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Weiqiang Zhan

Part I: Design, Synthesis and Biological Evaluation of C6-C8 Bridged Epothilone Analogs

Part II: Discovery of Small Molecule CXCR4 Antagonists

By

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Part I: Design, Synthesis and Biological Evaluation of C6-C8 Bridged Epothilone Analogs

Part II: Discovery of Small Molecule CXCR4 Antagonists

By

Weiqiang Zhan

M.E. Shanghai Jiao Tong University, 2003
B.E. Shanghai Jiao Tong University, 2000

Advisor: Dennis C. Liotta, Ph.D.

An Abstract of
a dissertation submitted to the
Faculty of the Graduate School of Emory University
in partial fulfillment of the requirements
of the degree of Doctor of Philosophy

Department of Chemistry

2008

Abstract

In the first part of this dissertation, a series of conformationally restrained epothilone analogs with a short bridge between methyl groups at C6 and C8 were designed to mimic the binding pose determined for our recently reported EpoA-microtubule binding model. A versatile synthetic route to these bridged epothilone analogs has been successfully devised and implemented. The key stereochemistry within the bridged C6-C8 sector was controlled by asymmetric allylboration followed by hydroxy-directed epoxidation and regio-controlled epoxide opening with a Grignard reagent. The biological evaluation of these bridged epothilone analogs against A2780 human ovarian cancer cell line suggested that the introduction of a bridge between C6-C8 made these epothilones less potent by 55-1000 fold in comparison with Taxol®. The biological results further confirmed the previous depicted structure-activity relationship (SAR) profile of epothilones, and provided significant SAR information arising from the C6-C8 sector.

The second part of this dissertation describes the discovery of novel small molecule CXCR4 antagonists. Compelling evidence is accumulating that the CXCR4/SDF-1 interaction and the resulting cell signaling cascade play a key role in metastasis by facilitating locomotion, chemoattraction, homing and adhesion of the metastatic cells to the defined organs, as well as supporting tumor growth and angiogenesis. In view of aspects of the molecular mechanism of the CXCR4 antagonist, AMD3100, we designed a template and identified G1 lead WZ13 by

means of an affinity binding assay against the ligand-mimicking CXCR4 antagonist, TN14003. Following a structure-activity profile around WZ13, the design and synthesis of a series of novel small molecule CXCR4 antagonists led to the discovery of G2 lead WZ811, which shows subnanomolar potency in an affinity binding assay and *in vivo* function assays. Attempts to improve the pharmacokinetic profile of WZ811 resulted in the discovery of MSX-122 (WZ40). Preclinical studies indicated that MSX-122 is a novel, safe, and highly effective agent with oral bioavailability to block cancer metastasis and tumor angiogenesis by antagonizing CXCR4. MSX-122 is currently in phase I clinical trials.

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DEDICATED TO MY FAMILY

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Part I: Design, Synthesis and Biological Evaluation of C6-C8 Bridged Epothilone Analogs

Part II: Discovery of Small Molecule CXCR4 Antagonists

Abbreviations

AIDS	Acquired Immune Deficiency Syndrome
9-BBN	9-Borabicyclo[3.3.1]nonane
Boc	*t*-Butoxycarbonyl
BORSM	Basis on Recycle Starting Material
calcd	Calculated
cAMP	Cyclic Adenosine Monophosphate
cat	Catalytic
compd	Compound
Cp	Cyclopentadienyl
CXCR4	CXC Chemokine receptor-4
DBU	8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DIBAL	Diisobutylaluminum Hydride
DMAP	N,N-Dimethylaminopyridine
DMDO	3,3-Dimethyldioxirane
EDCI	1-Ethyl-3-((dimethylamino)propyl)carbodiimide hydrochloride
EI-MS	Electron Ionization Mass Spectroscopy
EPO	Epothilone
equiv	Equivalents
EC	Effective Concentration
EC_{50}	Half maximal effective concentration
FDG-PET	Fluorodeoxyglucose-Positron Emission Tomography
G-CSF	Granulocyte-Colony Stimulating Factor
h	Hours
H&E	Hematoxylin and Eosin.
HIV	Human Immunodeficiency Virus
HMPA	Hexamethylphosphoramide
HRMS	High Resolution Mass Spectrometry
IC_{50}	Concentration that is required for 50% inhibition

i-Pr	*iso*-Propyl
IR	Infrared Spectroscopy
*m*CPBA	*meta*-Chloroperoxybenzoic Acid
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
Ph	Phenyl
PTS	*p*-Toluenesulfonic Acid
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SAR	Structure Activity Relationship
sat.	Saturated
SCCHN	Squamous Cell Carcinoma of Head and Neck
SDF-1	Stromal-Derived Factor-1
TBAF	Tetra-*n*-Butylammonium Fluoride
TBS	*tert*-butyldimethylsilyl
TFA	Trifluoroacetic Acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TPAP	Tetrapropylammonium Perruthenate
TR-FRET	Time Resolved-Fluorescence Resonance Energy Transfer
VEGF	Vascular Endothelial Growth Factor

Part I: Design, Synthesis and Biological Evaluation of C6-C8 Bridged Epothilone Analogs

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 α/β 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 α/β-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]

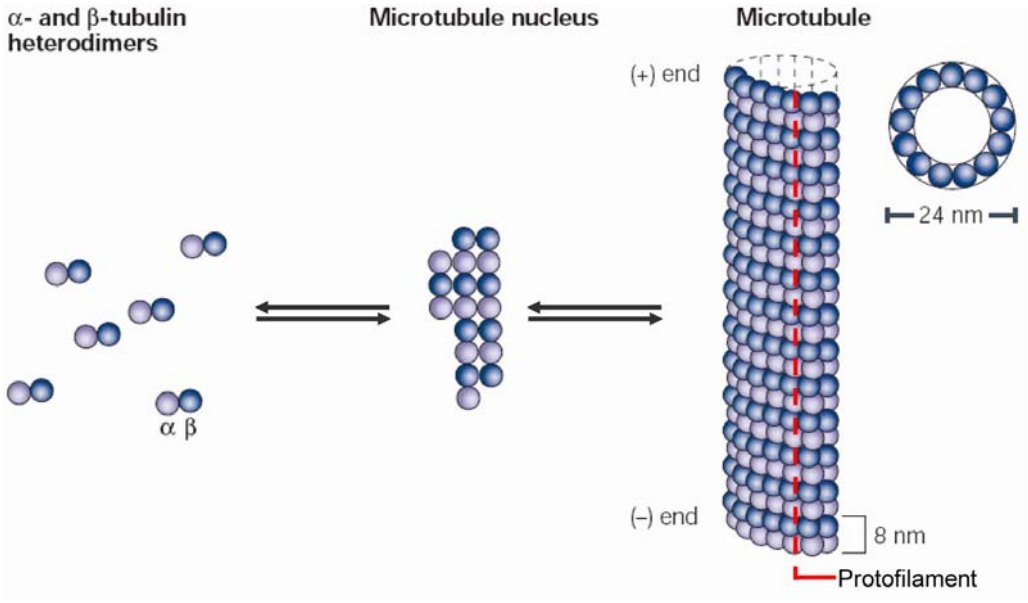


Figure 1. Polymerization of microtubules (Adapted from ref.6a)

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 microtubule-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)** and sarcodictyins (**8a** and **8b**) (Figure 2).

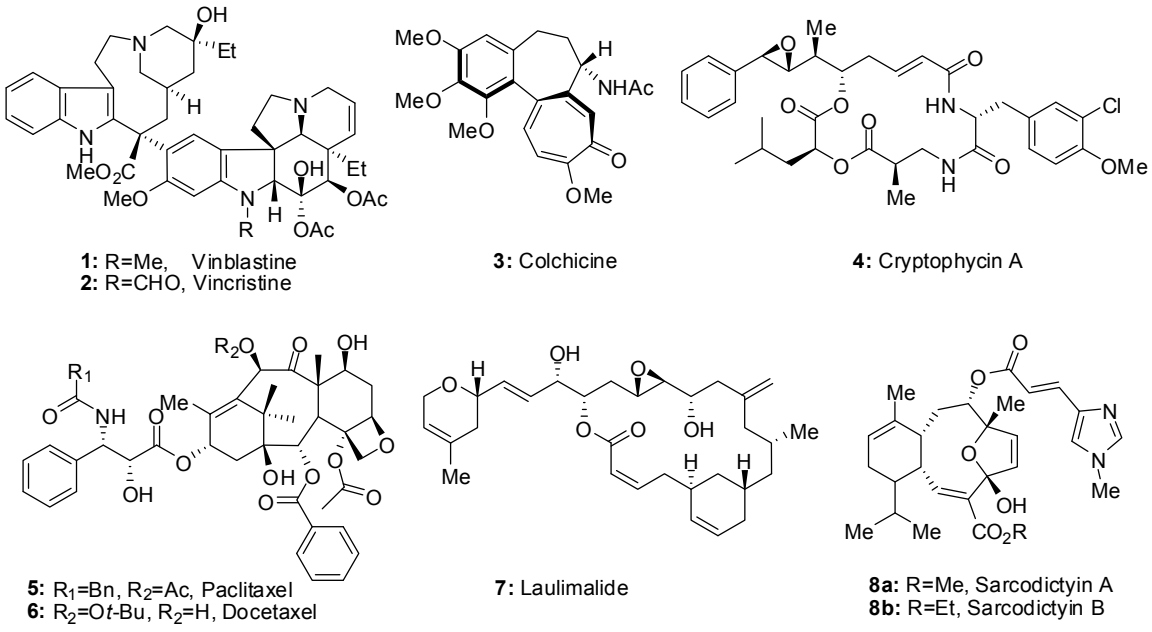


Figure 2. Structures of selected microtubule-interacting agents

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]

