether in hexane, to provide **45** (1.16g, 61%) as a pale yellow oil. $[\alpha]_D^{20}$ = +13.2 (c = 3.0, $CHCl_3$). IR (thin film) *vmax* 3376, 3079, 2952, 2930, 2887, 2857, 1712, 1461, 1437, 1289, 1250, 1220, 1150, 1047, 992, 917, 868, 835, 774, 665 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.69-5.55 (m, 1H), 4.99-4.88 (m, 2H), 3.88 (d, *J* = 10.3 Hz, 1H), 3.81-3.73 (m, 1H), 3.69 (td, *J* = 9.6, 3.6 Hz, 1H), 3.54 (s, 3H), 3.40 (d, *J* = 2.5 Hz, 1H), 2.41 (dd, *J* = 13.7, 6.9 Hz, 1H), 2.19 (dd, *J* = 13.7, 7.9 Hz, 1H), 1.63-1.48 (m, 1H), 1.38 (ddd, *J* = 14.2, 5.7, 2.4 Hz, 1H), 1.03 (s, 3H), 0.78 (s, 9H), -0.04 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.2, 134.3, 118.0, 75.8, 63.1, 51.7, 51.3, 40.8, 34.2, 25.9, 18.3, 16.2, -5.4, -5.4. HRMS (APCI) calcd for $C_{16}H_{33}O_4Si$ $[M+H]^+$: 317.21426, found 317.21401.

Preparation of primary alcohol 46. To the solution of **45** (3.34 g, 10.5 mmol) in dichloromethane (50 mL) was added 2,6-lutidine (1.94 mL, 16.9 mmol, 1.6 eq) and TBSOTf (3.7 mL, 15.4 mmol, 1.5 eq) at -78 ^oC and the resulting reaction mixture was stirred over 6 h. Sat. NH_4Cl solution (100 mL) was added to quench the reaction. Two layers were separated and the aqueous phase was extracted with dichloromethane (20 mL x 3). The combined organic phases were dried and concentrated to give crude product, which was subjected to silica gel chromatography with 3% ethyl acetate in hexane, to provide a bis-TBS ether

(4.1g, 91%) as colorless oil. $[\alpha]_D^{20}$ = +5.0 (c = 1.0, $CHCl_3$). IR (thin film) *vmax* 3078, 2953, 2930, 2886, 2857, 1738, 1463, 1385, 1254, 1209, 1096, 1033, 1003, 937, 833, 709, 677 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.74-5.60 (m, 1H), 5.01 (d, *J* = 12.9 Hz, 2H), 4.03 (dd, *J* = 7.8, 2.9 Hz, 1H), 3.62 (s, 3H), 3.58 (dd, *J* = 16.4, 8.5 Hz, 2H), 2.40 (dd, *J* = 13.3, 7.0 Hz, 1H), 2.25 (dd, *J* = 13.3, 7.8 Hz, 1H), 1.66-1.46 (m, 2H), 1.07 (s, 3H), 0.88 (s, 9H), 0.89, (s, 9H), 1.00 (s, 3H), 0.08 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.0, 134.5, 117.9, 73.6, 60.1, 52.8, 51.7, 42.3, 37.7, 26.3, 26.1, 18.6, 18.4 14.8, -3.8, -3.7, -5.1, -5.1. HRMS (APCI) calcd for $C_{22}H_{47}O_4Si_2$ $[M+H]^+$: 431.30074, found 431.30032.

To a solution of bis-TBS ether (2.08 g, 4.83 mmol) in CH_2Cl_2 (45 mL) at -78 ^oC, obtained from the above reaction, was added a solution of DIBAL-H (1 M, 17 mmol, 3.5 eq) dropwise, and the resulting reaction mixture was stirred for 45 min. CH_3OH (5 mL) was added and the reaction brought to room temperature. Then a saturated solution of Na, K-tartrates (50 mL) was added and stirred 30 min to fully quench the reaction. Two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (30 mL x 3). The combined organics were dried and concentrated to give crude product, which was subjected to silica gel chromatography with 3% EtOAc in hexane, to provide the primary alcohol (1.65 g, 85%)as a colorless oil. $[\alpha]_D^{20}$ = -2.7 (c = 3.9, $CHCl_3$). IR (thin film) *vmax* 3445, 3075, 2955, 2930, 2885, 2858, 1471, 1389, 1254, 1091, 1003, 938, 912, 835, 775, 669 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.79 (ddt, *J* = 20.2, 9.1, 7.5 Hz, 1H),

5.03 (dd, *J* = 13.6, 1.8 Hz, 2H), 3.74 (ddd, *J* = 11.2, 6.8, 3.4 Hz, 2H), 3.65 (ddd, *J* = 13.6, 10.1, 4.8 Hz, 2H), 3.31 (dd, *J* = 11.2, 7.1 Hz, 1H), 3.03 (dd, *J* = 7.1, 4.3 Hz, 1H), 2.06 – 1.88 (m, 3H), 1.69 – 1.56 (m, 1H), 0.95 (s, 3H), 0.88 (s, 9H), 0.89, (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), 0.05 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.5, 117.7, 76.0, 68.4, 60.7, 42.2, 39.7, 36.1, 26.2, 26.1, 19.33 , 18.40 , -3.8, -4.0, -5.2, -5.2. HRMS (APCI) calcd for $C_{21}H_{47}O_3Si_2$ $[M+H]^+$: 403.30583, found 403.30569.

Preparation of the ketone 38. To the solution of **15** (4.7 g, 10 mmol) in a 1:1 mixture of CH_2Cl_2 and DMSO (80 mL), was added triethylamine (6.96 mL, 50 mmol, 5 eq) followed by SO_3.Py (6.93 g, 50 mmol, 5 eq) at 0 ^oC and the resulting reaction mixture was stirred for 2h. Saturated NH_4Cl solution (100 mL) was added to quench the reaction. Two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (40 mL x 3). The combined organics were dried and concentrated to give crude product, which was subjected to silica gel chromatography, with 3% EtOAc in hexane, to provide the aldehyde (3.83, 94%) as a coloreless oil. $[\alpha]_D^{20}$ = +2.4 (c = 0.75, $CHCl_3$). IR (thin film) *vmax* 3079, 2954, 2930, 2887, 2857, 1730, 1463, 1378, 1253, 1104, 1080, 1006, 920, 833, 774, 671 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60 (s, 1H), 5.65 (m, 1H), 5.05 (dd, *J* = 17.2, 1.6 Hz, 2H), 4.00 (dd, *J* = 7.6, 3.2Hz, 1H), 3.62 (m, 2H), 2.50 (dd, *J* = 14.2, 6.8Hz, 1H), 2.25 (dd, *J* = 14.2, 6.8 Hz, 1H), 1.70 (m, 1H), 1.62 (m, 1H), 1.0 (s, 3H), 0.88 (2 singlets, 18H), 0.08 (s, 3H), 0.05 (s, 3H), 0.03 (2 singlets, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 206.7, 133.7, 118.4, 72.9, 59.7, 54.3, 37.2, 37.0, 26.2, 26.1, 18.5, 18.4, 15.7, -3.6, -4.0, -5.1, -5.1. HRMS (ESI) calcd for $C_{21}H_{43}O_3Si_2$ $[M-H]^-$: 399.27453, found 399.27405.

To the solution of the aldehyde (3.8 g, 9.45 mmol), obtained from the above reaction, in THF (40 mL) was added ethyl magnesium bromide (1 M, 16.1 mL, 16.1 mmol, 1.7 eq) at 0 ^oC and the resulting reaction mixture was stirred for 1 h. Saturated NH_4Cl solution (100 mL) was added to quench the reaction. Two layers were separated and the aqueous phase was extracted with EtOAc (40 mL x 3). The combined organic layers were dried and concentrated to give crude product, which was subjected to silica gel chromatography, with 3% EtOAc in hexane, to provide the product as a diastereomeric mixture (9:1) (64%). The crude product was subjected to the next reaction without purification.

DMSO (0.397 mL, 5.6 mmol, 4 eq) was added to a solution of oxalyl chloride (0.243 mL, 2.8 mmol, 2 eq) in CH_2Cl_2 (10 mL) at -78 ^oC and the resulting reaction mixture was stirred for 5-10 min. Then a solution of product obtained from the above reaction (0.6 g, 1.39 mmol, 1 eq) in CH_2Cl_2 (10 mL) was added and resulting reaction mixture was stirred for 2 h. Then, triethylamine (1.6 mL, 11.2 mmol, 8 eq) was added and the reaction mixture was brought to room temperature for 1 h. Saturated NH_4Cl solution (50 mL) was added to quench the reaction. Two layers were separated and the aqueous phase was extracted with ethyl acetate (30 mL x 3). The combined organics were dried and concentrated

to give crude product, which was subjected to silica gel chromatography, with 1.5% ether in hexane, to provide the ketone **38** (0.42g, 70%) as a yellow oil. $[\alpha]_D^{20}$ = -0.0 (c = 1.8, $CHCl_3$). IR (thin film) *vmax* 3077, 2954, 2929, 2885, 2857, 1705, 1463, 1384, 1254, 1005, 833, 773, 664 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.65-5.51 (m, 1H), 5.00 (dd, *J* = 13.6, 1.3 Hz, 2H), 4.06 (dd, *J* = 8.0, 2.5 Hz, 1H), 3.58 (dd, *J* = 7.8, 4.9 Hz, 2H), 2.56 -2.32 (m, 3H), 2.26 (dd, *J* = 13.8, 7.7 Hz, 1H), 1.56-1.33 (m, 2H), 1.09 (s, 3H), 0.97 (t, *J* = 7.1 Hz, 3H), 0.90 (s, 9H), 0.88 (s, 9H), 0.11(s, 3H), 0.10 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 214.6, 134.3, 117.9, 73.3, 59.8, 57.4, 42.3, 37.7, 32.8, 26.3, 26.0, 18.6, 18.4, 14.8, 7.6, -3.6, -3.7, -5.2, -5.2. HRMS (APCI) calcd for $C_{23}H_{49}O_3Si_2$ $[M+H]^+$: 429.32148, found 429.32133.

Preparation of α,β-unsaturated ester 47. To a solution of triethyl phosphonoacetate (2.4 mL, 12 mmol, 1.2 equiv) in THF was added BuLi (4.8mL of 2.5 M, 12 mmol, 1.2 equiv) dropwise at -78 ^oC over 5 min. After being stirred at -78 ^oC for 30 min, 4-pentenal (840mg, 10mmol, 1equiv) in 10 mL THF was then added dropwise to the resulting solution. The resulting mixture was allowed to warm up to room temperature and stir for another 2h before iced water was added to quech the reaction. Two layers were separated and the aqueous phase was extracted with ethyl acetate (30 mL x 3). The combined organics were dried and concentrated to give crude product, which was subjected to silica gel chromatography, with 5% ethyl acetate in hexane, to provide the desired α,β-unsaturated ester **47** (1.15 g, 75%) as a colorless oil. IR (thin film) *vmax* 3078,

2981, 2933, 2886, 1718, 1446, 1368, 1312, 1265,1173, 1042, 988, 914, 853, 711, 669 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (dt, *J* = 15.6, 6.7 Hz, 1H), 5.90 – 5.68 (m, 2H), 5.13 – 4.91 (m, 2H), 2.38 – 2.10 (m, 4H), 1.24 (t, *J* = 9.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6, 148.3, 137.1, 121.7, 115.6, 60.2, 32.1, 31.5, 14.3. HRMS (APCI) calcd for $C_9H_{15}O_2$ $[M+H]^+$: 155.10666, found 155.10654.

Preparation of allylic alcohol 48. To a solution of α,β-unsaturated ester **47** (1.15 g, 7.45 mmol) in CH_2Cl_2 (20 mL) at 0 ^{o}C, was added a solution of DIBAL-H (1 M, 16mL, 16mmol, 2.2 equiv) dropwise, and the resulting reaction mixture was stirred for 45 min. CH_3OH (5 mL) was added and the reaction brought to room temperature. Then a saturated solution of Na, K-tartrates (100 mL) was added and stirred 30 min to fully quench the reaction. Two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (30 mL x 3). The combined organics were dried and concentrated to give crude product, which was subjected to silica gel chromatography with 10% EtOAc in hexane, to provide the allylic alcohol **48** (775 mg, 93%) as a colorless oil. IR (thin film) *vmax* 3318, 3077, 2979, 2920, 2848, 1437,1299,1088, 996, 969, 910, 668 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 – 5.71 (m, 1H), 5.71 – 5.52 (m, 2H), 4.96 (dd, *J* = 21.2, 13.6 Hz, 2H), 4.02 (d, *J* = 4.6 Hz, 2H), 2.47 (s, 1H), 2.25 – 2.02 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.0, 131.8, 129.4, 114.7, 63.1, 33.2, 31.5. HRMS (ESI) calcd for $C_9H_{15}NaO_2$ $[M+Na]^+$: 135.07858, found 135.07773.

Preparation of epoxy alcohol 49. An oven-dried, 50 mL three-neck round-bottom flask was charged with magnetic stir bar, 500mg of 4A powdered activated molecular sieves and 10 mL of anhydrous CH_2Cl_2, under argon. The flask was cooled to -30 ^oC. L-(+)-diethyl tartrate(0.30 mL, 1.74 mmol, 0.3 equiv) and Ti(O-*i*-Pr)$_4$ (0.34 mL, 1.16 mmol, 0.2 equiv) were added sequentially with stirring. *tert*-Butylhydroperoxide (2.2 mL, 11.6 mmol, 2 equiv)was added dropwise slowly to the above reaction mixture while stirring the reaction at that temperature. The resulting mixture was stirred at -30 ^oC for 1 h. Freshly prepared allylic **48** (0.65 g, 5.79 mmol, 1equiv) in 6 mL anhydrous CH_2Cl_2 was added dropwise to the reaction mixture over a period of 10 min. The resulting mixture was allowed to stir for additional 10 h before 10 mL of 10% NaOH was added to quench the reaction. The reaction mixture was filtered through a Celite pad, eluting with dichloromethane (20 mL), and the filtrates were washed with aqueous Na_2SO_4 solution. The aqueous layer was re-extracted with ethyl acetate (20 mL x 3). The combined organics were dried and concentrated to give crude product, which was subjected to silica gel chromatography, eluting with 50% ethyl acetate in hexane, to give epoxy alcohol **49** (0.54 mg, 73%) as a coloress oil. $[\alpha]_D^{20}$ = -32 (c = 0.25, $CHCl_3$). IR (thin film) *vmax* 3404, 3078, 2980, 2926, 1446, 1246, 1083, 1027, 996, 912, 879, 718, 634 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.76 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.05 – 4.89 (m, 2H), 3.82 (ddd, *J* = 12.6, 6.0, 2.4 Hz, 1H), 3.51 (ddd, *J* = 12.6, 6.5, 4.8 Hz, 1H), 3.00 (t, *J* =

6.3 Hz, 1H), 2.89 (ddt, *J* = 9.1, 4.9, 2.4 Hz, 2H), 2.25 – 1.96 (m, 2H), 1.61 (ddd, *J* = 8.9, 6.2, 1.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.5, 115.3, 61.8, 58.8, 55.6, 30.9, 30.1. HRMS (APCI) calcd for $C_7H_{12}NaO_2$ $[M+Na]^+$: 151.07350, found 151.07257.

Preparation of 1,3-diol 50. Cuprous cyanide (1.25 g, 14 mmol, 4equiv) in 8 mL ether was treated dropwise under vigorous striring with methyllithium (20 mL of 1.4 M in ether, 28 mmol, 8 equiv) at -78 ^{o}C. After adding epoxy alcohol 49 (448 mg, 3.5 mmol, 1 equiv) dropwise from a canula, the resulting mixture was warmed up to -25 ^{o}C and stirred for another 15 h. Then a solution of ammonia chloride in concentrated ammonia was added. The reaction mixture was filtered through a Celite pad, eluting with ether (50 mL). After separation of two layers, the aqueous layer was re-extracted with ether (20 mL x 3). The combined organics were dried and concentrated to give crude mixture of 1,3-diol and 1,2-diol which was dissolved in a mixture of THF and water (v/v=4:1,15 mL). $NaIO_4$ (400 mg) was added portionwise to selectively cleave the 1,2-diol and the resulting mixture was allowed to stirred for 1 h before saturated sodium bicarbonate was added to quench the reaction. After separation of two layers, the aqueous layer was re-extracted with ethyl acetate (20 mL x 3). The combined organics were dried over $MgSO_4$ and concentrated to give a crude residue which was subjected to silica gel chromatography, eluting with 50% ethyl acetate in hexane, to give the 1,3-diol (230 mg, 50%) as a colorless oil. $[\alpha]_D^{20}$ = -

23 (c = 0.25, $CHCl_3$). IR (thin film) *vmax* 3334, 3078, 2921, 2886, 1448, 1417, 1329, 1274, 1073, 1024, 994, 910, 840, 617 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.84 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.16 – 4.91 (m, 2H), 3.75 (dd, *J* = 10.8, 3.7 Hz, 1H), 3.65 – 3.43 (m, 2H), 3.32 (s, 2H), 2.32 – 2.19 (m, 1H), 2.19 – 2.08 (m, 1H), 1.76 – 1.60 (m, 2H), 1.53 (dtd, *J* = 14.4, 8.9, 5.6 Hz, 1H), 0.87 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.7, 114.9, 76.7, 67.6, 39.9, 34.4, 29.7, 13.9. HRMS (APCI) calcd for $C_8H_{17}O_2$ $[M+H]^+$: 145.12231, found 145.12220.

Preparation of primary alcohol 51. To a solution of 1,3-diol **50** (0.23 g, 1.6 mmol, 1equiv) in CH_2Cl_2 (15 mL), was added *p*-anisaldehyde dimethyl acetal (0.33 mL, 1.9 mmol, 1.2 equiv) dropwise followed by CSA (37.2 mg, 0.16 mmol, 10 mol%), and the resulting reaction mixture was stirred for 2 h before saturated $NaHCO_3$ (10 mL) was added to quench the reaction. After separation of two layers, the aqueous layer was re-extracted with CH_2Cl_2 (10 mL x 3). The combined organics were dried over $MgSO_4$ and concentrated to give a crude residue which was subjected to silica gel chromatography, eluting with 5 % ethyl acetate in hexane, to give the PMP ketal (0.4 g, 96%) as a pale yellow oil. $[\alpha]_D^{20}$ = -48 (c = 0.26, $CHCl_3$). IR (thin film) *vmax* 3074, 2953, 2930, 2837, 1516, 1302, 1247, 1170, 1114, 1030, 985, 910, 826, 634 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 5.87 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.46 (s, 1H), 5.13 – 4.95 (m, 2H), 4.11 (dd, *J* = 11.3, 4.8 Hz, 1H), 3.80 (s, 3H), 3.54 – 3.39 (m, 2H), 2.45 – 2.30 (m, 1H), 2.28 – 2.14 (m, 1H), 1.97 –

1.74 (m, 2H), 1.73 – 1.57 (m, 1H), 0.80 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8, 138.6, 131.4, 127.3, 114.7, 113.6, 100.9, 82.3, 73.0, 55.3, 33.9, 31.9, 29.2, 12.5. HRMS (APCI) calcd for $C_{16}H_{23}O_3$ $[M+H]^+$: 263.16417, found 263.16407.

To a solution of the PMP ketal (0.4 g, 1.52 mmol, 1equiv) in CH_2Cl_2 (15 mL) at 0 ^oC, obtained from the above reaction, was added a solution of DIBAL-H (9 mL of 1 M in CH_2Cl_2, 9 mmol, 6 eq) dropwise, and the resulting reaction mixture was stirred for 3 h. CH_3OH (2 mL) was added and the reaction brought to room temperature. Then a saturated solution of Na, K-tartrates (30 mL) was added and stirred 30 min to fully quench the reaction. Two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (20 mL x 3). The combined organics were dried over $MgSO_4$ and concentrated to give crude product, which was subjected to silica gel chromatography with 30% EtOAc in hexane, to provide the primary alcohol **51** (0.39 g, 98%) as a colorless oil. $[\alpha]_D^{20}$ = +15.3 (c = 0.6, $CHCl_3$). IR (thin film) *vmax* 3424, 3074, 2934, 2838, 1512, 1301, 1246, 1173, 1071, 1032, 911, 820, 751 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.83 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.12 – 4.91 (m, 2H), 4.52 (d, *J* = 10.9 Hz, 1H), 4.40 (d, *J* = 10.9 Hz, 1H), 3.78 (s, 3H), 3.63 (d, *J* = 10.9 Hz, 1H), 3.59 – 3.50 (m, 1H), 3.43 (dd, *J* = 11.1, 6.0 Hz, 1H), 2.93 (s, 1H), 2.22 – 2.10 (m, 2H), 1.91 (hd, *J* = 6.9, 4.2 Hz, 1H), 1.78 – 1.57 (m, 2H), 0.91 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 138.6, 130.4,

129.5, 114.7, 113.9, 82.7, 71.5, 66.5, 55.3, 37.9, 30.0, 28.8, 13.9. HRMS (APCI) calcd for $C_{16}H_{24}NaO_3$ $[M+Na]^+$: 287.16177, found 287.16145.

Preparation of TBS ether 52. To a solution of the primary alcohol 51 (5.8 g, 22 mmol) in 200 mL of CH_2Cl_2 was added sequentially imidazole (2.4 g, 35 mmol, 1.6 equiv) and TBSCl (4.83 g, 33 mmol, 1.5 equiv). The resulting suspension was allowed at room temperature for 3 h before 100 mL of saturated NH_4Cl was added to quench the reaction. After separation of two layers, the aqueous layer was re-extracted with CH_2Cl_2 (50 mL x 3). The combined organics were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The residue was subjected to silica gel chromatography, eluting with 2% ethyl acetate in hexane, to give the TBS ether **52** (7.9 g, 98%) as a colorless oil. $[\alpha]_D^{20}$ = -10 (c = 0.23, $CHCl_3$). IR (thin film) *vmax* 3075, 2953, 2930, 2856, 1512, 1463, 1247, 1080, 1038, 937, 834, 774, 667 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.94 – 5.69 (m, 1H), 5.16 – 4.82 (m, 2H), 4.48 (d, *J* = 10.9 Hz, 1H), 4.41 (d, *J* = 11.0 Hz, 1H), 3.81 (s, 3H), 3.62 – 3.52 (m, 2H), 3.47 (dd, *J* = 11.5, 5.8 Hz, 1H), 2.33 – 2.17 (m, 1H), 2.15 – 1.94 (m, 2H), 1.61 – 1.47 (m, 2H), 0.91 (s, 9H), 0.90 (d, *J* = 6.9 Hz, 3H), 0.05(s, 3H), 0.04 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2, 139.2, 131.3, 129.6, 114.5, 113.8, 79.1, 71.6, 65.3, 55.4, 38.4, 29.9, 29.5, 26.1, 18.4, 12.4, -5.2, -5.3. HRMS (APCI) calcd for $C_{22}H_{39}O_3$ $[M+H]^+$: 379.26630, found 379.26581.

Preparation of the aldehyde 53. TBS ether **52** (378.6 mg, 1 mmol) was

dissolved in THF/*t*BuOH (1:1, 20 mL) and H_2O (2 mL). 4-Methylmorpholine *N*-oxide (NMO) (140.6 mg, 1.2 mmol, 1.2 equiv) was added at 0 °C, followed by OsO_4 (0.13 mL, solution in *t*BuOH 1.0 mol %, 2.5% by weight). The mixture was vigorously stirred for 2.5 h at 0 °C and then for 12 h at 25 °C. After completion of the reaction, Na_2SO_3 (1.0 g) was added at 0 °C, followed by H_2O (10 mL). Stirring was continued for another 30 min, and then ether (20 mL) was added, followed by saturated aqueous NaCl solution (2 x 10 mL). The organic phase was separated, and the aqueous phase was extracted with ether (2 x 10 mL). The combined organics were dried over $MgSO_4$ and concentrated to give crude product which was subjected to the next step without chromatographic purification.

The crude residue obtained from the above dihydroxylation step was dissolved in in a mixture of THF and water (v/v=4:1,10 mL). $NaIO_4$ (428 mg, 2 mmol, 2 equiv) was added portionwise to the reaction mixture which was stirred for 2 h before $NaHCO_3$ was added to quech the reaction. The organic phase was separated and the aqueous phase was extracted with ether (10 mL x 3). The combined organics were dried over $MgSO_4$ and concentrated to give crude product, which was subjected to silica gel chromatography with 50% EtOAc in hexane, to provide the desired aldehyde **53** (300 mg, 80 % over 2 steps) as a colorless oil. $[\alpha]_D^{20}$ = -11 (c = 0.15, $CHCl_3$). IR (thin film) *vmax* 2954, 2930, 2856, 1708, 1513, 1463, 1248, 1173, 1081, 1036, 834, 775, 669 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.72 (t, *J* = 1.7 Hz, 1H), 7.24 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.7

Hz, 2H), 4.45 (d, *J* = 11.0 Hz, 1H), 4.33 (d, *J* = 11.0 Hz, 1H), 3.80 (s, 3H), 3.64 – 3.41 (m, 3H), 2.57 – 2.36 (m, 2H), 2.07 – 1.91 (m, 1H), 1.85 (dddd, *J* = 9.6, 8.1, 6.6, 3.1 Hz, 1H), 1.73 (td, *J* = 14.7, 8.1 Hz, 1H), 0.89 (s, 9H), 0.88(d, *J* = 6.4Hz), 0.05(s, 3H), 0.04 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.9, 159.4, 130.9, 129.8, 113.9, 78.7, 71.3, 65.2, 55.5, 40.5, 38.3, 26.1, 22.9, 18.5, 12.2, -5.2, -5.2. HRMS (APCI) calcd for $C_{21}H_{36}O_3NaSi$ $[M+Na]^+$: 403.22751, found 403.22697.

Preparation of the primary alcohol 54. A solution of aldehyde **53** (300 mg, 0.79 mmol) in MeOH (10 mL) was treated with $NaBH_4$ (45 mg, 1.18 mmol, 1.5 equiv) at 0 °C for 15 min. The solution was diluted with ether (50 mL), and then saturated aqueous NH_4Cl solution (10 mL) was carefully added. The organic phase was separated and the aqueous phase was extracted with ether (50 mL x 3). The combined organics were dried over $MgSO_4$ and concentrated to give crude product, which was subjected to silica gel chromatography with 20% EtOAc in hexane, to provide the desired primary alcohol 54 (280 mg, 93 %). $[\alpha]_D^{20}$ = -1 (c = 0.3, $CHCl_3$). IR (thin film) *vmax* 3387, 2952, 2929, 2881, 2856, 1513, 1463, 1247, 1059, 1035, 834, 775, 775. 668 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 4.48 (d, *J* = 10.9 Hz, 1H), 4.40 (d, *J* = 11.0 Hz, 1H), 3.78 (s, 3H), 3.56 (qd, *J* = 9.9, 5.8 Hz, 4H), 3.50 – 3.44 (m, 1H), 2.54 (br s, 1H), 2.09 – 1.94 (m, 1H), 1.76 – 1.54 (m, 3H), 1.54 – 1.42 (m, 1H), 0.90 (s, 9H), 0.87 (d, *J* = 6.9 Hz, 3H), 0.05 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4, 130.9, 129.8, 114.0, 79.5, 71.4, 65.4, 63.1,

55.4, 38.1, 28.9, 26.6, 26.2, 18.5, 12.4, -5.1, -5.2. HRMS (APCI) calcd for $C_{21}H_{39}O_4Si$ $[M+H]^+$: 383.26122, found 383.26064.

Preparation of phosphonium salt 55. A solution of alcohol **26** (300 mg, 0.78 mmol) in ether : MeCN (3:1, 8 mL) was cooled to 0 °C. Imidazole (160 mg, 2.34 mmol, 3.0 equiv), Ph_3P (306 mg, 1.17 mmol, 1.5 equiv), and iodine (297 mg, 1.17 mmol, 1.5 equiv) were sequentially added, and the mixture was stirred for 0.5 h at 0 °C. A saturated aqueous solution of Na_2SO_3 (5 mL) was added, followed by the addition of ether (20 mL). The organic phase was separated and the aqueous phase was extracted with ether (50 mL x 3). The combined organics were dried over $MgSO_4$ and concentrated to give crude product, which was subjected to silica gel chromatography with 1% EtOAc in hexane, to provide the iodide (360 mg, 94%) to be a pale yellow oil. $[\alpha]_D^{20}$ = -7.0 (c = 0.35, $CHCl_3$). IR (thin film) *vmax* 2953, 2929, 2882, 2855, 1512, 1463, 1247, 1173, 1075, 1036, 834, 774, 668 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 4.48 (d, *J* = 11.1 Hz, 1H), 4.39 (d, *J* = 11.1 Hz, 1H), 3.81 (s, 3H), 3.57 (ddd, *J* = 23.1, 9.8, 5.8 Hz, 2H), 3.51 – 3.39 (m, 1H), 3.16 (td, *J* = 6.9, 1.6 Hz, 2H), 2.07 – 1.91 (m, 2H), 1.90 – 1.74 (m, 1H), 1.70 – 1.57 (m, 1H), 1.50 (tdd, *J* = 14.2, 9.0, 5.1 Hz, 1H), 0.92 (s, 9H), 0.90 (d, *J* = 7.0 Hz, 3H), 0.07 (s, 3H), 0.07 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2, 130.9, 129.6, 113.8, 78.3, 71.2, 65.1, 55.3, 38.1, 30.9, 29.6, 26.0, 18.4, 12.3, 7.8, -5.3, -5.3. HRMS (ESI) calcd for $C_{19}H_{37}O_2INaSi$ $[M+Na]^+$: 515.14490, found 515.14415.

A mixture of iodide (360 mg, 0.73 mmol) and Ph_3P (210 mg, 0.8 mmol, 1.1 equiv) was heated neat at 50 °C for 6 h. Purification by flash column chromatography (silica gel, CH_2Cl_2; then 10% MeOH in CH_2Cl_2) provided phosphonium salt **55** (418 mg, 76%) to be yellow solid. $[\alpha]_D^{20}$ = +1.1 (c = 0.4, $CHCl_3$). IR (thin film) *vmax* 2953, 2928, 2881, 2855, 1709, 1512, 1437, 1247, 1110, 1080, 1057, 1032, 834, 776, 748, 723, 689 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.74 (m, 3H), 7.73 – 7.61 (m, 12H), 7.09 (d, *J* = 7.7 Hz, 2H), 6.69 (d, *J* = 7.6 Hz, 2H), 5.27 (d, *J* = 1.1 Hz, 2H), 4.41 (d, *J* = 11.1 Hz, 1H), 4.27 (d, *J* = 11.2 Hz, 1H), 3.74 (d, *J* = 1.2 Hz, 3H), 3.50 (d, *J* = 5.5 Hz, 2H), 3.44 (d, *J* = 15.0 Hz, 2H), 1.97 (s, 1H), 1.84 (dt, *J* = 12.8, 6.3 Hz, 1H), 1.79 – 1.52 (m, 2H), 0.83 (d, *J* = 1.1 Hz, 9H), 0.80 (d, *J* = 6.8 Hz, 3H), 0.00 (d, *J* = 0.9 Hz, 3H), -0.01 (d, *J* = 1.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 135.2, 135.1, 133.7, 133.6, 130.9, 130.6, 130.5, 129.7, 118.5, 117.6, 113.7, 78.5, 70.8, 65.1, 55.4, 53.6, 38.1, 30.4, 30.2, 26.0, 23.4, 22.9, 18.6, 18.5, 18.3, 12.4, -5.2, -5.2. HRMS (APCI) calcd for $C_{39}H_{52}O_3PSi$ $[M+H]^+$: 627.33451, found 627.34003.

Preparation of the ylide 40. A solution of **55** (352 mg, 0.47 mmol) in THF (5 ml) was added drop wise KHMDS (0.5 M, 1.88 ml, 0.94mmol, 2eq) at 0^0C and the resulting solution was stirred for 40 min at 0^0C. Freshly distilled (sparged with argon for 15 min before use) methyl chloroformate (0.036 mL, 0.52 mmol, 1.1eq) was added to the above solution and brought to room temperature. The reaction mixture was portioned between dichloromethane and water (2:1). The organic

was washed with brine, dried and concentrated. The crude yield **40** (315 mg, 98%yield) was directly used for next reaction.

Preparation of aldehyde 56. To a solution of thiazole ester (1.71 g, 10 mmol, 1 equiv) in dry CH_2Cl_2 (40 mL) was added DIBAL-H (1.00 M in CH_2Cl_2, 16 mL, 16 mmol, 1.6 equiv) via syringe pump over 20 h at –78 ^oC. The resulting reaction solution was stirred until its completion was verified by ^1H NMR (*ca.* 1h). After addition of methanol (1 mL) at -78 ^oC to quench the reaction, the mixture was warmed to room temperature and saturated aqueous Rochelle salt (20 mL) was added. The organic phase was separated and the aqueous phase was extracted with ether (50 mL x 3). The combined organics were dried over $MgSO_4$ and concentrated to give crude product, which was subjected to silica gel chromatography with 30% EtOAc in hexane, to provide the aldehyde **56** (1.14 g, 90%) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 9.95 (s, 1H), 8.03 (s, 1H), 2.76 (s, 3H). ^{13}NMR (100 MHz, $CDCl_3$) δ 184.52, 167.79, 154.95, 128.40, 19.44.

Preparation of aldehyde 57. To a solution of aromatic aldehyde **52** (0.62 g, 4.9 mmol, 1.0 equiv) in benzene (10 mL), was added 2-(triphenylphosphoranilidenyl)-propionaldehyde (1.8 g, 5.7 mmol, 1.15 equiv) at room temperature. The resulting mixture was heated at reflux until the reaction was complete as monitored by TLC (ca. 5 h). Evaporation of the solvent under reduced pressure to give solid residue, which dissolved in diethyl ether and

filtrated. Condensation of the diethyl ether followed by flash column chromatography (hexane/ethyl acetate, 5/1) produced the desired aldehyde **57** (0.72 g, 88%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.56 (s, 1H), 7.45 (s, 1H), 7.26 (d, *J* = 1.2 Hz, 1H), 2.76 (s, 3H), 2.20 (d, *J* = 1.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.4, 165.9, 151.6, 141.1, 138.4, 123.0, 19.3, 11.1.

Preparation of allylic alcohol 58. Aldehyde **57** (167 mg, 1 mmol, 1.0 equiv.) was dissolved in dry ether (5 mL) and cooled to -100 °C. To this solution was added (+)-diisopinocampheylallylborane (6mL, ca. 0.25 M in pentane, 1.5 mol, 1.5 equiv) by cannulation during 10 min at -100 ^{o}C. [(+)-Diisopinocampheylallylborane (1.5 equiv) in pentane was typically prepared by the adaptation of the original method reported by Brown 102. Allylmagnesium bromide (1.5 mL, 1 M solution in ether, 1.5 mmol) was added dropwise over 1h to a well-stirred solution of (−)-*B*-chlorodiisopinocampheylborane (0.51 g, 1.6 mmol, 1.6 equiv) in ether (6 mL) at 0 °C. After the completion of the addition, the reaction mixture was stirred at room temperature for additional 1 h and the solvent was removed under reduced pressure. The residue dissolved in pentane (6 mL) under argon, and stirring was discontinued to allow precipitation of the magnesium salts. The clear pentane solution was cannulated into another flask using a double-ended needle through a Kramer filter and used without further purification.]. After stirring at that temperature for 3 h, methanol (0.2 mL) was added and the resulting mixture was allowed to warm up to room temperature

over 40 min. Aminoethanol (0.6 mL, 10 mmol, 10 equiv) was added and stirring was continued for another 15 hr before saturated NH_4Cl was added to fully quench the reaction. The organic phase was separated and the aqueous phase was extracted with ether (10 mL x 3). The combined organics were dried over $MgSO_4$ and concentrated to give crude product, which was subjected to silica gel chromatography with 30% EtOAc in hexane, to provide the desired allylic alcohol 58 (182mg, 87%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (s, 1H), 6.43 (s, 1H), 5.70 (ddt, *J* = 17.2, 10.1, 7.1 Hz, 1H), 5.18 – 4.78 (m, 2H), 4.09 (t, *J*=7.4, 1H), 2.58 (br s, 1H, OH), 2.57 (s, 3H), 2.39 – 2.11 (m, 2H), 1.89 (d, *J* = 1.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9, 152.9, 141.8, 134.9, 119.2, 117.9, 115.6, 76.7, 40.2, 19.3, 14.6.

Preparation of TBS ether 59. Alcohol **24** (0.3 g, 1.4 mmol) was dissolved in DMF (3 mL, 0.5 M), the solution was cooled to 0 °C, and imidazole (0.15 g, 2.1 mmol, 1.5 equiv) was added. After stirring for 5 min, *tert*-butyldimethylsilyl chloride (0.26 g, 1.7 mmol, 1.2 equiv) was added portionwise and the reaction mixture was allowed to stir at 0 °C for 45 min, and then at room temperature for 2.5 h, after which time no starting alcohol was detected by TLC. Ether (5 mL) was added followed by saturated aqueous NH_4Cl solution (20 mL), the organic phase was separated, and the aqueous phase was re-extracted with ether (2 x 10 mL). The combined organics were dried over $MgSO_4$ and concentrated to give crude product, which was subjected to silica gel chromatography with 2%

EtOAc in hexane to provide TBS ether **59** (0.43, 95%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 1H), 6.46 (s, 1H), 5.78 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1H), 5.11 – 4.93 (m, 2H), 4.15 (t, *J* = 6.4 Hz, 1H), 2.70 (s, 3H), 2.42 – 2.23 (m, 2H), 2.00 (s, 3H), 0.89 (s, 9H), 0.04 (s, 3H), -0.01 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.5, 153.2, 142.1, 135.4, 118.9, 116.7, 115.2, 78.6, 41.5, 25.9, 19.3, 18.4, 14.0, -4.5, -4.8.

Preparation of aldehyde 41. TBS ether **59** (250 mg, 0.77 mmol, 1equiv) was dissolved in THF/*t*BuOH (1:1, 6 mL) and H_2O (0.6 mL). 4-Methylmorpholine *N*-oxide (NMO) (110 mg, 0.94 mmol, 1.2 equiv) was added at 0 °C, followed by OsO_4 (0.08 mL, solution in *t*BuOH 1.0 mol %, 2.5% by weight). The mixture was vigorously stirred for 2.5 h at 0 °C and then for 12 h at 25 °C. After completion of the reaction, Na_2SO_3 (1.0 g) was added at 0 °C, followed by H_2O (10 mL). Stirring was continued for another 30 min, and then ether (10 mL) was added, followed by saturated aqueous NaCl solution (2 x 5 mL). The organic phase was separated, and the aqueous phase was extracted with ether (2 x 5 mL). The combined organics were dried over $MgSO_4$ and concentrated to give crude product which was subjected to the next step without chromatographic purification.