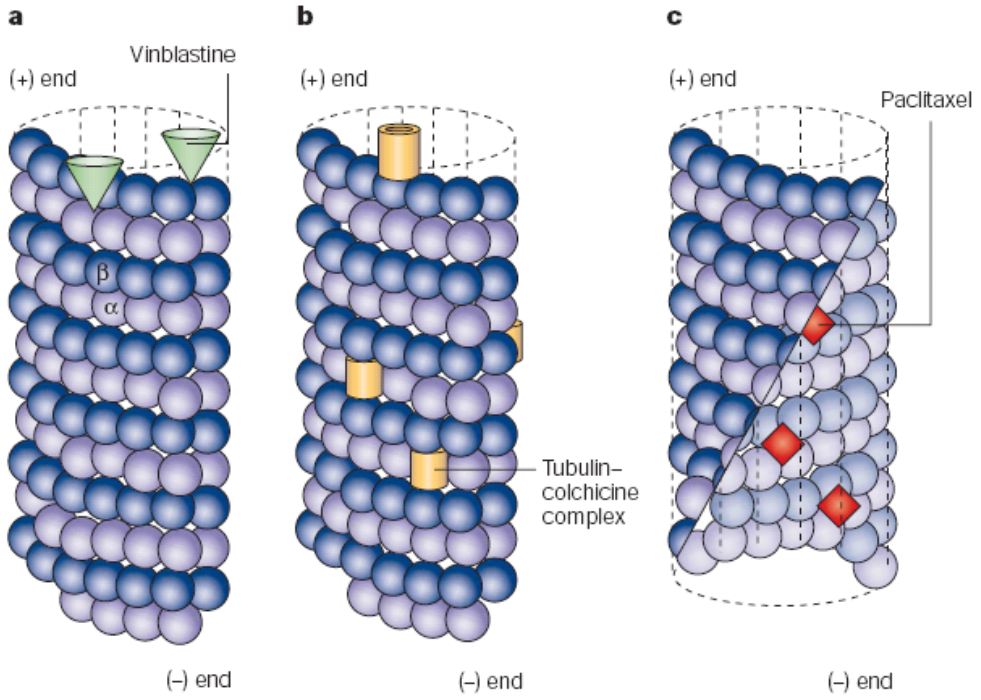


Figure 3. Microtubule-interacting agents bind to microtubules at diverse sites.

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 possess 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 1995, 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, **9**) and B (EpoB, **10**) (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, 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, **11**) and D (EpoD, **12**).[23-26]

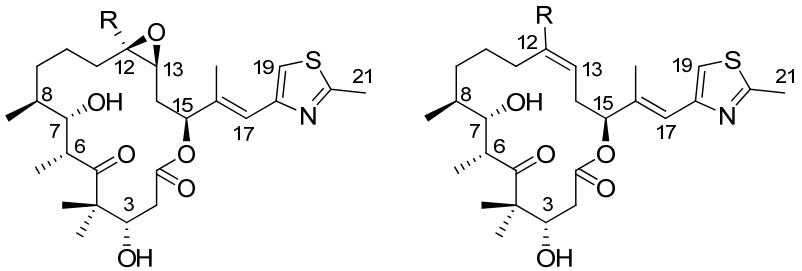


Figure 4 Structures of epothilones A, B, C, and D.

EpoA and EpoB were recognized shortly after their initial isolation to be potent inhibitors against breast and colon cancer cells.[21b] However, their action mechanism 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 polymerization 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 which induce the paclitaxel resistance.[28a] This suggests that epothilone-derived drugs might be useful in treating drug resistant tumors.

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

	Epo A	Epo B	Taxol
Microtubule protein polymerization (% of control)	69	90	49
EC50 (microtubule protein) [μM]	1.1	0.7	1.9
EC50 (pure tubulin) [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).

Cell line	Epo A	Epo B	Taxol
HCT-116 (colon)	2.51	0.32	2.79
PC-3M (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	9105
KB-31 (epidermoid)	2.1	0.19	2.31
KB-8511[b]	1.9	0.19	533

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

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 been arisen that have enabled the development of libraries of many 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 microtuules.[38-40]

In early SAR studies, Danishefsky structurally divided epothilones into three sectors: aryl (green), alkyl (blue), and acyl (red) sectors (Figure 5),[38] and found that the acyl sector constitutes a “hot spot” with great sensitivity to structural change. By contrast, the alkyl and aryl sectors exhibit significant tolerance, both in the tubulin assays and in cytotoxicity screens. In the last decade, a host of new synthetic analogs for SAR studies have been synthesized and much SAR data have been summarized in several excellent review articles.[21, 41]

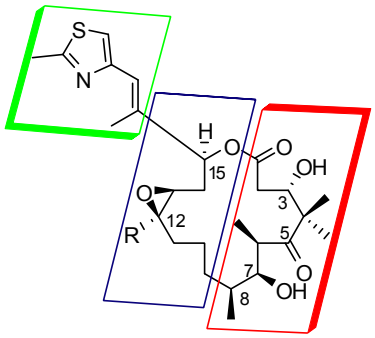


Figure 5. The three arbitrarily defined sectors of the epothilones: aryl (green), alkyl (blue), and acyl (red) sectors

The modifications around C12-C13 strongly suggest that the efficient microtubule stabilization and the potent anti-cancer properties of epothilones are not dependent on the epoxide moiety. 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 result was confirmed by the fact that "deoxyepothilones" (EpoC and EpoD) possess potent biological activity similar to that of epoxide-containing parent compounds[28c] and reinforced by the activities of cyclopropane-based epothilone analogs, in which the epoxide ring is replaced by a cyclopropane moiety.[42, 43] Modifications associated with the C12-C13 region also have shown retention of potent biological activity of the some nonnatural 12,13-*trans* analogs, especially for the EpoA/C analogs (**13**, Figure 6).[32, 44] Introduction of small and apolar substituents such as F, Cl, CH_3, or C_2H_5 onto the methyl at C12 produced analogs with slightly less potency than the parent compound.[38, 45]