The crude residue obtained from the above dihydroxylation step was dissolved in in a mixture of THF and water (v/v=4:1,10 mL). $NaIO_4$ (330 mg, 1.54 mmol, 2 equiv) was added portionwise to the reaction mixture which was stirred for 2 h

before $NaHCO_3$ was added to quech the reaction. The organic phase was separated and the aqueous phase was extracted with ether (10 mL x 3). The combined organics were dried over $MgSO_4$ and concentrated to give crude product, which was subjected to silica gel chromatography with 20% EtOAc in hexane, to provide the desired aldehyde **53** (178 mg, 71 % over 2 steps) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (dd, *J* = 2.8, 2.0 Hz, 1 H), 6.94 (s, 1 H,), 6.56 (s, 1 H), 4.69 (dd, *J* = 8.0, 3.6 Hz, 1 H), 2.75 (ddd, *J* = 15.2, 8.4, 2.8 Hz, 1 H), 2.71 (s, 3 H), 2.38 (ddd, *J* = 15.2, 4.4, 2.0 Hz, 1 H), 2.04 (d, *J* = 1.2 Hz, 3 H), 0.88 (s, 9 H), 0.08 (s, 3 H), 0.03 (s, 3 H) ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.6, 164.8, 152.7, 140.5, 119.4, 116.0, 74.0, 50.2, 25.8, 19.3, 18.2, 14.2, -4.5, -5.1.

Preparation of α,β-unsaturated ester 60. A solution of **40** (1.1 g, 1.45 mmol, 1.3 eq) and **41** (0.33 g, 1.12 mmol, 1eq) in benzene (12 ml, 0.1M solution) was refluxed at 120^{0}C over 16 h. The reaction mixture was brought to room temperature and filtered through small plug of silica gel, and washed out the silica gel plug with 60% ether in hexane. Filtrate was concentrated, and the crude on chromatography over silica gel with 10% ethyl acetate in hexane gave the α,β-unsaturated ester **60** (770 mg, 94%) as a pale yellow oil. $[\alpha]_D^{20}$ = +8.1 (c = 1.0, $CHCl_3$). IR (thin film) *vmax* 2952, 2929, 2856, 1712, 1609, 1512, 1463, 1248, 1199, 1073, 1035, 953, 834, 774, 668 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.22 (m, 2H), 6.90 (s, 1H), 6.83-6.79 (m, 1H), 6.82 (d, *J* = 8.7 Hz, 2H),

6.50 (s, 1H), 4.43 (d, *J* = 2.6 Hz, 2H), 4.22 (dd, *J* = 7.7, 4.8 Hz, 1H), 3.76 (s, 3H), 3.71 (s, 3H), 3.56 (d, *J* = 5.5 Hz, 2H), 3.41 (td, *J* = 6.7, 3.4 Hz, 1H), 2.70 (s, 3H), 2.58 – 2.26 (m, 4H), 2.00 (s, 3H), 1.95 (dd, *J* = 11.5, 7.5 Hz, 1H), 1.69 – 1.43 (m, 2H), 0.89 (s, 9H), 0.89 (d, *J* = 6.4 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 164.5, 159.1, 153.1, 141.7, 139.5, 133.6, 131.4, 129.4, 119.2, 115.6, 113.8, 79.3, 77.9, 71.0, 65.2, 55.3, 51.7, 38.3, 36.2, 29.6, 26.1, 25.9, 22.6, 19.4, 18.4, 18.3, 14.1, 12.8, -4.5, -4.9, -5.2, -5.3. HRMS (APCI) calcd for $C_{39}H_{66}O_6NSSi_2$ $[M+H]^+$: 732.41439, found 732.41346.

Preparation of allylic alcohol 61. To a solution of the α,β-unsaturated ester **60** (770 mg, 1.05 mmol, 1 equiv) in CH_2Cl_2 (10 mL) at -78 ^oC, obtained from the above reaction, was added a solution of DIBAL-H (4.2 mL of 1 M in CH_2Cl_2, 4.2 mmol, 4 eq) dropwise, and the resulting reaction mixture was stirred for 3 h. CH_3OH (2 mL) was added and the reaction brought to room temperature. Then a saturated solution of Na, K-tartrates (20 mL) was added and stirred 30 min to fully quench the reaction. Two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (10 mL x 3). The combined organics were dried over $MgSO_4$ and concentrated to give crude product, which was subjected to silica gel chromatography with 30% EtOAc in hexane, to provide the allylic alcohol **61** (649 mg, 88%) as a yellow oil. $[\alpha]_D^{20}$ = -2.0 (c = 0.2, $CHCl_3$). IR (thin film) *vmax* 3394, 3105, 2953, 2929, 2856, 1512, 1463, 1248, 1178, 1074, 1037, 1007, 941,

835, 775, 669 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 8.6 Hz, 2H), 6.89 (s, 1H), 6.83 (d, J = 8.6 Hz, 2H), 6.43 (s, 1H), 5.42 (t, J = 7.1 Hz, 1H), 4.42 (q, J = 11.0 Hz, 2H), 4.14 (t, J = 6.5 Hz, 1H), 4.00 (s, 2H), 3.77 (s, 3H), 3.60 – 3.48 (m, 2H), 3.47 – 3.36 (m, 1H), 2.69 (s, 3H), 2.34 (tt, J = 20.7, 7.4 Hz, 2H), 2.26 – 2.16 (m, 1H), 2.16 – 2.04 (m, 2H), 2.02 – 1.97 (m, 1H), 1.96 (s, 3H), 1.54 (ddd, J = 26.2, 16.5, 9.3 Hz, 2H), 0.89 (s, 18H), 0.86 (d, J = 7.0 Hz, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.5, 159.1, 153.1, 142.2, 140.9, 131.2, 129.5, 129.5, 123.3, 119.1, 115.1, 113.8, 79.7, 78.6, 71.2, 67.5, 65.3, 55.3, 38.2, 34.9, 28.8, 26.1, 26.0, 24.2, 19.3, 19.2, 18.4, 18.3, 14.0, 12.5, -4.5, -4.8, -5.2, -5.3. HRMS (APCI) calcd for $C_{38}H_{66}O_6NSSi_2$ $[M+H]^+$: 704.41948, found 704.41949.

Preparation of the bromide 62. To a solution of the allylic alcohol 61 (5.8 g, 8.25 mmol, 1 equiv) in CH_2Cl_2 (60 mL) at -30 ^oC was added sequentially *N*-bromosuccinimide (1.76 g, 9.90 mmol, 1.2 equiv) and triphenylphosphine (2.81 g, 10.7 mmol, 1.3 equiv). The resulting mixture was stirred for 5 min at -30 ^oC before saturated NH_4Cl (30 mL) was added to quench the reaction. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (20 mL x 3). The combined organics were dried over $MgSO_4$ and concentrated to give crude product, which was subjected to silica gel chromatography with 10% EtOAc in hexane, to provide the desired bromide **62** (5.59 g, 89%) as a yellow oil. $[\alpha]_D^{20}$ = +0.2 (c = 1.5, $CHCl_3$). IR (thin film) *vmax* 3105, 2953, 2928, 2896,

2855, 1512, 1463, 1248, 1075, 1037, 943, 834, 775, 668 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.8 Hz, 2H), 6.90 (s, 1H), 6.84 (d, *J* = 8.6 Hz, 2H), 6.46 (s, 1H), 4.43 (q, *J* = 11.0 Hz, 2H), 4.20 – 4.10 (m, 1H), 3.99 (s, 2H), 3.78 (s, 3H), 3.56 (qd, *J* = 9.8, 5.7 Hz, 2H), 3.42 (td, *J* = 7.1, 3.2 Hz, 1H), 2.70 (s, 3H), 2.30 (qdd, *J* = 19.4, 14.3, 6.5 Hz, 4H), 2.04 – 1.92 (m, 1H), 1.98 (s, 3H), 1.69 – 1.44 (m, 2H), 0.90 (s, 9H), 0.89 (s, 3H), 0.88 (d, *J*= 7.0 Hz), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.00 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.5, 159.1, 153.1, 142.0, 137.6, 131.2, 129.5, 128.7, 119.1, 115.4, 113.8, 79.4, 78.2, 71.4, 65.2, 55.4, 39.7, 38.3, 35.6, 28.6, 26.1, 26.0, 24.4, 19.4, 18.4, 18.3, 14.1, 12.6, -4.5, -4.8, -5.2, -5.3. HRMS (APCI) calcd for $C_{38}H_{65}O_4NBrSSi_2$ $[M+H]^+$: 766.33508, found 766.33528.

Preparation of the bis-TBS ether 63. To a solution of the bromide **62** (765 mg, 1 mmol, 1equiv) in THF (10 mL) at 0 ^{o}C was added lithium triethylborohydride (3 mL of 1M in THF, 3 mmol, 3 equiv) dropwise over 5 min. The resulting mixture was allow to stir at that temperature for addition 1 h before NH_4Cl (10 mL) was carefully added to quench the reaction. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (20 mL x 3). The combined organics were dried over $MgSO_4$ and concentrated to give crude product, which was subjected to silica gel chromatography with 20% EtOAc in hexane, to provide the desired bis-TBS ether **63** (652 mg, 95%) as a colorless oil. $[\alpha]_D^{20}$ = +2.3 (c = 3.2, $CHCl_3$). IR (thin film) *vmax* 3106, 2954, 2928, 2897, 2855, 1512,

1302, 1248, 1179, 1075, 1037, 940, 885, 834, 774, 668 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.6 Hz, 2H), 6.90 (s, 1H), 6.84 (d, *J* = 8.6 Hz, 2H), 6.46 (s, 1H), 5.14 (t, *J* = 6.8 Hz, 1H), 4.43 (q, *J* = 11.0 Hz, 2H), 4.14 – 4.05 (m, 1H), 3.78 (s, 3H), 3.56 (d, *J* = 5.8 Hz, 2H), 3.41 (dd, *J* = 10.5, 6.2 Hz, 1H), 2.71 (s, 3H), 2.39 – 2.17 (m, 2H), 2.10 (ddd, *J* = 20.1, 13.8, 6.9 Hz, 2H), 2.02 – 1.93 (m, 4H), 1.68 (s, 3H), 1.57 – 1.46 (m, 2H), 0.90 (s, 9H), 0.90(s, 9H) 0.88 (d, *J* = 7.0 Hz, 3H), 0.05 (s, 6H), 0.04 (s, 3H), 0.00 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 159.1, 153.6, 142.6, 137.0, 131.3, 129.5, 129.4, 121.7, 118.8, 115.1, 113.8, 79.7, 79.1, 71.3, 65.3, 55.3, 38.3, 35.4, 28.5, 27.9, 26.1, 26.0, 23.7, 19.3, 18.4, 18.34, 14.05, 12.61, -4.5, -4.8, -5.2, -5.3. HRMS (APCI) calcd for $C_{38}H_{66}O_4NSSi_2$ $[M+H]^+$: 688.42322, found 688.42384.

Preparation of primary alcohol 64. To a solution of bis-TBS ether **63** (953 mg, 1.39 mmol) in THF (15 mL) was added a buffered solution of HF.Py (3 mL) (stock solution was prepared by addition of 4 mL HF.Py to 11 mL pyridine in 22 mL of THF) at 0 °C, and the resulting reaction mixture was brought to room temperature and allowed to stir for overnigh. Sat $NaHCO_3$ solution was added to quench the reaction and two layers were separated. The aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organics were dried and concentrated to give crude mass, which was subjected to chromatography over silica gel, eluting with 40% ethyl acetate in hexane, to give the desired primary alcohol **64** (612 mg, 77%) as a colorless oil. $[\alpha]_D^{20}$ = +5.0 (c = 0.25, $CHCl_3$). IR

(thin film) *vmax* 3387, 3104, 2954, 2929, 2855, 1512, 1462, 1248, 1118, 1072, 1034, 939, 886, 834, 775, 731, 665 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J = 8.6 Hz, 2H), 6.90 (s, 1H), 6.84 (d, J = 8.5 Hz, 2H), 6.45 (s, 1H), 5.17 (t, J = 7.1 Hz, 1H), 4.53 (d, J = 10.9 Hz, 1H), 4.38 (d, J = 10.9 Hz, 1H), 4.09 (dd, J = 7.4, 5.4 Hz, 1H), 3.77 (s, 3H), 3.64 (dd, J = 10.8, 3.8 Hz, 1H), 3.55 (dd, J = 10.8, 6.7 Hz, 1H), 3.41 (dd, J = 11.4, 4.9 Hz, 1H), 2.69 (s, 3H), 2.37 – 2.17 (m, 2H), 2.17 – 2.02 (m, 2H), 1.97 (d, J = 8.4 Hz, 3H), 1.96 – 1.89 (m, 1H), 1.71 (d, J = 14.4 Hz, 3H), 1.65 (dd, J = 11.0, 5.9 Hz, 2H), 0.90 (d, J = 7.0 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 3H), -0.00 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.6, 159.3, 153.1, 142.7, 136.60, 130.4, 129.6, 122.0, 118.7, 118.7, 115.1, 114.0, 83.5, 79.2, 71.4, 66.7, 55.3, 37.6, 28.9, 26.9, 25.9, 23.7, 19.2, 18.3, 14.0, 13.9, -4.5, -4.8. HRMS (APCI) calcd for $C_{32}H_{52}O_4NSSi$ $[M+H]^+$: 574.33809, found 574.33736.

Preparation of aldehyde 39. To the solution of **64** (5.7 g, 10 mmol) in a 1:1 mixture of CH_2Cl_2 and DMSO (80 mL), was added triethylamine (6.96 mL, 50 mmol, 5 eq) followed by SO_3.Py (6.93 g, 50 mmol, 5 eq) at 0 ^{o}C and the resulting reaction mixture was stirred for 2h. Saturated NH_4Cl solution (100 mL) was added to quench the reaction. Two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (40 mL x 3). The combined organics were dried and concentrated to give crude product, which was subjected to silica gel chromatography, with 20% EtOAc in hexane, to provide the aldehyde **39** (4.28 g, 75%) as a pale yellow oil. $[\alpha]_D^{20}$ = +4.0 (c = 0.28, $CHCl_3$). IR (thin film) *vmax*

2953, 2929, 2855, 1735, 1513, 1462, 1373, 1301, 1246, 1176, 1069, 1036, 939, 834, 775, 668 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (d, *J* = 1.9 Hz, 1H), 7.23 (d, *J* = 8.6 Hz, 2H), 6.90 (s, 1H), 6.84 (d, *J* = 8.5 Hz, 2H), 6.46 (s, 1H), 5.17 (t, *J* = 6.2 Hz, 1H), 4.64 – 4.31 (m, 2H), 4.19 – 4.00 (m, 1H), 3.78 (s, 3H), 3.68 (dd, *J* = 10.8, 6.1 Hz, 1H), 2.76 – 2.62 (m, 4H), 2.39 – 2.16 (m, 2H), 2.16 – 2.05 (m, 2H), 1.98 (s, 3H), 1.68 (s, 3H), 1.65 – 1.53 (m, 2H), 1.08 (d, *J* = 7.0 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 3H), -0.00 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.6, 164.4, 159.3, 153.3, 142.5, 136.1, 130.3, 129.5, 122.3, 118.8, 115.2, 113.9, 79.0, 78.9, 71.3, 55.3, 49.3, 35.5, 29.3, 27.2, 26.0, 23.6, 19.3, 18.3, 14.1, 10.1, -4.5, -4.8. HRMS (APCI) calcd for $C_{32}H_{50}O_4NSSi$ $[M+H]^+$: 572.32244, found 572.32156.

Preparation of aldol adduct 65. To a solution of LHMDS (3mL of 1M in THF) in THF (2 mL) at -78 ^{o}C was added the ketone **38** (1g, 2.34 mmol, 2 equiv) in THF (5 mL) dropwise and the resulting mixture was stirred at -78 ^{o}C for 1 h before it was warmed up to -40 ^{o}C. After being stirred for additional 30 min at -40 ^{o}C, the reaction mixture was cooled back down to -78 ^{o}C and aldehyde 39 (0. 67 g, 1.17 mmol, 1 equiv) in THF (12 mL, *ca.* 0.1 M) was introduced to the reaction mixure very rapidly. The resulting solution was allowed to stir for 5 min before glacier acetic acid (0.3 mL in 1 mL THF) was added rapidly followed by addition of saturated NH_4Cl solution. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (20 mL x 3). The combined organics were

dried over $MgSO_4$ and concentrated to give crude product, which was subjected to silica gel chromatography with 3% to 20% EtOAc in hexane, to provide the desired aldol adduct **65** (570 mg, 61% brsm) as a colorless oil. $[\alpha]_D^{20}$ = -15.5 (c = 1.5, $CHCl_3$). IR (thin film) *vmax* 3507, 3074, 2954, 2929, 2886, 2856, 1682, 1512, 1463, 1375, 1248, 1180, 1074, 1039, 996, 834, 774, 666 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.23 (d, *J* = 8.6 Hz, 2H), 6.90 (s, 1H), 6.83 (d, *J* = 8.6 Hz, 2H), 6.44 (s, 1H), 5.76 – 5.57 (m, 1H), 5.13 (t, *J* = 7.0 Hz, 1H), 5.07 – 4.95 (m, 2H), 4.50 (d, *J* = 11.1 Hz, 1H), 4.35 (d, *J* = 11.1 Hz, 1H), 4.12 – 4.02 (m, 1H), 3.93 – 3.85 (m, 1H), 3.77 (s, 3H), 3.74 (s, 1H), 3.69 – 3.55 (m, 2H), 3.45 (d, *J* = 10.2 Hz, 1H), 3.40 (s, 1H), 3.13 (q, *J* = 6.8 Hz, 1H), 2.71 (s, 3H), 2.43 (dd, *J* = 13.8, 6.9 Hz, 1H), 2.31 (dt, *J* = 25.2, 8.9 Hz, 1H), 2.25 – 2.15 (m, 2H), 2.14 – 2.02 (m, 3H), 1.96 (d, *J* = 1.0 Hz, 2H), 1.76 – 1.56 (m, 2H), 1.67(s, 3H), 1.54 – 1.37 (m, 3H), 1.27 (s, 3H), 1.04 (s, 3H), 0.90 (s, 9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.78 (d, *J* = 6.9 Hz, 3H), 0.11(s, 3H), 0.10 (s, 3H), 0.03 (s, 9H), -0.01 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 221.6, 164.5, 159.1, 153.4, 142.9, 137.2, 134.3, 131.6, 129.4, 121.9, 118.8, 118.6, 115.1, 113.9, 79.6, 79.3, 74.4, 71.2, 71.2, 60.4, 57.8, 55.5, 42.7, 41.8, 38.0, 36.7, 35.5, 29.0, 27.4, 26.4, 26.1, 26.1, 23.7, 19.4, 18.6, 18.5, 18.4, 17.1, 14.1, 10.1, 8.9, -3.5, -3.8, -4.4, -4.7, -5.0, -5.1. HRMS (APCI) calcd for $C_{55}H_{98}O_7NSSi_3$ $[M+H]^+$: 1000.63664, found 1000.63880.

Preparation of primary alcohol 66. To the solution of **65** (370 mg, 0.36 mmol) in dichloromethane (4 mL) was added 2,6-lutidine (0.25 mL, 1.8 mmol, 5 eq) and

TBSOTf (0.42 mL, 1.8 mmol, 5 eq) at 0 ^{o}C and the resulting reaction mixture was warmed up to room temperature and stirred for 3 h. Sat. NH_4Cl solution (10 mL) was added to quench the reaction. Two layers were separated and the aqueous phase was extracted with dichloromethane (10 mL x 3). The combined organic phases were dried and concentrated to give crude product, which was subjected to silica gel chromatography with 3% ethyl acetate in hexane, to provide a tetrakis-TBS ether (365, 91%) as a colorless oil. $[\alpha]_D^{20}$ = -9.8 (c = 1.0, $CHCl_3$). IR (thin film) *vmax* 3074, 2954, 2929, 2886, 2856, 1692, 1513, 1463, 1386, 1250, 1077, 1038, 1003, 987, 929, 833, 773, 671 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.7 Hz, 2H), 6.88 (s, 1H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.45 (s, 1H), 5.62 (ddt, *J* = 17.4, 10.5, 7.2 Hz, 1H), 5.12 (t, *J* = 7.1 Hz, 1H), 5.00 – 4.85 (m, 2H), 4.41 (s, 2H), 4.08 (dd, *J* = 7.2, 5.6 Hz, 1H), 3.93 – 3.87 (m, 1H), 3.82 (dd, *J* = 7.6, 2.2 Hz, 1H), 3.78 (d, *J* = 1.3 Hz, 3H), 3.68 – 3.51 (m, 3H), 3.43 – 3.34 (m, 1H), 2.70 (s, 3H), 2.39 – 2.25 (m, 2H), 2.25 – 2.15 (m, 1H), 2.09 (dd, *J* = 14.8, 7.4 Hz, 3H), 1.97 (d, *J* = 1.1 Hz, 3H), 1.75 (dt, *J* = 7.1, 3.3 Hz, 1H), 1.67 (s, 3H), 1.66 – 1.59 (m, 2H), 1.53 – 1.38 (m, 2H), 1.08 (s, 3H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.94 (s, 9H), 0.89 (d, *J* = 7.0 Hz, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.87 (s, 9H), 0.09 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H), 0.04 (s, 6H), 0.02 (s, 6H), -0.01 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 217.9, 164.4, 159.1, 153.5, 142.7, 137.1, 134.5, 131.5, 129.4, 121.7, 118.9, 117.9, 115.2, 113.8, 79.3, 79.2, 75.5, 73.7, 70.8, 60.9, 56.9, 55.4, 46.5, 41.4, 41.2, 38.1, 35.6, 28.9, 27.2, 26.6, 26.4, 26.2, 26.1, 23.9, 19.5, 18.9, 18.7, 18.5, 18.4, 17.6, 14.7, 14.1, 13.8, -3.4, -3.4, -

3.6, -3.8, -4.4, -4.7, -5.0, -5.1. HRMS (APCI) calcd for $C_{61}H_{112}O_7NSSi_4$ $[M+H]^+$: 1114.72312, found 1114.72373.

To a solution of the tetrakis-TBS ether (300 mg, 0.27 mmol), obtained from above reaction, in THF (10 mL) was added a buffered solution of HF.Py (5 mL) (stock solution was prepared by addition of 4 mL HF.Py to 11 mL pyridine in 22 mL of THF) at 0 °C, and the resulting reaction mixture was brought to room temperature and allowed to stir for overnight. Sat $NaHCO_3$ solution was added to quench the reaction and two layers were separated. The aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organics were dried and concentrated to give crude mass, which was subjected to chromatography over silica gel, eluting with 30% ethyl acetate in hexane, to give the desired primary alcohol **66** (224 mg, 83%) as a colorless oil. $[\alpha]_D^{20}$ = -3.2 (c = 2.1, $CHCl_3$). IR (thin film) *vmax* 3406, 3074, 2953, 2929, 2886, 2856, 1688, 1513, 1463, 1249, 1179, 1074, 1039, 987, 939, 834, 774, 728, 673 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.18 (m, 2H), 6.89 (s, 1H), 6.85 – 6.77 (m, 2H), 6.44 (s, 1H), 5.57 (ddt, *J* = 17.2, 10.4, 6.9 Hz, 1H), 5.11 (t, *J* = 6.8 Hz, 1H), 4.96 (t, *J* = 12.6 Hz, 2H), 4.42 (q, *J* = 10.5 Hz, 2H), 4.08 (dd, *J* = 7.2, 5.6 Hz, 1H), 4.03 (dd, *J* = 5.8, 3.7 Hz, 1H), 3.91 (dd, *J* = 5.7, 2.5 Hz, 1H), 3.78 (s, 3H), 3.60 (br s, 3H), 3.53 – 3.41 (m, 1H), 2.70 (s, 3H), 2.40 – 2.24 (m, 2H), 2.24 – 2.12 (m, 2H), 2.11 – 2.01 (m, 2H), 1.97 (d, *J* = 0.9 Hz, 3H), 1.74 – 1.60 (m, 2H), 1.67 (s, 3H), 1.54 (dt, *J* = 7.2, 4.8 Hz, 2H), 1.50 – 1.38 (m, 1H), 1.01 (d, *J* = 7.1 Hz, 3H), 0.98 (s, 3H), 0.94 (s, 9H), 0.91 (d, *J* = 7.3 Hz, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.10 (s, 3H), 0.10 (s, 3H),

0.06 (s, 3H), 0.04 (s, 3H), 0.04 (s, 3H), -0.01 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 219.3, 164.4, 159.1, 153.3, 142.6, 136.9, 133.8, 131.3, 129.6, 121.7, 118.6, 117.9, 115.1, 113.7, 79.5, 79.1, 76.1, 71.9, 70.9, 60.5, 57.3, 55.4, 46.7, 41.2, 40.2, 38.5, 35.5, 29.1, 27.0, 26.6, 26.2, 25.9, 23.8, 19.4, 18.8, 18.5, 18.4, 16.2, 15.5, 14.6, 14.0, -3.5, -3.6, -3.7, -3.9, -4.5, -4.8. HRMS (APCI) calcd for $C_{55}H_{98}O_7NSSi_3$ $[M+H]^+$: 1000.63664, found 1000.63612.

Preparation of acid 67. To the solution of primary alcohol **66** (30 mg, 0.03 mmol) in 1:1 mixture of dichloromethane and DMSO (0.5 mL), was added triethylamine (6 μL, 0.15 mmol, 5eq) followed by SO_3.Py (6 mg, 0.15 mmol, 5 q) at 0 °C and the resulting reaction mixture was stirred for 1 h. Sat NH_4Cl solution (2 mL) was added to quench the reaction. Two layers were separated and the aqueous phase was extracted with dichloromethane (1 mL x 3). The combined organics were dried and concentrated to give crude mass, which was subjected to silica gel chromatography, eluting with 5% ethyl acetate in hexane, to provide an aldehyde (23 mg, 78%) as a pale yellow oil. $[\alpha]_D^{20}$ = -3.3 (c = 4.0, $CHCl_3$). IR (thin film) *vmax* 3075, 2954, 2930, 2887, 2856, 1727, 1693, 1513, 1463, 1250, 1077, 1038, 988, 939, 835, 775, 672 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 – 9.62 (m, 1H), 7.25 (d, *J* = 8.6 Hz, 2H), 6.88 (s, 1H), 6.82 (d, *J* = 8.7 Hz, 2H), 6.44 (s, 1H), 5.56 (ddt, *J* = 17.2, 10.3, 7.0 Hz, 1H), 5.11 (t, *J* = 6.8 Hz, 1H), 4.96 (dd, *J* = 24.0, 6.6 Hz, 2H), 4.42 (dt, *J* = 18.8, 8.7 Hz, 3H), 4.08 (dd, *J* = 7.3, 5.5 Hz, 1H), 3.92 – 3.84 (m, 1H), 3.77 (s, 3H), 3.66 – 3.56 (m, 1H), 3.50 (dt, *J* = 13.7,

6.9 Hz, 1H), 2.69 (s, 3H), 2.57 – 2.45 (m, 1H), 2.39 (ddd, *J* = 17.6, 5.3, 2.6 Hz, 1H), 2.35 – 1.98 (m, 6H), 1.96 (t, *J* = 5.0 Hz, 3H), 1.67 (s, 3H), 1.66 – 1.58 (m, 2H), 1.52 – 1.39 (m, 1H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.98 (s, 3H), 0.94 (s, 9H), 0.90 (d, *J* = 7.2 Hz, 3H), 0.88 (s, 9H), 0.84 (s, 9H), 0.09 (s, 6H), 0.05 (s, 3H), 0.03 (s, 3H), -0.01 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 218.4, 201.2, 164.4, 159.1, 153.3, 142.6, 136.8, 133.3, 131.3, 129.6, 121.7, 118.8, 118.4, 115.1, 113.7, 79.4, 79.1, 76.7, 70.9, 70.2, 56.5, 55.3, 49.3, 46.9, 40.9, 39.9, 35.5, 28.9, 26.6, 26.5, 26.1, 25.9, 23.8, 19.3, 18.8, 18.3, 18.3, 16.9, 15.8, 14.6, 14.0, -3.5, -3.6, -3.9, -4.3, -4.5, -4.8. HRMS (APCI) calcd for $C_{55}H_{96}O_7NSSi_3$ $[M+H]^+$: 998.62099, found 998.61966.

To a solution of the aldehyde (20 mg, 0.02 mmol), obtained in the preceding step, in ^{t}BuOH : H_2O (5:1, 0.6 mL) was added sequentially, 2-methyl-2-butene (0.5 mL of 2 M in THF, 1 mmol, 50 eq), $NaClO_2$ (5.4 mg, 0.06 mmol, 3 eq) and NaH_2PO_4 (3.6 mg, 0.03 mmol, 1.5 eq). The resulting reaction mixture was stirred for 1 h. Volatiles were removed and the residue was portioned between ethyl acetate and brine solution. Two layers were separated and the aqueous layer was extracted with ethyl acetate (1 mL x 3). The combined organics were dried and concentrated to give crude mass which was subjected to chromatography over silica gel, eluting with 40% ethyl acetate in hexane, to give acid **67** (19 mg, 94%) as a yellow oil. $[\alpha]_D^{20}$ = -1.0 (c = 0.8, $CHCl_3$). IR (thin film) *vmax* 3075, 2953, 2928, 2855, 1711, 1694, 1513, 1463, 1250, 1178, 1075, 1039, 988, 941, 833, 775, 675 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.5 Hz, 2H), 6.89

(s, 1H), 6.82 (d, *J* = 8.4 Hz, 2H), 6.51 (s, 1H), 5.68 – 5.48 (m, 1H), 5.11 (t, *J* = 7.0 Hz, 1H), 4.96 (t, *J* = 13.7 Hz, 2H), 4.38 (ddd, *J* = 13.8, 9.1, 6.3 Hz, 3H), 4.09 (dd, *J* = 7.5, 5.4 Hz, 1H), 3.92 – 3.83 (m, 1H), 3.78 (s, 3H), 3.61 (dd, *J* = 10.6, 5.8 Hz, 1H), 3.50 (dt, *J* = 13.3, 6.8 Hz, 1H), 2.70 (s, 3H), 2.48 (dd, *J* = 17.0, 2.1 Hz, 1H), 2.38 – 2.24 (m, 3H), 2.24 – 2.12 (m, 2H), 2.12 – 2.01 (m, 2H), 1.95 (s, 3H), 1.75 – 1.61 (m, 1H), 1.67 (s, 3H), 1.49 – 1.37 (m, 1H), 1.35 – 1.23 (m, 1H), 1.0 (s, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.94 (s, 9H), 0.89 (d, *J*= 7.0Hz, 3H), 0.88 (s, 9H), 0.84 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H), -0.01 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 218.1, 177.0, 164.8, 159.0, 153.1, 142.9, 137.0, 133.6, 131.4, 129.4, 121.6, 118.7, 118.3, 114.9, 113.7, 79.3, 79.2, 76.5, 72.5, 70.8, 56.8, 55.4, 46.7, 40.9, 40.0, 39.9, 35.5, 28.8, 26.7, 26.6, 26.2, 25.9, 23.8, 19.1, 18.8, 18.4, 18.4, 17.0, 15.5, 14.5, 14.0, -3.5, -3.5, -4.0, -4.5, -4.5, -4.8. HRMS (APCI) calcd for $C_{55}H_{96}O_8NSSi_3$ $[M+H]^+$: 1014.61590, found 1014.61564.

Preparation of hydroxy acid 37. To a solution of acid **67** (880 mg, 0.87mmol) in THF (15 mL) was added tetrabutyl ammonium bromide (0.1 M, 5.22 mL, 5.22 mmol, 6 eq) at 0 °C and the resulting reaction mixture was brought to 15 °C and left it without stirring for 8 h. Saturated NH_4Cl solution was added to quench the reaction and the product was extracted with ethyl acetate (30 mL x 3). The combined organics were dried and concentrated to give crude product, which was subjected to chromatography over silica gel, eluting with 40% ethyl acetate

in hexane, to give hydroxyl acid **37** (572 mg, 73%) as a white foam. $[\alpha]_D^{20}$ = -9.2 (c = 0.4, $CHCl_3$). IR (thin film) *vmax* 3074, 2953, 2929, 2856, 1710, 1513, 1463, 1380, 1250, 1179, 1077, 1038, 989, 955, 875, 833, 776, 670 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.6 Hz, 2H), 6.91 (s, 1H), 6.82 (d, *J* = 8.6 Hz, 2H), 6.57 (s, 1H), 5.66 – 5.48 (m, 1H), 5.15 (t, *J* = 6.9 Hz, 1H), 4.97 (t, *J* = 12.9 Hz, 2H), 4.42 (s, 2H), 4.35 (dd, *J* = 6.9, 2.5 Hz, 1H), 4.14 (dd, *J* = 7.2, 4.7 Hz, 1H), 3.88 (dd, *J* = 5.9, 2.6 Hz, 1H), 3.77 (s, 3H), 3.61 (dd, *J* = 14.2, 5.4 Hz, 1H), 3.48 (dt, *J* = 13.4, 6.8 Hz, 1H), 2.70 (s, 3H), 2.54 – 2.44 (m, 1H), 2.40 – 2.25 (m, 3H), 2.22 – 2.05 (m, 2H), 1.98 (d, *J* = 0.9 Hz, 3H), 1.82 – 1.62 (m, 1H), 1.71 (s, 3H), 1.45 (td, *J* = 13.9, 7.1 Hz, 1H), 1.37 – 1.18 (m, 1H), 1.01(s, 3H), 1.00 (d, *J* = 6.5 Hz, 3H), 0.94 (s, 9H), 0.90 (d, *J* = 7.2 Hz, 3H), 0.84 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), 0.05 (s, 3H), 0.00 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 217.9, 176.7, 164.9, 159.1, 152.8, 141.9, 139.6, 133.6, 131.3, 129.5, 120.2, 118.9, 118.4, 115.5, 113.7, 79.2, 76.5, 72.5, 70.9, 56.8, 55.4, 46.7, 40.9, 40.0, 39.9, 34.2, 29.8, 28.9, 26.7, 26.6, 26.2, 23.9, 19.1, 18.8, 18.4, 17.1, 15.4, 14.6, 14.5, -3.5, -3.5, -4.0, -4.5. HRMS (APCI) calcd for $C_{49}H_{82}O_8NSSi_2$ $[M+H]^+$: 900.52942, found 900.52828.

Preparation of the macrolactone 68. A slurry of seco acid **18** (380 mg, 0.42 mmol) and $NaHCO_3$ (9.0 g, 10.7 mmol) in CH_2Cl_2 (800 mL) was treated with solid 2-bromo-1-ethylpyridinium tetrafluoroborate **22** (2.3 g, 8.3 mmol) in one portion. The reaction mixture was vigorously stirred in the dark overnight, then

filtered and the filtrate was transferred directly onto a silica gel column and purified by flash chromatography to provide the macrolactone **68** (266 mg, 70%) as a white foam. $[\alpha]_D^{20}$ = -15 (c = 0.1, $CHCl_3$). IR (thin film) *vmax* 3074, 2952, 2929, 2855, 1739, 1694, 1514, 1462, 1389, 1300, 1249, 1184, 1109, 1075, 1039, 999, 938, 872, 831, 775, 670 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 2H), 6.92 (s, 1H), 6.90 (d, J = 8.5 Hz, 2H), 6.41 (s, 1H), 5.70 – 5.47 (m, 1H), 5.28 – 5.17 (m, 1H), 5.00 (d, J = 10.1 Hz, 1H), 4.90 (d, J = 16.8 Hz, 2H), 4.46 (d, J = 9.6 Hz, 2H), 4.37 – 4.09 (m, 2H), 4.09 – 3.93 (m, 1H), 3.77-3.79 (m, 2H), 3.74 (s, 3H), 3.41 – 3.21 (m, 1H), 3.03 (s, 2H), 2.80 – 2.74 (m, 1H), 2.71 (s, 3H), 2.31 (d, J = 16.7 Hz, 1H), 2.19 (d, J = 7.7 Hz, 2H), 2.12-2.01 (m, 1H), 2.08 (s, 3H), 1.99 – 1.80 (m, 2H), 1.79 – 1.56 (m, 2H), 1.71 (s, 3H), 1.38-1.23 (m, 1H), 1.07 (s, 3H), 0.99 (s, 9H), 0.94 (s, 3H), 0.82 (s, 9H), 0.18 (s, 3H), 0.16 (s, 3H), 0.07 (s, 3H), -0.14 (s, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 214.9, 171.9, 164.6, 159.2, 152.9, 139.1, 133.5, 131.7, 129.9, 129.7, 120.7, 118.6, 116.4, 113.9, 81.7, 80.2, 75.5, 56.6, 55.4, 40.8, 33.3, 29.9, 26.9, 26.5, 23.4, 19.8, 19.1, 18.9, 15.3, -3.4, -3.5. HRMS (APCI) calcd for $C_{49}H_{80}O_7NSSi_2$ $[M+H]^+$: 882.51886, found 882.51757.

Preparation of 69. To a solution of macrolactone **68** (226 mg, 0.26 mmol), obtained from the above step, in a mixture of CH_2Cl_2 (3 mL) and pH =7.0 buffer (0.15 mL) at 0 ^oC was added DDQ (88 mg, 0.56 mmol) and the resulting suspension was stirred at that temperature for additional 3 h before $NaHCO_3$

was added to quench the reaction. Two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (4 mL x 3). The combined organics were dried and concentrated to give crude product, which was subjected to silica gel chromatography, with 5 % ethyl acetate in hexane, to provide the desired **69** (131 mg, 67%) as colorless oil. $[\alpha]_D^{20}$ = -20 (c = 0.8, $CHCl_3$). IR (thin film) *vmax* 2953, 2929, 2856, 1734, 1693, 1463, 1389, 1188, 1098, 1039, 993, 828, 797, 731, 669 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 6.94 (s, 1H), 6.56 (s, 1H), 5.66 (dt, *J* = 16.9, 7.4 Hz, 1H), 5.26 – 5.13 (m, 1H), 5.12 – 5.02 (m, 2H), 4.90 (d, *J* = 9.3 Hz, 1H), 4.09 (d, *J* = 11.4 Hz, 1H), 3.99 (d, *J* = 9.9 Hz, 1H), 3.91 – 3.77 (m, 1H), 3.67 – 3.52 (m, 2H), 3.48 (t, *J* = 10.0 Hz, 1H), 3.09 (s, 1H), 2.82 (dd, *J* = 13.3, 9.4 Hz, 2H), 2.70 (s, 3H), 2.50 (dd, *J* = 14.0, 7.6 Hz, 1H), 2.34 (dd, *J* = 14.2, 6.3 Hz, 1H), 2.09 (d, *J* = 1.0 Hz, 3H), 2.03 (d, *J* = 9.7 Hz, 1H), 1.94 – 1.75 (m, 2H), 1.69 (s, 3H), 1.55-1.43 (m, 1H), 1.44 – 1.32 (m, 1H), 1.14 (s, 3H), 1.10 (d, *J* = 6.8 Hz, 3H), 0.97 (s, 9H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.84 (s, 9H), 0.18 (s, 3H), 0.13 (s, 3H), 0.10 (s, 3H), -0.14 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.0, 172.2, 164.6, 152.9, 140.4, 139.4, 132.9, 120.3, 119.1, 119.01, 116.0, 80.1, 76.2, 75.6, 57.0, 51.6, 42.6, 40.8, 38.1, 34.8, 33.0, 29.9, 27.7, 26.5, 26.5, 26.3, 23.6, 21.3, 19.4, 18.9, 18.7, 18.2, 15.5, -2.8, -3.2, -3.9, -5.7. HRMS (APCI) calcd for $C_{41}H_{72}O_6NSSi_2$ $[M+H]^+$: 762.46134, found 762.46284.