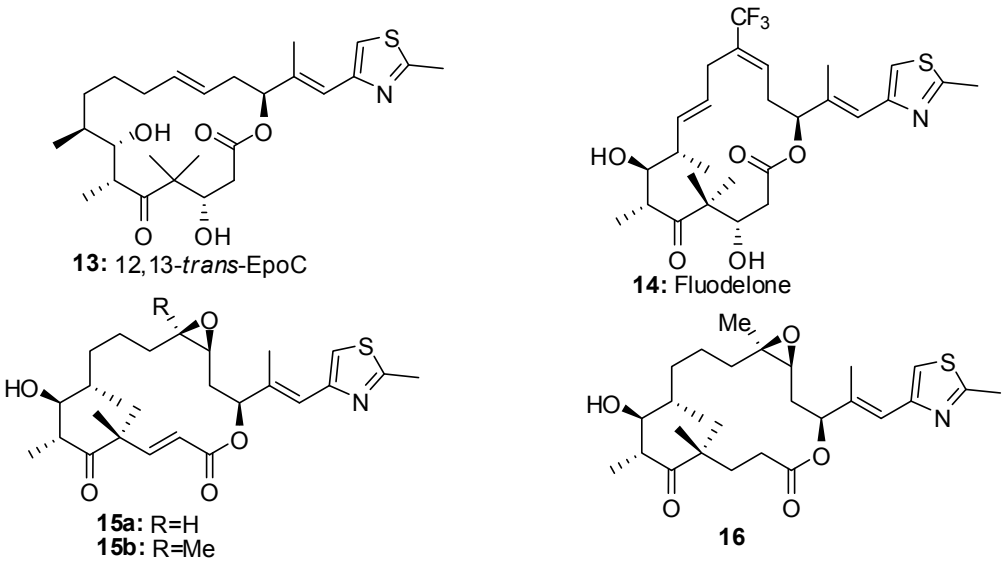


Figure 6. Selected epothilone analogs

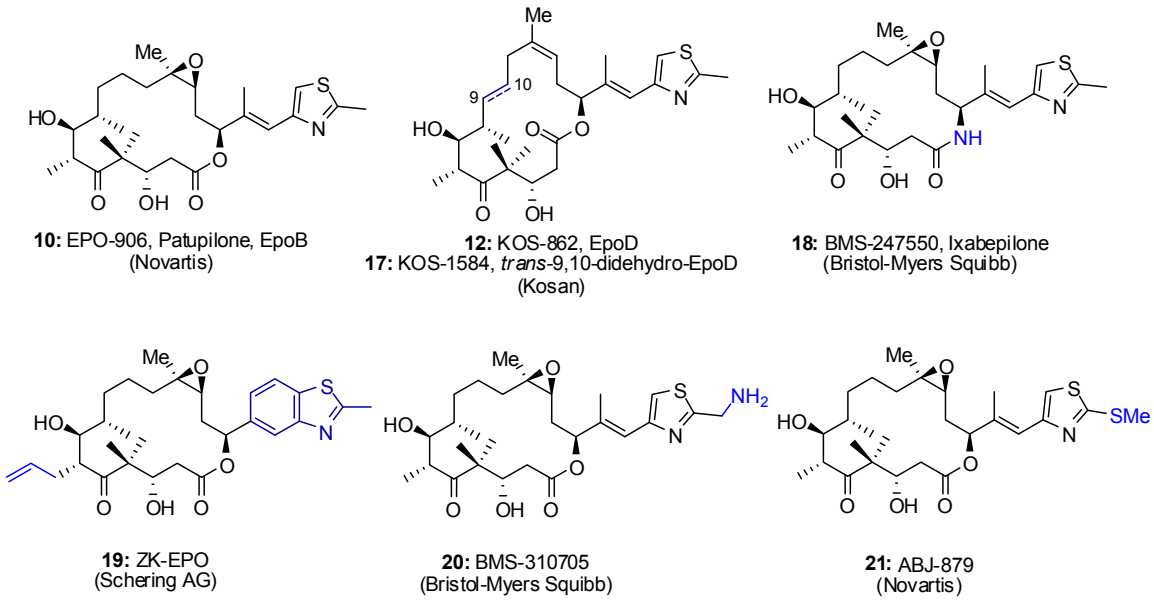
Early modification around the C9-C12 region indicated that both ring expansion and shrinkage (based on the incorporation or removal of a methylene group) would result in a substantial loss of potency.[38, 46] However, several analogs with *trans* double bonds either between C10-C11 or C9-C10 have shown potent antiproliferative activity *in vitro*, and even improved *in vivo* pharmacological profile over EpoB and EpoD.[21c] Following the finding of *trans*-9,10-didehydro-EpoD (**17**, Figure 7), *trans*-9,10-trifluoro-26-EpoD (**14**, Fludelone, Figure 6) discovered by Danishefsky and co-workers, has shown an excellent pharmacological profile with super *in vivo* antitumor activity without obvious lethality or irreversible toxicity.[47]

One of the most important achievements from the modifications around C1-C6 is the discovery of Ixabepilone® (**18**, BMS-247550, Figure 7). In compound **18**, the nitrogen atom replaces the bridging lactone oxygen in EpoB, thus transforming a macrolactone into a macrolactam ring.[48] Analogue **18** not only maintains the high biological activity of EpoB, but also is reported to overcome the limited stability of EpoB in rodent plasma.[48] More recently, Ixabepilone has been approved by the FDA for clinical use in humans.[21d] Another intriguing feature from C1-C6 modifications is the finding that the presence of a 3-hydroxyl group in epothilones is not a crucial requirement for potent biological activity.[49, 50] For example, 3-deoxy-2,3-dihehydro derivatives **15a/b** (Figure 6) retain most of the activity of the parent natural products,[50] while the 3-deoxyEpoB **16** retains highly potent biological activity, which is manifested in IC_{50} values for human cancer cell growth inhibition in the low nanomolar level.[49, 50]

The unsaturated heterocycle-bearing side chain has been heavily targeted

for SAR studies considering its ease for structural alterations which in turn modulate the physicochemical and pharmacokinetic profiles. The modifications include the replacement of the thiazole ring by other heterocyclic structures or aromatic rings, modification at the 2- and 4-positions of the thiazole ring, and the synthesis of C16-desmethyl EpoB.[21c] These SAR data have shown that the natural thiazole heterocycle is not an essential requirement for the biological activity. It could be replaced by other functionalized heterocycles such as oxazole pyrazole, imidazole, triazole, tetrazole,[38, 39, 51] or even 6-membered rings including pyridine-based heterocycles[52] and bulky heteroaromatics[51] without significant loss of biological potency. The rigidification of the entire side chain scaffold has led to the discovery of compound ZK-Epo (**19**, Figure 7) from the Novartis research group which is currently being studied in advanced clinical trial.[53]

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 (**18**, 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.[53]



10: EPO-906, Patupilone, EpoB (Novartis)

12: KOS-862, EpoD
17: KOS-1584, *trans*-9,10-didehydro-EpoD (Kosan)

18: BMS-247550, Ixabepilone (Bristol-Myers Squibb)

19: ZK-EPO (Schering AG)

20: BMS-310705 (Bristol-Myers Squibb)

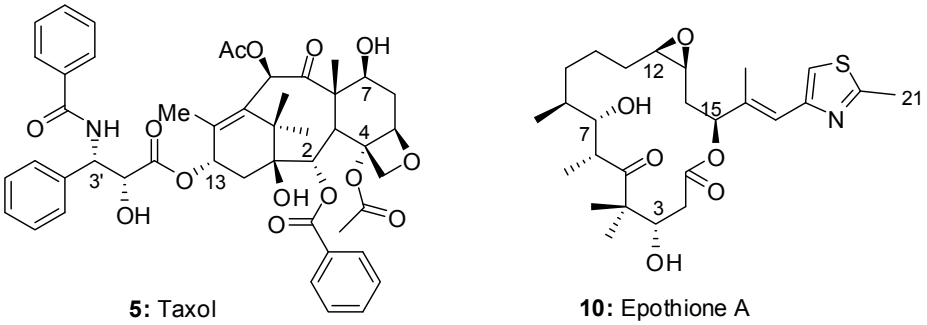
21: ABJ-879 (Novartis)

Figure 7. Epothilones in clinical trials (Publicly known)

1.1.4 Conformational and Modeling Studies of Epothilones

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.[54-57] A variety of epothilone conformations and binding modes on tubulin have been proposed by pharmacophore mapping,[54, 56] solution NMR,[58, 59] and the superposition of epothilones on taxanes in the electron crystallographic tubulin complex.[55, 57] 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[57] 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[56] proposed the C3'-phenyl and Ojima[54] proposed the C3'-benzoyloxyl phenyl as coincident with the thiazole ring from epothilones. All of these models can explain at least part of the obtained epothilone SAR data and may thus provide some useful guidance for the design of new analogs. However, further revision to these models is required in light of more recent structural data on the bioactive, β-tubulin-bound conformation of EpoA.[58, 60]



5: Taxol **10:** Epothione A

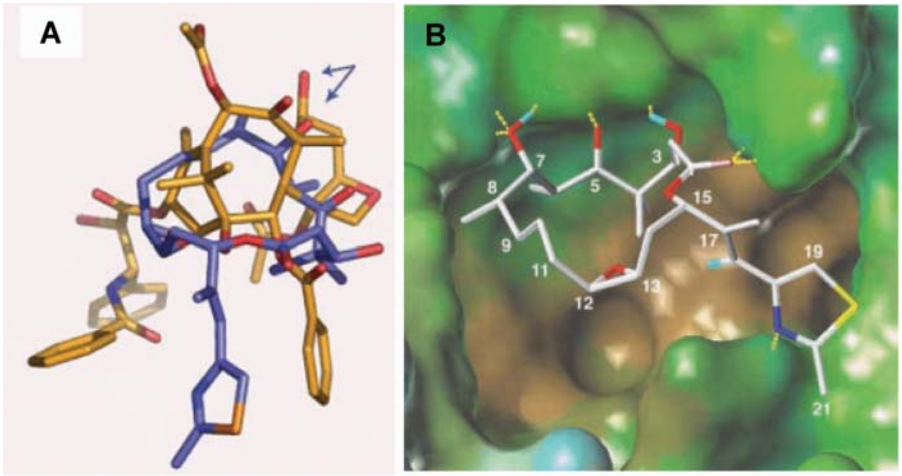


Figure 8. Upper: Structures of Taxol and EpoA; Bottom: Common binding site for epothilone and taxol: (**A**) Superposition of EpoA (blue) and Taxol (gold). (**B**) Hydrophobic to hydrophilic properties at binging site (white, EpoA). (Adapted from ref. 60)

Combining NMR spectroscopy, electron crystallography, and molecular modeling, an alternative model has been proposed by Nettles *et al.*[60] that contradicts the common pharmacophore model by referring to the tubulin binding cavity as promiscuous (Figure 8). According to the Nettles model, 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 overlapped with that of taxol bound to tubulin. The overlap 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.

1.2. Design and Synthesis of C6-C8 Bridged Epothilones

1.2.1 Design Rationale

As discussed above, our group recently proposed a unique EpoA conformation and microtubule binding model based on electron crystallography, NMR conformer deconvolution and SAR analysis.[60] A peculiar feature of the proposed binding conformer is the presence of a *syn*-pentane interaction between methyl groups at C-6 and C-8 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 series of conformationally restrained epothilone analogs with a short bridge between the

methyl groups at C6 and C8 (Figure 9) were designed to mimic the binding pose determined for the EpoA-microtubule binding model. Optimization of **22** and **23** in the proposed binding form indicated it was a stable local minimum. Furthermore, docking the structure into β-tubulin suggested that the additional CH_2 in the newly installed cyclohexane ring would not experience steric congestion with the protein and the shortest H---H contact is 2.5 Å (Figure 10).

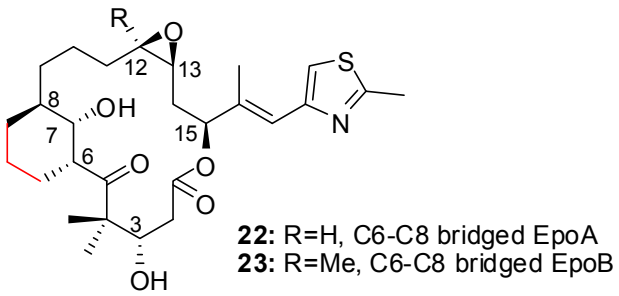


Figure 9. Structures of C6-C8 bridged EpoA and EpoB

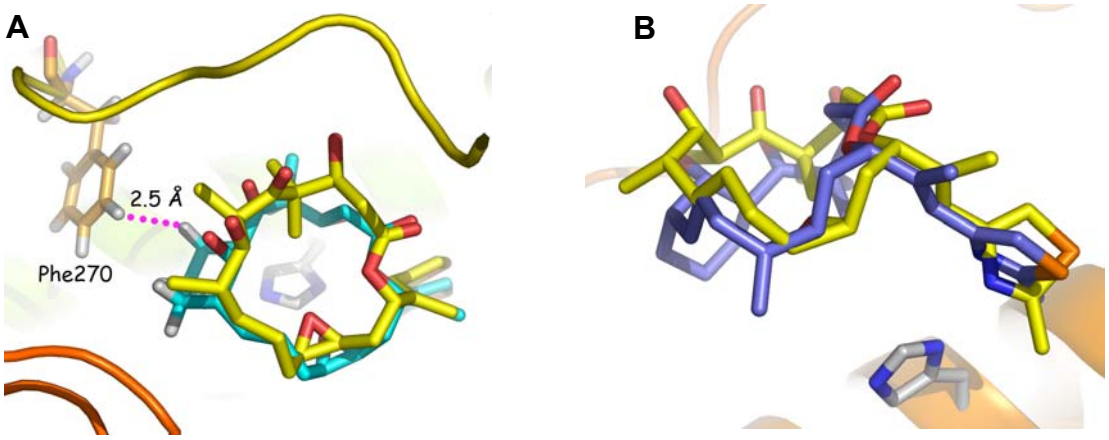


Figure 10. Docking poses of C6-C8 bridged epothilone analogs in the electron crystallography-determined tubulin binding site: (**A**) Docking poses of **10** (yellow) and **22** (cyan); (**B**) Docking poses of **10** (yellow) and **23** (blue).

In addition, although early SAR studies have suggested that the C1-C8 sector is critical for maintenance of biological activity and not amenable to significant change,[38] certain modifications within C1-C8 have yielded potent

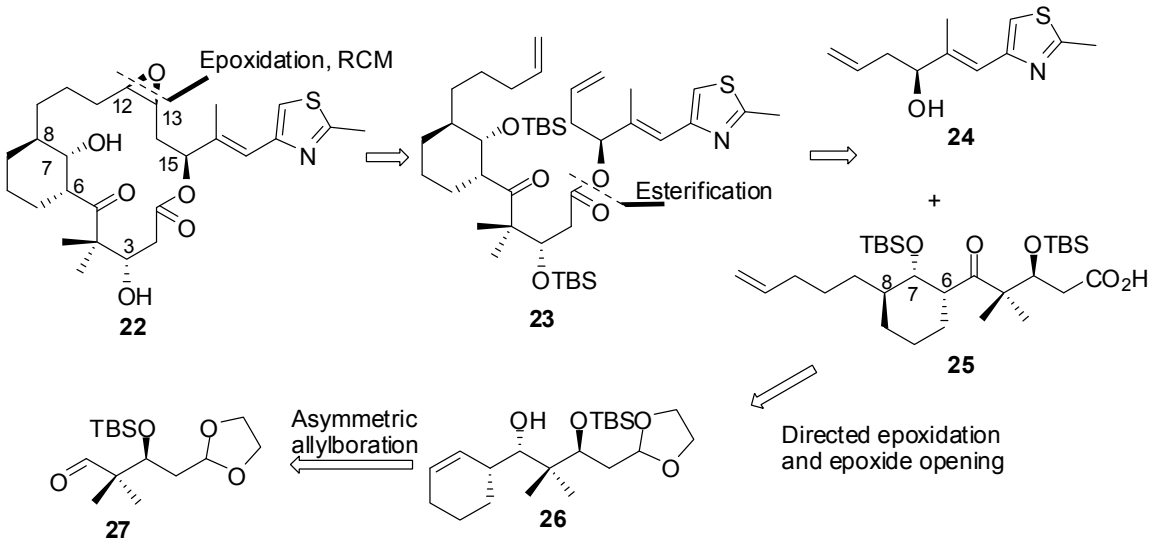
analogs (**17**, **18**, Figure 6).[49, 50] An important data point is available from the work of Martin *et al.* who introduced a 6-membered ring between C4-C6 from the *pro*-R methyl at C4 in the corresponding EpoB analog.[61] The compound proved to be inactive against the MCF-7 tumor cell line. The electron crystallographic structure suggests *pro*-S attachment to be the compatible link. Stereochemical inversion may then be responsible for the lack of activity. In this context, bridged epothilone analogs **22** and **23** suggested themselves as potential diagnostic tests of the electron crystallographic epothilone binding model.

1.2.2 Initial Synthesis via Ring Closure Metathesis

The first generation synthetic plan of the C6-C8 bridged epothilones, based on ring closure metathesis (RCM) as a key step, is summarized in Scheme 1 in which compound 22 was used as an example. Although RCM has been known to give both *cis* and *trans* isomers in total syntheses of Epo A/B,[33, 62] it was applied as a key step here considering the outcome diversity would be beneficial to the activity targeted medicinal chemistry. Following with general disconnections in epothilone synthesis,[33] the target compound **22** could be traced back to well known alcohol **24**[34] and the advanced intermediate, keto acid **25** after retrosynthetic epoxidation, RCM and esterification. The preparation of keto acid **25** would be the key step along this route, by which the cyclohexane core structure with three adjacent chiral centers would be constructed. First, the stereochemistry at C7 and C8 in **25** could be installed employing sequential substrate directed epoxidation [63] and regiocontrolled epoxide opening from

homoallylic alcohol **26**. Moving further along the retrosynthetic path, alcohol **26** could be envisioned to arise from aldehyde **27** utilizing Brown's asymmetric allylboration strategy to prepare 1-(2-cyclohexenyl)-1-alkanols.[64]

Scheme 1. Initial Retrosynthetic Analysis of C6-C8 Bridged EpoA (**22**)