Preparation of 76. To a stirred suspension of (ethyl)triphenylphosphonium iodide (1.673 g, 4.0 mmol, 2.0 equiv) in THF (20 mL) was added *n*-butyllithium

(1.6 mL, 2.5 M in hexane, 4.0 mmol, 2.0 equiv) at 0 ^{o}C. The resulting clear red solution was added dropwise to a solution of iodine (1.015 g, 4.0 mmol, 2.0 equiv) in THF (40 mL) at -78 ^{o}C. After warming to -30 ^{o}C, the mixture was treated with NaHMDS (3.8 mL, 1 M in THF, 3.8 mmol, 1.9 equiv). The mixture was stirred for 30 min, and cooled to -78 ^{o}C again, to which was added aldehyde **41** (0.651 g, 2.0 mmol, 1.0 equiv) in THF (10 mL) dropwise within 10 min. The mixture was warmed to -30 ^{o}C gradually, stirred for 10 min at -30 ^{o}C, and quenched with saturated aqueous NH_4Cl solution (5 mL). Half of the solvents were removed under reduced pressure and the concentrated mixture was diluted with pentane (100 mL), filtered through a small silica gel pad. The silica gel pad was eluted with pentane/Et_2O (4:1, 50 mL). The filtrate was concentrated, purified by flash chromatography (gradient elution, hexanes→10/1, hexanes/ethyl acetate) to afford vinyl iodide **76** (620, 67%) as a yellow oil. $[\alpha]_D^{20}$ = + 14.1 (*c* = 1.0, $CHCl_3$). IR (thin film) *vmax* 2953, 2927, 2855, 1653, 1504, 1471, 1250, 1183, 1065, 1030, 938, 833, 774, 730, 666, 573 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (s, 1H), 6.49 (s, 1H), 5.45 (td, *J* = 6.7, 1.3 Hz, 1H), 4.21 (t, *J* = 6.4 Hz, 1H), 2.70 (s, 3H), 2.48 (d, *J* = 1.1 Hz, 3H), 2.45 – 2.28 (m, 2H), 2.02 (s, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.5, 153.2, 141.8, 132.2, 119.0, 115.4, 102.5, 77.4, 43.8, 33.8, 25.9, 19.4, 18.3, 14.2, -4.5, -4.9. HRMS (APCI) calcd for $C_{18}H_{31}INOSSi$ $[M+H]^+$ 464.09403, found 464.09278.

Preparation of hydroxy vinyl iodide 72. To a solution of the vinyl iodide **76** (460 mg, 1 mmol), obtained from above reaction, in THF (10 mL) was added a solution of HF.Py (2 mL) at 0 °C, and the resulting reaction mixture was brought to room temperature and allowed to stir for 5 h. Sat $NaHCO_3$ solution was added to quench the reaction and two layers were separated. The aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organics were dried and concentrated to give crude mass, which was subjected to chromatography over silica gel, eluting with 40% ethyl acetate in hexane, to give the desired hydroxy vinyl iodide **72** (269 mg, 77%) as a yellow oil. IR (thin film) *vmax* 3286, 2948, 2914, 2854, 1507, 1428, 1188, 1053, 1025, 880, 731, 669 cm^{-1}. $[\alpha]_D^{20}$ = -9.0 (*c* = 0.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 1H), 6.56 (s, 1H), 5.53 (td, *J* = 6.5, 1.5 Hz, 1H), 4.24 (t, *J* = 6.4 Hz, 1H), 3.28 (s, 1H), 2.68 (s, 3H), 2.48 (d, *J* = 1.4 Hz, 3H), 2.41 (ddd, *J* = 8.6, 2.8, 1.4 Hz, 2H), 2.00 (d, *J* = 1.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.8, 152.6, 141.8, 131.7, 119.0, 115.5, 103.1, 76.2, 42.6, 33.8, 19.1, 14.6. HRMS (APCI) calcd for $C_{12}H_{17}ONIS$ $[M+H]^+$ 350.00701, found 350.00659.

Preparation of Weinreb amide 77. Methyl (*R*)-(-)-3-hydroxy-2-methylpropionate (1.0 g, 8.5 mmol) was dissolved in CH_2Cl_2 (30 ml), and the solution was sequentially treated with imidazole (691 mg, 10.2 mmol) and TBSCl (1.4 g, 9.3 mmol). The reaction mixture was stirred at room temperature for 5 h over which time imidazole-HCl precipitated out of solution. The reaction was then filtered,

and the filtrate was concentrated and purified by chromatography (EtOAc: Hexane, 1: 50) to provide a *tert*-butyldimethylsilyl ether (1.97 g, quant.) as colorless oil. $[\alpha]_D^{20}$ = - 17 (c = 0.3, $CHCl_3$). IR (thin film) *vmax* 2955, 2930, 2858, 1705, 1463, 1385, 1255, 1096, 1007, 940, 836, 775, 665 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 3.71 (ddd, *J* = 9.6, 6.9, 0.5 Hz, 1H), 3.63-3.55 (m, 4H), 2.66-2.50 (m, 1H), 1.07 (dd, *J* = 7.1, 0.5 Hz, 3H), 0.81 (d, *J* = 0.7 Hz, 9H), -0.03 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.5, 65.4, 51.6, 42.6, 25.89, 18.3, 13.6, -5.4, -5.4. HRMS (APCI) calcd for $C_{11}H_{25}O_3Si$ $[M+H]^+$ 233.15675, found 233.15670.

To a suspension of the *tert*-butyldimethylsilyl ether (10 g, 42.97 mmol), obtained from preceding step, and *N,O*-dimethylhydroxyamine hydrochlororide (6.3 g, 64.6 mmol) at -20 °C was added *i*-PrMgCl (65 mL of 2M in THF, 130 mmol) to create a homogeneous solution. After stirring at -10 °C for additional 30 min, the reaction was quenched by addition of an aqueous NH_4Cl solution (200 mL). The product was extracted with ethyl acetate (100 mL x 3). The combined organics were dried and concentrated to give crude product, which was subjected to chromatography over silica gel, eluting with 20% ethyl acetate in hexane, to give the desired Weinreb amide **77** (10.8 g, 97%) as pale yellow oil. $[\alpha]_D^{20}$ = - 4.1 (c = 1.0, $CHCl_3$). IR (thin film) *vmax* 2955, 2932, 2858, 1663, 1467, 1418, 1387, 1254, 1099, 997, 836, 776, 736, 665 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 3.85 – 3.76 (m, 1H), 3.68 (d, *J* = 1.9 Hz, 3H), 3.50 (ddd, *J* = 9.4, 6.1, 1.6 Hz, 1H), 3.17 (s, 3H), 3.14 – 3.08 (m, 1H), 1.04 (dd, *J* = 6.9, 1.8 Hz, 3H), 0.84 (d, *J* = 1.9 Hz, 8H), 0.01 (dd, *J* = 3.8, 1.7 Hz, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.2, 65.8,

61.6, 38.2, 32.1, 25.9, 18.4, 13.9, -5.3, -5.3. HRMS (APCI) calcd for $C_{12}H_{28}O_3NSi$ $[M+H]^+$ 262.18330, found 262.18323.

Preparation of propargyl ketone 78. Weinreb amide **77** (10 g, 38 mmol) was dissolved in THF (75 mL, 0.5 M), cooled to 0 °C and treated dropwise with ethylnylmagnesium bromide (115 mL of 0.5 M in THF, 57.5 mmol). The resulting solution was stirred at 0 °C for additional 2 h before quenching by addition of an aqueous NH_4Cl solution (100 mL). The product was extracted with ethyl acetate (100 mL x 3). The combined organics were dried and concentrated to give crude product, which was subjected to chromatography over silica gel, eluting with 3% ethyl acetate in hexane, to give the desired propargyl ketone **78** (7.2 g, 84%) as pale yellow oil. $[\alpha]_D^{20}$ = -13.3 (c = 1.0, $CHCl_3$). IR (thin film) *vmax* 3256, 2956, 2931, 2858, 2091, 1684, 1470, 1255, 1389, 1255, 1105, 1064, 1033, 837, 777, 668 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 3.95 – 3.75 (m, 2H), 3.23 (dd, *J* = 5.3, 0.6 Hz, 1H), 2.86 – 2.70 (m, 1H), 1.22 – 1.12 (m, 3H), 0.86 (t, *J* = 1.3 Hz, 9H), 0.03 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.8, 80.8, 79.2, 64.5, 51.2, 25.9, 18.4, 12.4, -5.4, -5.7. HRMS (APCI) calcd for $C_{12}H_{23}O_2Si$ $[M+H]^+$ 227.14619, found 227.14616.

Preparation of propargylic alcohol 79. Ketone **78** (2.26 g, 10 mmol) was dissolved in THF (50 mL, 0.2 M) and cooled to -30 °C. To this solution was added 2-methyl (*R*)-CBS oxazaborolidine (20 mL of 1 M in toluene, 20 mmol, 2 equiv), and boranedimethyl sulfide (15 mL of a 2 M in THF, 30 mmol, 3 equiv)

was added dropwise over 20 min. After the resulting reaction mixture was stirred for 1 h at -30 °C, the reaction was quenched by addition of ethanol (30 mL), warmed to room temperature, and diluted with water (100 mL) and diethyl ether (100 mL). The organic layer was dried ($MgSO_4$), concentrated, and purified by flash column chromatography, eluting with 3% ethyl acetate in hexane, to provide the desired propargylic alcohol **79** (2.17 g, 95%) as colorless oil. $[\alpha]_D^{20}$ = - 5.5 (c = 1.0, $CHCl_3$). IR (thin film) *vmax* 3425, 3311, 2955, 2929, 2857, 1471, 1389, 1253, 1092, 1025, 939, 834, 776, 654, 628 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 4.45 – 4.34 (m, 1H), 3.94 (dd, *J* = 10.1, 3.9 Hz, 1H), 3.66 – 3.52 (m, 2H), 2.50 – 2.42 (m, 1H), 2.00 – 1.87 (m, 1H), 1.67 (s, 1H), 1.03 (t, *J* = 6.2 Hz, 3H), 0.94 – 0.82 (m, 9H), 0.07 (s, 3H), 0.07 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 84.0, 73.4, 66.9, 40.5, 25.9, 18.3, 13.1, -5.5, -5.5. HRMS (APCI) calcd for $C_{12}H_{25}O_2Si$ $[M+H]^+$ 229.16184, found 229.16199.

Preparation of allylic alcohol 80. The propargylic alcohol **79** (300 mg, 1.3 mmol) was added to a proper flask for hydrogenation containing quinoline (0.3 mL, 2.6 mmol, 2 equiv) and Lindlar catalyst (125 mg) dispersed in absolute MeOH (50 mL). The mixture was cooled to 0 °C and shaken in a Parr hydrogenator for 10 min at 15 psi (reaction followed by TLC). The catalyst was removed by filtration through Celite and the product was purified by flash chromatography, eluting with 3% ethyl acetate in hexane, to provide the desired allylic alcohol **80** (275 mg, 91%) as colorless oil. $[\alpha]_D^{20}$ = - 15.2 (c = 1.0, $CHCl_3$).

IR (thin film) *vmax* 3422, 3105, 2956, 2930, 2858, 1469, 1390, 1254, 1085, 1006, 921, 834, 775, 667 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.00 – 5.67 (m, 1H), 5.41 – 5.00 (m, 2H), 4.11 – 3.90 (m, 1H), 3.90 – 3.69 (m, 2H), 3.60 – 3.51 (m, 1H), 1.90 (d, *J* = 12.1 Hz, 1H), 1.81 – 1.62 (m, 1H), 0.92 – 0.78 (m, 12H), 0.05 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.9, 115.6, 78.2, 67.9, 39.8, 25.9, 18.2, 13.6, -5.5, -5.5. HRMS (APCI) calcd for $C_{12}H_{27}O_2Si$ $[M+H]^+$ 231.17749, found 231.17746.

Preparation of primary alcohol 81. To a solution of the allylic alcohol **80** (275 mg, 1.19 mmol, 1 equiv) in CH_2Cl_2 (4 ml, 0.3 M) at room temperature was sequentially added freshely prepared 4-methoxybenzyltrichloroacetimidate (504 mg, 1.8 mmol, 1.5 equiv) and camphorsulfonic acid (13 mg, 0.06 mmol, 5 mol%). The resulting homogenous solution was allowed to stir for overnight before quenching by addition of an aqueous $NaHCO_3$ solution (5 mL). The aqueous layer was re-extracted with CH_2Cl_2 (5 mL x 3). The combined organics were dried and concentrated to give crude product, which was subjected to chromatography over silica gel, eluting with 1% ethyl acetate in hexane, to give the desired PMB ether (358 mg, 86%) as yellow oil. $[\alpha]_D^{20}$ = +15.5 (c = 1.0, $CHCl_3$). IR (thin film) *vmax* 3104, 2954, 2930, 2857, 1613, 1513, 1464, 1388, 1301, 1247, 1173, 1076, 1036, 1003, 925, 833, 774, 667 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 5.81 – 5.65 (m, 1H), 5.32 – 5.17 (m, 2H), 4.59(d, *J* = 11.2 Hz, 1H), 4.26 (d, *J* = 11.2 Hz, 1H),

3.81 (s, 3H), 3.73 (t, *J* = 8.0, Hz, 1H), 3.59 (d, *J* = 5.6 Hz, 2H), 1.86 (m, 1H), 0.90 (s, 9H), 0.88 (d, *J* = 6.9 Hz, 3H), 0.05 (dd, *J* = 5.7, 2.7 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2, 137.3, 131.2, 129.4, 118.4, 113.9, 81.6, 70.1, 64.8, 55.5, 40.3, 26.2, 18.5, 13.1, -5.2，-5.2. HRMS (APCI) calcd for $C_{20}H_{35}O_3Si$ $[M+H]^+$ 351.23500, found 351.23483.

To a solution of the PMB ether (358 mg, 1.02 mmol) in THF (10 ml) was added tetrabutylammonia fluoride (1.32 mL, 1.32 mmol, 1.3 equiv). The resulting mixture was stirred for 5 h before quenching by addition of aqueous NH_4Cl (10 mL). The aqueous layer was re-extracted with ethyl acetate (10 mL x 3). The combined organics were dried and concentrated to give crude product, which was subjected to chromatography over silica gel, eluting with 50% ethyl acetate in hexane, to give the desired primary alcohol **81** (236 mg, 98%) as colorless oil. $[\alpha]_D^{20}$ = + 56.8 (c = 1.0, $CHCl_3$). IR (thin film) *vmax* 3471, 3103, 2966, 2931, 2879, 1727, 1682, 1506, 1456, 1376, 1255, 1209, 1177, 1058, 995, 913, 732, 669, 650 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* =8.8 Hz, 2H), 6.91 (d, *J* =8.8 Hz, 2H), 5.81 – 5.61 (m, 1H), 5.38 – 5.14 (m, 2H), 4.53 (dd, *J* = 11.1, 1H), 4.25 (d, *J* = 11.4 Hz, 1H), 3.77 (s, 3H), 3.65 – 3.55 (m, 3H), 3.19 (br s, 1H), 1.96 – 1.75 (m, 1H), 0.81 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2, 137.2, 130.1, 129.4, 118.9, 113.9, 85.8, 69.9, 67.1, 55.2, 39.6, 13.6. HRMS (ESI) calcd for $C_{14}H_{20}O_3Na$ $[M+Na]^+$ 259.13047, found 259.13036.

Preparation of aldehyde 74. To the solution of **81** (41.8 g, 7.63 mmol) in a 1:1 mixture of CH_2Cl_2 and DMSO (50 mL), was added triethylamine (5.3 mL, 38

mmol, 5 eq) followed by SO_3.Py (5.3 g, 38 mmol, 5 eq) at 0 ^oC and the resulting reaction mixture was stirred for 2h. Saturated NH_4Cl solution (150 mL) was added to quench the reaction. Two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (20 mL x 3). The combined organics were dried and concentrated to give crude product, which was subjected to silica gel chromatography, with 10% EtOAc in hexane, to provide the aldehyde **74** (1.29 g, 72%) as colorless oil. $[\alpha]_D^{20}$ = + 66.5 (c = 1.0, $CHCl_3$). IR (thin film) *vmax* 3103, 2964, 2936, 2837, 1725, 1612, 1513, 1462, 1301, 1246, 1174, 1062, 1033, 995, 933, 819, 757, 706 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.69 (d, *J* = 2.6 Hz, 1H), 7.20 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 5.83 – 5.59 (m, 1H), 5.47 – 5.18 (m, 2H), 4.55 (d, *J* = 11.5 Hz, 1H), 4.28 (d, *J* = 11.5 Hz, 1H), 3.91 (t, *J* = 8.1 Hz, 1H), 3.79 (s, 3H), 2.61 – 2.50 (m, 1H), 0.98 (dd, *J* = 8.6, 4.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.0, 159.3, 135.9, 130.2, 129.5, 119.9, 113.9, 80.9, 69.9, 55.3, 50.5, 10.7. HRMS (ESI) calcd for $C_{14}H_{18}O_3Na$ $[M+Na]^+$ 257.11482, found 257.11480.

Preparation of 82. A solution of freshly prepared LDA (2 M, 3.85 mL, 7.71 mmol, 2.6 eq) in THF was added to a solution of **44** (0.78 g, 2.97 mmol) in THF (20 mL) at -78 ^oC, and the resulting solution was stirred brought to -20 ^oC and stirred for 30 min. Prenyl bromide (0.4 mL, 4.4 mmol, 1.5 eq) in HMPA (1.48 mL, 8.28 mmol, 1.08 eq to LDA) was added to the above reaction at -78 ^oC and the reaction mixture was brought to -20 ^oC and stirred for 1 h. Sat NH_4Cl (50 mL)

was added to quench the above reaction. The two layers were separated and aqueous phase was extracted with ether (20 x 3). The combined organics were washed with water, brine, dried and concentrated to give the crude mass, which was subjected to silica gel chromatography, with 5% ethyl acetate in hexane, to provide the prenyl derivative (686 mg, 70%) as a pale yellow oil. $[\alpha]_D^{20}$ = -3.0 (c = 2.6, $CHCl_3$). IR (thin film) *vmax* 3504, 2953, 2929, 2885, 2857, 1735, 1462, 1385, 1361, 1253, 1163, 1089, 938, 833, 776, 663 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.04 (dddd, *J* = 7.3, 6.0, 2.8, 1.4 Hz, 1H), 3.97 – 3.89 (m, 1H), 3.89 – 3.81 (m, 1H), 3.77 (ddd, *J* = 10.2, 7.5, 4.6 Hz, 1H), 3.66 (d, *J* = 8.9 Hz, 3H), 3.42 (d, *J* = 5.2 Hz, 1H), 2.53 – 2.41 (m, 1H), 2.39 – 2.19 (m, 2H), 1.76 – 1.62 (m, 2H), 1.66 (s, 3H), 1.59 (s, 3H), 0.93 – 0.82 (m, 9H), 0.04 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4, 134.2, 120.6, 71.3, 61.8, 51.7, 51.6, 36.8, 27.6, 26.1, 25.9, 18.3, 17.8, -5.4, -5.4. HRMS (APCI) calcd for $C_{17}H_{35}O_4Si$ $[M+H]^+$ 331.22991, found 331.23007.

To a freshly prepared solution of LDA (0.6 M, 5.5 mmol, 2.6 eq) in THF (24 mL), a solution of the prenyl derivative, obtained from the above reaction, (686 mg, 2.08 mmol) in THF (55 mL) was added at -78 ^oC, and the resulting solution was brought to -20 ^oC and stirred for 4 h. Then a solution of methyl iodide (0.21 mL, 3.39 mmol, 1.6 eq) in HMPA (5.95 mmol, 1.08 eq to LDA) was added to the above reaction at -78 ^oC, then, the reaction mixture was brought to -20 ^oC and stirred for 48 h. Saturated NH_4Cl (20 mL) was added to quench the above reaction. The two layers were separated and aqueous phase was extracted with

ether (10 x 3). The combined organic phases were washed with water, brine, dried, and concentrated to give the crude mass, which was subjected to silica gel chromatography, with 5% ethyl acetate in hexane, to provide **82** (465 mg, 65%) as yellow oil. $[\alpha]_D^{20}$ = -0.5 (c = 0.71, $CHCl_3$). IR (thin film) *vmax* 3512, 2952, 2929, 2857, 1727, 1463, 1385, 1361, 1255, 1227, 1195, 1174, 1083, 988, 836, 777, 683 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.12 (t, *J* = 7.4 Hz, 1H), 3.91 (ddd, *J* = 10.6, 5.2, 1.3 Hz, 1H), 3.87 – 3.72 (m, 2H), 3.67 (s, 2H), 3.17 (d, *J* = 5.2 Hz, 1H), 2.34 (tt, *J* = 22.8, 7.6 Hz, 2H), 1.80 – 1.63 (m, 2H), 1.66 (s, 3H), 1.59 (d, *J* = 7.9 Hz, 3H), 1.56 – 1.42 (m, 1H), 0.86 (d, *J* = 2.8 Hz, 9H), 0.83 (dd, *J* = 12.6, 5.1 Hz, 3H), 0.04 (s, 6H).^{13}C NMR (101 MHz, $CDCl_3$) δ 176.6, 134.5, 119.6, 75.9, 63.1, 51.7, 51.7, 34.9, 34.4, 26.2, 26.0, 18.3, 18.0, 16.1, -5.4, -5.4. HRMS (APCI) calcd for $C_{18}H_{37}O_4Si$ $[M+H]^+$ 345.24556, found 345.24582.

Preparation of 83. To the solution of **82** (1.23 g, 3.57 mmol) in dichloromethane (17 mL) was added 2,6-lutidine (0.66 mL, 5.75 mmol, 1.6 eq) and TBSOTf (1.26 mL, 5.24 mmol, 1.5 eq) at -78 ^oC and the resulting reaction mixture was stirred over 6 h. Sat NH_4Cl solution (30 mL) was added to quench the reaction. Two layers were separated and the aqueous phase was extracted with dichloromethane (8 mL x 3). The combined organic phases were dried and concentrated to give crude product, which was subjected to silica gel chromatography with 2% ethyl acetate in hexane, to provide a bis-TBS ether (1.42 g, 87 %) as colorless oil. $[\alpha]_D^{20}$ = + 1.2 (c = 4.0, $CHCl_3$). IR (thin film) *vmax* 2953, 2928, 2856, 1738, 1462, 1385, 1253, 1165, 1090, 1035, 939, 833, 772,

710, 678 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.00 – 4.90 (m, 1H), 4.01 (dt, *J* = 8.1, 4.1 Hz, 1H), 3.67 – 3.52 (m, 2H), 3.61 (s, 3H), 2.34 – 2.20 (m, 2H), 1.66 (s, 3H), 1.64 – 1.54 (m, 1H), 1.57(s, 3H), 1.54 – 1.43 (m, 1H), 1.04 (s, 3H), 0.94 – 0.83 (m, 18H), 0.04 (dt, *J* = 6.1, 2.4 Hz, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.4, 134.3, 119.9, 73.7, 60.1, 53.1, 51.6, 37.8, 36.6, 26.2, 26.1, 26.0, 18.5, 18.4, 18.1, 14.3, -3.6, -3.7, -5.1, -5.1. HRMS (APCI) calcd for $C_{24}H_{51}O_4Si_2$ $[M+H]^+$ 459.33204, found 459.33241.

To a solution of bis-TBS ether (1.42 g, 3.1 mmol) in CH_2Cl_2 (30 mL) at -78 ^oC, obtained from the above reaction, was added a solution of DIBAL-H (1 M, 11 mL, 11 mmol, 3.5 eq) dropwise, and the resulting reaction mixture was stirred for 45 min. CH_3OH (3 mL) was added and the reaction brought to room temperature. Then a saturated solution of Na, K-tartrates (30 mL) was added and stirred 30 min to fully quench the reaction. Two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (10 mL x 3). The combined organics were dried and concentrated to give crude product, which was subjected to silica gel chromatography with 3% EtOAc in hexane, to provide the primary alcohol **83** (1.21 g, 91%)as a colorless oil. $[\alpha]_D^{20}$ = -10.7 (c = 1.0, $CHCl_3$). IR (thin film) *vmax* 3463, 2955, 2928, 2883, 2856, 1472, 1463, 1387, 1253, 1080, 1035, 1004, 938, 832, 772, 667 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.14 (ddd, *J* = 7.7, 4.5, 1.3 Hz, 1H), 3.83 – 3.70 (m, 2H), 3.66 (ddt, *J* = 8.8, 6.2, 4.2 Hz, 2H), 3.30 (dd, *J* = 11.1, 7.3 Hz, 1H), 3.03 (dd, *J* = 7.3, 4.0 Hz, 1H), 2.04 – 1.80 (m, 3H), 1.70 (s, 3H), 1.69 – 1.53 (m, 1H), 1.59 (s, 3H), 0.94 (s, 3H), 0.89

(d, *J* = 1.4 Hz, 18H), 0.07 (dd, *J* = 19.3, 2.6 Hz, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.8, 119.8, 76.3, 68.6, 60.8, 42.9, 36.2, 33.3, 26.2, 26.2, 26.1, 19.3, 18.4, 18.4, 18.0, -3.8, -4.0, -5.2, -5.1. HRMS (APCI) calcd for $C_{23}H_{51}O_3Si_2$ $[M+H]^+$ 431.33713, found 431.33743.

Preparation of the ketone 75. To the solution of **83** (2.2 g, 5.12 mmol) in a 1:1 mixture of CH_2Cl_2 and DMSO (4 mL), was added triethylamine (1.82 mL, 25.5 mmol, 5 eq) followed by SO_3.Py (1.82 g, 25.5 mmol, 5 eq) at 0 ^oC and the resulting reaction mixture was stirred for 2h. Saturated NH_4Cl solution (50 mL) was added to quench the reaction. Two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (20 mL x 3). The combined organics were dried and concentrated to give crude product, which was subjected to silica gel chromatography, with 2% EtOAc in hexane, to provide the aldehyde (1.86 g, 94%) as a coloreless oil. $[\alpha]_D^{20}$ = -0.8 (c = 1.0, $CHCl_3$). IR (thin film) *vmax* 2954, 2929, 2857, 1726, 1463, 1387, 1254, 1093, 1036, 1006, 939, 834, 807, 774, 668 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.57 (s, 1H), 5.01 (t, *J* = 6.9 Hz, 1H), 4.01 (dd, *J* = 7.4, 3.5 Hz, 1H), 3.68- 3.55 (m, 2H), 2.39 (dd, *J* = 14.7, 6.9 Hz, 1H), 2.24 (dd, *J* = 14.7, 8.1 Hz, 1H), 1.73-1.54 (m, 2H), 1.67 (s, 3H), 1.60 (s, 3H), 0.98 (s, 3H), 0.89 (d, *J* = 4.2 Hz, 18H), 0.11 - 0.01 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.3, 134.6, 118.9, 72.8, 59.7, 55.1, 37.2, 31.4, 26.2, 26.1, 26.0, 18.5, 18.4, 18.1, 15.0, -3.8, -4.1, -5.2, -5.2. HRMS (APCI) calcd for $C_{23}H_{47}O_3Si_2$ $[M-H]^-$ 427.30583, found 427.30631.

To the solution of the aldehyde (1.86 g, 4.35 mmol), obtained from the above reaction, in THF (20 mL) was added ethyl magnesium bromide (1 M, 7.4 mL, 7.4 mmol, 1.7 eq) at 0 ^{o}C and the resulting reaction mixture was stirred for 1 h. Saturated NH_4Cl solution (50 mL) was added to quench the reaction. Two layers were separated and the aqueous phase was extracted with EtOAc (20 mL x 3). The combined organic layers were dried and concentrated to give crude product, which was subjected to silica gel chromatography, with 3% EtOAc in hexane, to provide the product (1.27 g) as a diastereomeric mixture (9:1) (64%). The crude product was subjected to the next reaction without purification.

DMSO (0.794 mL, 11.2 mmol, 4 eq) was added to a solution of oxalyl chloride (0.486 mL, 5.6 mmol, 2 eq) in CH_2Cl_2 (20 mL) at -78 ^{o}C and the resulting reaction mixture was stirred for 5-10 min. Then a solution of product obtained from the above reaction (1.27 g, 2.79 mmol, 1 eq) in CH_2Cl_2 (20 mL) was added and resulting reaction mixture was stirred for 2 h. Then, triethylamine (3.2 mL, 22.4 mmol, 8 eq) was added and the reaction mixture was brought to room temperature for 1 h. Saturated NH_4Cl solution (100 mL) was added to quench the reaction. Two layers were separated and the aqueous phase was extracted with ethyl acetate (60 mL x 3). The combined organics were dried and concentrated to give crude product, which was subjected to silica gel chromatography, with 1.5% ether in hexane, to provide the ketone **75** (0.89 g, 70%) as yellow oil. $[\alpha]_D^{20}$ = +1.0 (c = 1.0, $CHCl_3$). IR (thin film) *vmax* 2954, 2928, 2884, 2957, 1705, 1472, 1462, 1378, 1253, 1086, 1005, 972, 938, 833, 772,

710, 667 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.84 (td, *J* = 6.6, 1.3 Hz, 1H), 4.08 (dd, *J* = 8.2, 2.4 Hz, 1H), 3.63 – 3.50 (m, 2H), 2.52 – 2.33 (m, 2H), 2.33 – 2.20 (m, 2H), 1.65 (s, 3H), 1.56 (s, 3H), 1.49 (ddt, *J* = 13.2, 8.3, 5.0 Hz, 1H), 1.35 (dtd, *J* = 10.3, 7.9, 2.4 Hz, 1H), 1.03 (s, 3H), 0.96 (t, *J* = 7.1 Hz, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H), 0.01 (s, 3H), 0.00 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.2, 134.2, 119.7, 73.3, 59.8, 57.8, 37.9, 36.6, 32.5, 26.3, 26.0, 26.0, 18.5, 18.4, 18.1, 14.2, 7.7, -3.5, -3.71, -5.2, -5.2. HRMS (APCI) calcd for $C_{25}H_{53}O_3Si_2$ $[M+H]^+$ 457.35278, found 457.35331.

Preparation of aldol adduct 84. LHMDS (1.3 mL of 1M in THF, 1.3 mmol) was added to THF (1 mL) and cooled to -78 °C for 15 min. To the resulting solution was added the ketone **75** (0.457 g, 1.0 mmol) in Tetrahydrofuran (3 mL) dropwise and stirred at -78 °C for 1hr. The resulting mixture was then brought to -40 C° for another 30 min. Adehyde **74** (0.117 g, 0.5 mmol) in THF (5 mL, 0.1 M) was then rapidly introduced to the reaction mixture and strired for 5 min. AcOH (4.8 eq, 0.3 mL) was then rapidly added to quench the reaction followed by addition of NH_4Cl (6 mL) immediately. Two layers were separated and the aqueous phase was extracted with ethyl acetate (60 mL x 3). The combined organics were dried and concentrated to give crude product, which was subjected to silica gel chromatography (ethyl acetate : hexane, 1: 50 to 1:30) to provide the desired aldol adduct **84** (0.237 g, 65% brsm) as colorless oil. $[\alpha]_D^{20}$ = -10.2 (c = 1.5, $CHCl_3$). IR (thin film) *vmax* 3505, 3105, 2954, 2928, 2884, 2856,

1677, 1614, 1514, 1471, 1301, 1247, 1092, 1036, 991, 949, 833, 773, 710, 667 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 5.76 (ddd, *J* = 18.0, 10.4, 7.8 Hz, 1H), 5.38 – 5.26 (m, 2H), 4.98 (t, *J* = 7.3 Hz, 1H), 4.50 (d, *J* = 11.2 Hz, 1H), 4.32 (d, *J* = 11.2 Hz, 1H), 4.24 (dd, *J* = 7.8, 4.1 Hz, 1H), 3.95 (dd, *J* = 6.6, 3.6 Hz, 1H), 3.79 (s, 3H), 3.71 – 3.62 (m, 1H), 3.62 – 3.53 (m, 1H), 3.60(s, 1H) 3.40 (d, *J* = 10.2 Hz, 1H), 3.01 (q, *J* = 6.9 Hz, 1H), 2.31 (dd, *J* = 13.9, 7.2 Hz, 1H), 2.12 (dd, *J* = 14.0, 7.8 Hz, 1H), 2.02 (ddd, *J* = 10.6, 6.9, 3.9 Hz, 1H), 1.66 (s, 3H), 1.61 – 1.47 (m, 5H), 1.25 (s, 3H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.80 (d, *J* = 6.9 Hz, 3H), 0.10 (s, 3H), 0.08 (s, 3H), 0.03 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 222.6, 159.1, 135.4, 134.6, 131.2, 129.2, 119.5, 118.9, 113.8, 80.9, 74.2, 71.2, 70.1, 60.6, 58.2, 55.4, 42.3, 39.6, 38.1, 37.0, 29.8, 26.3, 26.2, 26.1, 18.5, 18.4, 18.1, 15.7, 10.2, 8.8, -3.5, -3.8, -5.1, -5.2. HRMS (APCI) calcd for $C_{39}H_{71}O_6Si_2$ $[M+H]^+$ 691.48022, found 691.47998.

Preparation of allylic alcohol 85. To a solution of the aldol adduct **84** (55 mg, 0.08 mmol) in 2 mL anhydrous pyridine was sequentially added acetic anhydride (11.3 μL, 0.12 mmol, 1.5 equiv) and DMAP (1 mg, 10 mol%). The resulting mixture was stirred under refluxing for 3 h. The solvent was then removed under reduced pressure and the resulting residue was subjected to chromatography to provide an acetate intermediate (50 mg, 85%) as colorless oil.

To the acetate intermediate (50 mg, 0.068 mmol) in a mixture of CH_2Cl_2 (0.8 mL) and pH =7.0 buffer (0.04 mL) at ^{o}C was added DDQ (23 mg, 0.1 mmol) and the

resulting suspension was stirred at that temperature for additional 3 h before $NaHCO_3$ was added to quench the reaction. Two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 mL x 3). The combined organics were dried and concentrated to give crude product, which was subjected to silica gel chromatography, with 10 % ethyl acetate in hexane, to provide the desired allylic **85** (30 mg, 73%) as colorless oil. $[\alpha]_D^{20}$ = -75 (c = 0.28, $CHCl_3$). IR (thin film) *vmax* 3104, 2955, 2930, 2886, 2858, 1705, 1463, 1385, 1255, 1096, 1035, 1007, 940, 836, 775 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.83 (ddd, *J* = 17.2, 10.6, 5.1 Hz, 1H), 5.14 (ddt, *J* = 24.2, 10.7, 1.5 Hz, 2H), 5.04 – 4.87 (m, 2H), 4.11 (s, 1H), 3.73 (dd, *J* = 7.8, 2.2 Hz, 1H), 3.68 – 3.50 (m, 2H), 3.41 – 3.29 (m, 1H), 2.23 (dd, *J* = 14.7, 7.1 Hz, 1H), 2.04 (ddd, *J* = 10.3, 8.8, 5.4 Hz, 3H), 1.99 (s, 3H), 1.80 – 1.70 (m, 1H), 1.68 (s, 3H), 1.57 (s, 3H), 1.32 (s, 3H), 1.29 – 1.20 (m, 1H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 7.0 Hz, 3H), 0.88 (s, 9H), 0.86 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), 0.00 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.4, 171.1, 138.3, 134.0, 119.9, 115.1, 75.3, 73.8, 72.5, 60.2, 57.3, 42.7, 40.4, 37.6, 34.3, 26.3, 26.1, 21.3, 18.5, 18.3, 12.7, 9.8, -3.1, -4.4, -5.2, -5.2. HRMS (APCI) calcd for $C_{33}H_{65}O_6Si_2$ $[M+H]^+$ 613.43276, found 613.43242.

Preparation of 87. To a solution of the aldol adduct **84** (100mg, 0.145 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C was sequentially added triethylamine (30.3 µl, 0.217 mmol) and TBSOTf (43.2 µl, 0.188 mmol). The resulting mixture was stirred at 0 °C for 15 min before warmed up to room temperature. After stirring at room

temperature for additional 5 h, the reaction was quenched by addition of aqueous NH_4Cl solution. Two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 mL x 3). The combined organics were dried and concentrated to give crude product, which was subjected to silica gel chromatography, with 10 % ethyl acetate in hexane, to provide the desired **87** as pale yellow oil. IR (thin film) *vmax* 2955, 2928, 2856, 1687, 1514, 1468, 1385, 1252, 1078, 1038, 988, 835, 776, 669 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 5.72 – 5.43 (m, 1H), 5.20 (ddd, J = 18.9, 13.8, 1.7 Hz, 2H), 4.98 (t, J = 6.2 Hz, 1H), 4.44 (d, J = 10.7 Hz, 1H), 4.19 (d, J = 10.7 Hz, 1H), 3.95 – 3.82 (m, 3H), 3.80 (s, 3H), 3.67 (td, J = 9.4, 4.7 Hz, 1H), 3.62 – 3.47 (m, 2H), 2.22 (dd, J = 15.4, 6.1 Hz, 1H), 2.05 (dd, J = 15.6, 6.6 Hz, 1H), 1.63 (s, 5H), 1.51 (s, 3H), 1.49 – 1.38 (m, 1H), 1.26 (s, 2H), 1.25 – 1.19 (m, 1H), 1.05 (s, 3H), 1.00 (d, J = 6.9 Hz, 3H), 0.88 (s, 9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.82 (d, J = 7.3 Hz, 3H), 0.11 (s, 3H), 0.09 (s, 3H), 0.06 (s, 3H), 0.03 (s, 6H), 0.01 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 218.7, 159.0, 137.9, 133.2, 131.4, 129.4, 120.0, 117.7, 113.7, 82.3, 76.1, 73.1, 70.1, 61.2, 57.1, 55.4, 46.7, 43.0, 38.3, 34.9, 29.9, 26.5, 26.3, 26.1, 18.8, 18.6, 18.5, 18.3, 17.2, 15.9, 14.6, -3.6, -3.7, -3.9, -5.1. HRMS (APCI) calcd for $C_{45}H_{85}O_6Si_3$ $[M+H]^+$ 805.56485, found 805.56622.

Preparation of 91 and 92. To a slurry of the aldol adduct (345mg, 0.43 mmol) and $NaHCO_3$ (179 mg, 2.14 mmol) in CH_2Cl_2 (5 mL) was added *m*-CPBA (221

mg, 1.28 mol) portionwise at 0 °C. The reaction mixture was vigourously stirred and monitored by TLC. After ca. 3 h, saturated aq. NH_4Cl was added to quench the reaction. Two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 mL x 3). The combined organics were dried and concentrated to give crude product **88** (275 mg, *ca.* 90%) without chromatography.

To the crude epoxide **88**, obtained from previous step, in CH_2Cl_2 (2 mL) was added $NaIO_4$ (190 mg, 0.89 mmol, 2equiv) portionwise at 23 °C. The resulting mixture was allowed to stir overnight. Aqueous $NaHCO_3$ solution was added to quench the reaction. The aldehyde product become ca. 1:1 lactol and aldehyde upon chromatographic purification. The mixture (207 mg, *ca.* 80%) was subject to the next step.

Finely grounded K_2CO_3 (0.25 g, 1.8 mmol) and 18-crown-6 (0.95 g, 3.6 mmol) were stirred for 1 hr at room temperature and then cooled to -20 °C. The mixture of aldehyde and lactol (207 mg, 0.3 mmol) and ylide (0.084 mL, 0.39 mmol) were added and the mixture was stirred at -20 °C for 2 h. Saturated NH_4Cl was added and the product was extracted with ether. The ether extracts were dried over $MgSO_4$ and concentrated under reduced pressure to give crude product which was subjected to flash chromatography, with 10 % ethyl acetate in hexane, to provide both **91** (86 mg, 40%) and **92** (65 mg, 30%). **91**. $[\alpha]_D^{20}$ = -6.9 (c = 0.9, $CHCl_3$). IR (thin film) *vmax* 3505, 3076, 2954, 2930, 2885, 2857, 1723, 1681, 1514, 1440, 1301, 1250, 1196, 1175, 1096, 1037, 1000, 836, 776, 678 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 6.12

(ddd, *J* = 11.6, 9.0, 5.9 Hz, 1H), 5.81 (d, *J* = 11.7 Hz, 1H), 5.77 – 5.65 (m, 1H), 5.28 (dd, *J* = 8.7, 6.8 Hz, 2H), 4.50 (d, *J* = 11.3 Hz, 1H), 4.30 (d, *J* = 11.3 Hz, 1H), 4.14 (dd, *J* = 7.9, 4.8 Hz, 1H), 3.94 (dd, *J* = 7.4, 2.5 Hz, 1H), 3.79 (s, 3H), 3.69 (s, 3H), 3.68 – 3.54 (m, 3H), 3.39 (d, *J* = 9.9 Hz, 1H), 3.23 – 3.14 (m, 1H), 3.01 (dd, *J* = 15.4, 10.1 Hz, 1H), 2.95 – 2.80 (m, 1H), 2.07 – 1.88 (m, 1H), 1.69 (dtd, *J* = 10.4, 7.9, 2.5 Hz, 1H), 1.56 – 1.39 (m, 1H), 1.26 (s, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.88 (s, 9H), 0.88 (s, 9H), 0.80 (d, *J* = 6.9 Hz, 3H), 0.10 (s, 3H), 0.09 (s, 3H), 0.03 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 220.1, 166.8, 159.2, 146.2, 135.5, 131.0, 129.4, 121.4, 119.2, 114.0, 81.7, 74.2, 71.9, 70.2, 60.5, 57.7, 55.5, 51.3, 42.4, 39.9, 37.9, 29.9, 26.3, 26.2, 18.6, 18.5, 17.9, 10.8, 9.2, -3.5, -3.8, -5.1, -5.0. HRMS (APCI) calcd for $C_{39}H_{68}O_8NaSi_2$ $[M+Na]^+$ 743.43449, found 743.43389. **92**. $[\alpha]_D^{20}$ = -22.8 (c = 1.0, $CHCl_3$). IR (thin film) *vmax* 3506, 3078, 2954, 2930, 2857, 1727, 1681, 1513, 1463, 1249, 1095, 1036, 993, 936, 884, 775, 709, 668 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 6.84-6.77 (m, 1H), 5.80 (d, J = 15.5 Hz, 1H), 5.77 – 5.65 (m, 1H), 5.30 (d, J = 5.1 Hz, 1H), 5.29 – 5.23 (m, 1H), 4.49 (d, J = 11.2 Hz, 1H), 4.31 (d, J = 11.2 Hz, 1H), 4.15 (dd, J = 7.8, 4.7 Hz, 1H), 3.89 (dd, J = 7.6, 2.4 Hz, 1H), 3.78 (s, 3H), 3.69 (d, J = 7.6 Hz, 3H), 3.67 – 3.53 (m, 3H), 3.49 (s, 1H), 3.39 (d, J = 10.0 Hz, 1H), 3.12 (d, J = 6.8 Hz, 1H), 2.60 (dd, J = 13.7, 7.3 Hz, 1H), 2.21 (dd, J = 13.6, 8.4 Hz, 1H), 1.98 (ddd, J = 9.8, 7.0, 4.7 Hz, 1H), 1.61 (dt, J = 13.6, 6.8 Hz, 1H), 1.54 – 1.37 (m, 1H), 1.27 (s, 3H), 1.02 (d, J = 6.8 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.79 (d, J = 6.9 Hz, 3H), 0.11 (s, 3H), 0.09 (s, 3H), 0.02 (s, 6H). ^{13}C

NMR (101 MHz, $CDCl_3$) δ 219.9, 166.4, 159.1, 144.9, 135.3, 131.0, 129.3, 124.2, 119.1, 113.8, 81.5, 74.6, 71.6, 70.1, 60.1, 57.5, 55.4, 51.5, 42.7, 39.9, 39.7, 37.7, 26.2, 26.0, 18.5, 18.4, 17.3, 10.6, 8.9, -3.6, -3.9, -5.2, -5.2. HRMS (APCI) calcd for $C_{39}H_{68}O_8NaSi_2$ $[M+Na]^+$ 743.43450, found 743.43341.

Preparation of allylic alcohol 93. To a solution of **91** (300 mg, 0.42 mmol) in CH_2Cl_2 (4 mL) at 0 °C was sequentially added triethylamine (91 µl, 0.6 mmol) and TBSOTf (129 µl, 0.57 mmol). The resulting mixture was stirred at 0 °C for 15 min before warmed up to room temperature. After stirring at room temperature for additional 5 h, the reaction was quenched by addition of aqueous NH_4Cl solution. Two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (5 mL x 3). The combined organics were dried and concentrated to give crude product, which was subjected to silica gel chromatography, with 2 % ethyl acetate in hexane, to provide a tri-TBS ether (312 mg, 89%) as a colorless oil. $[\alpha]_D^{20}$ = -12.0 (c = 0.3, $CHCl_3$). IR (thin film) *vmax* 3075, 2953, 2930, 2886, 2856, 1724, 1685, 1514, 1387, 1249, 1194, 1174, 1090, 1035, 987, 832, 773, 669 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 6.30 – 6.10 (m, 1H), 5.81 – 5.66 (m, 1H), 5.53 (ddd, *J* = 17.2, 10.2, 8.3 Hz, 1H), 5.17 (ddd, *J* = 18.8, 13.7, 1.7 Hz, 2H), 4.44 (d, *J* = 10.7 Hz, 1H), 4.13 (d, *J* = 10.7 Hz, 1H), 3.96 – 3.89 (m, 2H), 3.82-3.77 (m, 1H), 3.80 (s, 3H), 3.68 (s, 3H), 3.67 – 3.61 (m, 1H), 3.61 – 3.52 (m, 2H), 3.01 – 2.69 (m, 2H), 1.60 (ddd, *J* = 16.4, 9.8, 2.5 Hz, 1H), 1.47 (dtd, *J* = 13.5, 8.5, 3.3 Hz, 2H), 1.01 (t, *J* = 3.4 Hz,

6H), 0.93 (s, 9H), 0.87 (s, 9H), 0.86 (s, 9H), 0.80 (d, *J* = 7.2 Hz, 3H), 0.10 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.02 (s, 3H), 0.02 (s, 3H), 0.00 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 218.3, 166.5, 159.1, 146.7, 137.9, 131.2, 129.6, 120.5, 117.9, 113.7, 82.5, 76.1, 72.5, 70.1, 61.1, 56.7, 55.4, 51.1, 46.6, 42.8, 38.1, 35.1, 26.5, 26.15, 18.7, 18.4, 18.5, 16.9, 15.8, 15.0, -3.4, -3.7, -3.8, -3.8, -5.1, -5.1. HRMS (APCI) calcd for $C_{45}H_{82}O_8NaSi_3$ $[M+Na]^+$ 857.52098, found 857.52197.

To the tri-TBS ether (312 mg, 0.37 mmol), obtained from the above step, in a mixture of CH_2Cl_2 (3 mL) and pH =7.0 buffer (0.15 mL) at 0 ^oC was added DDQ (126 mg, 0.56 mmol) and the resulting suspension was stirred at that temperature for additional 3 h before $NaHCO_3$ was added to quench the reaction. Two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (4 mL x 3). The combined organics were dried and concentrated to give crude product, which was subjected to silica gel chromatography, with 5 % ethyl acetate in hexane, to provide the desired allylic alcohol **93** (214 mg, 81%). $[\alpha]_D^{20}$ = -2.0 (c = 0.3, $CHCl_3$). IR (thin film) *vmax* 3514, 3078, 2954, 2930, 2886, 2857, 1724, 1696, 1486, 1439, 1386, 1362, 1254, 1196, 1176, 1095, 1029, 988, 834, 775, 670 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.20 (dt, *J* = 11.8, 6.9 Hz, 1H), 5.75 (ddd, *J* = 17.2, 14.4, 9.3 Hz, 2H), 5.22 – 5.05 (m, 2H), 3.95 (ddd, *J* = 9.4, 7.3, 2.4 Hz, 2H), 3.88 (dd, *J* = 11.9, 5.0 Hz, 1H), 3.74 – 3.64 (m, 1H), 3.68(s, 3H), 3.64 – 3.54 (m, 1H), 3.37 (p, *J* = 6.9 Hz, 1H), 3.06 – 2.79 (m, 2H), 1.80 – 1.64 (m, 1H), 1.49 (dtd, *J* = 12.2, 7.3, 4.9 Hz, 1H), 1.44 – 1.36 (m, 1H), 1.33 (s, 3H), 1.09 (s,

3H), 0.92 (s, 9H), 0.87 (s, 18H), 0.81 (d, *J* = 7.1 Hz, 3H), 0.11 (s, 3H), 0.11 (s, 3H), 0.09 (s, 3H), 0.06 (s, 3H), 0.03 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 217.4, 166.7, 146.3, 139.4, 121.0, 115.9, 77.3, 75.7, 73.3, 60.8, 57.1, 51.2, 47.8, 44.4, 37.9, 34.8, 26.3, 26.2, 26.1, 18.5, 18.5, 18.4, 15.8, 15.3 , -3.5, -3.8, -3.7, -4.0 , -5.1, -5.2. HRMS (APCI) calcd for $C_{37}H_{74}O_7NaSi_3$ $[M+Na]^+$ 737.46346, found 737.46288.

Preparation of allylic diol 94. To a solution of allylic alcohol **93** (320 mg, 0.45 mmol) in toluene (5 mL) was added DIBAL-H (0.49 ml, 0.49 mmol) dropwise over 30 min at -78 °C. The resulting mixture was allowed to stir at -78 °C for 1.5 h until starting material was consumed based on TLC monitoring. Methanol (0.1 mL)was then added to quench the reaction followed by addition of Roche's salt. Two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (4 mL x 3). The combined organics were dried and concentrated to give crude product, which was subjected to silica gel chromatography, with 5% ethyl acetate in hexane, to provide the desired allylic diol **94** (232 mg, 75%) as colorless oil. $[\alpha]_D^{20}$ = -11.0 (c = 0.3, $CHCl_3$). IR (thin film) *vmax* 3363, 3079, 2954, 2930, 2886, 2857, 1693, 1469, 1386, 1254, 1096, 1023, 988, 834, 803, 774, 670 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (ddd, *J* = 17.1, 10.4, 6.7 Hz, 1H), 5.72 – 5.58 (m, 1H), 5.51 – 5.37 (m, 1H), 5.25 – 5.09 (m, 2H), 4.23 (dd, *J* = 12.7, 7.1 Hz, 1H), 4.08 (dd, *J* = 12.7, 6.5 Hz, 1H), 3.96 – 3.76 (m, 3H), 3.73 – 3.52 (m, 2H), 3.30 (p, *J* = 6.9 Hz, 1H), 3.04 (br s, 1H), 2.62 (dd, *J* = 14.7, 8.2 Hz,

1H), 2.18 (br s, 1H), 1.93 (dd, *J* = 14.4, 6.3 Hz, 1H), 1.86 – 1.66 (m, 1H), 1.55 – 1.35 (m, 2H), 1.36 (s, 3H), 1.08 (d, *J* = 6.8 Hz, 3H), 0.91 (s, 9H), 0.89 (s, 9H), 0.87(s, 9H), 0.82 (d, *J* = 7.1 Hz, 3H), 0.11(s, 3H), 0,10 (s, 3H), 0.09 (s, 6H), 0.03 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 218.0, 139.3, 131.3, 127.6, 115.9, 77.7, 75.5, 74.9, 60.6, 58.6, 57.3, 47.9, 44.2, 37.5, 33.9, 26.3, 26.2, 26.1, 19.2, 18.6, 18.4, 18.4, 15.7, 15.3, -3.5, -3.6, -3.9, -4.0, -5.1, -5.2. HRMS (APCI) calcd for $C_{36}H_{74}O_6NaSi_3$ $[M+Na]^+$ 709.46855, found 709.46820.

Preparation of hydroxy acid 73. To a solution of **94** (220 mg, 0.32 mmol) in CH_2Cl_2 (3.5 mL) was sequentially added TEMPO (15.01 mg, 0.096 mmol) and $PhI(OAc)_2$ (124 mg, 0.384 mmol). The resulting mixture was allowed to stir at 23 °C for another 5 h before the starting material was consumed based on TLC monitor before quenching by addition of aqueous $NaHCO_3$ solution (4 mL). Two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (4 mL x 3). The combined organics were dried and concentrated to give crude product, which was subjected to silica gel chromatography, with 5 % ethyl acetate in hexane, to provide the desired aldehyde (201 mg, 92%) as colorless oil. $[\alpha]_D^{20}$ = -13.0 (c = 0.2, $CHCl_3$). IR (thin film) *vmax* 3080, 2955, 2930, 2886, 2857, 1696, 1472, 1388, 1255, 1096, 1035, 1004, 836, 775, 670 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 10.02 (d, *J* = 7.9 Hz, 1H), 6.54 (dt, *J* = 11.3, 8.0 Hz, 1H), 6.01 – 5.90 (m, 1H), 5.73 (ddd, *J* = 17.1, 10.4, 6.6 Hz, 1H), 5.18 (d, *J* = 17.1 Hz, 1H), 5.10 (d, *J* = 10.4 Hz, 1H), 3.97 – 3.84 (m, 3H), 3.83 – 3.52 (m, 2H), 3.38 (p,

J = 6.8 Hz, 1H), 3.09 – 2.95 (m, 1H), 2.80 (d, *J* = 2.4 Hz, 1H), 2.59 (ddd, *J* = 15.1, 8.3, 1.2 Hz, 1H), 1.92 – 1.64 (m, 1H), 1.54 – 1.31 (m, 2H), 1.38 (s, 3H), 1.08 (d, *J* = 6.8 Hz, 3H), 0.91 (s, 9H), 0.88 (s, 9H), 0.86(s, 9H), 0.80 (d, *J* = 7.1 Hz, 3H), 0.09 (s, 6H), 0.09 (s, 3H), 0.08(s, 3H), 0.01 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 216.7, 191.0, 148.5, 139.2, 131.7, 116.0, 77.5, 75.5, 74.4, 60.2, 57.1, 47.9, 44.5, 37.5, 33.9, 26.2, 26.2, 26.0, 19.1, 18.5, 18.4, 18.3, 15.9, 15.1, -3.4, -3.6, -3.8, -4.0, -5.2, -5.2. HRMS (APCI) calcd for $C_{36}H_{72}O_6NaSi_3$ $[M+Na]^+$ 707.45290, found 707.45386.

To a solution of the aldehyde (220 mg, 0.32 mmol) in a mixture of *t*-BuOH and water (7.5 mL / 1.5 mL) at 0 °C was sequentially added 2-methyl-2-butene (1701 µl, 16.05 mmol), sodium chlorite (87 mg, 0.96 mmol) and sodium phosphate monobasic (57.8 mg, 0.48 mmol). The reaction mixture was allowed to stir at 0 °C for 30 min and then allowed to warm up to room temperature. After 2 h, the reaction was then quenched by addition of aqueous sodium bicarbonate and ethyl ether. Two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (4 mL x 3). The combined organics were dried and concentrated to give crude product, which was subjected to silica gel chromatography, with 60 % ethyl acetate in hexane, to provide the desired hydroxy acid **73** (201 mg, 90%) as colorless oil. $[\alpha]_D^{20}$ = -10.5 (c = 0.5, $CHCl_3$). IR (thin film) *vmax* 3079, 2955, 2931, 2886, 2858, 1697, 1641, 1469, 1387, 1255, 1098, 1031, 988, 938, 836, 776, 669 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.39 – 6.24 (m, 1H), 5.80 (d, *J* = 11.8 Hz, 1H), 5.73 (ddd, *J* = 17.2, 10.3, 6.8 Hz, 1H), 5.18 (d, *J* = 17.1 Hz, 1H),

5.09 (d, *J* = 10.4 Hz, 1H), 3.99 – 3.90 (m, 2H), 3.86 (dd, *J* = 16.8, 9.5 Hz, 1H), 3.72 – 3.62 (m, 1H), 3.62 – 3.54 (m, 1H), 3.48 – 3.32 (m, 1H), 3.03 – 2.75 (m, 2H), 1.79 – 1.41 (m, 2H), 1.41 – 1.29 (m, 2H), 1.33(s, 3H), 1.08 (d, *J* = 6.7 Hz, 3H), 0.92 (s, 9H), 0.86 – 0.75 (s, 18H), 0.80 (d, *J* = 7.1 Hz, 3H), 0.10 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H), 0.01 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 217.5, 171.4, 148.6, 139.2, 120.9, 116.1, 77.3, 75.8, 73.2, 60.8, 57.2, 47.9, 44.5, 37.9, 35.2, 26.3, 26.2, 26.1, 18.5, 18.5, 18.4, 15.8 , 15.2, -3.5, -3.7, -3.8, -4.0, -5.1, -5.2. HRMS (APCI) calcd for $C_{36}H_{72}O_7NaSi_3$ $[M+Na]^+$ 723.44781, found 723.44757.

Preparation of unsaturated macrolactone 71. To a slurry of seco-acid **73** (20.3 mg, 29 μmol) and $NaHCO_3$ (600 mg, 7.1 mmol) in CH_2Cl_2 (60 mL) was treated with solid 2-bromo-1-ethyl pridinium tetrafluoroborate (150 mg, 0.55 mmol) in one portion at 23 °C. The reaction mixture was vigorously stirred in the dark overnight, then transferred directly onto a silica gel column and purified by flash chromatography to provide the unsaturated macrolactone **71** (12.3 mg, 62%) as colorless oil. $[\alpha]_D^{20}$ = -33 (c = 0.27, $CHCl_3$). IR (thin film) *vmax* 3080, 2955, 2931, 2886, 2857, 1720, 1696, 1256, 1102, 986, 863, 835, 775, 669 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.19 (dd, *J* = 20.0, 9.4 Hz, 1H), 5.87 (d, *J* = 11.7 Hz, 2H), 5.29 – 5.08 (m, 3H), 3.94 (s, 1H), 3.78 – 3.51 (m, 2H), 3.02 (s, 1H), 2.53 (s, 1H), 1.75 – 1.44 (m, 2H), 1.25 (d, *J* = 7.7 Hz, 4H), 1.06 (dd, *J* = 13.4, 4.9 Hz, 3H), 1.03 – 0.93 (m, 3H), 0.89 (s, 9H), 0.88 (d, *J* = 3.9 Hz, 9H), 0.87 (s, 9H),

0.13 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 218.6, 165.2, 149.0, 136.1, 124.6, 118.0, 73.9, 61.3, 57.4, 38.8, 29.9, 26.3, 26.3, 26.2, 18.6, 18.5, -3.4, -3.9, -5.0. HRMS (APCI) calcd for $C_{36}H_{71}O_6Si_3$ $[M+H]^+$ 683.45530, found 683.45749.

Preparation of 95. To a solution of **71** (30 mg, 0.044 mmol) in THF (0.1mL) was added dropwise 9-BBN (6.43 mg, 0.053 mmol). In a separate flask, the vinyl iodide **72** (18.40 mg, 0.053 mmol) was dissolved in DMF (0.3 mL). $CsCO_3$ (25.8 mg, 0.079 mmol) was then added with vigorous stirring followed by sequential addition of tripheynyarsen (3.23 mg, 10.54 μmol), $Pd(dppf)Cl_2$ (7.71 mg, 10.54 μmol) and water (38.0 mg, 2.108 mmol)The resulting red suspension was purged with a stream of argon for 20 min. After 1.5 h, the borane in THF was added rapidly to the vigorously stirred iodide mixture in DMF. The reaction quickly turned dark brown in color. After stirring at room temperature for additional 2 h, the reaction was quenched by addition of aqueous NH_4Cl (0.5 mL). Two layers were separated and the aqueous phase was extracted with ethyl acetate (0.5 mL x 3). The combined organics were dried and concentrated to give crude product, which was subjected to silica gel chromatography, with 40 % ethyl acetate in hexane, to provide the desired Suzuki coupling product **95** (25 mg, 63%) as yellow oil. $[\alpha]_D^{20}$ = -13.2 (c = 0.4, $CHCl_3$). IR (thin film) *vmax* 3362, 3041, 2954, 2929, 2887, 2856, 1716, 1698, 1470, 1461, 1388, 1255, 1101, 1035, 1007, 986, 865, 835, 775, 670 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 6.92 (s, 1H), 6.53 (s, 1H), 6.16 (m, 1H), 5.87 (d, J = 11.6 Hz, 1H), 5.15 (s, 1H), 4.82 (m, 1H), 4.41 (m, 1H),

4.13 (t, J = 6.1 Hz, 1H), 3.90 (d, J = 4.3 Hz, 1H), 3.75 – 3.52 (m, 2H), 3.02 (m, 1H), 2.89 – 2.72 (m, 1H), 2.69 (s, 3H), 2.51 (d, J = 11.7 Hz, 1H), 2.30 (s, 2H), 2.03-1.92 (m, 3H), 2.01 (s, 3H), 1.70 (s, 5H), 1.52 (m, 2H), 1.24 (d, J = 3.5 Hz, 3H), 1.04 (s, 3H), 0.94 (d, J = 6.4 Hz, 3H), 0.88 (s, 9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.11 (s, 3H), 0.08 (s, 9H), 0.02 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 216.7, 165.9, 164.5, 153.1, 143.8, 141.7, 137.9, 124.4, 121.1, 119.1, 115.5, 82.2, 78.1, 77.4, 74.6, 69.8, 60.9, 57.2, 50.2, 43.2, 38.4, 36.2, 34.1, 31.1, 28.9, 26.2, 26.1, 23.7, 19.3, 18.5, 18.4, 16.9, 15.0, 14.5, 11.7, -3.6, -3.8, -4.4, -4.6, -5.1. HRMS (APCI) calcd for $C_{48}H_{87}O_7NSSi_3$ $[M+H]^+$ 906.55839, found 906.55957.

Preparation of hydroxy acid 70. To a solution of **95** (300 mg, 0.3 mmol), obtained from above reaction, in THF (10 mL) was added a buffered solution of HF.Py (5 mL) (stock solution was prepared by addition of 4 mL HF.Py to 11 mL pyridine in 22 mL of THF) at 0 °C, and the resulting reaction mixture was brought to room temperature and allowed to stir for overnight. Sat $NaHCO_3$ solution was added to quench the reaction and two layers were separated. The aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organics were dried and concentrated to give crude mass, which was subjected to chromatography over silica gel, eluting with 60% ethyl acetate in hexane, to give a primary alcohol (176 mg, 74%) as a colorless oil. $[\alpha]_D^{20}$ = -13 (c = 0.29, $CHCl_3$). IR (thin film) *vmax* 3371, 2954, 2929, 2887, 2856, 1714, 1694, 1463, 1379, 1077, 1020, 986, 867, 836, 775, 730 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (s, 1H), 6.54 (s,

1H), 6.16 (s, 1H), 5.87 (d, *J* = 10.9 Hz, 1H), 5.16 (s, 1H), 4.76 (s, 1H), 4.33 (s, 1H), 4.13 (t, *J* = 6.1 Hz, 1H), 4.09 – 3.99 (m, 1H), 3.66 (s, 2H), 3.04 (s, 1H), 2.68 (s, 3H), 2.80-2.40 (m, 3H), 2.30 (m, 2H), 2.11 – 1.87 (m, 3H), 1.99 (s, 3H), 1.69 (s, 3H), 1.62 (m, 2H), 1.24 (s, 3H), 1.06 (s, 3H), 0.95 (d, *J* = 7.0 Hz, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H), 0.07 (s, 3H), 0.07 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 217.9, 165.9, 164.7, 152.9, 142.8, 141.9, 137.7, 124.6, 121.3, 119.0, 115.5, 82.2, 78.4, 77.4, 73.6, 69.9, 60.3, 57.6, 50.9, 43.5, 38.6, 36.2, 34.2, 31.2, 28.9, 26.1, 26.2, 23.7, 19.2, 18.5, 17.0, 15.3, 14.5, 11.9, -3.4, -3.4, -4.1, -4.1. HRMS (APCI) calcd for $C_{42}H_{74}O_7NSSi_2$ $[M+H]^+$ 792.47191, found 792.47112.

To a solution of the primary alchol (176 mg, 0.22 mmol), obtained from the preceding step, in CH_2Cl_2 (2.5 mL) was sequentially added TEMPO (10.4 mg, 0.067 mmol) and $PhI(OAc)_2$ (85.6 mg, 0.265 mmol). The resulting mixture was allowed to stir at 23 °C for another 5 h before the starting material was consumed based on TLC monitor before quenching by addition of aqueous $NaHCO_3$ solution (2 mL). Two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 mL x 3). The combined organics were dried and concentrated to give crude product, which was subjected to silica gel chromatography, with 40 % ethyl acetate in hexane, to provide an aldehyde (122 mg, 76%) as colorless oil. $[\alpha]_D^{20}$ = -23 (c = 0.3, $CHCl_3$). IR (thin film) *vmax* 3407, 3039, 2954, 2929, 2856, 1717, 1693, 1463, 1378, 1280, 1255, 1221, 1095, 1078, 987, 866, 836, 776, 637 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (s, 1H), 6.92 (s,

1H), 6.52 (s, 1H), 6.17 (s, 1H), 5.90 (d, J = 11.5 Hz, 1H), 5.15 (s, 1H), 5.13-4.96 (m, 1H), 4.83 (s, 1H), 4.49 (s, 1H), 4.37 (s, 1H), 4.16 – 4.09 (m, 1H), 3.65 (s, 1H), 3.20 (s, 1H), 3.02 (s, 1H), 2.86-2.63 (m, 1H), 2.68 (s, 3H), 2.52-2.40 (m, 2H), 2.45 (s, 1H), 2.29 (s, 3H), 2.06-1.91 (m, 2H), 2.00 (s, 3H), 1.69 (s, 3H), 1.23 (s, 3H), 1.04 (s, 3H), 0.94 (d, J = 5.9 Hz, 3H), 0.87 (s, 9H), 0.86 (s, 9H), 0.11 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 217.0, 201.1, 165.7, 164.5, 153.0, 142.4, 141.7, 137.6, 124.8, 121.2, 119.1, 115.5, 81.8, 78.1, 77.3, 73.9, 69.7, 56.7, 49.2, 43.5, 36.2, 34.1, 31.1, 28.9, 26.0, 26.0, 23.7, 19.3, 18.3, 17.1, 15.1, 14.5, 14.3, 11.7, -3.8, -3.8, -4.5, -4.5. HRMS (APCI) calcd for $C_{42}H_{72}O_7NSSi_2$ $[M+H]^+$ 790.45626, found 790.45746.

To a solution of the aldehyde (122 mg, 0.15 mmol), obtained from the preceding step, in a mixture of *t*-BuOH and water (3.5 mL / 0.7 mL) at 0 °C was sequentially added 2-methyl-2-butene (0.85 mL, 8 mmol), sodium chlorite (44 mg, 0.48 mmol) and sodium phosphate monobasic (28.9 mg, 0.24 mmol). The reaction mixture was allowed to stir at 0 °C for 30 min and then allowed to warm up to room temperature. After 2 h, the reaction was then quenched by addition of aqueous sodium bicarbonate and ethyl ether. Two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 mL x 3). The combined organics were dried and concentrated to give crude product, which was subjected to silica gel chromatography, with 60 % ethyl acetate in hexane, to provide the desired hydroxy acid **70** (112 mg, 93%) as colorless oil. $[\alpha]_D^{20}$ = +3 (c = 0.27, $CHCl_3$). IR (thin film) *vmax* 3473, 2955, 2930, 2895, 2856, 1708, 1693,

1464, 1403, 1283, 1255, 1183, 1078, 1053, 988, 867, 836, 776, 630 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (s, 1H), 6.56 (s, 1H), 6.21 (s, 1H), 5.91 (d, J = 11.6 Hz, 1H), 5.15 (s, 1H), 5.10-4.86 (m, 1H), 4.42 (s, 1H), 4.16 (s, 1H), 3.67 (s, 1H), 3.19 (s, 1H), 3.02 (s, 1H), 2.83-2.65 (m, 1H), 2.70 (s, 3H), 2.60-2.20 (m, 4H), 2.14 – 1.82 (m, 3H), 1.96 (s, 3H), 1.69 (s, 3H), 1.25 (d, J = 8.2 Hz, 3H), 1.07 (s, 3H), 0.94 (d, J = 6.7 Hz, 3H), 0.87 (s, 18H), 0.12 (s, 3H), 0.06 (s, 6H), 0.05 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 216.8, 176.3, 165.9, 165.3, 152.6, 142.9, 142.5, 137.7, 124.7, 121.1, 119.1, 115.3, 82.2, 73.9, 69.9, 56.5, 50.7, 43.5, 40.4, 36.3, 33.9, 32.5, 31.3, 29.1, 26.3, 23.7, 19.2, 18.9, 18.3, 17.5, 15.6, 14.4, 11.6, -3.9, -3.9 -4.8, -4.8. HRMS (APCI) calcd for $C_{42}H_{72}O_8NSSi_2$ $[M+H]^+$ 806.45117, found 806.45053.

Preparation of macrolactone 96. To a slurry of seco-acid **70** (120 mg, 0.15 mmol) and $NaHCO_3$ (3 g, 35.5 mmol) in CH_2Cl_2 (300 mL) was treated with solid 2-bromo-1-ethyl pridinium tetrafluoroborate (750 mg, 2.75 mmol) in one portion at 23 °C. The reaction mixture was vigorously stirred in the dark overnight, then transferred directly onto a silica gel column and purified by flash chromatography with 2% ethyl acetate in hexane to provide the desired macrolactone **96** (77 mg, 65%) as colorless oil. $[\alpha]_D^{20}$ = +103 (c = 0.1, $CHCl_3$). IR (thin film) *vmax* 3106, 2954, 2929, 2856, 1723, 1462, 1376, 1276, 1253, 1196, 1027, 1077, 1027, 983, 866, 855, 836, 774, 672 cm^{-1}. **Major**: (2 extra protons) ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (s, 1H), 6.63 (s, 1H), 6.38 (dd, *J* = 19.8, 9.6 Hz, 1H), 5.92 (d, *J* =

11.7 Hz, 1H), 5.25 (d, *J* = 9.6 Hz, 1H), 5.00 (d, *J* = 11.2 Hz, 2H), 4.66 (d, *J* = 7.3 Hz, 1H), 4.26 (dd, *J* = 9.5, 2.5 Hz, 1H), 2.97 (ddd, *J* = 25.0, 14.1, 8.3 Hz, 2H), 2.69 (s, 3H), 2.57 – 2.21 (m, 5H), 2.09 (s, 3H), 2.06 – 1.94 (m, 3H), 1.90 – 1.71 (m, 2H), 1.66 (s, 3H), 1.59 – 1.42 (m, 2H), 1.36 (s, 3H), 1.13 (d, *J* = 6.6 Hz, 3H), 1.03 (d, *J* = 7.2 Hz, 3H), 0.90 (s, 9H), 0.87 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 212.9, 170.6, 165.9, 164.6, 153.0, 141.9, 137.3, 137.2, 124.5, 122.0, 119.8, 116.6, 81.9, 75.6, 71.5, 57.7, 45.0, 43.2, 42.2, 31.5, 31.3, 29.5, 26.2, 26.0, 24.1, 20.1, 19.5, 19.4, 18.4, 18.2, 13.6, 11.5, -2.4, -4.1, -4.3, -4.5. **Minor**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (s, 1H), 6.53 (s, 1H), 6.21 (dd, *J* = 20.8, 9.0 Hz, 1H), 5.81 (d, *J* = 12.1 Hz, 1H), 5.10 (d, *J* = 9.6 Hz, 1H), 5.00 (m, 1H), 4.82 – 4.69 (m, 2H), 3.72 – 3.48 (m, 2H), 3.21 – 3.09 (m, 1H), 2.68 (s, 3H), 2.56 – 2.20 (m, 5H), 2.09 (s, 3H), 2.07 – 1.93 (m, 3H), 1.61 (s, 3H), 1.59 – 1.42 (m, 2H), 1.22 (s, 3H), 1.06 (d, *J* = 7.6 Hz, 3H), 0.96 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 213.9, 170.9, 165.9, 164.6, 153.2, 140.6, 139.2, 137.6, 125.3, 121.3, 118.6, 116.5, 82.6, 76.0, 71.9, 71.6, 57.1, 47.2, 42.5, 37.7, 33.4, 32.0, 26.2, 26.0, 25.9, 23.4, 21.2, 18.7, 18.4, 18.3, 14.0, 11.6, -2.2, -3.9, -4.4, -4.6. HRMS (APCI) calcd for $C_{42}H_{70}O_7NSSi_2$ $[M+H]^+$ 788.44061, found 788.44094.

Preparation of 97. To a solution of macrolactone **96** (120 mg, 0.15 mmol) in THF (15 mL) was added HF.Py (70%, 10 mL) at 0 °C and the resulting reaction mixture was brought to room temperature and stirred over 36 h. Sat $NaHCO_3$

was added carefully to quench the reaction and extracted with ethyl acetate (10 mL x 3). The combined organics were dried and concentrated to give crude mass, which was subjected to chromatography over silica gel, eluting with 55% ethyl acetate in hexane, to give the Michael adduct (61 mg, 72%) as a white foam. $[\alpha]_D^{20}$ = -25.9 (c = 0.5, $CHCl_3$). IR (thin film) *vmax* 3074, 2954, 2930, 2885, 2857, 1724, 1613, 1513, 1464, 1301, 1247, 1173, 1076, 1036, 1003, 925, 833, 774, 667 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 6.87 (s, 1H), 6.58 (s, 1H), 5.18 (dd, *J* = 10.6, 3.1 Hz, 1H), 5.12 (dd, *J* = 10.8, 4.5 Hz, 1H), 4.93 (d, *J* = 10.7 Hz, 1H), 4.67 (d, *J* = 10.5 Hz, 1H), 4.50 – 4.41 (m, 1H), 4.37 (d, *J* = 7.9 Hz, 1H), 3.48 (dq, *J* = 10.4, 6.9 Hz, 3H), 3.06 – 2.85 (m, 3H), 2.77 (dd, *J* = 18.6, 4.3 Hz, 1H), 2.71 – 2.58 (m, 4H), 2.43 (ddd, *J* = 23.7, 18.0, 9.3 Hz, 2H), 2.25 – 1.94 (m, 5H), 2.06 (s, 3H), 1.77 (t, *J* = 11.1 Hz, 2H), 1.65 (s, 3H), 1.55 – 1.38 (m, 1H), 1.21 (s, 3H), 1.15 (d, *J* = 6.9 Hz, 3H), 1.01 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 219.6, 170.9, 170.2, 164.5, 153.0, 138.9, 137.5, 120.8, 119.3, 116.0, 79.5, 79.3, 77.8, 72.2, 65.9, 57.5, 42.5, 42.4, 40.1, 37.8, 33.0, 30.5, 27.8, 25.9, 22.5, 19.4, 19.3, 17.8, 15.4, 14.6. HRMS (APCI) calcd for $C_{30}H_{42}O_7NS$ $[M+H]^+$ 560.26765, found 560.26723.