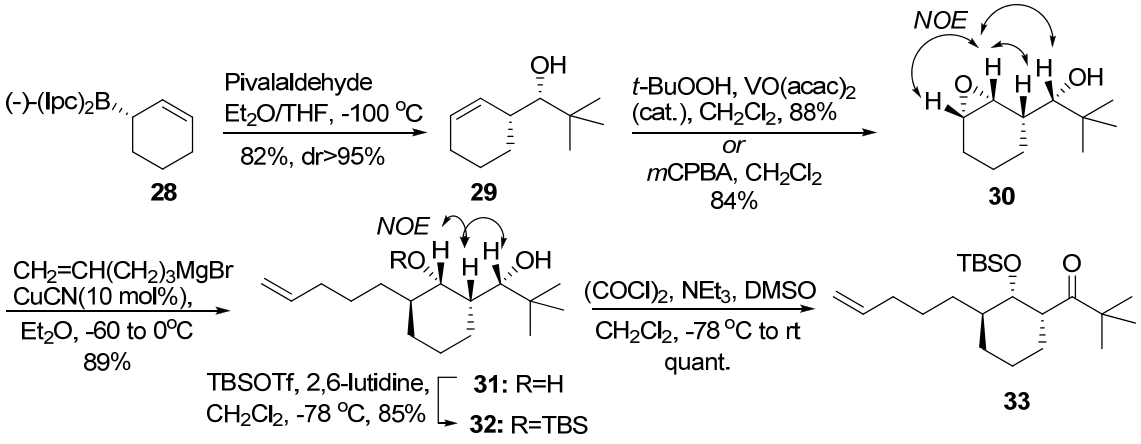


To test the feasibility of the substrate directed epoxidation and subsequent regio-controlled epoxide opening strategy, a simplified model system was studied as shown in Scheme 2. The model study started from (-)-*B*-2-cyclohexen-1-yldiisopinocampheylborane **28**, which was prepared by treating cyclohexa-1,3-diene with diisopinocampheylborane derived from (+)-α-pinene at -25 ^{o}C in tetrahydrofuran (THF) as described by Brown.[64] In accordance to the literature procedure,[64b] the freshly prepared solution of borane **28** in THF was cooled down to -100 ^{o}C, and treated with pivalaldehyde. After oxidation with H_2O_2 in presence of $NaHCO_3$, homoallylic alcohol **29** was obtained in 82% yield (*dr*>95% by ^{1}H NMR).[65]

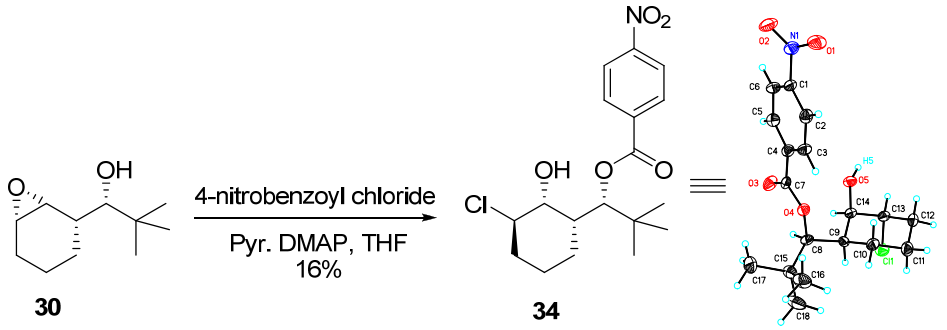
The highly stereoselective epoxidation of **29** was first achieved by a

homoallylic alcohol directed vanadium-catalyzed epoxidation strategy [66] to afford hydroxy epoxide **30** in 88% yield as only one isomer. Further study indicated that *m*CPBA-based epoxidation also delivered the desired epoxide **30** in 84% yield. The relative configuration was confirmed by NOE. Considering the difference of optical rotation value of **29** from the literature data ($[\alpha]_D^{25}$= -3.4, c 1.0, $CHCl_3$, Lit.[64b] +6.83 *l* 0.5, neat), a *p*-nitro-benzoyl derivative **34** was prepared and the X-ray crystallography of **34** further confirmed the absolute configuration of hydroxy epoxide **30** (Scheme 3). The position where the chloride anion attacked the epoxide also further supports the original design for the regioselective nucleophilic opening of the hydroxy epoxide.

Scheme 2. Synthesis of Cyclohexane Model System **33**

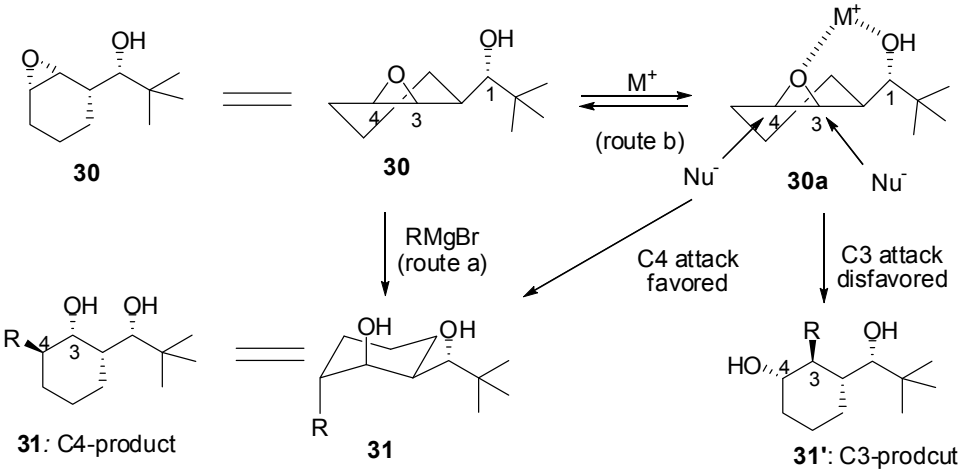


Scheme 3. Confirmation of Stereochemistry of **30**.



With the successful stereoselective epoxidation, the next key step in Scheme 2 is to open the epoxide with an alkyl nucleophile in a regioselective manner. Fortunately, this transformation was successfully performed by treatment of **30** with freshly prepared 4-pentenylmaganesium bromide[67] in the presence of CuCN (10 mol%) and the desired diol **31** was obtained exclusively in 89% yield. As suggested by Crotti and co-workers,[68, 69] we agreed that the regioselectivity of this metal catalyzed epoxide opening was not only controlled by the Fürst-Plattner rule (Route a, Scheme 4),[70] which favors a diaxial orientation, but it also could be reinforced by a chelation process (Route b, Scheme 4). In the chelation process, the initial coordination between the metal ion and oxygen atoms from the hydroxy and oxirane of **30** provides the bidentate structure **30a**. The nucleophilic attack on the C-4 oxirane carbon of **30** to give the C4 product will be favored due to stereoelectronic factors implicated in the chelation controlled ring opening of 3,4-epoxy-1-alkanol derivatives.[68]

Scheme 4. Regioselective opening of epoxide **30**.



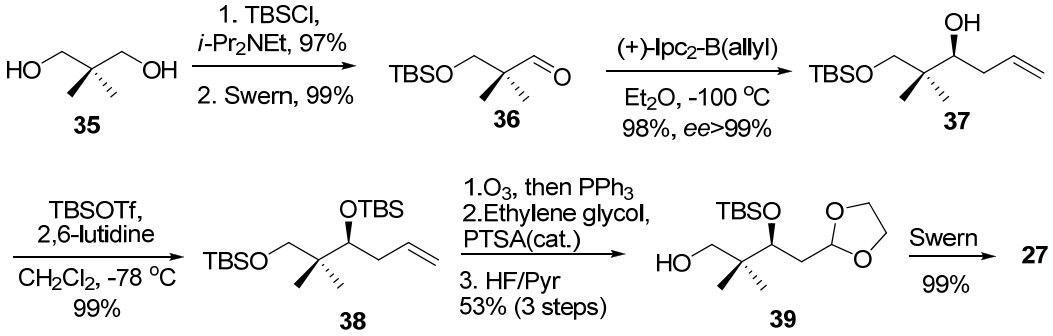
With the fantastic success of the two key steps in the model study, we turned

our attention to test the regioselective protection of the two secondary hydroxy groups in **31** and the following oxidation of the sterically hindered secondary alcohol in the model system. The pursuit of selective silylation of the sterically less hindered OH group in **31** was achieved by slow addition of *tert*-butyldimethylsilyl triflate (TBSOTf) into a solution of **31** in CH_2Cl_2 at -78 ^oC in the presence of 2,6-lutidine, giving mono-silyl ether **32** in 85% yield. Surprising to us, neither sterically hindered hydroxy monosilylated nor bissilylated product was detected when even 1.5 equiv of TBSOTf was added. At this stage, a NOESY analysis on silyl ether **32** suggested the previous regioselectivity of the oxirane opening and selective TBS protection (Scheme 2). The oxidation of the sterically hindered alcohol was furnished by Swern oxidation protocol to afford the desired keto olefin **33** almost in quantitative yield.

Encouraged by the results from the model studies described above, we proceeded to construct carboxylic acid **25**. In pursuit of this advanced intermediate, the known aldehyde **9**[71] was prepared in 96% yield (2 steps) following a two-step sequence from the commercially available neopentyl glycol **35** (Scheme 5). The aldehyde was then converted to an enantiomerically enriched homoallylic alcohol **37** (98% yield, *ee*> 95%, Mosher ester determination) by reaction with (+)-Ipc_2B(allyl) prepared from (-)-Ipc_2BCl and allylmagnesium bromide.[34, 72] Subsequent silylation of **37** by treatment with TBSOTf in the presence of 2,6-lutidine furnished silyl ether **38** almost in quantitative yield (Scheme 2). The silyl ether was subjected to ozonolysis, followed by an acid catalyzed acetal protection with ethylene glycol and selective desilylation[73] to

afford the primary alcohol **39** in 56% yield over three steps. Exposure of **39** to oxidative conditions produced the desired aldehyde **27** in quantitative yield.