Preparation of 98. To a solution of the Michael adduct (**97**) (20 mg, 0.036 mmol, 1.0 equiv) in CH_2Cl_2 (0.4 mL) at -78 ^oC was added freshly prepared 3,3-dimethyldioxirane [103] (1.0 mL, ca. 0.08 mmol,ca. 0.08 M in acetone, 2.2 equiv) dropwise. The resulting solution was warmed to -30 ^oC for 1 h, and another

portion of dimethyldioxirane (1 mL, 0.08 mmol) was added. After stirring at -50 ^{o}C for additional 2.5 h, A stream of argon was then bubbled through the solution at -30 ^{o}C to remove excess dimethyldioxirane and solvent. The resulting residue was purified by preparative thin-layer chromatography (CH_2Cl_2/MeOH, 30/1) to afford bridged epothilone **98** as a single diastereomer. IR (thin film) *vmax* 3421, 2960, 2931, 2858, 1612, 1513, 1459, 1301, 1247, 1174, 1034, 995, 930, 822, 669 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 1H), 6.63 (s, 1H), 5.21 (d, J = 10.1 Hz, 1H), 5.02 (d, J = 4.6 Hz, 1H), 4.69 (d, J = 10.7 Hz, 1H), 4.47 (dd, J = 6.8, 3.1 Hz, 2H), 3.64 – 3.46 (m, 1H), 3.13 – 2.86 (m, 3H), 2.76 (d, J = 8.6 Hz, 1H), 2.72 – 2.61 (m, 1H), 2.68 (s, 3H), 2.45 (dd, J = 16.6, 11.2 Hz, 1H), 2.25 – 2.10 (m, 2H), 2.08 (s, 3H), 1.94 – 1.79 (m, 3H), 1.79 – 1.67 (m, 2H), 1.64 – 1.52 (m, 1H), 1.29 (s, 3H), 1.24 (d, J = 7.0 Hz, 3H), 1.17 (d, J = 6.9 Hz, 3H), 1.03 (d, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 219.6, 170.7, 170.1, 164.6, 152.8, 137.7, 120.1, 116.4, 79.3, 78.4, 77.7, 72.8, 70.0, 63.1, 60.7, 57.2, 42.8, 42.5, 40.2, 37.7, 33.0, 28.4, 27.9, 25.8, 22.0, 19.4, 19.4, 17.5, 14.6, 11.6. HRMS (APCI) calcd for $C_{30}H_{42}O_8NS$ $[M+H]^+$ 576.26257, found 576.26293.

1.5.2. Molecular Modeling

The 3-D structures of bridged epothilones **35** were constructed based on the electron crystallographic (EC) pose of EpoA bound to tubulin. The resulting structures of **35** was then fully optimized with the MMFF/GBSA/H_2O force field to provide the nearest local minimum.

1.5.3. Cytotoxicity Assay

Human ovarian cancer cells (A2780) grown to 95% confluency were harvested and resuspended in growth medium (RPMI1640 supplemented with 10% fetal bovine serum and 2 mM L-glutamine). Cells were counted using a hemacytometer and a solution containing 2.5x105 cells per mL was prepared in growth media. Eleven columns of a 96 well microtitre plate were seeded with 199 µl of cell suspension per well, and the remaining column contained media only (one hundred percent inhibition control). The plate was incubated for 3 hs at 37ºC/5%CO_2 to allow the cells to adhere to the wells. Following this incubation, potential cytotoxic agents, prepared in DMSO, were added to the wells in an appropriate series of concentrations, 1 µl per well. One column of wells was left with no inhibitor (zero percent inhibition control), and 4 dilutions of a known compound (taxol or actinomycin) was included as a positive control. The plate was incubated for 2 days at 37ºC/5%CO_2, then the media gently shaken from the wells and replaced with reaction media (supplemented growth medium containing 1% alamarBlue), and incubated for another 3 hs. The level of alamarBlue converted to a fluorescent compound by living cells was then analyzed using a Cytofluor Series 4000 plate reader (Perseptive Biosystems) with an excitation wavelength of 530 nm, an emission wavelength of 590 nm, and gain of 45. The percent inhibition of cell growth was calculated using the zero percent and one hundred percent controls present on the plate, and an IC50 value (concentration of cytotoxic agent which produces 50% inhibition) was

calculated using a linear extrapolation of the data which lie either side of the 50% inhibition level. Samples were analyzed in triplicate on at least two separate occasions to produce a reliable IC_{50} value.

1.6.4. X-ray Crystallography Data

1.6.4.1 Allylic alcohol 85.

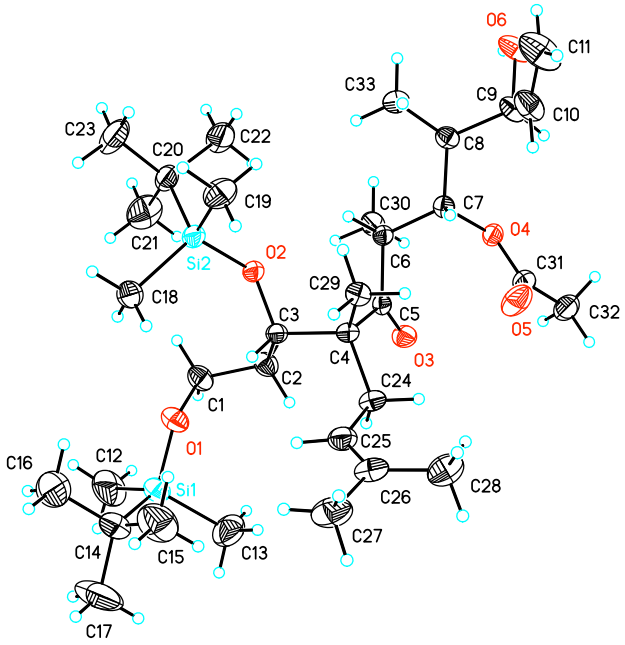


Figure S1. Thermal ellipsoid diagram of **85** with 50% displacement ellipsoids.

Table S1. Crystal data and structure refinement for **85**.

Empirical formula	C33 H64 O6 Si2	
Formula weight	613.02	
Temperature	173(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 12.5983(6) Å	α= 90°.
	b = 13.3257(6) Å	β= 90°.
	c = 23.0775(11) Å	γ = 90°.
Volume	3874.3(3) $Å^3$	
Z	4	
Density (calculated)	1.051 Mg/m^3	
Absorption coefficient	1.112 mm^{-1}	
F(000)	1352	
Crystal size	0.35 x 0.32 x 0.18 mm^3	
Theta range for data collection	3.83 to 68.14°.	
Index ranges	-13<=h<=15, -16<=k<=15, -27<=l<=27	
Reflections collected	43386	
Independent reflections	6697 [R(int) = 0.0190]	
Completeness to theta = 68.14°	98.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.8249 and 0.6969	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6697 / 0 / 370	
Goodness-of-fit on F^2	1.047	
Final R indices [I>2sigma(I)]	R1 = 0.0372, wR2 = 0.1053	
R indices (all data)	R1 = 0.0378, wR2 = 0.1060	
Absolute structure parameter	0.01(2)	
Largest diff. peak and hole	0.518 and -0.247 $e.Å^{-3}$	

Table S2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for **85**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	3993(2)	11680(2)	637(1)	41(1)
C(2)	4054(2)	10551(1)	546(1)	37(1)
C(3)	4177(1)	9964(1)	1109(1)	27(1)
C(4)	3976(1)	8807(1)	1034(1)	27(1)
C(5)	4699(1)	8439(1)	546(1)	26(1)
C(6)	5877(1)	8230(1)	667(1)	27(1)
C(7)	6061(1)	7096(1)	773(1)	28(1)
C(8)	7226(1)	6843(1)	893(1)	32(1)
C(9)	7423(2)	5693(2)	934(1)	39(1)
C(10)	6939(2)	5232(2)	1460(1)	52(1)
C(11)	7460(3)	4802(2)	1881(1)	75(1)
C(12)	2486(3)	13706(2)	344(2)	83(1)
C(13)	1386(2)	11696(2)	186(1)	74(1)
C(14)	1208(2)	12802(2)	1373(1)	60(1)
C(15)	949(3)	11821(3)	1688(2)	86(1)
C(16)	1801(3)	13492(3)	1790(2)	90(1)
C(17)	164(3)	13304(4)	1179(2)	112(2)
C(18)	4654(2)	11690(2)	2157(1)	50(1)
C(19)	5730(2)	9788(2)	2540(1)	55(1)
C(20)	6967(2)	11228(2)	1746(1)	43(1)
C(21)	6861(2)	12026(2)	1267(1)	74(1)
C(22)	7689(2)	10388(2)	1525(1)	69(1)
C(23)	7471(2)	11700(3)	2281(1)	73(1)
C(24)	2802(1)	8606(2)	858(1)	37(1)
C(25)	1994(2)	8930(2)	1283(1)	44(1)
C(26)	1238(2)	8376(2)	1534(1)	46(1)
C(27)	453(2)	8831(2)	1944(1)	64(1)
C(28)	1074(2)	7284(2)	1413(1)	57(1)

C(29)	4197(1)	8259(1)	1604(1)	32(1)
C(30)	6540(2)	8638(1)	167(1)	39(1)
C(31)	4770(2)	6142(1)	245(1)	37(1)
C(32)	4541(2)	5707(2)	-338(1)	48(1)
C(33)	7623(2)	7375(2)	1437(1)	42(1)
O(1)	3101(1)	11938(1)	980(1)	44(1)
O(2)	5226(1)	10134(1)	1327(1)	30(1)
O(3)	4372(1)	8362(1)	53(1)	36(1)
O(4)	5753(1)	6555(1)	253(1)	31(1)
O(5)	4177(1)	6153(1)	649(1)	55(1)
O(6)	8532(1)	5501(1)	944(1)	52(1)
Si(1)	2062(1)	12535(1)	723(1)	47(1)
Si(2)	5614(1)	10703(1)	1929(1)	34(1)

Table S3. Bond lengths [Å] and angles [°] for **85**.

C(1)-O(1)	1.417(2)	O(4)-C(7)-C(6)	108.29(13)
C(1)-C(2)	1.522(3)	C(8)-C(7)-C(6)	112.78(13)
C(1)-H(1A)	0.9900	O(4)-C(7)-H(7A)	109.5
C(1)-H(1B)	0.9900	C(8)-C(7)-H(7A)	109.5
C(2)-C(3)	1.525(2)	C(6)-C(7)-H(7A)	109.5
C(2)-H(2A)	0.9900	C(33)-C(8)-C(7)	111.14(14)
C(2)-H(2B)	0.9900	C(33)-C(8)-C(9)	110.79(15)
C(3)-O(2)	1.4329(19)	C(7)-C(8)-C(9)	112.39(15)
C(3)-C(4)	1.572(2)	C(33)-C(8)-H(8A)	107.4
C(3)-H(3A)	1.0000	C(7)-C(8)-H(8A)	107.4
C(4)-C(5)	1.529(2)	C(9)-C(8)-H(8A)	107.4
C(4)-C(29)	1.530(2)	O(6)-C(9)-C(10)	108.35(17)
C(4)-C(24)	1.557(2)	Si(1)-C(12)-H(12B)	109.5
C(5)-O(3)	1.214(2)	H(12A)-C(12)-H(12B)	109.5
C(5)-C(6)	1.535(2)	Si(1)-C(12)-H(12C)	109.5

C(6)-C(30)	1.524(2)	H(12A)-C(12)-H(12C)	109.5
C(6)-C(7)	1.548(2)	H(12B)-C(12)-H(12C)	109.5
C(6)-H(6A)	1.0000	Si(1)-C(13)-H(13A)	109.5
C(7)-O(4)	1.452(2)	Si(1)-C(13)-H(13B)	109.5
C(7)-C(8)	1.531(2)	H(13A)-C(13)-H(13B)	109.5
C(7)-H(7A)	1.0000	Si(1)-C(13)-H(13C)	109.5
C(8)-C(33)	1.527(3)	H(13A)-C(13)-H(13C)	109.5
C(8)-C(9)	1.556(3)	H(13B)-C(13)-H(13C)	109.5
C(8)-H(8A)	1.0000	C(16)-C(14)-C(15)	108.6(3)
C(9)-O(6)	1.421(2)	C(16)-C(14)-C(17)	109.9(3)
C(9)-C(10)	1.492(3)	C(15)-C(14)-C(17)	109.0(3)
C(9)-H(9A)	1.0000	C(16)-C(14)-Si(1)	109.7(2)
C(10)-C(11)	1.304(4)	C(15)-C(14)-Si(1)	109.82(19)
C(10)-H(10)	0.9239	C(17)-C(14)-Si(1)	109.8(2)
C(11)-H(11A)	0.9366	C(14)-C(15)-H(15A)	109.5
C(11)-H(11B)	0.9712	C(14)-C(15)-H(15B)	109.5
C(12)-Si(1)	1.865(3)	H(15A)-C(15)-H(15B)	109.5
C(12)-H(12A)	0.9800	C(14)-C(15)-H(15C)	109.5
C(12)-H(12B)	0.9800	H(15A)-C(15)-H(15C)	109.5
C(12)-H(12C)	0.9800	H(15B)-C(15)-H(15C)	109.5
C(13)-Si(1)	1.875(3)	C(14)-C(16)-H(16A)	109.5
C(13)-H(13A)	0.9800	C(14)-C(16)-H(16B)	109.5
C(13)-H(13B)	0.9800	H(16A)-C(16)-H(16B)	109.5
C(13)-H(13C)	0.9800	C(14)-C(16)-H(16C)	109.5
C(14)-C(16)	1.527(4)	H(16A)-C(16)-H(16C)	109.5
C(14)-C(15)	1.531(5)	H(16B)-C(16)-H(16C)	109.5
C(14)-C(17)	1.542(4)	C(14)-C(17)-H(17A)	109.5
C(14)-Si(1)	1.881(3)	C(14)-C(17)-H(17B)	109.5
C(15)-H(15A)	0.9800	H(17A)-C(17)-H(17B)	109.5
C(15)-H(15B)	0.9800	C(14)-C(17)-H(17C)	109.5
C(15)-H(15C)	0.9800	H(17A)-C(17)-H(17C)	109.5
C(16)-H(16A)	0.9800	H(17B)-C(17)-H(17C)	109.5
C(16)-H(16B)	0.9800	Si(2)-C(18)-H(18A)	109.5
C(16)-H(16C)	0.9800	Si(2)-C(18)-H(18B)	109.5

C(17)-H(17A)	0.9800	H(18A)-C(18)-H(18B)	109.5
C(17)-H(17B)	0.9800	Si(2)-C(18)-H(18C)	109.5
C(17)-H(17C)	0.9800	H(18A)-C(18)-H(18C)	109.5
C(18)-Si(2)	1.862(2)	H(18B)-C(18)-H(18C)	109.5
C(18)-H(18A)	0.9800	Si(2)-C(19)-H(19A)	109.5
C(18)-H(18B)	0.9800	Si(2)-C(19)-H(19B)	109.5
C(18)-H(18C)	0.9800	H(19A)-C(19)-H(19B)	109.5
C(19)-Si(2)	1.871(2)	Si(2)-C(19)-H(19C)	109.5
C(19)-H(19A)	0.9800	H(19A)-C(19)-H(19C)	109.5
C(19)-H(19B)	0.9800	H(19B)-C(19)-H(19C)	109.5
C(19)-H(19C)	0.9800	C(23)-C(20)-C(22)	108.9(2)
C(20)-C(23)	1.525(3)	C(23)-C(20)-C(21)	109.4(2)
C(20)-C(22)	1.530(3)	C(22)-C(20)-C(21)	108.5(2)
C(20)-C(21)	1.539(4)	C(23)-C(20)-Si(2)	110.27(15)
C(20)-Si(2)	1.890(2)	C(22)-C(20)-Si(2)	109.89(15)
C(21)-H(21A)	0.9800	C(21)-C(20)-Si(2)	109.81(16)
C(21)-H(21B)	0.9800	C(20)-C(21)-H(21A)	109.5
C(21)-H(21C)	0.9800	C(20)-C(21)-H(21B)	109.5
C(22)-H(22A)	0.9800	H(21A)-C(21)-H(21B)	109.5
C(22)-H(22B)	0.9800	C(20)-C(21)-H(21C)	109.5
C(22)-H(22C)	0.9800	H(21A)-C(21)-H(21C)	109.5
C(23)-H(23A)	0.9800	H(21B)-C(21)-H(21C)	109.5
C(23)-H(23B)	0.9800	C(20)-C(22)-H(22A)	109.5
C(23)-H(23C)	0.9800	C(20)-C(22)-H(22B)	109.5
C(24)-C(25)	1.476(3)	H(22A)-C(22)-H(22B)	109.5
C(24)-H(24A)	0.9900	C(20)-C(22)-H(22C)	109.5
C(24)-H(24B)	0.9900	H(22A)-C(22)-H(22C)	109.5
C(25)-C(26)	1.337(3)	H(22B)-C(22)-H(22C)	109.5
C(25)-H(25A)	0.9500	C(20)-C(23)-H(23A)	109.5
C(26)-C(28)	1.496(4)	C(20)-C(23)-H(23B)	109.5
C(26)-C(27)	1.497(3)	H(23A)-C(23)-H(23B)	109.5
C(27)-H(27A)	0.9800	C(20)-C(23)-H(23C)	109.5
C(27)-H(27B)	0.9800	H(23A)-C(23)-H(23C)	109.5
C(27)-H(27C)	0.9800	H(23B)-C(23)-H(23C)	109.5

C(28)-H(28A)	0.9800	C(25)-C(24)-C(4)	109.5
C(28)-H(28B)	0.9800	C(25)-C(24)-H(24A)	109.5
C(28)-H(28C)	0.9800	C(4)-C(24)-H(24A)	115.64(15)
C(29)-H(29A)	0.9800	C(25)-C(24)-H(24B)	108.4
C(29)-H(29B)	0.9800	C(4)-C(24)-H(24B)	108.4
C(29)-H(29C)	0.9800	H(24A)-C(24)-H(24B)	108.4
C(30)-H(30A)	0.9800	C(26)-C(25)-C(24)	108.4
C(30)-H(30B)	0.9800	C(26)-C(25)-H(25A)	107.4
C(30)-H(30C)	0.9800	C(24)-C(25)-H(25A)	128.1(2)
C(31)-O(5)	1.196(2)	C(25)-C(26)-C(28)	115.9
C(31)-O(4)	1.355(2)	C(25)-C(26)-C(27)	115.9
C(31)-C(32)	1.355(2)	C(28)-C(26)-C(27)	123.7(2)
C(32)-H(32A)	0.9800	C(26)-C(27)-H(27A)	121.4(2)
C(32)-H(32B)	0.9800	C(26)-C(27)-H(27B)	114.8(2)
C(32)-H(32C)	0.9800	H(27A)-C(27)-H(27B)	109.5
C(33)-H(33A)	0.9800	C(26)-C(27)-H(27C)	109.5
C(33)-H(33B)	0.9800	H(27A)-C(27)-H(27C)	109.5
C(33)-H(33C)	0.9800	H(27B)-C(27)-H(27C)	109.5
O(1)-Si(1)	1.6428(14)	C(26)-C(28)-H(28A)	109.5
O(2)-Si(2)	1.6563(12)	C(26)-C(28)-H(28B)	109.5
O(6)-H(6B)	0.8400	H(28A)-C(28)-H(28B)	109.5
O(1)-C(1)-C(2)	110.97(16)	C(26)-C(28)-H(28C)	109.5
O(1)-C(1)-H(1A)	109.4	H(28A)-C(28)-H(28C)	109.5
C(2)-C(1)-H(1A)	109.4	H(28B)-C(28)-H(28C)	109.5
O(1)-C(1)-H(1B)	109.4	C(4)-C(29)-H(29A)	109.5
C(2)-C(1)-H(1B)	109.4	C(4)-C(29)-H(29B)	109.5
H(1A)-C(1)-H(1B)	108.0	H(29A)-C(29)-H(29B)	109.5
C(1)-C(2)-C(3)	113.20(15)	C(4)-C(29)-H(29C)	109.5
C(1)-C(2)-H(2A)	108.9	H(29A)-C(29)-H(29C)	109.5
C(3)-C(2)-H(2A)	108.9	H(29B)-C(29)-H(29C)	109.5
C(1)-C(2)-H(2B)	108.9	C(6)-C(30)-H(30A)	109.5
C(3)-C(2)-H(2B)	108.9	C(6)-C(30)-H(30B)	109.5
H(2A)-C(2)-H(2B)	107.8	H(30A)-C(30)-H(30B)	109.5
O(2)-C(3)-C(2)	108.18(14)	C(6)-C(30)-H(30C)	109.5

O(2)-C(3)-C(4)	109.99(13)	H(30A)-C(30)-H(30C)	109.5
C(2)-C(3)-C(4)	113.09(13)	H(30B)-C(30)-H(30C)	109.5
O(2)-C(3)-H(3A)	108.5	O(5)-C(31)-O(4)	123.71(18)
C(2)-C(3)-H(3A)	108.5	O(5)-C(31)-C(32)	125.95(17)
C(4)-C(3)-H(3A)	108.5	O(4)-C(31)-C(32)	110.32(16)
C(5)-C(4)-C(29)	111.84(13)	C(31)-C(32)-H(32A)	109.5
C(5)-C(4)-C(24)	108.65(13)	C(31)-C(32)-H(32B)	109.5
C(29)-C(4)-C(24)	108.26(14)	H(32A)-C(32)-H(32B)	109.5
C(5)-C(4)-C(3)	107.49(13)	C(31)-C(32)-H(32C)	109.5
C(29)-C(4)-C(3)	110.11(13)	H(32A)-C(32)-H(32C)	109.5
C(24)-C(4)-C(3)	110.50(14)	H(32B)-C(32)-H(32C)	109.5
O(3)-C(5)-C(4)	120.95(15)	C(8)-C(33)-H(33A)	109.5
O(3)-C(5)-C(6)	118.91(15)	C(8)-C(33)-H(33B)	109.5
C(4)-C(5)-C(6)	120.01(13)	H(33A)-C(33)-H(33B)	109.5
C(30)-C(6)-C(5)	109.10(14)	C(8)-C(33)-H(33C)	109.5
C(30)-C(6)-C(7)	112.69(14)	H(33A)-C(33)-H(33C)	109.5
C(5)-C(6)-C(7)	110.55(13)	H(33B)-C(33)-H(33C)	109.5
C(30)-C(6)-H(6A)	108.1	C(1)-O(1)-Si(1)	123.15(12)
C(5)-C(6)-H(6A)	108.1	C(3)-O(2)-Si(2)	129.73(10)
C(7)-C(6)-H(6A)	108.1	C(31)-O(4)-C(7)	117.26(14)
O(4)-C(7)-C(8)	107.26(13)	C(9)-O(6)-H(6B)	109.5
O(6)-C(9)-C(8)	109.60(17)	O(1)-Si(1)-C(12)	110.29(13)
C(10)-C(9)-C(8)	112.93(16)	O(1)-Si(1)-C(13)	108.19(12)
O(6)-C(9)-H(9A)	108.6	C(12)-Si(1)-C(13)	108.66(16)
C(10)-C(9)-H(9A)	108.6	O(1)-Si(1)-C(14)	104.98(10)
C(8)-C(9)-H(9A)	108.6	C(12)-Si(1)-C(14)	112.26(15)
C(11)-C(10)-C(9)	125.5(2)	C(13)-Si(1)-C(14)	112.34(14)
C(11)-C(10)-H(10)	125.3	O(2)-Si(2)-C(18)	111.62(8)
C(9)-C(10)-H(10)	109.1	O(2)-Si(2)-C(19)	110.91(9)
C(10)-C(11)-H(11A)	116.0	C(18)-Si(2)-C(19)	107.37(11)
C(10)-C(11)-H(11B)	119.4	O(2)-Si(2)-C(20)	104.34(7)
H(11A)-C(11)-H(11B)	124.2	C(18)-Si(2)-C(20)	112.80(10)
Si(1)-C(12)-H(12A)	109.5	C(19)-Si(2)-C(20)	109.84(11)

Table S4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **85**. The anisotropic
displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	44(1)	35(1)	44(1)	8(1)	4(1)	6(1)
C(2)	42(1)	35(1)	33(1)	3(1)	-1(1)	6(1)
C(3)	24(1)	30(1)	28(1)	-2(1)	-2(1)	2(1)
C(4)	22(1)	31(1)	28(1)	2(1)	-1(1)	1(1)
C(5)	28(1)	22(1)	29(1)	0(1)	-2(1)	-1(1)
C(6)	24(1)	27(1)	30(1)	-2(1)	1(1)	-1(1)
C(7)	29(1)	29(1)	28(1)	-1(1)	3(1)	0(1)
C(8)	28(1)	34(1)	33(1)	3(1)	5(1)	2(1)
C(9)	40(1)	35(1)	43(1)	2(1)	6(1)	12(1)
C(10)	48(1)	40(1)	68(1)	14(1)	14(1)	8(1)
C(11)	78(2)	75(2)	70(2)	36(2)	28(1)	24(2)
C(12)	96(2)	44(1)	110(2)	25(2)	-3(2)	12(1)
C(13)	77(2)	70(2)	73(2)	-1(1)	-32(2)	-7(2)
C(14)	43(1)	63(2)	74(2)	-10(1)	0(1)	16(1)
C(15)	72(2)	87(2)	97(2)	5(2)	30(2)	7(2)
C(16)	70(2)	106(3)	96(2)	-42(2)	8(2)	8(2)
C(17)	66(2)	147(4)	122(3)	-9(3)	0(2)	58(2)
C(18)	43(1)	59(1)	48(1)	-23(1)	-1(1)	11(1)
C(19)	60(1)	67(1)	37(1)	1(1)	-12(1)	-3(1)
C(20)	32(1)	48(1)	51(1)	-18(1)	2(1)	-6(1)
C(21)	60(2)	75(2)	86(2)	11(2)	7(1)	-27(1)

C(22)	31(1)	79(2)	97(2)	-42(2)	10(1)	-3(1)
C(23)	50(1)	94(2)	75(2)	-43(2)	2(1)	-21(1)
C(24)	25(1)	45(1)	40(1)	0(1)	-4(1)	-2(1)
C(25)	30(1)	52(1)	49(1)	-5(1)	-1(1)	2(1)
C(26)	29(1)	67(1)	41(1)	1(1)	-4(1)	-1(1)
C(27)	38(1)	96(2)	59(1)	-5(1)	10(1)	-6(1)
C(28)	51(1)	73(2)	48(1)	6(1)	0(1)	-13(1)
C(29)	30(1)	35(1)	30(1)	4(1)	4(1)	1(1)
C(30)	34(1)	34(1)	49(1)	7(1)	10(1)	-1(1)
C(31)	30(1)	34(1)	47(1)	-2(1)	1(1)	-4(1)
C(32)	38(1)	52(1)	56(1)	-15(1)	-2(1)	-6(1)
C(33)	34(1)	44(1)	48(1)	-2(1)	-9(1)	3(1)
O(1)	44(1)	42(1)	46(1)	4(1)	-1(1)	13(1)
O(2)	25(1)	32(1)	34(1)	-6(1)	0(1)	0(1)
O(3)	36(1)	43(1)	29(1)	-4(1)	-5(1)	5(1)
O(4)	28(1)	30(1)	36(1)	-6(1)	2(1)	-2(1)
O(5)	39(1)	68(1)	59(1)	-12(1)	11(1)	-20(1)
O(6)	44(1)	58(1)	54(1)	17(1)	14(1)	24(1)
Si(1)	44(1)	39(1)	58(1)	5(1)	-10(1)	9(1)
Si(2)	28(1)	39(1)	34(1)	-10(1)	-1(1)	1(1)

Table S5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for **85**.

	x	y	z	U(eq)
H(1A)	4649	11915	831	49
H(1B)	3942	12020	257	49
H(2A)	4665	10399	290	44
H(2B)	3402	10324	346	44
H(3A)	3655	10231	1397	33
H(6A)	6082	8600	1026	32

H(7A)	5615	6868	1106	34
H(8A)	7652	7101	559	38
H(9A)	7112	5364	583	47
H(10)	6208	5279	1435	62
H(11A)	7047	4470	2159	89
H(11B)	8229	4769	1863	89
H(12A)	2933	13532	12	125
H(12B)	2888	14129	613	125
H(12C)	1857	14071	210	125
H(13A)	1861	11572	-143	110
H(13B)	735	12019	47	110
H(13C)	1207	11056	372	110
H(15A)	498	11964	2024	128
H(15B)	1609	11503	1818	128
H(15C)	574	11368	1423	128
H(16A)	1351	13634	2127	136
H(16B)	1978	14121	1593	136
H(16C)	2456	13162	1919	136
H(17A)	-278	13441	1520	167
H(17B)	-218	12855	915	167
H(17C)	323	13935	980	167
H(18A)	3969	11379	2248	75
H(18B)	4561	12174	1841	75
H(18C)	4926	12036	2500	75
H(19A)	5027	9521	2635	82
H(19B)	6026	10128	2881	82
H(19C)	6200	9237	2426	82
H(21A)	7565	12293	1172	110
H(21B)	6404	12572	1403	110
H(21C)	6548	11720	920	110
H(22A)	8388	10666	1429	103
H(22B)	7375	10085	1178	103
H(22C)	7767	9875	1826	103
H(23A)	8171	11969	2180	109

H(23B)	7548	11190	2584	109
H(23C)	7017	12245	2423	109
H(24A)	2661	8952	487	44
H(24B)	2715	7877	791	44
H(25A)	2014	9617	1391	52
H(27A)	618	9543	1998	96
H(27B)	492	8484	2318	96
H(27C)	-264	8762	1784	96
H(28A)	1624	7047	1146	85
H(28B)	373	7185	1238	85
H(28C)	1117	6906	1776	85
H(29A)	4072	7539	1551	47
H(29B)	3722	8517	1905	47
H(29C)	4936	8371	1719	47
H(30A)	7293	8509	243	58
H(30B)	6423	9362	131	58
H(30C)	6330	8304	-194	58
H(32A)	3828	5413	-338	73
H(32B)	5064	5186	-427	73
H(32C)	4579	6238	-631	73
H(33A)	7494	8098	1402	63
H(33B)	8386	7254	1483	63
H(33C)	7244	7115	1776	63
H(6B)	8825	5804	668	78

Table S6. Torsion angles [°] for **85**.

O(1)-C(1)-C(2)-C(3)	-61.2(2)	C(3)-C(4)-C(24)-C(25)	-61.7(2)
C(1)-C(2)-C(3)-O(2)	-71.24(19)	C(4)-C(24)-C(25)-C(26)	-123.6(2)
C(1)-C(2)-C(3)-C(4)	166.67(15)	C(24)-C(25)-C(26)-C(28)	-0.8(3)
O(2)-C(3)-C(4)-C(5)	-67.51(16)	C(24)-C(25)-C(26)-C(27)	-178.0(2)
C(2)-C(3)-C(4)-C(5)	53.57(17)	C(2)-C(1)-O(1)-Si(1)	-110.50(16)
O(2)-C(3)-C(4)-C(29)	54.55(17)	C(2)-C(3)-O(2)-Si(2)	115.11(14)

C(2)-C(3)-C(4)-C(29)	175.62(14)	C(4)-C(3)-O(2)-Si(2)	-120.92(13)
O(2)-C(3)-C(4)-C(24)	174.09(13)	O(5)-C(31)-O(4)-C(7)	-4.2(3)
C(2)-C(3)-C(4)-C(24)	-64.84(18)	C(32)-C(31)-O(4)-C(7)	174.26(15)
C(29)-C(4)-C(5)-O(3)	142.90(16)	C(8)-C(7)-O(4)-C(31)	140.26(15)
C(24)-C(4)-C(5)-O(3)	23.5(2)	C(6)-C(7)-O(4)-C(31)	-97.75(16)
C(3)-C(4)-C(5)-O(3)	-96.12(18)	C(1)-O(1)-Si(1)-C(12)	-52.8(2)
C(29)-C(4)-C(5)-C(6)	-41.3(2)	C(1)-O(1)-Si(1)-C(13)	65.94(19)
C(24)-C(4)-C(5)-C(6)	-160.69(14)	C(1)-O(1)-Si(1)-C(14)	-173.92(16)
C(3)-C(4)-C(5)-C(6)	79.72(17)	C(16)-C(14)-Si(1)-O(1)	62.9(2)
O(3)-C(5)-C(6)-C(30)	38.2(2)	C(15)-C(14)-Si(1)-O(1)	-56.4(2)
C(4)-C(5)-C(6)-C(30)	-137.74(15)	C(17)-C(14)-Si(1)-O(1)	-176.2(3)
O(3)-C(5)-C(6)-C(7)	-86.27(19)	C(16)-C(14)-Si(1)-C(12)	-56.9(3)
C(4)-C(5)-C(6)-C(7)	97.81(17)	C(15)-C(14)-Si(1)-C(12)	-176.2(2)
C(30)-C(6)-C(7)-O(4)	-61.20(17)	C(17)-C(14)-Si(1)-C(12)	63.9(3)
C(5)-C(6)-C(7)-O(4)	61.18(17)	C(16)-C(14)-Si(1)-C(13)	-179.7(2)
C(30)-C(6)-C(7)-C(8)	57.33(19)	C(15)-C(14)-Si(1)-C(13)	61.0(2)
C(5)-C(6)-C(7)-C(8)	179.71(13)	C(17)-C(14)-Si(1)-C(13)	-58.9(3)
O(4)-C(7)-C(8)-C(33)	-179.59(14)	C(3)-O(2)-Si(2)-C(18)	-29.14(17)
C(6)-C(7)-C(8)-C(33)	61.28(19)	C(3)-O(2)-Si(2)-C(19)	90.54(16)
O(4)-C(7)-C(8)-C(9)	-54.78(18)	C(3)-O(2)-Si(2)-C(20)	-151.25(15)
C(6)-C(7)-C(8)-C(9)	-173.91(14)	C(23)-C(20)-Si(2)-O(2)	-174.98(18)
C(33)-C(8)-C(9)-O(6)	-65.07(19)	C(22)-C(20)-Si(2)-O(2)	-54.94(19)
C(7)-C(8)-C(9)-O(6)	169.92(15)	C(21)-C(20)-Si(2)-O(2)	64.34(17)
C(33)-C(8)-C(9)-C(10)	55.8(2)	C(23)-C(20)-Si(2)-C(18)	63.7(2)
C(7)-C(8)-C(9)-C(10)	-69.2(2)	C(22)-C(20)-Si(2)-C(18)	-176.27(18)
O(6)-C(9)-C(10)-C(11)	5.2(3)	C(21)-C(20)-Si(2)-C(18)	-56.99(19)
C(8)-C(9)-C(10)-C(11)	-116.4(3)	C(23)-C(20)-Si(2)-C(19)	-56.1(2)
C(5)-C(4)-C(24)-C(25)	-179.38(16)	C(22)-C(20)-Si(2)-C(19)	64.0(2)
C(29)-C(4)-C(24)-C(25)	59.0(2)	C(21)-C(20)-Si(2)-C(19)	-176.73(17)

Table S7. Hydrogen bonds for **85** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)

O(6)-H(6B)...O(3)#1	0.84	2.12	2.9512(19)	172.8

Symmetry transformations used to generate equivalent atoms:
#1 x+1/2,-y+3/2,-z

1.8.2. Bis-TBS ether **96**.

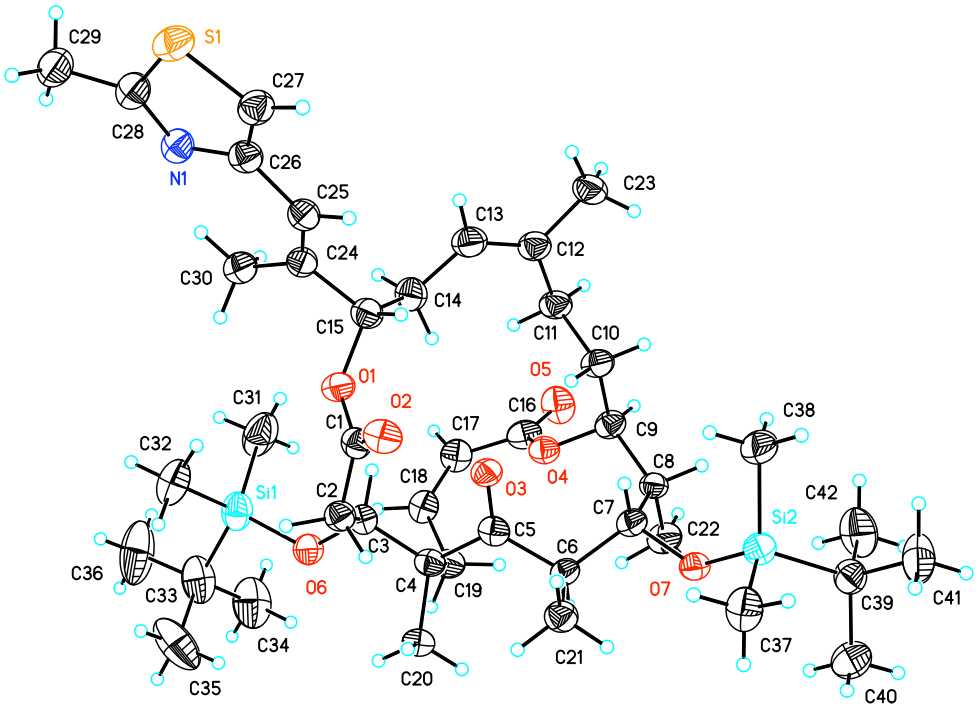


Figure S2. Thermal ellipsoid diagram of **96** with 50% displacement ellipsoids.

Table S8. Crystal data and structure refinement for **96**.