Scheme 5. Synthesis of Aldehyde **27**.

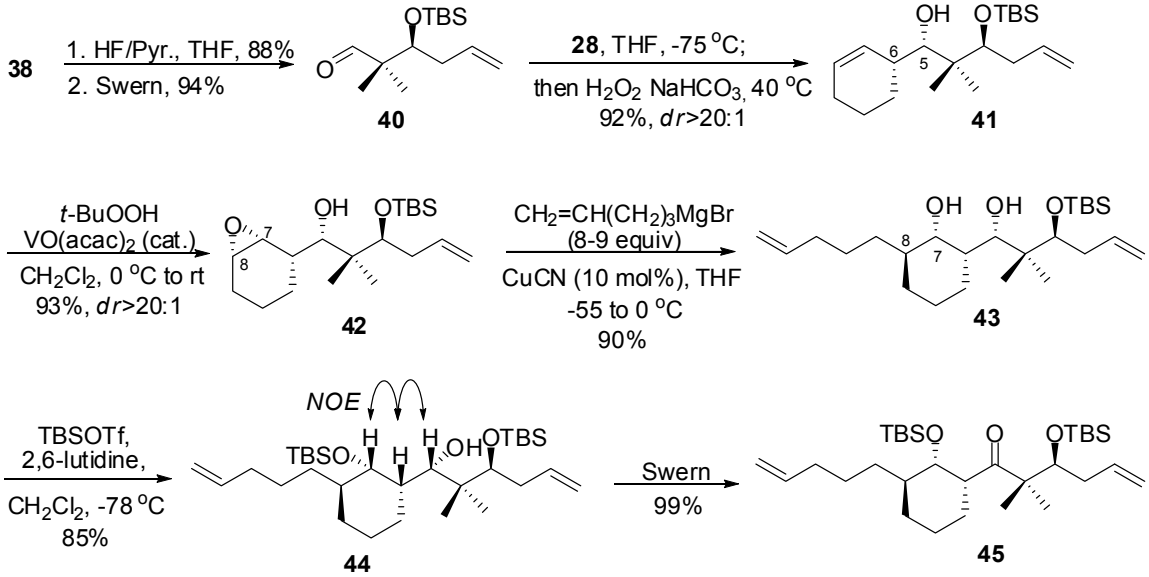


We are now in a position to probe the feasibility of establishing the C5-C6 bond by Brown's protocol.[64] Unfortunately, when aldehyde **27** was subjected to the standard Brown conditions,[64] no workable amounts of product **26** could be separated, while over 90% of aldehyde **27** was recovered before the oxidation. Attempts to facilitate the reaction by increasing temperature (-25 ^{o}C) and reaction time (one week) did not lead to satisfactory results. The allylboration could be not only disfavored from the steric hindrance of the α-quaternary carbon of aldehyde, but also suffered from the coordination between the borane and acetal oxygen atoms, which in turn interrupted the interaction between the borane and aldehyde.

To address the above problem, we turned our attention to aldehyde **40**, in which a terminal alkene displaced the acetal in **27** to avoid the potential coordination described above. Selective desilylation and subsequent Swern oxidation converted silyl ether **38** into the desired aldehyde **40** (Scheme 6). Upon treatment of the modified aldehyde **40** with freshly prepared borane **28**, the desired homoallylic alcohol **41** was obtained in remarkable yield and selectivity

(96%, *dr*>20:1 by ^{1}H NMR) as shown in Scheme 6. Surprising, both the C-C bond formation and oxidative cleavage of B-O bond were still unexpectedly sluggish (over ca. 3 weeks totally). Stereochemistry at C5 and C6 was assigned on the basis of Brown's study on asymmetric synthesis of diastereomeric 1-(2-cyclohexenyl)-1-alkanols.[64]

Scheme 6. Synthesis of Keto Diene **45**.



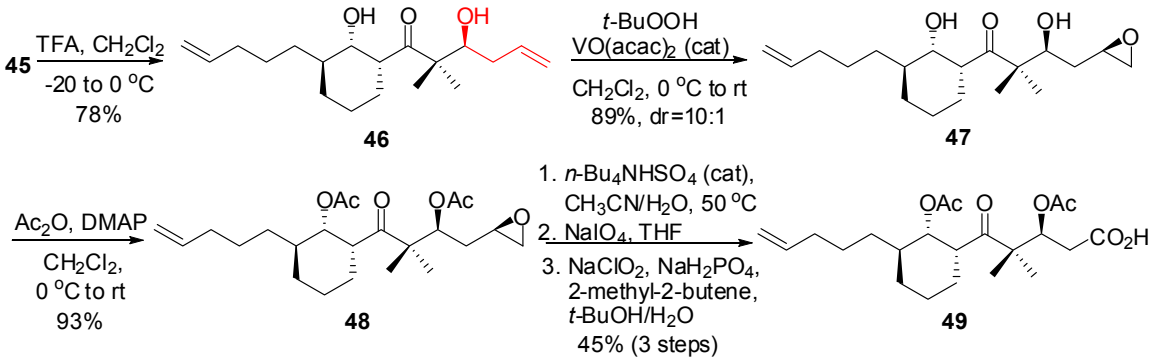
With this chemistry in hand, the next phase involved crucial stereoselective epoxidation followed by regioselective oxirane ring opening. For this purpose, model studies were performed to prove the feasibility of the strategy. Alcohol **41** was epoxidized by the vanadium-catalysis strategy to provide the hydroxy epoxide **42** in 93% yield (*dr*>20:1 by ^{1}H NMR), while the following copper-catalyzed epoxide opening with Grignard reagent furnished diol **43** in 90% yield and only one isomer was isolated (Scheme 6). It is worth noting that an excess of Grignard reagent (8-9 equiv) was required to reduce the potential side product, bromohydrin.[74] Selective silylation of the sterically less hindered OH

group in **43** furnished silyl ether **44** (85% yield). The relative stereochemistry of compound **44** was confirmed on the basis of NOESY experiments, while this assignment was confirmed by comparisons with its analogue **73** (Scheme 15) whose stereochemistry was determined by X-ray crystallography of its derivative. In practice, the conversion from **41** to **44** could be completed in 93% yield over three steps without purification of the intermediates **42** and **44**. To finish scheme 6, the subsequent Swern oxidation converted the secondary alcohol into ketone **45** in quantitative yield.

This is clear that aldehyde **40** has obvious advantages over aldehyde **39** in terms of the allylboration step. However, the application of aldehyde **40** raised a second challenging problem of differentiating between the two terminal olefins with high structural similarity in **45**. As will be shown, the right terminal olefin would be selectively converted to a carboxylic acid. Fortunately, we noticed that there is a hydroxy group at the homoallylic carbon of the right olefin in **45**. With this scenario in mind, we turned our attention to the hydroxy directed epoxidation giving a carboxylic acid precursor. To pursue this strategy, desilylation of **45** with trifluoroacetic acid afforded diol **46** (78% yield).[34] Subsequently, vanadium catalyzed chemoselective epoxidation[66] of **46** led, as expected, to β-hydroxy epoxide **47** in 89% total yield as a mixture of two diastereomeric epoxides (ca. 10:1 by ^{1}H NMR). The stereochemistry of the epoxide is tentatively defined as the proposed model by Mihelich and coworkers.[66a] Considering the following cleavage of the epoxide, the diastereomeric epoxides underwent the next step without separation.

At this stage, we initially attempted to reinstall the TBS silyl ether on **47** following with the original synthetic plan (Scheme 1). However, all attempts with classical conditions failed to give satisfactory results. For instance, when epoxy alcohol **47** was exposed to *tert*-butyldimethylsilyl chloride (TBSCl),[75] over 90% of starting epoxide was recycled, while increasing the temperature led to the epoxide opening by chloride[76] and other complex mixtures. In the case of the more active TBSOTf, complex mixtures were achieved with a major furan product derived from the intramolecular epoxide opening by β-hydroxyl (The structure of the furan product was undefined).

Scheme 7. Preparation of Keto Acid **49**.