Empirical formula	C42 H69 N O7 S Si2	
Formula weight	788.22	
Temperature	173(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 10.6266(5) Å	α= 90°.
	b = 17.1019(8) Å	β= 90°.
	c = 25.9204(12) Å	γ = 90°.
Volume	4710.6(4) $Å^3$	
Z	4	
Density (calculated)	1.111 Mg/m^3	
Absorption coefficient	1.446 mm^{-1}	
F(000)	1712	
Crystal size	0.47 x 0.09 x 0.05 mm^3	
Theta range for data collection	3.10 to 69.24°.	
Index ranges	-12<=h<=10, -20<=k<=16, -30<=l<=30	
Reflections collected	33950	
Independent reflections	8128 [R(int) = 0.0758]	
Completeness to theta = 69.24°	95.1 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9378 and 0.5497	

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8128 / 0 / 479
Goodness-of-fit on F^2	1.060
Final R indices [I>2sigma(I)]	R1 = 0.0623, wR2 = 0.1449
R indices (all data)	R1 = 0.1096, wR2 = 0.1729
Absolute structure parameter	0.01(3)
Extinction coefficient	0.00145(15)
Largest diff. peak and hole	0.467 and -0.249 e.$Å^{-3}$

Table S9. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for **96**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	230(4)	1081(3)	9695(2)	53(1)
C(2)	1429(4)	621(3)	9625(2)	55(1)
C(3)	1685(4)	308(2)	9070(2)	51(1)
C(4)	2677(4)	775(3)	8784(2)	52(1)
C(5)	2266(4)	1641(3)	8745(2)	51(1)
C(6)	3180(4)	2279(2)	8584(2)	49(1)
C(7)	2551(4)	2964(3)	8297(2)	51(1)
C(8)	2113(4)	2851(3)	7732(2)	52(1)
C(9)	925(4)	2366(3)	7633(2)	57(1)
C(10)	-245(4)	2612(3)	7944(2)	59(1)
C(11)	-1401(4)	2113(3)	7815(2)	61(1)
C(12)	-2502(4)	2286(3)	8159(2)	61(1)
C(13)	-2776(5)	1865(3)	8579(2)	69(1)
C(14)	-2069(5)	1187(3)	8774(2)	69(1)
C(15)	-1885(4)	1174(3)	9360(2)	58(1)
C(16)	923(5)	1015(3)	7405(2)	67(1)
C(17)	1092(5)	219(3)	7598(2)	68(1)
C(18)	1885(5)	-6(3)	7964(2)	64(1)
C(19)	2918(4)	454(3)	8217(2)	59(1)
C(20)	3968(4)	708(3)	9051(2)	57(1)
C(21)	3744(4)	2595(3)	9094(2)	61(1)
C(22)	3195(4)	2574(3)	7379(2)	67(1)
C(23)	-3293(5)	2971(3)	8004(2)	74(2)
C(24)	-2935(4)	797(3)	9660(2)	55(1)
C(25)	-3664(4)	1256(3)	9956(2)	54(1)
C(26)	-4748(4)	1037(3)	10281(2)	58(1)
C(27)	-5397(4)	1582(3)	10555(2)	64(1)
C(28)	-6116(5)	237(3)	10656(2)	65(1)

C(29)	-6755(5)	-505(3)	10809(2)	79(2)
C(30)	-3060(4)	-77(3)	9601(2)	65(1)
C(31)	-41(6)	-1343(4)	8657(2)	114(2)
C(32)	405(6)	-1289(3)	9807(2)	95(2)
C(33)	2383(7)	-2080(3)	9113(3)	102(2)
C(34)	3101(8)	-2004(4)	8596(3)	123(3)
C(35)	3360(9)	-2011(4)	9551(3)	148(4)
C(36)	1734(10)	-2884(3)	9128(3)	157(4)
C(37)	3914(6)	4709(3)	9100(2)	80(2)
C(38)	1508(5)	4742(3)	8470(2)	80(2)
C(39)	4023(5)	5136(3)	7960(2)	67(1)
C(40)	5442(5)	4983(4)	7969(3)	101(2)
C(41)	3791(6)	6006(3)	8085(3)	103(2)
C(42)	3482(7)	4967(4)	7412(2)	105(2)
N(1)	-5158(4)	277(2)	10336(1)	60(1)
O(1)	-732(3)	725(2)	9449(1)	58(1)
O(2)	144(3)	1675(2)	9931(1)	66(1)
O(3)	1204(3)	1813(2)	8879(1)	55(1)
O(4)	1193(3)	1560(2)	7754(1)	56(1)
O(5)	529(4)	1161(2)	6973(1)	85(1)
O(6)	2088(3)	-486(2)	9086(1)	60(1)
O(7)	3440(2)	3604(2)	8281(1)	55(1)
S(1)	-6579(1)	1138(1)	10899(1)	74(1)
Si(1)	1206(2)	-1274(1)	9166(1)	76(1)
Si(2)	3201(1)	4523(1)	8450(1)	63(1)

Table S10. Bond lengths [Å] and angles [°] for **96**.

C(1)-O(2)	1.188(5)	C(12)-C(11)-H(11A)	109.1
C(1)-O(1)	1.351(5)	C(10)-C(11)-H(11A)	109.1
C(1)-C(2)	1.509(6)	C(12)-C(11)-H(11B)	109.1
C(2)-C(3)	1.559(6)	C(10)-C(11)-H(11B)	109.1
C(2)-H(2A)	0.9900	H(11A)-C(11)-H(11B)	107.8

C(2)-H(2B)	0.9900	C(13)-C(12)-C(23)	121.2(5)
C(3)-O(6)	1.424(5)	C(13)-C(12)-C(11)	123.1(5)
C(3)-C(4)	1.516(6)	C(23)-C(12)-C(11)	115.6(4)
C(3)-H(3A)	1.0000	C(12)-C(13)-C(14)	126.4(5)
C(4)-C(20)	1.540(5)	C(12)-C(13)-H(13A)	116.8
C(4)-C(5)	1.549(6)	C(14)-C(13)-H(13A)	116.8
C(4)-C(19)	1.589(6)	C(13)-C(14)-C(15)	114.7(4)
C(5)-O(3)	1.217(5)	C(13)-C(14)-H(14A)	108.6
C(5)-C(6)	1.520(6)	C(15)-C(14)-H(14A)	108.6
C(6)-C(7)	1.539(6)	C(13)-C(14)-H(14B)	108.6
C(6)-C(21)	1.550(6)	C(15)-C(14)-H(14B)	108.6
C(6)-H(6A)	1.0000	H(14A)-C(14)-H(14B)	107.6
C(7)-O(7)	1.447(5)	O(1)-C(15)-C(24)	108.3(4)
C(7)-C(8)	1.548(6)	O(1)-C(15)-C(14)	105.6(4)
C(7)-H(7A)	1.0000	C(24)-C(15)-C(14)	115.1(4)
C(8)-C(9)	1.532(6)	O(1)-C(15)-H(15A)	109.2
C(8)-C(22)	1.542(6)	C(24)-C(15)-H(15A)	109.2
C(8)-H(8A)	1.0000	C(14)-C(15)-H(15A)	109.2
C(9)-O(4)	1.442(5)	O(5)-C(16)-O(4)	123.7(5)
C(9)-C(10)	1.539(6)	O(5)-C(16)-C(17)	123.1(5)
C(9)-H(9A)	1.0000	O(4)-C(16)-C(17)	113.1(5)
C(10)-C(11)	1.533(6)	C(18)-C(17)-C(16)	126.4(5)
C(10)-H(10A)	0.9900	C(18)-C(17)-H(17A)	116.8
C(10)-H(10B)	0.9900	C(16)-C(17)-H(17A)	116.8
C(11)-C(12)	1.501(6)	C(17)-C(18)-C(19)	128.7(5)
C(11)-H(11A)	0.9900	C(17)-C(18)-H(18A)	115.6
C(11)-H(11B)	0.9900	C(19)-C(18)-H(18A)	115.6
C(12)-C(13)	1.337(6)	C(18)-C(19)-C(4)	117.9(4)
C(12)-C(23)	1.496(7)	C(18)-C(19)-H(19A)	107.8
C(13)-C(14)	1.471(7)	C(4)-C(19)-H(19A)	107.8
C(13)-H(13A)	0.9500	C(18)-C(19)-H(19B)	107.8
C(14)-C(15)	1.533(6)	C(4)-C(19)-H(19B)	107.8
C(14)-H(14A)	0.9900	H(19A)-C(19)-H(19B)	107.2
C(14)-H(14B)	0.9900	C(4)-C(20)-H(20A)	109.5

C(15)-O(1)	1.464(5)	C(4)-C(20)-H(20B)	109.5
C(15)-C(24)	1.505(6)	H(20A)-C(20)-H(20B)	109.5
C(15)-H(15A)	1.0000	C(4)-C(20)-H(20C)	109.5
C(16)-O(5)	1.222(6)	H(20A)-C(20)-H(20C)	109.5
C(16)-O(4)	1.329(6)	H(20B)-C(20)-H(20C)	109.5
C(16)-C(17)	1.462(7)	C(6)-C(21)-H(21A)	109.5
C(17)-C(18)	1.324(6)	C(6)-C(21)-H(21B)	109.5
C(17)-H(17A)	0.9500	H(21A)-C(21)-H(21B)	109.5
C(18)-C(19)	1.502(6)	C(6)-C(21)-H(21C)	109.5
C(18)-H(18A)	0.9500	H(21A)-C(21)-H(21C)	109.5
C(19)-H(19A)	0.9900	H(21B)-C(21)-H(21C)	109.5
C(19)-H(19B)	0.9900	C(8)-C(22)-H(22A)	109.5
C(20)-H(20A)	0.9800	C(8)-C(22)-H(22B)	109.5
C(20)-H(20B)	0.9800	H(22A)-C(22)-H(22B)	109.5
C(20)-H(20C)	0.9800	C(8)-C(22)-H(22C)	109.5
C(21)-H(21A)	0.9800	H(22A)-C(22)-H(22C)	109.5
C(21)-H(21B)	0.9800	H(22B)-C(22)-H(22C)	109.5
C(21)-H(21C)	0.9800	C(12)-C(23)-H(23A)	109.5
C(22)-H(22A)	0.9800	C(12)-C(23)-H(23B)	109.5
C(22)-H(22B)	0.9800	H(23A)-C(23)-H(23B)	109.5
C(22)-H(22C)	0.9800	C(12)-C(23)-H(23C)	109.5
C(23)-H(23A)	0.9800	H(23A)-C(23)-H(23C)	109.5
C(23)-H(23B)	0.9800	H(23B)-C(23)-H(23C)	109.5
C(23)-H(23C)	0.9800	C(25)-C(24)-C(15)	118.1(4)
C(24)-C(25)	1.343(6)	C(25)-C(24)-C(30)	125.9(4)
C(24)-C(30)	1.508(6)	C(15)-C(24)-C(30)	116.0(4)
C(25)-C(26)	1.476(6)	C(24)-C(25)-C(26)	128.9(5)
C(25)-H(25A)	0.9500	C(24)-C(25)-H(25A)	115.5
C(26)-C(27)	1.358(7)	C(26)-C(25)-H(25A)	115.5
C(26)-N(1)	1.378(6)	C(27)-C(26)-N(1)	115.7(4)
C(27)-S(1)	1.717(5)	C(27)-C(26)-C(25)	121.4(5)
C(27)-H(27)	0.9500	N(1)-C(26)-C(25)	123.0(4)
C(28)-N(1)	1.315(6)	C(26)-C(27)-S(1)	109.8(4)
C(28)-C(29)	1.493(7)	C(26)-C(27)-H(27)	125.1

C(28)-S(1)	1.735(5)	S(1)-C(27)-H(27)	125.1
C(29)-H(29A)	0.9800	N(1)-C(28)-C(29)	124.3(5)
C(29)-H(29B)	0.9800	N(1)-C(28)-S(1)	113.8(4)
C(29)-H(29C)	0.9800	C(29)-C(28)-S(1)	121.9(4)
C(30)-H(30A)	0.9800	C(28)-C(29)-H(29A)	109.5
C(30)-H(30B)	0.9800	C(28)-C(29)-H(29B)	109.5
C(30)-H(30C)	0.9800	H(29A)-C(29)-H(29B)	109.5
C(31)-Si(1)	1.873(6)	C(28)-C(29)-H(29C)	109.5
C(31)-H(31A)	0.9800	H(29A)-C(29)-H(29C)	109.5
C(31)-H(31B)	0.9800	H(29B)-C(29)-H(29C)	109.5
C(31)-H(31C)	0.9800	C(24)-C(30)-H(30A)	109.5
C(32)-Si(1)	1.868(6)	C(24)-C(30)-H(30B)	109.5
C(32)-H(32A)	0.9800	H(30A)-C(30)-H(30B)	109.5
C(32)-H(32B)	0.9800	C(24)-C(30)-H(30C)	109.5
C(32)-H(32C)	0.9800	H(30A)-C(30)-H(30C)	109.5
C(33)-C(36)	1.538(9)	H(30B)-C(30)-H(30C)	109.5
C(33)-C(35)	1.543(10)	Si(1)-C(31)-H(31A)	109.5
C(33)-C(34)	1.547(9)	Si(1)-C(31)-H(31B)	109.5
C(33)-Si(1)	1.867(7)	H(31A)-C(31)-H(31B)	109.5
C(34)-H(34A)	0.9800	Si(1)-C(31)-H(31C)	109.5
C(34)-H(34B)	0.9800	H(31A)-C(31)-H(31C)	109.5
C(34)-H(34C)	0.9800	H(31B)-C(31)-H(31C)	109.5
C(35)-H(35A)	0.9800	Si(1)-C(32)-H(32A)	109.5
C(35)-H(35B)	0.9800	Si(1)-C(32)-H(32B)	109.5
C(35)-H(35C)	0.9800	H(32A)-C(32)-H(32B)	109.5
C(36)-H(36A)	0.9800	Si(1)-C(32)-H(32C)	109.5
C(36)-H(36B)	0.9800	H(32A)-C(32)-H(32C)	109.5
C(36)-H(36C)	0.9800	H(32B)-C(32)-H(32C)	109.5
C(37)-Si(2)	1.875(5)	C(36)-C(33)-C(35)	110.5(6)
C(37)-H(37A)	0.9800	C(36)-C(33)-C(34)	108.6(6)
C(37)-H(37B)	0.9800	C(35)-C(33)-C(34)	107.4(7)
C(37)-H(37C)	0.9800	C(36)-C(33)-Si(1)	111.0(6)
C(38)-Si(2)	1.839(5)	C(35)-C(33)-Si(1)	109.9(4)
C(38)-H(38A)	0.9800	C(34)-C(33)-Si(1)	109.4(5)

C(38)-H(38B)	0.9800	C(33)-C(34)-H(34A)	109.5
C(38)-H(38C)	0.9800	C(33)-C(34)-H(34B)	109.5
C(39)-C(40)	1.530(7)	H(34A)-C(34)-H(34B)	109.5
C(39)-C(41)	1.542(7)	C(33)-C(34)-H(34C)	109.5
C(39)-C(42)	1.559(7)	H(34A)-C(34)-H(34C)	109.5
C(39)-Si(2)	1.864(5)	H(34B)-C(34)-H(34C)	109.5
C(40)-H(40A)	0.9800	C(33)-C(35)-H(35A)	109.5
C(40)-H(40B)	0.9800	C(33)-C(35)-H(35B)	109.5
C(40)-H(40C)	0.9800	H(35A)-C(35)-H(35B)	109.5
C(41)-H(41A)	0.9800	C(33)-C(35)-H(35C)	109.5
C(41)-H(41B)	0.9800	H(35A)-C(35)-H(35C)	109.5
C(41)-H(41C)	0.9800	H(35B)-C(35)-H(35C)	109.5
C(42)-H(42A)	0.9800	C(33)-C(36)-H(36A)	109.5
C(42)-H(42B)	0.9800	C(33)-C(36)-H(36B)	109.5
C(42)-H(42C)	0.9800	H(36A)-C(36)-H(36B)	109.5
O(6)-Si(1)	1.655(3)	C(33)-C(36)-H(36C)	109.5
O(7)-Si(2)	1.650(3)	H(36A)-C(36)-H(36C)	109.5
O(2)-C(1)-O(1)	124.8(4)	H(36B)-C(36)-H(36C)	109.5
O(2)-C(1)-C(2)	125.0(4)	Si(2)-C(37)-H(37A)	109.5
O(1)-C(1)-C(2)	110.3(4)	Si(2)-C(37)-H(37B)	109.5
C(1)-C(2)-C(3)	116.0(4)	H(37A)-C(37)-H(37B)	109.5
C(1)-C(2)-H(2A)	108.3	Si(2)-C(37)-H(37C)	109.5
C(3)-C(2)-H(2A)	108.3	H(37A)-C(37)-H(37C)	109.5
C(1)-C(2)-H(2B)	108.3	H(37B)-C(37)-H(37C)	109.5
C(3)-C(2)-H(2B)	108.3	Si(2)-C(38)-H(38A)	109.5
H(2A)-C(2)-H(2B)	107.4	Si(2)-C(38)-H(38B)	109.5
O(6)-C(3)-C(4)	107.9(3)	H(38A)-C(38)-H(38B)	109.5
O(6)-C(3)-C(2)	110.7(4)	Si(2)-C(38)-H(38C)	109.5
C(4)-C(3)-C(2)	113.0(4)	H(38A)-C(38)-H(38C)	109.5
O(6)-C(3)-H(3A)	108.4	H(38B)-C(38)-H(38C)	109.5
C(4)-C(3)-H(3A)	108.4	C(40)-C(39)-C(41)	108.6(5)
C(2)-C(3)-H(3A)	108.4	C(40)-C(39)-C(42)	110.3(5)
C(3)-C(4)-C(20)	111.2(4)	C(41)-C(39)-C(42)	108.1(5)
C(3)-C(4)-C(5)	109.9(4)	C(40)-C(39)-Si(2)	110.8(4)

C(20)-C(4)-C(5)	110.6(4)	C(41)-C(39)-Si(2)	108.9(4)
C(3)-C(4)-C(19)	112.5(4)	C(42)-C(39)-Si(2)	110.1(4)
C(20)-C(4)-C(19)	104.2(3)	C(39)-C(40)-H(40A)	109.5
C(5)-C(4)-C(19)	108.4(3)	C(39)-C(40)-H(40B)	109.5
O(3)-C(5)-C(6)	119.9(4)	H(40A)-C(40)-H(40B)	109.5
O(3)-C(5)-C(4)	118.3(4)	C(39)-C(40)-H(40C)	109.5
C(6)-C(5)-C(4)	121.7(4)	H(40A)-C(40)-H(40C)	109.5
C(5)-C(6)-C(7)	113.7(3)	H(40B)-C(40)-H(40C)	109.5
C(5)-C(6)-C(21)	105.1(3)	C(39)-C(41)-H(41A)	109.5
C(7)-C(6)-C(21)	108.4(4)	C(39)-C(41)-H(41B)	109.5
C(5)-C(6)-H(6A)	109.8	H(41A)-C(41)-H(41B)	109.5
C(7)-C(6)-H(6A)	109.8	C(39)-C(41)-H(41C)	109.5
C(21)-C(6)-H(6A)	109.8	H(41A)-C(41)-H(41C)	109.5
O(7)-C(7)-C(6)	107.8(3)	H(41B)-C(41)-H(41C)	109.5
O(7)-C(7)-C(8)	105.3(3)	C(39)-C(42)-H(42A)	109.5
C(6)-C(7)-C(8)	119.5(4)	C(39)-C(42)-H(42B)	109.5
O(7)-C(7)-H(7A)	107.9	H(42A)-C(42)-H(42B)	109.5
C(6)-C(7)-H(7A)	107.9	C(39)-C(42)-H(42C)	109.5
C(8)-C(7)-H(7A)	107.9	H(42A)-C(42)-H(42C)	109.5
C(9)-C(8)-C(22)	110.5(4)	H(42B)-C(42)-H(42C)	109.5
C(9)-C(8)-C(7)	118.2(4)	C(28)-N(1)-C(26)	111.0(4)
C(22)-C(8)-C(7)	112.0(4)	C(1)-O(1)-C(15)	118.1(3)
C(9)-C(8)-H(8A)	105.0	C(16)-O(4)-C(9)	118.7(4)
C(22)-C(8)-H(8A)	105.0	C(3)-O(6)-Si(1)	127.6(3)
C(7)-C(8)-H(8A)	105.0	C(7)-O(7)-Si(2)	127.8(3)
O(4)-C(9)-C(8)	108.6(3)	C(27)-S(1)-C(28)	89.8(3)
O(4)-C(9)-C(10)	107.9(4)	O(6)-Si(1)-C(33)	102.3(3)
C(8)-C(9)-C(10)	115.5(4)	O(6)-Si(1)-C(32)	112.4(2)
O(4)-C(9)-H(9A)	108.2	C(33)-Si(1)-C(32)	111.1(3)
C(8)-C(9)-H(9A)	108.2	O(6)-Si(1)-C(31)	111.4(2)
C(10)-C(9)-H(9A)	108.2	C(33)-Si(1)-C(31)	112.1(3)
C(11)-C(10)-C(9)	112.4(4)	C(32)-Si(1)-C(31)	107.6(3)
C(11)-C(10)-H(10A)	109.1	O(7)-Si(2)-C(38)	110.7(2)
C(9)-C(10)-H(10A)	109.1	O(7)-Si(2)-C(39)	106.4(2)

C(11)-C(10)-H(10B)	109.1	C(38)-Si(2)-C(39)	111.3(2)
C(9)-C(10)-H(10B)	109.1	O(7)-Si(2)-C(37)	109.7(2)
H(10A)-C(10)-H(10B)	107.8	C(38)-Si(2)-C(37)	109.5(3)
C(12)-C(11)-C(10)	112.7(4)	C(39)-Si(2)-C(37)	109.1(3)

Table S11. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **96**. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	53(3)	57(3)	50(3)	5(2)	1(2)	0(2)
C(2)	52(3)	63(3)	51(3)	1(2)	-4(2)	-1(2)
C(3)	51(3)	53(3)	49(3)	-3(2)	-2(2)	-1(2)
C(4)	46(2)	63(3)	48(3)	0(2)	-1(2)	3(2)
C(5)	51(3)	63(3)	38(3)	-5(2)	-5(2)	4(2)
C(6)	42(2)	59(3)	47(3)	-2(2)	4(2)	-2(2)
C(7)	46(2)	58(3)	51(3)	-2(2)	1(2)	-4(2)
C(8)	41(2)	61(3)	54(3)	7(2)	-2(2)	3(2)
C(9)	48(3)	70(3)	52(3)	0(2)	-1(2)	-6(2)
C(10)	44(3)	74(3)	59(3)	3(3)	0(2)	0(2)
C(11)	49(3)	76(3)	56(3)	4(3)	-9(2)	-1(2)
C(12)	49(3)	74(3)	59(3)	3(3)	-4(2)	-1(2)
C(13)	48(3)	80(4)	79(4)	-1(3)	3(2)	5(3)
C(14)	67(3)	80(4)	61(3)	8(3)	7(2)	3(3)
C(15)	51(3)	62(3)	60(3)	0(2)	-1(2)	5(2)
C(16)	58(3)	79(4)	64(4)	-13(3)	2(2)	-4(3)
C(17)	76(4)	68(3)	61(4)	-10(3)	-7(3)	-10(3)
C(18)	72(3)	60(3)	60(3)	-5(3)	3(3)	-6(3)
C(19)	54(3)	70(3)	54(3)	-2(2)	4(2)	6(2)
C(20)	44(3)	61(3)	67(3)	-2(2)	-5(2)	6(2)
C(21)	58(3)	65(3)	58(3)	2(2)	-6(2)	-2(2)

C(22)	59(3)	90(4)	53(3)	0(3)	7(2)	-1(3)
C(23)	55(3)	94(4)	72(4)	18(3)	-4(2)	7(3)
C(24)	49(3)	60(3)	57(3)	3(2)	-8(2)	-6(2)
C(25)	52(3)	58(3)	51(3)	1(2)	-8(2)	-2(2)
C(26)	52(3)	69(3)	52(3)	1(3)	-8(2)	-1(3)
C(27)	55(3)	69(3)	69(4)	0(3)	-4(2)	-4(3)
C(28)	61(3)	84(4)	49(3)	3(3)	-7(2)	-14(3)
C(29)	71(3)	89(4)	78(4)	11(3)	2(3)	-15(3)
C(30)	58(3)	71(3)	64(3)	0(3)	2(2)	-2(3)
C(31)	124(6)	123(5)	95(5)	9(4)	-25(4)	-66(5)
C(32)	113(5)	78(4)	93(5)	0(3)	17(4)	-35(4)
C(33)	154(7)	69(4)	83(5)	-1(4)	16(5)	7(4)
C(34)	173(8)	71(4)	123(6)	-14(4)	31(6)	16(4)
C(35)	200(10)	117(6)	126(7)	10(5)	-23(6)	83(6)
C(36)	266(11)	56(4)	148(7)	-1(4)	72(7)	-10(6)
C(37)	107(4)	75(3)	58(3)	-5(3)	-7(3)	-11(3)
C(38)	61(3)	80(4)	100(4)	2(3)	15(3)	-1(3)
C(39)	65(3)	70(3)	65(3)	9(3)	14(2)	-1(3)
C(40)	64(4)	112(5)	126(5)	21(4)	33(3)	2(4)
C(41)	126(5)	58(3)	126(6)	16(3)	43(4)	5(4)
C(42)	152(6)	106(5)	56(4)	16(3)	-2(4)	-1(5)
N(1)	60(3)	71(3)	50(3)	1(2)	-2(2)	-5(2)
O(1)	45(2)	66(2)	64(2)	-2(2)	0(1)	-1(2)
O(2)	64(2)	73(2)	59(2)	-8(2)	-3(2)	9(2)
O(3)	44(2)	66(2)	54(2)	4(2)	9(1)	7(2)
O(4)	50(2)	65(2)	53(2)	-4(2)	-6(1)	0(2)
O(5)	109(3)	85(3)	60(3)	-4(2)	-24(2)	-9(2)
O(6)	57(2)	57(2)	66(2)	-2(2)	-1(2)	0(2)
O(7)	42(2)	62(2)	62(2)	1(2)	2(1)	1(2)
S(1)	57(1)	94(1)	70(1)	-6(1)	8(1)	-2(1)
Si(1)	96(1)	62(1)	69(1)	-1(1)	-2(1)	-15(1)
Si(2)	54(1)	63(1)	71(1)	4(1)	6(1)	2(1)

Table S12. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **96**.

x	y	z	U(eq)
H(2A)	1410	170	9864	66
H(2B)	2146	956	9728	66
H(3A)	882	334	8869	61
H(6A)	3863	2051	8365	59
H(7A)	1808	3136	8504	62
H(8A)	1902	3388	7607	62
H(9A)	715	2401	7258	68
H(10A)	-59	2564	8317	71
H(10B)	-436	3167	7871	71
H(11A)	-1647	2209	7452	73
H(11B)	-1178	1553	7848	73
H(13A)	-3497	2019	8770	83
H(14A)	-1232	1179	8607	83
H(14B)	-2517	704	8670	83
H(15A)	-1761	1721	9487	69
H(17A)	582	-176	7447	82
H(18A)	1788	-529	8081	77
H(19A)	3114	907	7993	71
H(19B)	3679	120	8227	71
H(20A)	4216	156	9070	86
H(20B)	3913	925	9400	86
H(20C)	4597	999	8852	86
H(21A)	4155	2167	9281	91
H(21B)	3069	2814	9308	91
H(21C)	4363	3003	9017	91
H(22A)	2884	2519	7025	101
H(22B)	3510	2069	7502	101
H(22C)	3877	2960	7387	101

H(23A)	-3972	3043	8255	111
H(23B)	-3655	2875	7662	111
H(23C)	-2770	3443	7993	111
H(25A)	-3453	1795	9955	65
H(27)	-5222	2126	10556	77
H(29A)	-6367	-945	10627	119
H(29B)	-7649	-475	10719	119
H(29C)	-6667	-581	11182	119
H(30A)	-3771	-263	9808	97
H(30B)	-2284	-331	9719	97
H(30C)	-3205	-206	9238	97
H(31A)	-643	-914	8701	171
H(31B)	-482	-1844	8689	171
H(31C)	348	-1308	8315	171
H(32A)	1037	-1257	10082	142
H(32B)	-73	-1776	9843	142
H(32C)	-169	-842	9833	142
H(34A)	3710	-2432	8565	184
H(34B)	3547	-1502	8587	184
H(34C)	2503	-2029	8309	184
H(35A)	3978	-2434	9519	222
H(35B)	2932	-2052	9885	222
H(35C)	3788	-1505	9527	222
H(36A)	2368	-3297	9091	236
H(36B)	1127	-2921	8845	236
H(36C)	1295	-2946	9458	236
H(37A)	3492	4383	9358	120
H(37B)	3811	5262	9190	120
H(37C)	4812	4579	9091	120
H(38A)	1101	4411	8729	120
H(38B)	1135	4640	8131	120
H(38C)	1386	5294	8561	120
H(40A)	5856	5312	7711	151
H(40B)	5603	4432	7892	151

H(40C)	5774	5108	8312	151
H(41A)	4214	6333	7828	155
H(41B)	4126	6124	8429	155
H(41C)	2885	6112	8079	155
H(42A)	3912	5297	7158	157
H(42B)	2579	5084	7408	157
H(42C)	3613	4416	7325	157

Table S13. Torsion angles [°] for **96**.

O(2)-C(1)-C(2)-C(3)	-136.1(5)	O(1)-C(15)-C(24)-C(30)	-48.3(5)
O(1)-C(1)-C(2)-C(3)	43.5(5)	C(14)-C(15)-C(24)-C(30)	69.6(5)
C(1)-C(2)-C(3)-O(6)	-134.9(4)	C(15)-C(24)-C(25)-C(26)	179.5(4)
C(1)-C(2)-C(3)-C(4)	104.0(4)	C(30)-C(24)-C(25)-C(26)	-1.1(8)
O(6)-C(3)-C(4)-C(20)	-58.6(5)	C(24)-C(25)-C(26)-C(27)	-179.4(5)
C(2)-C(3)-C(4)-C(20)	64.1(5)	C(24)-C(25)-C(26)-N(1)	1.7(7)
O(6)-C(3)-C(4)-C(5)	178.7(3)	N(1)-C(26)-C(27)-S(1)	-0.1(6)
C(2)-C(3)-C(4)-C(5)	-58.6(5)	C(25)-C(26)-C(27)-S(1)	-179.1(3)
O(6)-C(3)-C(4)-C(19)	57.9(4)	C(29)-C(28)-N(1)-C(26)	-178.2(5)
C(2)-C(3)-C(4)-C(19)	-179.4(3)	S(1)-C(28)-N(1)-C(26)	1.0(5)
C(3)-C(4)-C(5)-O(3)	-8.8(6)	C(27)-C(26)-N(1)-C(28)	-0.6(6)
C(20)-C(4)-C(5)-O(3)	-131.9(4)	C(25)-C(26)-N(1)-C(28)	178.4(4)
C(19)-C(4)-C(5)-O(3)	114.5(4)	O(2)-C(1)-O(1)-C(15)	14.9(7)
C(3)-C(4)-C(5)-C(6)	166.7(4)	C(2)-C(1)-O(1)-C(15)	-164.7(3)
C(20)-C(4)-C(5)-C(6)	43.7(5)	C(24)-C(15)-O(1)-C(1)	-115.6(4)
C(19)-C(4)-C(5)-C(6)	-70.0(5)	C(14)-C(15)-O(1)-C(1)	120.6(4)
O(3)-C(5)-C(6)-C(7)	-35.2(6)	O(5)-C(16)-O(4)-C(9)	4.6(7)
C(4)-C(5)-C(6)-C(7)	149.3(4)	C(17)-C(16)-O(4)-C(9)	-172.8(4)
O(3)-C(5)-C(6)-C(21)	83.2(5)	C(8)-C(9)-O(4)-C(16)	-128.4(4)
C(4)-C(5)-C(6)-C(21)	-92.2(5)	C(10)-C(9)-O(4)-C(16)	105.7(4)
C(5)-C(6)-C(7)-O(7)	165.9(3)	C(4)-C(3)-O(6)-Si(1)	-157.5(3)

C(21)-C(6)-C(7)-O(7)	49.4(4)	C(2)-C(3)-O(6)-Si(1)	78.4(4)
C(5)-C(6)-C(7)-C(8)	-74.1(5)	C(6)-C(7)-O(7)-Si(2)	-129.2(3)
C(21)-C(6)-C(7)-C(8)	169.4(4)	C(8)-C(7)-O(7)-Si(2)	102.2(4)
O(7)-C(7)-C(8)-C(9)	-164.3(4)	C(26)-C(27)-S(1)-C(28)	0.5(4)
C(6)-C(7)-C(8)-C(9)	74.5(5)	N(1)-C(28)-S(1)-C(27)	-0.9(4)
O(7)-C(7)-C(8)-C(22)	65.5(5)	C(29)-C(28)-S(1)-C(27)	178.3(4)
C(6)-C(7)-C(8)-C(22)	-55.7(5)	C(3)-O(6)-Si(1)-C(33)	177.5(4)
C(22)-C(8)-C(9)-O(4)	61.5(5)	C(3)-O(6)-Si(1)-C(32)	-63.2(4)
C(7)-C(8)-C(9)-O(4)	-69.3(5)	C(3)-O(6)-Si(1)-C(31)	57.6(4)
C(22)-C(8)-C(9)-C(10)	-177.2(4)	C(36)-C(33)-Si(1)-O(6)	-174.9(5)
C(7)-C(8)-C(9)-C(10)	52.0(6)	C(35)-C(33)-Si(1)-O(6)	62.5(5)
O(4)-C(9)-C(10)-C(11)	-59.7(5)	C(34)-C(33)-Si(1)-O(6)	-55.1(5)
C(8)-C(9)-C(10)-C(11)	178.6(4)	C(36)-C(33)-Si(1)-C(32)	65.0(6)
C(9)-C(10)-C(11)-C(12)	173.3(4)	C(35)-C(33)-Si(1)-C(32)	-57.6(6)
C(10)-C(11)-C(12)-C(13)	-96.4(6)	C(34)-C(33)-Si(1)-C(32)	-175.2(5)
C(10)-C(11)-C(12)-C(23)	83.6(5)	C(36)-C(33)-Si(1)-C(31)	-55.5(6)
C(23)-C(12)-C(13)-C(14)	-179.4(5)	C(35)-C(33)-Si(1)-C(31)	-178.1(5)
C(11)-C(12)-C(13)-C(14)	0.6(8)	C(34)-C(33)-Si(1)-C(31)	64.3(6)
C(12)-C(13)-C(14)-C(15)	137.5(5)	C(7)-O(7)-Si(2)-C(38)	-18.5(4)
C(13)-C(14)-C(15)-O(1)	-153.3(4)	C(7)-O(7)-Si(2)-C(39)	-139.6(3)
C(13)-C(14)-C(15)-C(24)	87.3(5)	C(7)-O(7)-Si(2)-C(37)	102.5(4)
O(5)-C(16)-C(17)-C(18)	154.5(5)	C(40)-C(39)-Si(2)-O(7)	-62.8(5)
O(4)-C(16)-C(17)-C(18)	-28.1(8)	C(41)-C(39)-Si(2)-O(7)	177.9(4)
C(16)-C(17)-C(18)-C(19)	-9.3(9)	C(42)-C(39)-Si(2)-O(7)	59.5(4)
C(17)-C(18)-C(19)-C(4)	103.9(6)	C(40)-C(39)-Si(2)-C(38)	176.5(4)
C(3)-C(4)-C(19)-C(18)	23.5(6)	C(41)-C(39)-Si(2)-C(38)	57.2(5)
C(20)-C(4)-C(19)-C(18)	144.0(4)	C(42)-C(39)-Si(2)-C(38)	-61.2(5)
C(5)-C(4)-C(19)-C(18)	-98.2(5)	C(40)-C(39)-Si(2)-C(37)	55.5(5)
O(1)-C(15)-C(24)-C(25)	131.2(4)	C(41)-C(39)-Si(2)-C(37)	-63.8(5)
C(14)-C(15)-C(24)-C(25)	-110.9(5)	C(42)-C(39)-Si(2)-C(37)	177.8(4)

1.8.3. Michael adduct 97.

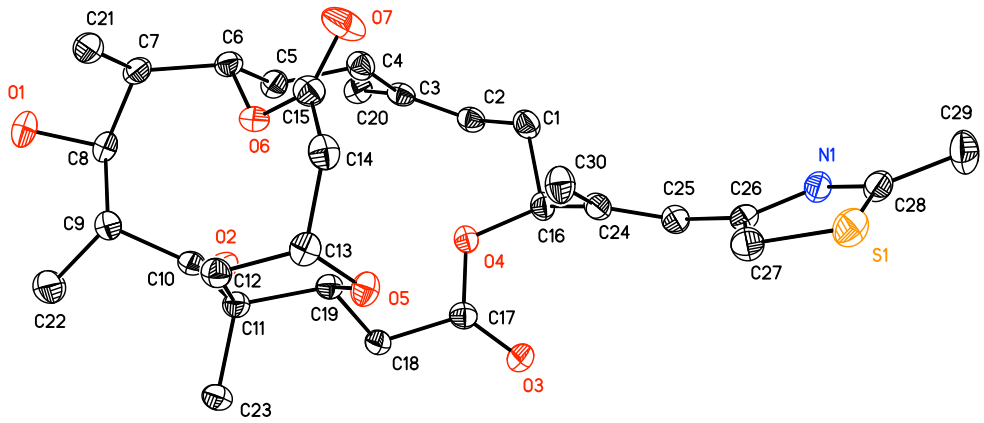


Figure S3. Thermal ellipsoid diagram of **97** with 50% displacement ellipsoids.

Table S14. Crystal data and structure refinement for **97**.

Empirical formula	C30 H41 N O7 S	
Formula weight	559.70	
Temperature	173(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 10.4617(3) Å	α= 90°.
	b = 13.9431(4) Å	β= 90°.
	c = 19.6338(5) Å	γ = 90°.
Volume	2863.95(14) $Å^3$	
Z	4	
Density (calculated)	1.298 Mg/m^3	
Absorption coefficient	1.396 mm^{-1}	
F(000)	1200	
Crystal size	0.27 x 0.27 x 0.03 mm^3	
Theta range for data collection	3.89 to 69.35°.	
Index ranges	-12<=h<=12, -15<=k<=16, -23<=l<=23	
Reflections collected	27445	
Independent reflections	5191 [R(int) = 0.0234]	
Completeness to theta = 69.35°	97.7 %	

Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9593 and 0.7043
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5191 / 0 / 360
Goodness-of-fit on F^2	1.036
Final R indices [I>2sigma(I)]	R1 = 0.0311, wR2 = 0.0855
R indices (all data)	R1 = 0.0320, wR2 = 0.0865
Absolute structure parameter	0.026(14)
Largest diff. peak and hole	0.363 and -0.321 e.$Å^{-3}$

Table S15. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for **97**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	502(2)	-271(1)	2532(1)	32(1)
C(2)	1173(2)	-870(1)	3061(1)	29(1)
C(3)	1840(2)	-543(1)	3591(1)	28(1)
C(4)	2047(2)	514(1)	3729(1)	32(1)
C(5)	3350(2)	740(1)	4038(1)	29(1)
C(6)	3645(2)	1806(1)	4094(1)	27(1)
C(7)	4848(2)	2039(1)	4501(1)	29(1)
C(8)	6089(2)	1482(1)	4326(1)	29(1)
C(9)	6733(2)	1741(1)	3641(1)	30(1)
C(10)	6112(2)	1212(1)	3051(1)	26(1)
C(11)	5830(2)	1692(1)	2366(1)	25(1)
C(12)	5582(2)	2789(1)	2380(1)	28(1)
C(13)	4284(2)	2935(1)	2025(1)	29(1)
C(14)	3166(2)	3239(1)	2480(1)	31(1)
C(15)	2826(2)	2723(1)	3136(1)	31(1)
C(16)	1148(2)	-249(1)	1833(1)	28(1)
C(17)	3255(2)	91(1)	1421(1)	26(1)
C(18)	4581(2)	399(1)	1641(1)	26(1)
C(19)	4552(2)	1292(1)	2081(1)	24(1)
C(20)	2403(2)	-1229(1)	4103(1)	33(1)
C(21)	5079(2)	3124(1)	4540(1)	37(1)
C(22)	8153(2)	1431(2)	3637(1)	57(1)
C(23)	6967(2)	1457(1)	1891(1)	32(1)
C(24)	468(2)	438(1)	1362(1)	28(1)
C(25)	-379(2)	84(1)	918(1)	29(1)
C(26)	-1186(2)	632(1)	451(1)	28(1)
C(27)	-889(2)	1447(1)	108(1)	37(1)
C(28)	-3038(2)	853(1)	-83(1)	33(1)

C(29)	-4392(2)	716(2)	-284(1)	51(1)
C(30)	737(2)	1486(1)	1473(1)	37(1)
N(1)	-2412(1)	288(1)	328(1)	31(1)
O(1)	6951(1)	1684(1)	4874(1)	38(1)
O(2)	5919(1)	353(1)	3098(1)	35(1)
O(3)	2954(1)	-111(1)	849(1)	38(1)
O(4)	2460(1)	54(1)	1959(1)	28(1)
O(5)	4036(1)	2052(1)	1675(1)	31(1)
O(6)	3802(1)	2225(1)	3408(1)	26(1)
O(7)	1786(1)	2787(1)	3389(1)	51(1)
S(1)	-2168(1)	1823(1)	-371(1)	41(1)

Table S16. Bond lengths [Å] and angles [°] for **97**.

C(1)-C(2)	1.506(2)	C(9)-C(8)-H(8A)	108.6
C(1)-C(16)	1.531(2)	C(7)-C(8)-H(8A)	108.6
C(1)-H(1A)	0.9900	C(10)-C(9)-C(22)	105.74(15)
C(1)-H(1B)	0.9900	C(10)-C(9)-C(8)	111.38(14)
C(2)-C(3)	1.334(2)	C(22)-C(9)-C(8)	110.94(16)
C(2)-H(2A)	0.9500	C(10)-C(9)-H(9A)	109.6
C(3)-C(20)	1.507(2)	C(22)-C(9)-H(9A)	109.6
C(3)-C(4)	1.515(2)	C(8)-C(9)-H(9A)	109.6
C(4)-C(5)	1.525(2)	O(2)-C(10)-C(9)	119.31(15)
C(4)-H(4A)	0.9900	O(2)-C(10)-C(11)	117.68(15)
C(4)-H(4B)	0.9900	C(9)-C(10)-C(11)	122.74(15)
C(5)-C(6)	1.521(2)	C(10)-C(11)-C(23)	106.82(13)
C(5)-H(5A)	0.9900	C(10)-C(11)-C(12)	116.58(13)
C(5)-H(5B)	0.9900	C(23)-C(11)-C(12)	110.37(14)
C(6)-O(6)	1.4769(19)	C(10)-C(11)-C(19)	108.96(13)
C(6)-C(7)	1.527(2)	C(23)-C(11)-C(19)	111.69(12)
C(6)-H(6A)	1.0000	C(12)-C(11)-C(19)	102.47(13)
C(7)-C(21)	1.534(2)	C(13)-C(12)-C(11)	105.71(13)
C(7)-C(8)	1.551(2)	C(13)-C(12)-H(12A)	110.6

C(7)-H(7A)	1.0000	C(11)-C(12)-H(12A)	110.6
C(8)-O(1)	1.4312(19)	C(13)-C(12)-H(12B)	110.6
C(8)-C(9)	1.547(2)	C(11)-C(12)-H(12B)	110.6
C(8)-H(8A)	1.0000	H(12A)-C(12)-H(12B)	108.7
C(9)-C(10)	1.519(2)	O(5)-C(13)-H(13A)	107.5
C(9)-C(22)	1.548(2)	C(14)-C(13)-H(13A)	107.5
C(9)-H(9A)	1.0000	C(12)-C(13)-H(13A)	107.5
C(10)-O(2)	1.219(2)	C(15)-C(14)-C(13)	122.86(15)
C(10)-C(11)	1.530(2)	C(15)-C(14)-H(14A)	108.9(12)
C(11)-C(23)	1.546(2)	C(13)-C(14)-H(14A)	107.1(12)
C(11)-C(12)	1.551(2)	C(15)-C(14)-H(14B)	107.5(12)
C(11)-C(19)	1.553(2)	C(13)-C(14)-H(14B)	105.7(12)
C(12)-C(13)	1.540(2)	H(14A)-C(14)-H(14B)	103.1(17)
C(12)-H(12A)	0.9900	O(7)-C(15)-O(6)	124.28(17)
C(12)-H(12B)	0.9900	O(7)-C(15)-C(14)	121.90(17)
C(13)-O(5)	1.434(2)	O(6)-C(15)-C(14)	113.79(14)
C(13)-C(14)	1.531(3)	O(4)-C(16)-C(24)	111.33(14)
C(13)-H(13A)	1.0000	O(4)-C(16)-C(1)	105.63(13)
C(14)-C(15)	1.519(3)	C(24)-C(16)-C(1)	110.70(14)
C(14)-H(14A)	0.92(2)	O(4)-C(16)-H(16A)	109.7
C(14)-H(14B)	0.92(2)	C(24)-C(16)-H(16A)	109.7
C(15)-O(7)	1.199(2)	C(1)-C(16)-H(16A)	109.7
C(15)-O(6)	1.345(2)	O(3)-C(17)-O(4)	124.23(15)
C(16)-O(4)	1.458(2)	O(3)-C(17)-C(18)	125.00(15)
C(16)-C(24)	1.509(2)	O(4)-C(17)-C(18)	110.75(13)
C(16)-H(16A)	1.0000	C(17)-C(18)-C(19)	112.09(13)
C(17)-O(3)	1.200(2)	C(17)-C(18)-H(18A)	109.2
C(17)-O(4)	1.344(2)	C(19)-C(18)-H(18A)	109.2
C(17)-C(18)	1.515(2)	C(17)-C(18)-H(18B)	109.2
C(18)-C(19)	1.517(2)	C(19)-C(18)-H(18B)	109.2
C(18)-H(18A)	0.9900	H(18A)-C(18)-H(18B)	107.9
C(18)-H(18B)	0.9900	O(5)-C(19)-C(18)	107.33(12)
C(19)-O(5)	1.4312(19)	O(5)-C(19)-C(11)	105.04(12)
C(19)-H(19A)	1.0000	C(18)-C(19)-C(11)	118.83(13)

C(20)-H(20A)	0.9800	O(5)-C(19)-H(19A)	108.4
C(20)-H(20B)	0.9800	C(18)-C(19)-H(19A)	108.4
C(20)-H(20C)	0.9800	C(11)-C(19)-H(19A)	108.4
C(21)-H(21A)	0.9800	C(3)-C(20)-H(20A)	109.5
C(21)-H(21B)	0.9800	C(3)-C(20)-H(20B)	109.5
C(21)-H(21C)	0.9800	H(20A)-C(20)-H(20B)	109.5
C(22)-H(22A)	0.9800	C(3)-C(20)-H(20C)	109.5
C(22)-H(22B)	0.9800	H(20A)-C(20)-H(20C)	109.5
C(22)-H(22C)	0.9800	H(20B)-C(20)-H(20C)	109.5
C(23)-H(23A)	0.9800	C(7)-C(21)-H(21A)	109.5
C(23)-H(23B)	0.9800	C(7)-C(21)-H(21B)	109.5
C(23)-H(23C)	0.9800	H(21A)-C(21)-H(21B)	109.5
C(24)-C(25)	1.336(2)	C(7)-C(21)-H(21C)	109.5
C(24)-C(30)	1.505(2)	H(21A)-C(21)-H(21C)	109.5
C(25)-C(26)	1.462(2)	H(21B)-C(21)-H(21C)	109.5
C(25)-H(25A)	0.9500	C(9)-C(22)-H(22A)	109.5
C(26)-C(27)	1.358(3)	C(9)-C(22)-H(22B)	109.5
C(26)-N(1)	1.390(2)	H(22A)-C(22)-H(22B)	109.5
C(27)-S(1)	1.7166(19)	C(9)-C(22)-H(22C)	109.5
C(27)-H(27)	0.9500	H(22A)-C(22)-H(22C)	109.5
C(28)-N(1)	1.304(2)	H(22B)-C(22)-H(22C)	109.5
C(28)-C(29)	1.483(3)	C(11)-C(23)-H(23A)	109.5
C(28)-S(1)	1.724(2)	C(11)-C(23)-H(23B)	109.5
C(29)-H(29A)	0.9800	H(23A)-C(23)-H(23B)	109.5
C(29)-H(29B)	0.9800	C(11)-C(23)-H(23C)	109.5
C(29)-H(29C)	0.9800	H(23A)-C(23)-H(23C)	109.5
C(30)-H(30A)	0.9800	H(23B)-C(23)-H(23C)	109.5
C(30)-H(30B)	0.9800	C(25)-C(24)-C(30)	125.23(16)
C(30)-H(30C)	0.9800	C(25)-C(24)-C(16)	118.50(16)
C(30)-H(30D)	0.9800	C(30)-C(24)-C(16)	116.10(15)
C(30)-H(30E)	0.9800	C(24)-C(25)-C(26)	126.82(17)
C(30)-H(30F)	0.9800	C(24)-C(25)-H(25A)	116.6
O(1)-H(1D)	0.8400	C(26)-C(25)-H(25A)	116.6
C(2)-C(1)-C(16)	115.03(14)	C(27)-C(26)-N(1)	114.41(16)

C(2)-C(1)-H(1A)	108.5	C(27)-C(26)-C(25)	128.05(17)
C(16)-C(1)-H(1A)	108.5	N(1)-C(26)-C(25)	117.53(15)
C(2)-C(1)-H(1B)	108.5	C(26)-C(27)-S(1)	110.39(14)
C(16)-C(1)-H(1B)	108.5	C(26)-C(27)-H(27)	124.8
H(1A)-C(1)-H(1B)	107.5	S(1)-C(27)-H(27)	124.8
C(3)-C(2)-C(1)	126.34(16)	N(1)-C(28)-C(29)	124.51(19)
C(3)-C(2)-H(2A)	116.8	N(1)-C(28)-S(1)	114.28(14)
C(1)-C(2)-H(2A)	116.8	C(29)-C(28)-S(1)	121.19(15)
C(2)-C(3)-C(20)	120.57(16)	C(28)-C(29)-H(29A)	109.5
C(2)-C(3)-C(4)	123.15(16)	C(28)-C(29)-H(29B)	109.5
C(20)-C(3)-C(4)	116.25(15)	H(29A)-C(29)-H(29B)	109.5
C(3)-C(4)-C(5)	113.57(15)	C(28)-C(29)-H(29C)	109.5
C(3)-C(4)-H(4A)	108.9	H(29A)-C(29)-H(29C)	109.5
C(5)-C(4)-H(4A)	108.9	H(29B)-C(29)-H(29C)	109.5
C(3)-C(4)-H(4B)	108.9	C(24)-C(30)-H(30A)	109.5
C(5)-C(4)-H(4B)	108.9	C(24)-C(30)-H(30B)	109.5
H(4A)-C(4)-H(4B)	107.7	H(30A)-C(30)-H(30B)	109.5
C(6)-C(5)-C(4)	114.31(15)	C(24)-C(30)-H(30C)	109.5
C(6)-C(5)-H(5A)	108.7	H(30A)-C(30)-H(30C)	109.5
C(4)-C(5)-H(5A)	108.7	H(30B)-C(30)-H(30C)	109.5
C(6)-C(5)-H(5B)	108.7	C(24)-C(30)-H(30D)	109.5
C(4)-C(5)-H(5B)	108.7	H(30A)-C(30)-H(30D)	141.1
H(5A)-C(5)-H(5B)	107.6	H(30B)-C(30)-H(30D)	56.3
O(6)-C(6)-C(5)	110.10(13)	H(30C)-C(30)-H(30D)	56.3
O(6)-C(6)-C(7)	107.57(13)	C(24)-C(30)-H(30E)	109.5
C(5)-C(6)-C(7)	114.36(14)	H(30A)-C(30)-H(30E)	56.3
O(6)-C(6)-H(6A)	108.2	H(30B)-C(30)-H(30E)	141.1
C(5)-C(6)-H(6A)	108.2	H(30C)-C(30)-H(30E)	56.3
C(7)-C(6)-H(6A)	108.2	H(30D)-C(30)-H(30E)	109.5
C(6)-C(7)-C(21)	111.44(15)	C(24)-C(30)-H(30F)	109.5
C(6)-C(7)-C(8)	117.87(13)	H(30A)-C(30)-H(30F)	56.3
C(21)-C(7)-C(8)	111.88(14)	H(30B)-C(30)-H(30F)	56.3
C(6)-C(7)-H(7A)	104.8	H(30C)-C(30)-H(30F)	141.1
C(21)-C(7)-H(7A)	104.8	H(30D)-C(30)-H(30F)	109.5

C(8)-C(7)-H(7A)	104.8	H(30E)-C(30)-H(30F)	109.5
O(1)-C(8)-C(9)	109.50(14)	C(28)-N(1)-C(26)	111.27(15)
O(1)-C(8)-C(7)	105.21(13)	C(8)-O(1)-H(1D)	109.5
C(9)-C(8)-C(7)	116.13(14)	C(17)-O(4)-C(16)	117.45(12)
O(1)-C(8)-H(8A)	108.6	C(19)-O(5)-C(13)	107.51(12)
O(5)-C(13)-C(14)	112.29(14)	C(15)-O(6)-C(6)	118.76(13)
O(5)-C(13)-C(12)	105.16(13)	C(27)-S(1)-C(28)	89.61(9)
C(14)-C(13)-C(12)	116.54(14)		

Table S17. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **97**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	25(1)	35(1)	37(1)	0(1)	1(1)	-4(1)
C(2)	26(1)	28(1)	33(1)	0(1)	5(1)	-3(1)
C(3)	24(1)	28(1)	31(1)	1(1)	8(1)	-2(1)
C(4)	29(1)	29(1)	38(1)	-2(1)	1(1)	-3(1)
C(5)	32(1)	29(1)	27(1)	1(1)	0(1)	-5(1)
C(6)	29(1)	30(1)	23(1)	-2(1)	5(1)	-3(1)
C(7)	35(1)	30(1)	23(1)	-4(1)	3(1)	-5(1)
C(8)	33(1)	27(1)	25(1)	-2(1)	-6(1)	-3(1)
C(9)	26(1)	35(1)	30(1)	-2(1)	-2(1)	0(1)
C(10)	22(1)	29(1)	28(1)	-3(1)	3(1)	5(1)
C(11)	26(1)	26(1)	25(1)	-1(1)	2(1)	-2(1)
C(12)	28(1)	25(1)	31(1)	0(1)	3(1)	-3(1)
C(13)	36(1)	24(1)	29(1)	4(1)	-2(1)	-2(1)
C(14)	31(1)	24(1)	38(1)	3(1)	-5(1)	3(1)
C(15)	30(1)	25(1)	38(1)	-2(1)	2(1)	2(1)
C(16)	24(1)	29(1)	31(1)	-2(1)	-4(1)	-2(1)
C(17)	26(1)	23(1)	31(1)	-2(1)	0(1)	5(1)
C(18)	23(1)	28(1)	27(1)	-3(1)	2(1)	1(1)
C(19)	24(1)	25(1)	22(1)	1(1)	2(1)	1(1)
C(20)	36(1)	30(1)	31(1)	1(1)	2(1)	-2(1)

C(21)	33(1)	32(1)	44(1)	-12(1)	3(1)	-4(1)
C(22)	31(1)	100(2)	42(1)	-12(1)	-7(1)	11(1)
C(23)	26(1)	38(1)	32(1)	-4(1)	7(1)	-3(1)
C(24)	23(1)	30(1)	32(1)	-3(1)	1(1)	0(1)
C(25)	27(1)	27(1)	32(1)	-2(1)	-1(1)	1(1)
C(26)	29(1)	31(1)	25(1)	-6(1)	1(1)	1(1)
C(27)	35(1)	40(1)	34(1)	5(1)	0(1)	-3(1)
C(28)	36(1)	37(1)	26(1)	-2(1)	-4(1)	4(1)
C(29)	41(1)	63(1)	50(1)	7(1)	-18(1)	2(1)
C(30)	36(1)	30(1)	44(1)	0(1)	-8(1)	-3(1)
N(1)	32(1)	34(1)	29(1)	-3(1)	-5(1)	1(1)
O(1)	43(1)	36(1)	35(1)	-5(1)	-14(1)	-4(1)
O(2)	50(1)	25(1)	29(1)	-2(1)	-2(1)	6(1)
O(3)	32(1)	53(1)	31(1)	-15(1)	-3(1)	2(1)
O(4)	23(1)	35(1)	27(1)	-1(1)	-2(1)	-3(1)
O(5)	35(1)	26(1)	31(1)	0(1)	-8(1)	2(1)
O(6)	26(1)	26(1)	26(1)	0(1)	4(1)	2(1)
O(7)	33(1)	61(1)	59(1)	11(1)	12(1)	15(1)
S(1)	50(1)	41(1)	33(1)	9(1)	-4(1)	3(1)

Table S18. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for **97**.

	x	y	z	U(eq)
H(1A)	436	395	2704	38
H(1B)	-379	-519	2476	38
H(2A)	1117	-1547	3011	35
H(4A)	1372	743	4043	38
H(4B)	1956	872	3296	38
H(5A)	3393	453	4499	35
H(5B)	4019	432	3757	35

H(6A)	2902	2128	4319	33
H(7A)	4640	1845	4979	35
H(8A)	5894	780	4328	34
H(9A)	6673	2448	3563	36
H(12A)	5550	3026	2854	34
H(12B)	6266	3135	2133	34
H(13A)	4400	3445	1672	35
H(14A)	2450(20)	3269(15)	2208(10)	33(5)
H(14B)	3314(17)	3871(14)	2586(9)	23(4)
H(16A)	1144	-907	1630	34
H(18A)	5108	524	1232	31
H(18B)	4988	-130	1899	31
H(19A)	3960	1175	2473	28
H(20A)	2209	-1889	3967	49
H(20B)	2035	-1102	4553	49
H(20C)	3332	-1141	4122	49
H(21A)	4276	3450	4652	55
H(21B)	5393	3355	4099	55
H(21C)	5715	3261	4893	55
H(22A)	8541	1603	3199	86
H(22B)	8210	735	3703	86
H(22C)	8609	1758	4006	86
H(23A)	7755	1722	2084	48
H(23B)	6815	1740	1441	48
H(23C)	7051	760	1846	48
H(25A)	-465	-594	905	34
H(27)	-87	1765	129	44
H(29A)	-4724	130	-73	77
H(29B)	-4450	660	-781	77
H(29C)	-4898	1267	-132	77
H(30A)	1394	1559	1825	55
H(30B)	-47	1810	1619	55
H(30C)	1040	1773	1047	55
H(30D)	197	1869	1169	55

H(30E)	1639	1618	1374	55
H(30F)	551	1655	1947	55
H(1D)	7647	1400	4805	57

Table S19. Torsion angles [°] for **97**.

C(16)-C(1)-C(2)-C(3)	106.90(19)	O(4)-C(17)-C(18)-C(19)	-49.63(18)
C(1)-C(2)-C(3)-C(20)	176.60(15)	C(17)-C(18)-C(19)-O(5)	-62.63(17)
C(1)-C(2)-C(3)-C(4)	-1.6(3)	C(17)-C(18)-C(19)-C(11)	178.55(14)
C(2)-C(3)-C(4)-C(5)	-145.18(16)	C(10)-C(11)-C(19)-O(5)	151.29(12)
C(20)-C(3)-C(4)-C(5)	36.5(2)	C(23)-C(11)-C(19)-O(5)	-90.94(16)
C(3)-C(4)-C(5)-C(6)	172.32(14)	C(12)-C(11)-C(19)-O(5)	27.20(15)
C(4)-C(5)-C(6)-O(6)	-67.85(17)	C(2)-C(1)-C(16)-C(24)	-174.91(14)
C(4)-C(5)-C(6)-C(7)	170.91(14)	O(3)-C(17)-C(18)-C(19)	131.77(18)
O(6)-C(6)-C(7)-C(21)	57.78(17)	C(10)-C(11)-C(19)-C(18)	-88.72(16)
C(5)-C(6)-C(7)-C(21)	-179.60(14)	C(23)-C(11)-C(19)-C(18)	29.0(2)
O(6)-C(6)-C(7)-C(8)	-73.56(18)	C(12)-C(11)-C(19)-C(18)	147.19(14)
C(5)-C(6)-C(7)-C(8)	49.1(2)	O(4)-C(16)-C(24)-C(25)	144.70(15)
C(6)-C(7)-C(8)-O(1)	-167.39(14)	C(1)-C(16)-C(24)-C(25)	-98.12(18)
C(21)-C(7)-C(8)-O(1)	61.47(17)	O(4)-C(16)-C(24)-C(30)	-39.8(2)
C(6)-C(7)-C(8)-C(9)	71.37(19)	C(1)-C(16)-C(24)-C(30)	77.41(19)
C(21)-C(7)-C(8)-C(9)	-59.78(19)	C(30)-C(24)-C(25)-C(26)	1.0(3)
O(1)-C(8)-C(9)-C(10)	158.41(14)	C(16)-C(24)-C(25)-C(26)	176.10(16)
C(7)-C(8)-C(9)-C(10)	-82.66(18)	C(24)-C(25)-C(26)-C(27)	36.6(3)
O(1)-C(8)-C(9)-C(22)	40.9(2)	C(24)-C(25)-C(26)-N(1)	-144.05(17)
C(7)-C(8)-C(9)-C(22)	159.85(17)	N(1)-C(26)-C(27)-S(1)	1.3(2)
C(22)-C(9)-C(10)-O(2)	72.8(2)	C(25)-C(26)-C(27)-S(1)	-179.29(14)
C(8)-C(9)-C(10)-O(2)	-47.8(2)	C(29)-C(28)-N(1)-C(26)	-176.42(18)
C(22)-C(9)-C(10)-C(11)	-101.07(19)	S(1)-C(28)-N(1)-C(26)	1.83(19)
C(8)-C(9)-C(10)-C(11)	138.33(15)	C(27)-C(26)-N(1)-C(28)	-2.1(2)

O(2)-C(10)-C(11)-C(23)	-78.47(18)	C(25)-C(26)-N(1)-C(28)	178.50(15)
C(9)-C(10)-C(11)-C(23)	95.51(17)	O(3)-C(17)-O(4)-C(16)	-0.2(2)
O(2)-C(10)-C(11)-C(12)	157.62(15)	C(18)-C(17)-O(4)-C(16)	-178.86(13)
C(9)-C(10)-C(11)-C(12)	-28.4(2)	C(24)-C(16)-O(4)-C(17)	-62.57(18)
O(2)-C(10)-C(11)-C(19)	42.33(19)	C(1)-C(16)-O(4)-C(17)	177.21(13)
C(9)-C(10)-C(11)-C(19)	-143.69(14)	C(18)-C(19)-O(5)-C(13)	-166.52(13)
C(10)-C(11)-C(12)-C(13)	-125.83(15)	C(11)-C(19)-O(5)-C(13)	-39.16(15)
C(23)-C(11)-C(12)-C(13)	112.10(15)	C(14)-C(13)-O(5)-C(19)	-93.50(15)
C(19)-C(11)-C(12)-C(13)	-6.97(16)	C(12)-C(13)-O(5)-C(19)	34.19(16)
C(11)-C(12)-C(13)-O(5)	-15.38(16)	O(7)-C(15)-O(6)-C(6)	-6.6(3)
C(11)-C(12)-C(13)-C(14)	109.70(16)	C(14)-C(15)-O(6)-C(6)	171.50(14)
O(5)-C(13)-C(14)-C(15)	71.3(2)	C(5)-C(6)-O(6)-C(15)	100.98(16)
C(12)-C(13)-C(14)-C(15)	-50.1(2)	C(7)-C(6)-O(6)-C(15)	-133.81(15)
C(13)-C(14)-C(15)-O(7)	-159.46(18)	C(26)-C(27)-S(1)-C(28)	-0.25(15)
C(13)-C(14)-C(15)-O(6)	22.4(2)	N(1)-C(28)-S(1)-C(27)	-0.94(15)
C(2)-C(1)-C(16)-O(4)	-54.28(18)	C(29)-C(28)-S(1)-C(27)	177.38(17)

1.8.4. Epoxide 98.

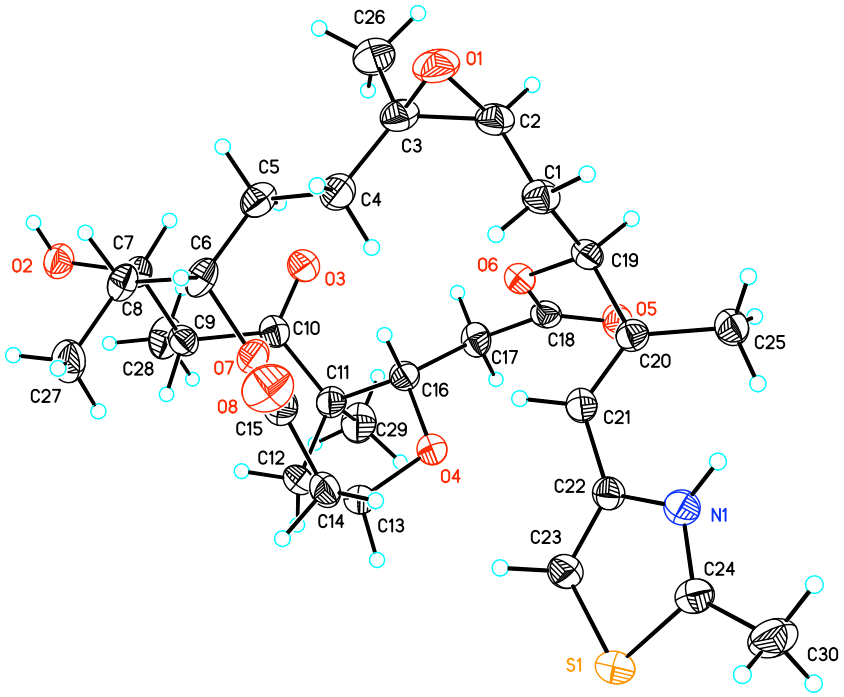


Figure S4. Thermal ellipsoid diagram of **98** with 50% displacement ellipsoids.

Table S20. Crystal data and structure refinement for **98**.

Empirical formula	C32 H47 N O9 S	
Formula weight	621.77	
Temperature	173(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 9.0832(3) Å	α= 90°.
	b = 16.7951(6) Å	β= 90°.
	c = 22.7579(8) Å	γ = 90°.

Volume	3471.8(2) $Å^3$
Z	4
Density (calculated)	1.190 Mg/m^3
Absorption coefficient	1.243 mm^{-1}
F(000)	1336
Crystal size	0.32 x 0.14 x 0.05 mm^3
Theta range for data collection	3.27 to 69.27°.
Index ranges	-10<=h<=10, -19<=k<=14, -27<=l<=24
Reflections collected	23769
Independent reflections	5919 [R(int) = 0.0334]
Completeness to theta = 69.27°	95.6 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9405 and 0.6919
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5919 / 0 / 385
Goodness-of-fit on F^2	1.053
Final R indices [I>2sigma(I)]	R1 = 0.0687, wR2 = 0.1914
R indices (all data)	R1 = 0.0774, wR2 = 0.2003
Absolute structure parameter	0.01(3)
Largest diff. peak and hole	1.137 and -0.401 $e.Å^{-3}$

Table S21. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **98**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	10074(5)	10616(2)	10900(2)	38(1)
C(2)	10259(5)	11283(2)	10471(2)	40(1)
C(3)	9089(5)	11571(2)	10071(2)	40(1)
C(4)	7558(5)	11190(2)	10080(2)	41(1)
C(5)	6676(5)	11254(2)	9514(2)	40(1)
C(6)	5205(5)	10839(2)	9529(2)	38(1)
C(7)	4253(5)	10933(2)	8979(2)	40(1)
C(8)	4971(5)	10747(2)	8380(2)	35(1)
C(9)	5334(5)	9863(2)	8250(2)	36(1)
C(10)	6804(4)	9630(2)	8524(2)	33(1)
C(11)	7070(5)	8835(2)	8822(2)	36(1)
C(12)	5721(5)	8420(3)	9102(2)	46(1)
C(13)	6138(5)	8288(3)	9755(2)	44(1)
C(14)	5283(5)	8786(3)	10210(2)	49(1)
C(15)	5153(5)	9675(3)	10166(2)	42(1)
C(16)	8106(4)	8978(2)	9357(2)	32(1)
C(17)	9736(4)	8910(2)	9258(2)	35(1)
C(18)	10619(4)	9072(2)	9807(2)	30(1)
C(19)	10763(5)	9831(2)	10680(2)	34(1)
C(20)	10515(4)	9165(2)	11124(2)	32(1)
C(21)	9197(4)	8820(2)	11144(2)	34(1)
C(22)	8679(4)	8189(2)	11535(2)	32(1)
C(23)	7662(5)	7634(2)	11364(2)	40(1)
C(24)	8528(5)	7503(2)	12370(2)	38(1)
C(25)	11824(5)	8974(3)	11486(2)	40(1)
C(26)	9578(6)	12000(3)	9527(2)	58(1)
C(27)	2781(5)	10515(3)	9052(2)	50(1)
C(28)	5468(6)	9715(3)	7589(2)	54(1)

C(29)	7787(6)	8275(3)	8365(2)	53(1)
C(30)	8789(7)	7266(3)	13001(2)	56(1)
N(1)	9150(4)	8099(2)	12111(1)	36(1)
O(1)	9460(4)	12007(2)	10605(2)	52(1)
O(2)	3965(3)	11049(2)	7948(1)	41(1)
O(3)	7853(3)	10077(2)	8467(1)	42(1)
O(4)	7697(3)	8401(2)	9787(1)	41(1)
O(5)	11738(3)	8719(2)	9939(1)	42(1)
O(6)	10049(3)	9667(2)	10122(1)	30(1)
O(7)	5442(3)	9977(2)	9622(1)	37(1)
O(8)	4774(5)	10066(2)	10567(2)	62(1)
S(1)	7315(1)	6979(1)	11925(1)	45(1)
O(1S)	923(7)	4059(4)	8081(3)	45(1)
C(1S)	276(18)	5299(9)	7797(6)	83(4)
C(2S)	-217(11)	4510(5)	7981(4)	47(2)
C(3S)	529(10)	3296(5)	8258(4)	42(2)
C(4S)	1862(11)	2794(6)	8280(4)	49(2)
O(2S)	-1547(7)	4299(3)	8027(3)	42(1)

Table S22. Bond lengths [Å] and angles [°] for **98**.

C(1)-C(2)	1.496(6)	O(2)-C(8)-H(8A)	108.1
C(1)-C(19)	1.544(6)	C(7)-C(8)-H(8A)	108.1
C(1)-H(1A)	0.9900	C(9)-C(8)-H(8A)	108.1
C(1)-H(1B)	0.9900	C(10)-C(9)-C(28)	107.0(4)
C(2)-O(1)	1.448(5)	C(10)-C(9)-C(8)	110.7(3)
C(2)-C(3)	1.480(6)	C(28)-C(9)-C(8)	111.1(3)
C(2)-H(2A)	1.0000	C(10)-C(9)-H(9A)	109.3
C(3)-O(1)	1.459(5)	C(28)-C(9)-H(9A)	109.3
C(3)-C(26)	1.500(6)	C(8)-C(9)-H(9A)	109.3
C(3)-C(4)	1.530(6)	O(3)-C(10)-C(11)	117.7(4)
C(4)-C(5)	1.520(6)	O(3)-C(10)-C(9)	118.8(3)
C(4)-H(4A)	0.9900	C(11)-C(10)-C(9)	123.3(4)

C(4)-H(4B)	0.9900	C(10)-C(11)-C(29)	107.6(4)
C(5)-C(6)	1.507(7)	C(10)-C(11)-C(12)	117.0(3)
C(5)-H(5A)	0.9900	C(29)-C(11)-C(12)	109.7(4)
C(5)-H(5B)	0.9900	C(10)-C(11)-C(16)	108.1(3)
C(6)-O(7)	1.478(5)	C(29)-C(11)-C(16)	111.4(3)
C(6)-C(7)	1.530(6)	C(12)-C(11)-C(16)	103.0(3)
C(6)-H(6A)	1.0000	C(11)-C(12)-C(13)	105.5(3)
C(7)-C(27)	1.519(7)	C(11)-C(12)-H(12A)	110.6
C(7)-C(8)	1.543(6)	C(13)-C(12)-H(12A)	110.6
C(7)-H(7A)	1.0000	C(11)-C(12)-H(12B)	110.6
C(8)-O(2)	1.435(5)	C(13)-C(12)-H(12B)	110.6
C(8)-C(9)	1.550(5)	H(12A)-C(12)-H(12B)	108.8
C(8)-H(8A)	1.0000	O(4)-C(13)-C(14)	113.1(4)
C(9)-C(10)	1.525(6)	O(4)-C(13)-C(12)	105.8(4)
C(9)-C(28)	1.530(6)	C(14)-C(13)-C(12)	116.4(4)
C(9)-H(9A)	1.0000	O(4)-C(13)-H(13A)	107.0
C(10)-O(3)	1.221(5)	C(14)-C(13)-H(13A)	107.0
C(10)-C(11)	1.516(5)	C(12)-C(13)-H(13A)	107.0
C(11)-C(29)	1.545(6)	C(15)-C(14)-C(13)	122.3(4)
C(11)-C(12)	1.548(6)	C(15)-C(14)-H(14A)	106.7
C(11)-C(16)	1.558(5)	C(13)-C(14)-H(14A)	106.7
C(12)-C(13)	1.548(7)	C(15)-C(14)-H(14B)	106.7
C(12)-H(12A)	0.9900	C(13)-C(14)-H(14B)	106.7
C(12)-H(12B)	0.9900	H(14A)-C(14)-H(14B)	106.6
C(13)-O(4)	1.431(5)	O(8)-C(15)-O(7)	123.6(4)
C(13)-C(14)	1.541(7)	O(8)-C(15)-C(14)	121.8(4)
C(13)-H(13A)	1.0000	O(7)-C(15)-C(14)	114.6(4)
C(14)-C(15)	1.502(7)	O(4)-C(16)-C(17)	108.0(3)
C(14)-H(14A)	0.9900	O(4)-C(16)-C(11)	105.9(3)
C(14)-H(14B)	0.9900	C(17)-C(16)-C(11)	117.8(3)
C(15)-O(8)	1.176(6)	O(4)-C(16)-H(16A)	108.3
C(15)-O(7)	1.363(5)	C(17)-C(16)-H(16A)	108.3
C(16)-O(4)	1.426(5)	C(11)-C(16)-H(16A)	108.3
C(16)-C(17)	1.502(6)	C(16)-C(17)-C(18)	112.7(3)

C(16)-H(16A)	1.0000	C(16)-C(17)-H(17A)	109.1
C(17)-C(18)	1.509(5)	C(18)-C(17)-H(17A)	109.1
C(17)-H(17A)	0.9900	C(16)-C(17)-H(17B)	109.1
C(17)-H(17B)	0.9900	C(18)-C(17)-H(17B)	109.1
C(18)-O(5)	1.215(5)	H(17A)-C(17)-H(17B)	107.8
C(18)-O(6)	1.334(5)	O(5)-C(18)-O(6)	123.9(4)
C(19)-O(6)	1.452(5)	O(5)-C(18)-C(17)	124.1(3)
C(19)-C(20)	1.524(5)	O(6)-C(18)-C(17)	111.9(3)
C(19)-H(19A)	1.0000	O(6)-C(19)-C(20)	112.0(3)
C(20)-C(21)	1.330(6)	O(6)-C(19)-C(1)	105.4(3)
C(20)-C(25)	1.483(6)	C(20)-C(19)-C(1)	110.6(3)
C(21)-C(22)	1.463(5)	O(6)-C(19)-H(19A)	109.6
C(21)-H(21A)	0.9500	C(20)-C(19)-H(19A)	109.6
C(22)-C(23)	1.369(6)	C(1)-C(19)-H(19A)	109.6
C(22)-N(1)	1.386(5)	C(21)-C(20)-C(25)	127.5(4)
C(23)-S(1)	1.714(4)	C(21)-C(20)-C(19)	118.4(4)
C(23)-H(23A)	0.9900	C(25)-C(20)-C(19)	114.1(3)
C(23)-H(23B)	0.9900	C(20)-C(21)-C(22)	128.7(4)
C(24)-N(1)	1.293(5)	C(20)-C(21)-H(21A)	115.6
C(24)-C(30)	1.509(6)	C(22)-C(21)-H(21A)	115.6
C(24)-S(1)	1.737(5)	C(23)-C(22)-N(1)	113.7(3)
C(25)-H(25A)	0.9800	C(23)-C(22)-C(21)	122.5(4)
C(25)-H(25B)	0.9800	N(1)-C(22)-C(21)	123.8(4)
C(25)-H(25C)	0.9800	C(22)-C(23)-S(1)	110.5(3)
C(26)-H(26A)	0.9800	C(22)-C(23)-H(23A)	109.6
C(26)-H(26B)	0.9800	S(1)-C(23)-H(23A)	109.6
C(26)-H(26C)	0.9800	C(22)-C(23)-H(23B)	109.6
C(27)-H(27A)	0.9800	S(1)-C(23)-H(23B)	109.6
C(27)-H(27B)	0.9800	H(23A)-C(23)-H(23B)	108.1
C(27)-H(27C)	0.9800	N(1)-C(24)-C(30)	124.7(4)
C(28)-H(28A)	0.9800	N(1)-C(24)-S(1)	113.8(3)
C(28)-H(28B)	0.9800	C(30)-C(24)-S(1)	121.5(3)
C(28)-H(28C)	0.9800	C(20)-C(25)-H(25A)	109.5
C(29)-H(29A)	0.9800	C(20)-C(25)-H(25B)	109.5