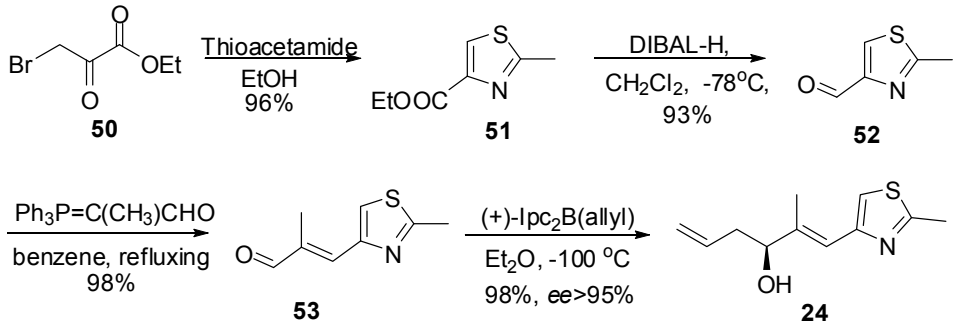


Thus, at this point we temporarily gave up the TBS silyl ether, and chose instead to use acetate as protection for the alcohol. Fortunately, acetyl epoxide **48** was cleanly obtained in 93% yield by treatment of alcohol **47** with acetic anhydride and 4-dimethylaminopyridine (DMAP). At this stage, it was timely to transfer the primary epoxide to the carboxylic acid. This conversion was accomplished by a three step sequence. The epoxide first underwent tetrabutylammonium bisulfate catalyzed hydrolysis,[77] followed by $NaIO_4$ cleavage of the resulting diol to furnish

an aldehyde intermediate. Purification of the aldehyde via silica gel flash column chromatography was unmanageable due to its instability. Thus, an immediate Pinnick oxidation[78] of the crude aldehyde with $NaClO_2$ in the presence of 2-methyl-2-butene and NaH_2PO_4 in *t*-BuOH/H_2O provided the desired carboxylic acid **49** in 45% yield over three steps (Scheme 7).

The stage was now set to construct the thiazole-containing secondary alcohol **24**. The synthesis of this terminal alkene was conducted following a literature reported procedure[34, 79] as summarized in Scheme 8. Condensation between bromide **50** and thioacetamide gave thiazole derivative **51** (96% yield), followed by DIBAL-H reduction and Wittig olefination to afford aldehyde **53** in 91% yield (2 steps). The aldehyde was converted to alcohol **24** in 98% (*ee*> 95% by Mosher ester) by Brown's allylboration protocol.[72]

Scheme 8. Synthesis of Alcohol **24**.



With the appropriate building bocks at hand, our attention would next be directed to the feasibility of the olefin metathesis strategy. Therefore, the coupling of alcohol **24** with the previously described acid **49** was performed under the influence of 1-ethyl-3-((dimethylamino)propyl)carbodiimide hydrochloride (EDCI) and DMAP to the proposed metathesis precursor **54** in 58% yield as depicted in

Scheme 9. In this coupling reaction, a serious β-elimination from the β-acetate of the carboxylic acid was responsible for the mild yield. However, this β-elimination was completely suppressed by a modified Yonemitsu-Yamaguchi protocol,[80] giving ester **54** in 86% yield. Exposure of **54** to metathesis catalysts **58-61** (Scheme 10) under highly dilute conditions resulted in clean formation of a single *trans*-product **55** (*J*=14.4 Hz) (Table 3). Grubbs catalysts **58** and **59** with Hoveyda catalyst **61** gave the *trans*-product in high yields, while the reaction seems to be inactive with Hoveyda catalyst **60** (Entry 5, Table 3). It has been widely realized that the *E/Z* selectivity of the ring closure metathesis depends on many factors including substrate, solvent, temperature and concentration.[81] In this specific case, attempts to modify the geometric outcome of the reaction by choosing solvents and temperatures were temporarily unsuccessesful (Table 3).

Scheme 9. Synthesis of **54** via Olefin Metathesis

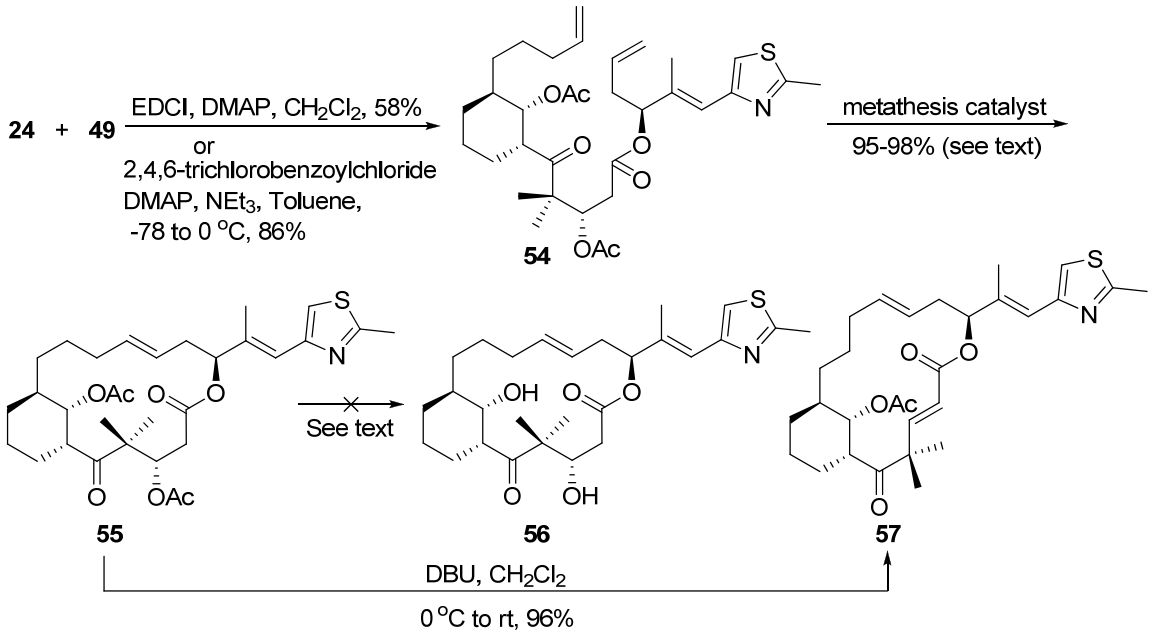
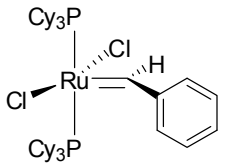


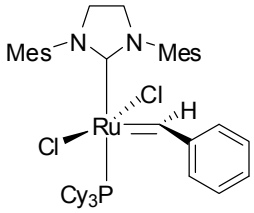
Table 3. RCM Studies of **54** on Basis of Different Conditions

Entry	Catalysts	Conditions	Yields (%)
1	**58**	CH_2Cl_2, rt, 12h	84
2	**58**	Toluene, 80 ^oC, 12h	76
3	**59**	CH_2Cl_2, rt, 12h	100
4	**59**	Toluene, 80 ^oC, 12h	100
5	**60**	CH_2Cl_2, rt, 12h	<5
6	**61**	CH_2Cl_2, rt, 12h	95

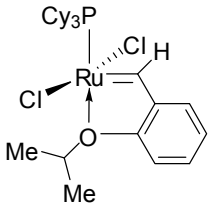
Scheme 10. Structures of Metathesis Catalysts.



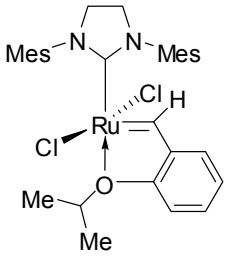
58: G1Grubb's Cat.



59: G2 Grubbs Cat.



60: G1 Hoveyda Cat.



61: G2 Hoveyda Cat.