C(29)-H(29B)	0.9800	H(25A)-C(25)-H(25B)	109.5
C(29)-H(29C)	0.9800	C(20)-C(25)-H(25C)	109.5
C(30)-H(30A)	0.9800	H(25A)-C(25)-H(25C)	109.5
C(30)-H(30B)	0.9800	H(25B)-C(25)-H(25C)	109.5
C(30)-H(30C)	0.9800	C(3)-C(26)-H(26A)	109.5
N(1)-H(1C)	0.8800	C(3)-C(26)-H(26B)	109.5
O(2)-H(2B)	0.8400	H(26A)-C(26)-H(26B)	109.5
O(1S)-C(2S)	1.304(11)	C(3)-C(26)-H(26C)	109.5
O(1S)-C(3S)	1.391(11)	H(26A)-C(26)-H(26C)	109.5
C(1S)-C(2S)	1.459(17)	H(26B)-C(26)-H(26C)	109.5
C(1S)-H(1SA)	0.9800	C(7)-C(27)-H(27A)	109.5
C(1S)-H(1SB)	0.9800	C(7)-C(27)-H(27B)	109.5
C(1S)-H(1SC)	0.9800	H(27A)-C(27)-H(27B)	109.5
C(2S)-O(2S)	1.263(12)	C(7)-C(27)-H(27C)	109.5
C(3S)-C(4S)	1.477(13)	H(27A)-C(27)-H(27C)	109.5
C(3S)-H(3SA)	0.9900	H(27B)-C(27)-H(27C)	109.5
C(3S)-H(3SB)	0.9900	C(9)-C(28)-H(28A)	109.5
C(4S)-H(4SA)	0.9800	C(9)-C(28)-H(28B)	109.5
C(4S)-H(4SB)	0.9800	H(28A)-C(28)-H(28B)	109.5
C(4S)-H(4SC)	0.9800	C(9)-C(28)-H(28C)	109.5
C(2)-C(1)-C(19)	112.4(3)	H(28A)-C(28)-H(28C)	109.5
C(2)-C(1)-H(1A)	109.1	H(28B)-C(28)-H(28C)	109.5
C(19)-C(1)-H(1A)	109.1	C(11)-C(29)-H(29A)	109.5
C(2)-C(1)-H(1B)	109.1	C(11)-C(29)-H(29B)	109.5
C(19)-C(1)-H(1B)	109.1	H(29A)-C(29)-H(29B)	109.5
H(1A)-C(1)-H(1B)	107.9	C(11)-C(29)-H(29C)	109.5
O(1)-C(2)-C(3)	59.8(3)	H(29A)-C(29)-H(29C)	109.5
O(1)-C(2)-C(1)	115.7(4)	H(29B)-C(29)-H(29C)	109.5
C(3)-C(2)-C(1)	124.4(4)	C(24)-C(30)-H(30A)	109.5
O(1)-C(2)-H(2A)	115.0	C(24)-C(30)-H(30B)	109.5
C(3)-C(2)-H(2A)	115.0	H(30A)-C(30)-H(30B)	109.5
C(1)-C(2)-H(2A)	115.0	C(24)-C(30)-H(30C)	109.5
O(1)-C(3)-C(2)	59.0(3)	H(30A)-C(30)-H(30C)	109.5
O(1)-C(3)-C(26)	112.2(4)	H(30B)-C(30)-H(30C)	109.5

C(2)-C(3)-C(26)	116.8(4)	C(24)-N(1)-C(22)	112.4(4)
O(1)-C(3)-C(4)	114.1(4)	C(24)-N(1)-H(1C)	123.8
C(2)-C(3)-C(4)	120.5(4)	C(22)-N(1)-H(1C)	123.8
C(26)-C(3)-C(4)	118.8(4)	C(2)-O(1)-C(3)	61.2(3)
C(5)-C(4)-C(3)	116.0(4)	C(8)-O(2)-H(2B)	109.5
C(5)-C(4)-H(4A)	108.3	C(16)-O(4)-C(13)	108.3(3)
C(3)-C(4)-H(4A)	108.3	C(18)-O(6)-C(19)	116.0(3)
C(5)-C(4)-H(4B)	108.3	C(15)-O(7)-C(6)	117.8(3)
C(3)-C(4)-H(4B)	108.3	C(23)-S(1)-C(24)	89.6(2)
H(4A)-C(4)-H(4B)	107.4	C(2S)-O(1S)-C(3S)	112.4(7)
C(6)-C(5)-C(4)	114.5(3)	C(2S)-C(1S)-H(1SA)	109.5
C(6)-C(5)-H(5A)	108.6	C(2S)-C(1S)-H(1SB)	109.5
C(4)-C(5)-H(5A)	108.6	H(1SA)-C(1S)-H(1SB)	109.5
C(6)-C(5)-H(5B)	108.6	C(2S)-C(1S)-H(1SC)	109.5
C(4)-C(5)-H(5B)	108.6	H(1SA)-C(1S)-H(1SC)	109.5
H(5A)-C(5)-H(5B)	107.6	H(1SB)-C(1S)-H(1SC)	109.5
O(7)-C(6)-C(5)	109.1(3)	O(2S)-C(2S)-O(1S)	125.6(8)
O(7)-C(6)-C(7)	107.5(3)	O(2S)-C(2S)-C(1S)	124.9(10)
C(5)-C(6)-C(7)	115.7(3)	O(1S)-C(2S)-C(1S)	109.5(10)
O(7)-C(6)-H(6A)	108.1	O(1S)-C(3S)-C(4S)	109.0(8)
C(5)-C(6)-H(6A)	108.1	O(1S)-C(3S)-H(3SA)	109.9
C(7)-C(6)-H(6A)	108.1	C(4S)-C(3S)-H(3SA)	109.9
C(27)-C(7)-C(6)	111.1(4)	O(1S)-C(3S)-H(3SB)	109.9
C(27)-C(7)-C(8)	112.0(4)	C(4S)-C(3S)-H(3SB)	109.9
C(6)-C(7)-C(8)	117.6(3)	H(3SA)-C(3S)-H(3SB)	108.3
C(27)-C(7)-H(7A)	104.9	C(3S)-C(4S)-H(4SA)	109.5
C(6)-C(7)-H(7A)	104.9	C(3S)-C(4S)-H(4SB)	109.5
C(8)-C(7)-H(7A)	104.9	H(4SA)-C(4S)-H(4SB)	109.5
O(2)-C(8)-C(7)	105.4(3)	C(3S)-C(4S)-H(4SC)	109.5
O(2)-C(8)-C(9)	110.0(3)	H(4SA)-C(4S)-H(4SC)	109.5
C(7)-C(8)-C(9)	116.9(3)	H(4SB)-C(4S)-H(4SC)	109.5

Table S23. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **98**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	45(2)	34(2)	35(2)	-6(2)	-2(2)	-4(2)
C(2)	47(2)	31(2)	41(2)	-5(2)	-2(2)	-6(2)
C(3)	52(3)	30(2)	38(2)	-2(2)	-1(2)	-1(2)
C(4)	44(3)	38(2)	42(2)	1(2)	-2(2)	3(2)
C(5)	54(3)	31(2)	34(2)	0(2)	-5(2)	4(2)
C(6)	44(2)	34(2)	35(2)	0(2)	4(2)	15(2)
C(7)	39(2)	37(2)	45(2)	3(2)	0(2)	12(2)
C(8)	35(2)	34(2)	35(2)	6(2)	-7(2)	1(2)
C(9)	32(2)	38(2)	39(2)	-2(2)	-4(2)	-3(2)
C(10)	34(2)	34(2)	31(2)	-6(2)	-2(2)	1(2)
C(11)	39(2)	28(2)	41(2)	-7(2)	-7(2)	3(2)
C(12)	37(2)	37(2)	63(3)	4(2)	-16(2)	-10(2)
C(13)	36(2)	37(2)	58(3)	13(2)	-10(2)	-8(2)
C(14)	26(2)	61(3)	59(3)	26(2)	-4(2)	-5(2)
C(15)	33(2)	53(3)	39(2)	13(2)	5(2)	1(2)
C(16)	31(2)	28(2)	37(2)	-4(2)	-1(2)	1(2)
C(17)	30(2)	37(2)	37(2)	-7(2)	4(2)	8(2)
C(18)	28(2)	28(2)	36(2)	2(2)	5(2)	-3(2)
C(19)	33(2)	33(2)	35(2)	0(2)	-4(2)	-6(2)
C(20)	34(2)	29(2)	32(2)	-1(2)	1(2)	1(2)
C(21)	30(2)	38(2)	35(2)	3(2)	-3(2)	-1(2)
C(22)	30(2)	29(2)	36(2)	-1(2)	1(2)	1(2)
C(23)	33(2)	38(2)	48(2)	5(2)	3(2)	-2(2)

C(24)	42(2)	35(2)	38(2)	5(2)	3(2)	-2(2)
C(25)	34(2)	45(2)	41(2)	3(2)	-2(2)	-1(2)
C(26)	62(3)	51(3)	61(3)	17(2)	-1(3)	-9(3)
C(27)	36(2)	62(3)	51(2)	10(2)	8(2)	9(2)
C(28)	64(3)	55(3)	42(2)	-11(2)	-13(2)	16(2)
C(29)	59(3)	42(2)	59(3)	-22(2)	-14(2)	12(2)
C(30)	76(4)	51(3)	40(2)	13(2)	-3(2)	-14(3)
N(1)	40(2)	33(2)	36(2)	-3(1)	-4(2)	-2(2)
O(1)	70(2)	27(1)	60(2)	-10(1)	-6(2)	-4(2)
O(2)	39(2)	43(2)	41(2)	8(1)	-5(1)	5(1)
O(3)	36(2)	42(2)	49(2)	3(1)	2(1)	-1(1)
O(4)	33(2)	41(2)	50(2)	13(1)	-7(1)	-4(1)
O(5)	33(2)	44(2)	50(2)	-3(1)	-5(1)	4(1)
O(6)	30(1)	31(1)	30(1)	-4(1)	1(1)	-1(1)
O(7)	36(2)	35(1)	41(2)	9(1)	6(1)	6(1)
O(8)	76(3)	67(2)	43(2)	8(2)	15(2)	1(2)
S(1)	41(1)	41(1)	52(1)	7(1)	-2(1)	-11(1)

Table S24. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **98**.

	x	y	z	U(eq)
H(1A)	9011	10532	10974	45
H(1B)	10539	10767	11278	45
H(2A)	11287	11365	10325	48
H(4A)	7671	10619	10178	50
H(4B)	6981	11439	10400	50
H(5A)	6513	11824	9426	48
H(5B)	7266	11027	9189	48
H(6A)	4637	11050	9872	45
H(7A)	4007	11513	8962	49
H(8A)	5905	11060	8351	41

H(9A)	4538	9517	8414	43
H(12A)	5521	7905	8906	55
H(12B)	4835	8760	9070	55
H(13A)	5942	7715	9846	52
H(14A)	4268	8572	10220	58
H(14B)	5726	8669	10598	58
H(16A)	7894	9519	9520	38
H(17A)	10033	9293	8949	42
H(17B)	9966	8368	9115	42
H(19A)	11843	9907	10616	41
H(21A)	8499	9010	10866	41
H(23A)	8037	7340	11018	47
H(23B)	6737	7904	11249	47
H(25A)	11585	8539	11757	60
H(25B)	12117	9445	11711	60
H(25C)	12637	8811	11229	60
H(26A)	10575	12209	9586	87
H(26B)	8903	12441	9446	87
H(26C)	9578	11630	9194	87
H(27A)	2366	10646	9438	75
H(27B)	2924	9938	9023	75
H(27C)	2105	10691	8743	75
H(28A)	5686	9152	7518	80
H(28B)	6264	10044	7428	80
H(28C)	4539	9855	7396	80
H(29A)	8639	8540	8188	80
H(29B)	7068	8147	8058	80
H(29C)	8106	7784	8559	80
H(30A)	9511	7628	13178	83
H(30B)	9165	6720	13016	83
H(30C)	7861	7298	13220	83
H(1C)	9800	8412	12280	43
H(2B)	3781	11529	8019	62
H(1SA)	-581	5641	7728	124

H(1SB)	848	5253	7433	124
H(1SC)	893	5533	8105	124
H(3SA)	-190	3068	7978	51
H(3SB)	64	3317	8651	51
H(4SA)	1595	2257	8410	73
H(4SB)	2571	3025	8556	73
H(4SC)	2304	2765	7887	73

Table S25. Torsion angles [°] for **98**.

C(19)-C(1)-C(2)-O(1)	171.3(3)	C(12)-C(11)-C(16)-O(4)	23.8(4)
C(19)-C(1)-C(2)-C(3)	101.7(5)	C(10)-C(11)-C(16)-C(17)	-90.8(4)
C(1)-C(2)-C(3)-O(1)	102.0(4)	C(29)-C(11)-C(16)-C(17)	27.2(5)
O(1)-C(2)-C(3)-C(26)	101.0(4)	C(12)-C(11)-C(16)-C(17)	144.7(4)
C(1)-C(2)-C(3)-C(26)	-157.0(4)	O(4)-C(16)-C(17)-C(18)	-61.0(4)
O(1)-C(2)-C(3)-C(4)	-101.5(4)	C(11)-C(16)-C(17)-C(18)	179.2(3)
C(1)-C(2)-C(3)-C(4)	0.5(6)	C(16)-C(17)-C(18)-O(5)	142.8(4)
O(1)-C(3)-C(4)-C(5)	138.4(4)	C(16)-C(17)-C(18)-O(6)	-39.2(5)
C(2)-C(3)-C(4)-C(5)	-154.6(4)	C(2)-C(1)-C(19)-O(6)	-57.3(4)
C(26)-C(3)-C(4)-C(5)	2.4(6)	C(2)-C(1)-C(19)-C(20)	-178.6(3)
C(3)-C(4)-C(5)-C(6)	177.2(3)	O(6)-C(19)-C(20)-C(21)	-39.2(5)
C(4)-C(5)-C(6)-O(7)	-62.1(4)	C(1)-C(19)-C(20)-C(21)	78.0(4)
C(4)-C(5)-C(6)-C(7)	176.7(3)	O(6)-C(19)-C(20)-C(25)	140.2(3)
O(7)-C(6)-C(7)-C(27)	59.8(4)	C(1)-C(19)-C(20)-C(25)	-102.6(4)
C(5)-C(6)-C(7)-C(27)	-178.1(4)	C(25)-C(20)-C(21)-C(22)	2.3(7)
O(7)-C(6)-C(7)-C(8)	-71.2(4)	C(19)-C(20)-C(21)-C(22)	-178.4(4)
C(5)-C(6)-C(7)-C(8)	50.9(5)	C(20)-C(21)-C(22)-C(23)	-147.9(4)
C(27)-C(7)-C(8)-O(2)	61.8(4)	C(20)-C(21)-C(22)-N(1)	32.7(6)
C(6)-C(7)-C(8)-O(2)	-167.6(3)	N(1)-C(22)-C(23)-S(1)	-1.1(5)
C(27)-C(7)-C(8)-C(9)	-60.7(5)	C(21)-C(22)-C(23)-S(1)	179.4(3)
C(6)-C(7)-C(8)-C(9)	69.8(5)	C(30)-C(24)-N(1)-C(22)	-178.4(4)
O(2)-C(8)-C(9)-C(10)	156.8(3)	S(1)-C(24)-N(1)-C(22)	1.1(5)

C(7)-C(8)-C(9)-C(10)	-83.1(4)	C(23)-C(22)-N(1)-C(24)	0.0(5)
O(2)-C(8)-C(9)-C(28)	38.1(5)	C(21)-C(22)-N(1)-C(24)	179.5(4)
C(7)-C(8)-C(9)-C(28)	158.2(4)	C(1)-C(2)-O(1)-C(3)	-116.5(4)
C(28)-C(9)-C(10)-O(3)	75.7(5)	C(26)-C(3)-O(1)-C(2)	-108.8(5)
C(8)-C(9)-C(10)-O(3)	-45.6(5)	C(4)-C(3)-O(1)-C(2)	112.4(4)
C(28)-C(9)-C(10)-C(11)	-98.9(4)	C(17)-C(16)-O(4)-C(13)	-162.5(3)
C(8)-C(9)-C(10)-C(11)	139.9(4)	C(11)-C(16)-O(4)-C(13)	-35.5(4)
O(3)-C(10)-C(11)-C(29)	-78.6(4)	C(14)-C(13)-O(4)-C(16)	-96.6(4)
C(9)-C(10)-C(11)-C(29)	96.0(5)	C(12)-C(13)-O(4)-C(16)	31.8(4)
O(3)-C(10)-C(11)-C(12)	157.4(4)	O(5)-C(18)-O(6)-C(19)	-6.2(5)
C(9)-C(10)-C(11)-C(12)	-28.0(5)	C(17)-C(18)-O(6)-C(19)	175.8(3)
O(3)-C(10)-C(11)-C(16)	41.8(5)	C(20)-C(19)-O(6)-C(18)	-68.8(4)
C(9)-C(10)-C(11)-C(16)	-143.6(4)	C(1)-C(19)-O(6)-C(18)	170.9(3)
C(10)-C(11)-C(12)-C(13)	-123.4(4)	O(8)-C(15)-O(7)-C(6)	-2.5(7)
C(29)-C(11)-C(12)-C(13)	113.7(4)	C(14)-C(15)-O(7)-C(6)	174.5(4)
C(16)-C(11)-C(12)-C(13)	-5.0(4)	C(5)-C(6)-O(7)-C(15)	104.6(4)
C(11)-C(12)-C(13)-O(4)	-15.2(4)	C(7)-C(6)-O(7)-C(15)	-129.2(4)
C(11)-C(12)-C(13)-C(14)	111.3(4)	C(22)-C(23)-S(1)-C(24)	1.4(3)
O(4)-C(13)-C(14)-C(15)	70.4(5)	N(1)-C(24)-S(1)-C(23)	-1.5(4)
C(12)-C(13)-C(14)-C(15)	-52.3(6)	C(30)-C(24)-S(1)-C(23)	178.1(4)
C(13)-C(14)-C(15)-O(8)	-164.1(5)	C(3S)-O(1S)-C(2S)-O(2S)	-0.9(13)
C(13)-C(14)-C(15)-O(7)	18.9(6)	C(3S)-O(1S)-C(2S)-C(1S)	-180.0(9)
C(10)-C(11)-C(16)-O(4)	148.3(3)	C(2S)-O(1S)-C(3S)-C(4S)	172.0(8)
C(29)-C(11)-C(16)-O(4)	-93.7(4)		

Table S26. Hydrogen bonds for **98** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1C)...O(2)#1	0.88	2.10	2.935(4)	159.4

Symmetry transformations used to generate equivalent atoms:
#1 -x+3/2,-y+2,z+1/2

1.6. Reference:

1. (a) Burns, R. G. *Cell Motil. Cytoskeleton* **1991**, *20*, 181. (b) Amos, L.; Klug, A. *J. Cell Sci.* **1974**, *14*, 523. (c) For a recent review, see: Wade, R. H. *Methods Mol. Med.* **2007**, *137*, 1.
2. (a) Mitchison, T.; Kirschner, M. *Nature* **1984**, *312*, 237. (b) Kirschner, M. W.; Mitchison, T. *Nature* **1986**, *324*, 621.
3. Desai, A.; Mitchison, T. J. *Annu. Rev. Cell. Dev. Biol.* **1997**, *13*, 83.
4. (a) Margolis, R. L.; Wilson, L. *Cell* **1978**, *13*, 1. (b) Rodionov, V. I.; Borisy, G. G. *Science* **1997**, *275*, 215. (c) Shaw, S. L.; Kamyar, R.; Ehrhardt, D. W. *Science* **2003**, *300*, 1715.
5. (a) Rusan, N. M.; Fagerstrom, C. J.; Yvon, A. M.; Wadsworth, P. *Mol. Biol. Cell.* **2001**, *12*, 971. (b) Zhou, J.; Yao, J.; Joshi, H. C. *J. Cell Sci.* **2002**, *115*, 3547.
6. For recent reviews on microtubule as target for anticancer drugs, see: (a) Jordan, M. A.; Wilson, L. *Nat. Rev. Cancer* **2004**, *4*, 253. (b) Zhou, J.; Giannakakou, P. *Curr. Med. Chem. Anticancer Agents* **2005**, *5*, 65.
7. Altmann, K. H.; Gertsch, J. *Nat. Prod. Rep.* **2007**, *24*, 327.
8. (a) Jordan, M. A.; Wendell, K.; Gardiner, S.; Derry, W. B.; Copp, H.; Wilson, L. *Cancer Res.* **1996**, *56*, 816. (b) Yvon, A. M.; Wadsworth, P.; Jordan, M. A. *Mol. Biol. Cell.* **1999**, *10*, 947. (c) For recent review, see: Jordan, M. A. *Curr. Med. Chem. Anticancer Agents* **2002**, *2*, 1.
9. Hamel, E. *Med. Res. Rev.* **1996**, *16*, 207.

10. Feng, Y.; Broder, C. C.; Kennedy, P. E.; Berger, E. A. *Science* **1996**, *272*, 872.

11. Oberlin, E.; Amara, A.; Bachelerie, F.; Bessia, C.; Virelizier, J. L.; Arenzana-Seisdedos, F.; Schwartz, O.; Heard, J. M.; Clark-Lewis, I.; Legler, D. F.; Loetscher, M.; Baggiolini, M.; Moser, B. *Nature* **1996**, *382*, 833.

12. Tachibana, K.; Hirota, S.; Iizasa, H.; Yoshida, H.; Kawabata, K.; Kataoka, Y.; Kitamura, Y.; Matsushima, K.; Yoshida, N.; Nishikawa, S.; Kishimoto, T.; Nagasawa, T. *Nature* **1998**, *393*, 591.

13. Muller, A.; Homey, B.; Soto, H.; Ge, N.; Catron, D.; Buchanan, M. E.; McClanahan, T.; Murphy, E.; Yuan, W.; Wagner, S. N.; Barrera, J. L.; Mohar, A.; Verastegui, E.; Zlotnik, A. *Nature* **2001**, *410*, 50.

14. Liang, Z.; Wu, T.; Lou, H.; Yu, X.; Taichman, R. S.; Lau, S. K.; Nie, S.; Umbreit, J.; Shim, H. *Cancer Res.* **2004**, *64*, 4302.

15. Kucia, M.; Jankowski, K.; Reca, R.; Wysoczynski, M.; Bandura, L.; Allendorf, D. J.; Zhang, J.; Ratajczak, J.; Ratajczak, M. Z. *J. Mol. Histol.* **2004**, *35*, 233.

16. Doranz, B. J.; Grovit-Ferbas, K.; Sharron, M. P.; Mao, S. H.; Goetz, M. B.; Daar, E. S.; Doms, R. W.; O'Brien, W. A. *J. Exp. Med.* **1997**, *186*, 1395.

17. Fujii, N.; Oishi, S.; Hiramatsu, K.; Araki, T.; Ueda, S.; Tamamura, H.; Otaka, A.; Kusano, S.; Terakubo, S.; Nakashima, H.; Broach, J. A.; Trent, J. O.; Wang, Z. X.; Peiper, S. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 3251.

18. Tamamura, H.; Hiramatsu, K.; Ueda, S.; Wang, Z.; Kusano, S.; Terakubo, S.; Trent, J. O.; Peiper, S. C.; Yamamoto, N.; Nakashima, H.; Otaka, A.; Fujii, N. *J. Med. Chem.* **2005**, *48*, 380.

19. Ueda, S.; Oishi, S.; Wang, Z. X.; Araki, T.; Tamamura, H.; Cluzeau, J.; Ohno, H.; Kusano, S.; Nakashima, H.; Trent, J. O.; Peiper, S. C.; Fujii, N. *J. Med. Chem.* **2007**, *50*, 192.

20. Tamamura, H.; Ojida, A.; Ogawa, T.; Tsutsumi, H.; Masuno, H.; Nakashima, H.; Yamamoto, N.; Hamachi, I.; Fujii, N. *J. Med. Chem.* **2006**, *49*, 3412.

21. Tamamura, H.; Tsutsumi, H.; Masuno, H.; Mizokami, S.; Hiramatsu, K.; Wang, Z.; Trent, J. O.; Nakashima, H.; Yamamoto, N.; Peiper, S. C.; Fujii, N. *Org. Biomol. Chem.* **2006**, *4*, 2354.

22. Liang, X.; Sadler, P. J. *Chem. Soc. Rev.* **2004**, *33*, 246.

23. Princen, K.; Hatse, S.; Vermeire, K.; Aquaro, S.; De Clercq, E.; Gerlach, L. O.; Rosenkilde, M.; Schwartz, T. W.; Skerlj, R.; Bridger, G.; Schols, D. *J. Virol.* **2004**, *78*, 12996.

24. Hatse, S.; Princen, K.; De Clercq, E.; Rosenkilde, M. M.; Schwartz, T. W.; Hernandez-Abad, P. E.; Skerlj, R. T.; Bridger, G. J.; Schols, D. *Biochem. Pharmacol.* **2005**, *70*, 752.

25. Hu, J. S.; Freeman, C. M.; Stolberg, V. R.; Chiu, B. C.; Bridger, G. J.; Fricker, S. P.; Lukacs, N. W.; Chensue, S. W. *Am. J. Pathol.* **2006**, *169*, 424.

26. Schwarz, M. K.; Wells, T. N. *Nat. Rev. Drug. Discov.* **2002**, *1*, 347.

27. Scozzafava, A.; Mastrolorenzo, A.; Supuran, C. T. *J. Enzyme Inhib. Med. Chem.* **2002**, *17*, 69.

28. Hendrix, C. W.; Flexner, C.; MacFarland, R. T.; Giandomenico, C.; Fuchs, E. J.; Redpath, E.; Bridger, G.; Henson, G. W. *Antimicrob Agents Chemother* **2000**, *44*, 1667.

29. Princen, K.; Schols, D. *Cytokine Growth Factor Rev.* **2005**, *16*, 659.

30. De Clercq, E. *Int. J. Biochem. Cell Biol.* **2004**, *36*, 1800.

31. Seely, D. M.; Wu, P.; Mills, E. J. *BMC Cardiovasc. Disord.* **2005**, *5*, 32.

32. Selig, R. A.; White, L.; Gramacho, C.; Sterling-Levis, K.; Fraser, I. W.; Naidoo, D. *Cancer Res.* **1998**, *58*, 473.

33. Grier, M. T.; Meyers, D. G. *Ann. Pharmacother* **1993**, *27*, 1504.

34. Gerlach, L. O.; Jakobsen, J. S.; Jensen, K. P.; Rosenkilde, M. R.; Skerlj, R. T.; Ryde, U.; Bridger, G. J.; Schwartz, T. W. *Biochemistry* **2003**, *42*, 710.

35. Liang, X.; Parkinson, J. A.; Weishaupl, M.; Gould, R. O.; Paisey, S. J.; Park, H. S.; Hunter, T. M.; Blindauer, C. A.; Parsons, S.; Sadler, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 9105.

36. Braun, C. E.; Erit, J. D.; Crooks, G. C. *J. Org. Chem.* **1938**, *3*, 146.

37. Murdock, K. C.; Child, R. G.; Lin, Y.; Warren, J. D.; Fabio, P. F.; Lee, V. J.; Izzo, P. T.; Lang, S. A., Jr.; Angier, R. B.; Citarella, R. V.; Wallace, R. E.; Durr, F. E. *J. Med. Chem.* **1982**, *25*, 505.

38. Linton, B. R.; Goodman, M. S.; Fan, E.; van Arman, S. A.; Hamilton, A. D. *J. Org. Chem.* **2001**, *66*, 7313.

39. Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849.

40. Micovic, V. M.; Mihailovic, M. L. *J. Org. Chem.* **1953**, *18*, 1190.

41. Nicolaou, K. C.; Vourloumis, D.; Li, T. H.; Pastor, J.; Winssinger, N. et al. *Angew. Chem. Int. Ed.* **1997***, 36*, 2097.

42. Taylor, R. E.; Zajicek, J. *J. Org. Chem.* **1999***, 64*, 7224.

43. Taylor, R. E.; Chen, Y.; Galvin, G. M.; Pabba, P. K. *Org. and Biomol. Chem.* **2004***, 2*, 127.

44. Tang, L.; Qiu, R. G.; Li, Y.; Katz, L. *J. Antibiot.* **2003***, 56*, 16.

45. Njardarson, J. T.; Biswas, K.; Danishefsky, S. J. *Chem. Commun.* **2002**, 2759.

46. Nicolaou, K. C.; Sarabia, F.; Ninkovic, S.; Finlay, M. R. V.; Boddy, C. N. C. *Angew. Chem. Int. Ed.* **1998***, 37*, 81.

47. Biswas, K.; Lin, H.; Njardarson, J. T.; Chappell, M. D.; Chou, T. C. et al. *J. Am. Chem. Soc.* **2002***, 124*, 9825.

48. Rivkin, A.; Yoshimura, F.; Gabarda, A. E.; Chou, T. C.; Dong, H. J. et al. *J. Am. Chem. Soc.* **2003***, 125*, 2899.

49. Wu, K. D.; Cho, Y. S.; Katz, J.; Ponomarev, V.; Chen-Kiang, S.; Danishefsky, S. J.; Moore, M. A. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 10640.

50. Meng, D. F.; Su, D. S.; Balog, A.; Bertinato, P.; Sorensen, E. J. et al. *J. Am. Chem. Soc.* **1997***, 119*, 2733.

51. Wang, M. M.; Xia, X. Y.; Kim, Y.; Hwang, D.; Jansen, J. M.; Botta, M.; Liotta, D. C.; Snyder, J. P. *Org. Lett.* **1999**, *1*, 43.

52. Nicolaou, K. C.; Sasmal, P. K.; Rassias, G.; Reddy, M. V.; Altmann, K. H. et al. *Angew. Chem. Int. Ed.* **2003***, 42*, 3515.

53. Nicolaou, K. C.; Ritzen, A.; Namoto, K.; Buey, R. M.; Diaz, J. F. et al. *Tetrahedron* **2002***, 58*, 6413.

54. Nicolaou, K. C.; Namoto, K.; Ritzen, A.; Ulven, T.; Shoji, M. et al. *J. Am. Chem. Soc.* **2001***, 123*, 9313.

55. Regueiro-Ren, A.; Borzilleri, R. M.; Zheng, X. P.; Kim, S. H.; Johnson, J. A. et al. *Org. Lett.* **2001***, 3*, 2693.

56. Rivkin, A.; Biswas, K.; Chou, T. C.; Danishefsky, S. J. *Org. Lett.* **2002***, 4*, 4081.

57. Chou, T. C.; Dong, H. J.; Rivkin, A.; Yoshimura, F.; Gabarda, A. E. et al. *Angew. Chem. Int. Ed.* **2003***, 42*, 4761.

58. Regueiro-Ren, A.; Leavitt, K.; Kim, S. H.; Hofle, G.; Kiffe, M.; Gougoutas, J. Z.; DiMarco, J. D.; Lee, F. Y. F.; Fairchild, C. R.; Long, B. H.; Vite, G. D. *Org. Lett.* **2002**, *4*, 3815.

59. Su, D. S.; Meng, D. F.; Bertinato, P.; Balog, A.; Sorensen, E. J. et al. *Angew. Chem. Int. Ed.* **1997***, 36*, 757.

60. Nicolaou, K. C.; Scarpelli, R.; Bollbuck, B.; Werschkun, B.; Pereira, M. M.

A. et al. *Chem. Biol.* **2000***, 7*, 593.

61. Nicolaou, K. C.; He, Y.; Roschangar, F.; King, N. P.; Vourloumis, D. et al. *Angew. Chem. Int. Ed.* **1998***, 37*, 84.

62. Klar, U.; Buchmann, B.; Schwede, W.; Skuballa, W.; Hoffinann, J.; Lichtner, R. B. *Angew. Chem., Int. Ed.* **2006**, *45*, 7942.

63. Nicolaou, K. C.; Vallberg, H.; King, N. P.; Roschangar, F.; He, Y. et al. Q *Chem. Eur. J.* **1997***, 3*, 1957.

64. Ojima, I.; Chakravarty, S.; Inoue, T.; Lin, S. N.; He, L. F. et al. *Proc. Natl. Acad. Sci. U. S. A.* **1999***, 96*, 4256.

65. Borzilleri, R. M.; Zheng, X. P.; Schmidt, R. J.; Johnson, J. A.; Kim, S. H.; DiMarco, J. D.; Fairchild, C. R.; Gougoutas, J. Z.; Lee, F. Y. F.; Long, B. H.; Vite, G. D. *J. Am. Chem. Soc.* **2000**, *122*, 8890.

66. D. W. Heinz, W. D. Schubert, G. Hofle, *Angew. Chem. Int. Ed*. **2005**, *44*, 1298 .

67. He, L.; Jagtap, P. G.; Kingston, D. G.; Shen, H. J.; Orr, G. A.; Horwitz, S. B. *Biochemistry* **2000**, *39*, 3972.

68. Giannakakou, P.; Gussio, R.; Nogales, E.; Downing, K. H.; Zaharevitz, D.; Bollbuck, B.; Poy, G.; Sackett, D.; Nicolaou, K. C.; Fojo, T. *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 2904.

69. Carlomagno, T.; Blommers, M. J.; Meiler, J.; Jahnke, W.; Schupp, T.; Petersen, F.; Schinzer, D.; Altmann, K. H.; Griesinger, C. *Angew. Chem. Int. Ed.* **2003**, *42*, 2511.

70. Ni, F. *Prog. Nucl. Magn. Reson. Spectrosc.* **1994**, *26*, 517.

71. Carlomagno, T.; Felli, I. C.; Czech, M.; Fischer, R.; Sprinzl, M.; Griesinger, C. *J. Am. Chem. Soc.* **1999**, *121*, 1945.

72. Blommers, M. J. J.; Stark, W.; Jones, C. E.; Head, D.; Owen, C. E.; Jahnke, W. *J. Am. Chem. Soc.* **1999**, *121*, 1949.

73. Sanchez-Pedregal, V. M.; Reese,M.; Meiler,J.; Blommers, M. J.; Griesinger, C.; Carlomagno, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 4172.

74. Snyder, J. P.; Nettles, J. H.; Cornett, B.; Downing, K. H.; Nogales, E. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 5312.

75. Nettles, J. H.; Li, H.; Cornett, B.; Krahn, J. M.; Snyder J. P.; Downing K. H. *Science* **2004**, *305*, 866.

76. (a) Metaferia, B. B.; Hoch, J.; Glass, T. E.; Bane, S. L.; Chatterjee, S. K.; Snyder, J. P.; Lakdawala, A.; Cornett, B.; Kingston, D. G. I. *Org. Lett.* **2001**, *3*, 2461. (b) Ganesh, T.; Guza, RC.; Bane, S.; Ravindra, R.; Shanker, N.; Lakdawala, A. S.; Snyder, J. P.; Kingston, D. G. I. *Proc. Natl. Acad. Sci. USA.* **2004**, *101*, 10006. (c) Ganesh, T.; Norris, A.; Sharma, S.; Bane, S.; Alcaraz, A. A.; Snyder, J. P.; Kingston, D. G. I. *Bioorg. Med. Chem*. **2006**, *14*, 3447.

77. (a) Chen, Q.-H.; Ganesh, T.; Brodie, P. J.; Jiang, Y.; Bane, S. L.; Snyder, J. P.; Kingston, D. G. I. *Org. Biomol. Chem.* **2008,** *6*, 4542. (b) Chen, Q.-H.; Ganesh, T.; Jiang, Y.; Bane, S. L.; Snyder, J. P.; Kingston, D. G. I. *Chem. Commun.* **2010**, *46*, 2019.

78. Zhan, W.; Jiang, Y.; Brodie, P. J.; Kingston, D. G. I.; Liotta, D. C.; Snyder, J. P. *Org. Lett.* 2008, *10*, 1565.

79. Nicolaou, K. C.; Ninkovic, S.; Sarabia, F.; Vourloumis, D.; He, Y.; Vallberg, H.; Finlay, M. R. V.; Yang, Z. *J. Am. Chem. Soc.* **1997**, *119,* 7974.

80. Noyori, R.; Ohkuma T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.*, **1987**, *109*, 5856.

81. (a) Horner, L.; Hoffmann, H. M. R.; Wippel, H. G. *Ber.* **1958**, *91*, 61. (b) Wadsworth, W. S. Jr.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733.

82. Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.

83. Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J Org. Chem.* **1986**, *51*, 432.

84. For a review of selective deprotection of silyl ethers, see: Nelson, T. D.; Crouch, R. D. *Synthesis* **1996**, 1031.

85. Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

86. Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.

87. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *53*, 1989.

88. (a) Xu, J.-C.; Li, P. *Tetrahedron* **2000**, *56*, 8119. (b) Folmer, J. J.; Acero, C.; Thai, D. L.; Rapoport, H. *J. Org. Chem.* **1998**, *63*, 8170.

89. (a) Meng, D. F.; Bertinato, P.; Balog, A.; Su, D. S.; Kamenecka, T.;

Sorensen, E. J.; Danishefsky, S. J. *J. Am. Chem Soc.* **1997**, *119*, 10073. (b) For a review on Suzuki-Miyaura coupling reaction in natural product synthesis, see: Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544.

90. Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 2173.

91. Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E. J. J. *Tetrahedron Lett*. **1995**, *36*, 5461.

92. Trost, B. M.; Gunzner, J. L.; Dirat, O.; Rhee, Y. H. *J. Am. Chem. Soc.* **2002**, *124*, 10396.

93. (a) Fráter G. *Helvetica Chimica Acta* **1979**, *62*, 2825. (b) Fráter, G.; Müller, U.; Günther, W. *Tetrahedron***, 1984,** *40,* 1269. (c) Seebach, D.; Wasmuth, D. *Helvetica Chimica Acta* **1980**, *63*, 197.

94. Evans, D. A.; Dart, M. J.; Duffy, J. L.; Rieger, D. L. *J. Am. Chem. Soc.*, **1995**, *117*, 9073.

95. Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G.; Livingston, A. B. *J. Am. Chem. Soc.* **1995**, *117*, 6619.

96. White, J. D.; Carter, R. G.; Sundermann, K. F.; Wartmann, M. *J. Am. Chem. Soc.* **2001**, *123,* 5407.

97. Rchnovsky D. S., Rogers B., Yang G. *J. Org. Chem,* **1993**, *58*, 3511.

98. Still, W.C., Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.

99. De Nooy, A. E. J.; Besemer, A. C.; Van Bekkum, H. *Synthesis* **1996**, 1153.

100. Smith, A. B., III.; Dong, S.; Brenneman, J. B.; and Fox, R. J. *J. Am. Chem. Soc.* **2009**, *131*, 12109.

101. Behrens, B. C.; Hamilton, T. C.; Masuda, H.; Grotzinger, K. R.; Whang-Peng, J.; Louie, K. G.; Knutsen, T.; McKoy, W. M.; Young, R. C.; Ozols, R. F. *Cancer Res.* **1987**, *47*, 414.

102. Liu, C.; Strobl, J. S.; Bane, S.; Schilling, J. K.; McCracken, M.; Chatterjee, S. K.; Rahim-Bata, R.; Kingston, D. G. *J. Nat. Prod.* **2004**, *67*, 152.

103. Adam, W.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377.