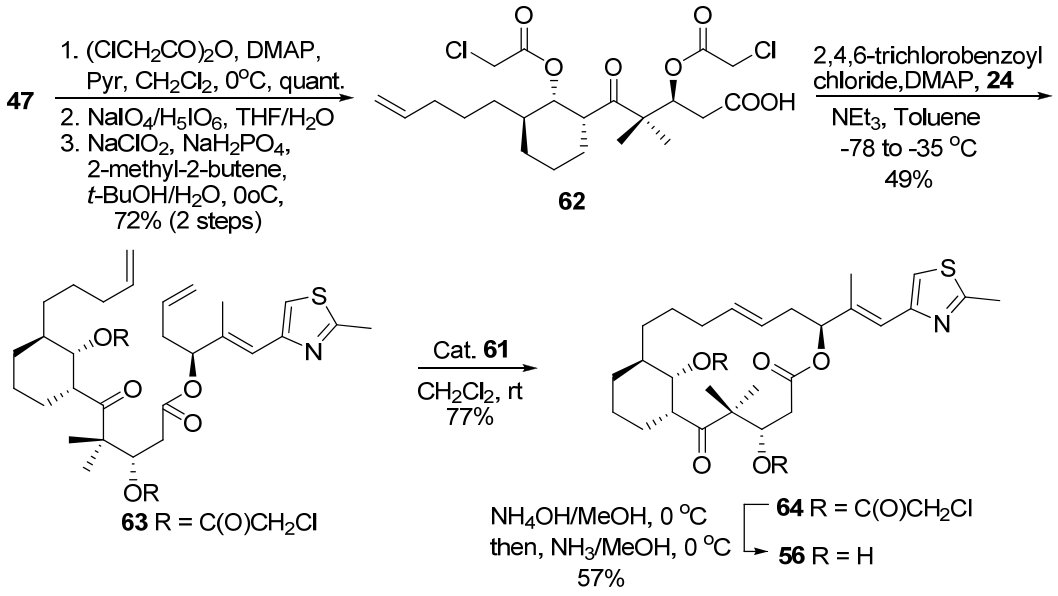
The disheartening results from olefin metathesis temporarily directed our attention to the 12,13-*trans*-6,8-bridged EpoC (**56**, Scheme 9). Early SAR studies of epothilones have suggested that nonnatural epothilone analogue 12,13-*trans*-EpoC (**13**, Figure 6) was only slightly less active then the natural EpoC.[32, 44] The C6-C8 bridged analogue **56** could provide the interesting structural information that we pursued in the program. With this scenario in mind, we turned to the deacylation of **55** (Scheme 9). Surprisingly, at no point were we able to accomplish this deprotection to produce the dihydroxyl lactone. In all cases, either unreacted acetate was recovered or decomposition took place. One of the major side reactions arising from the deacylation was the β-elimination leading to lactone **57**, which could be alternatively prepared from **55** in 96% yield by treatment with 8-diazabicyclo[5.4.0]undec-7-ene (DBU).[50] This β-elimination took place even in extremely mild condition such as potassium cyanide (KCN)

catalyzed transesterification which is suitable for acid- or base-sensitive deacylation.[82] This elimination was documented and the approximate 180^{o} torsion angle of the C2-C3 could be responsible for this elimination.[21, 50]

The infeasible deacylation could also arise from the competition between hydrolysis and elimination of the β-acetate. In this specific case, the β-elimination could be much faster than the hydrolysis of the acetate. To facilitate the deacylation, we envisioned introducing a substituent to the acetyl which could increase the acetyl hydrolysis rate while not increasing its ability as a leaving group. With this scenario in mind, chloroacetyl was introduced, which is 350-700 fold more quickly hydrolyzed than the acetyl depending on different intermediates.[83] As shown in Scheme 11, chloroacetate intermediate was first prepared from epoxy alcohol **47** in quantitative yield. Subsequent exposure of this intermediate to $NaIO_4/H_5IO_6$ in aqueous THF generated an aldehyde [84] that was then followed by Pinnick oxidation[78] to furnish the carboxylic acid **62** in 72% overall yield. The esterification between alcohol **24** and acid **62** was achieved in mild yield via the modified Yonemitsu-Yamaguchi protocol,[80] while only trace amounts of product was detectable through the classical EDCI coupling procedure together with large amounts of β-eliminated side products. With no surprise, the following olefin metathesis cleanly led to *trans*-product **64** (*J*=14.8 Hz). For example, a 72% yield of **64** was achieved with Hoveyda's second generation metathesis catalyst **61**. After screening various conditions to the crucial deacylation step, we were lucky to discover that it was successfully performed by careful treatment of **64** with ammonium hydroxide in methanol (1/10,

v/v) followed by treatment with ammonia in methanol to afford the 12,13-*trans*-6,8-bridged EpoC analogue **56** in 57% yield (Scheme 11).

Scheme 11. Synthesis of Epothilone **56**.



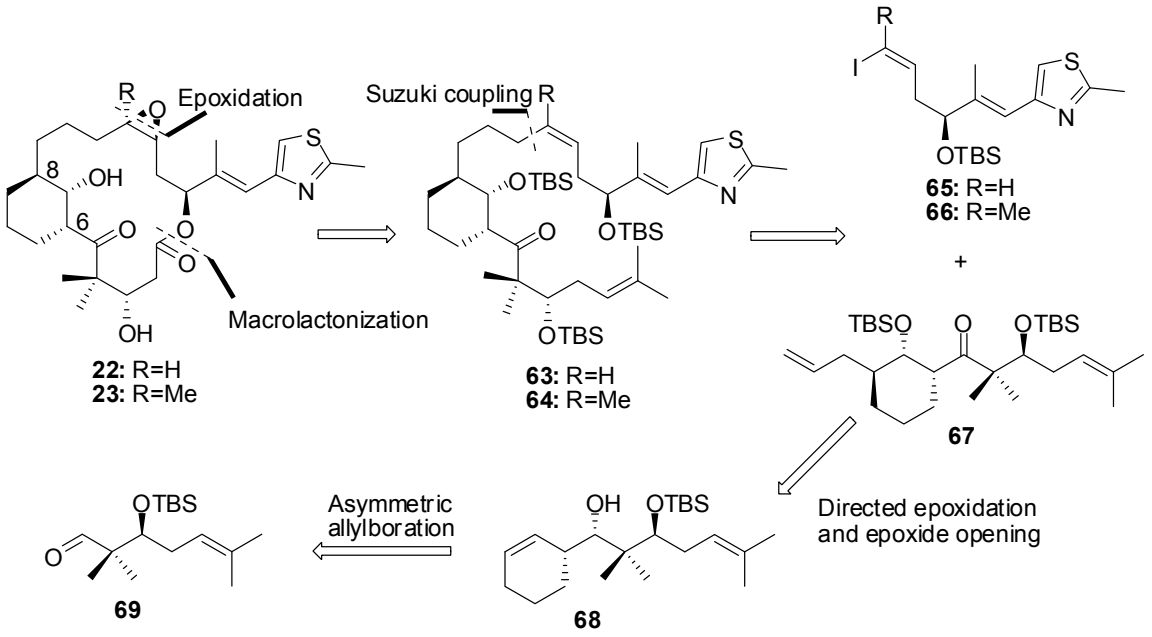
To end the program, we initially attempted to regioselectively isomerize the C12-C13 *trans* double to the desired *cis* geometry.[85] Unfortunately, in all attempts, such as photoirradiated isomerization,[86] iodine-catalyzed free radical isomerization,[85, 87] and Vedejs isomerization,[88] no workable amounts of isomerized product was separated (assuming isomerization occurred). In many cases, either unreacted *trans*-olefin was recovered or decomposition happened.

1.2.3 Second Generation Synthesis via Suzuki Coupling

As discussed above, some surprising limitations surfaced in the ring forming olefin metathesis reaction. Although there is still much space to optimize reaction conditions and alternative catalysts such as the molybdenum based Schrock catalyst,[89] it was recognized even in the epothilone literature[33, 35, 90] that the

stereochemical outcome of the RCM process is highly substrate dependent. With these discouraging results, it was imperative that we discover a reliable method to access the desired *Z*-stereochemistry. An important alternative to introduce the Z-double bond at C12-C13 in epothilone synthesis was Danishefsky's *B*-alkyl Suzuki coupling strategy.[36, 91] Given the widespread application of this strategy in epothilone synthesis, it was not unnatural that we proposed a Suzuki coupling based approach to our targets.

Scheme 12. G2 Retrosynthesis for Bridged Epothilones **22** and **23**

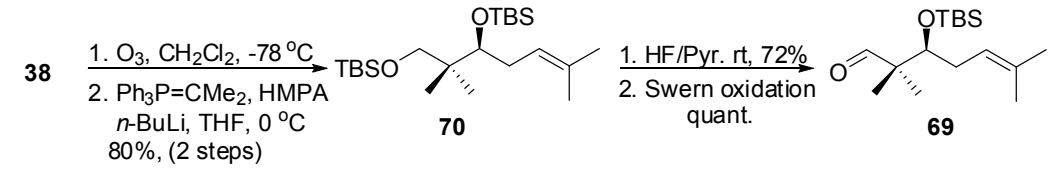


The retrosynthesis for bridged epothilones **22** and **23** via the second generation Suzuki coupling strategy is summarized in Scheme 12. The key disconnection along with this route is at the C11-C12 bond, leading to vinyl iodide **65** and olefin **67** as the two Suzuki coupling partners. The keto diene **67** was conceived to derive from aldehyde **69** via intermediate **68** following a similar sequence for the synthesis of dienyl ketone **45** in Scheme 6. Different the

previous keto diene **45**, a gem dimethyls were introduced to the right terminal olefin of keto diene **67** in order to easily differentiate the two olefins.

To pursue this modified route, aldehyde **69** was accomplished from silyl ether **38** as shown in Scheme 13. Ozonolysis of **38** followed by a Wittig reaction furnished the desired *gem*-dimethyl olefin **70** in 80% yield (2 steps).[92] HF/pyridine mediated selective desilyation of the primary silyl ether from **70** was achieved in 72% yield affording the hydroxy intermediate, which was subjected to Swern oxidation to give aldehyde **69** in quantitative yield.

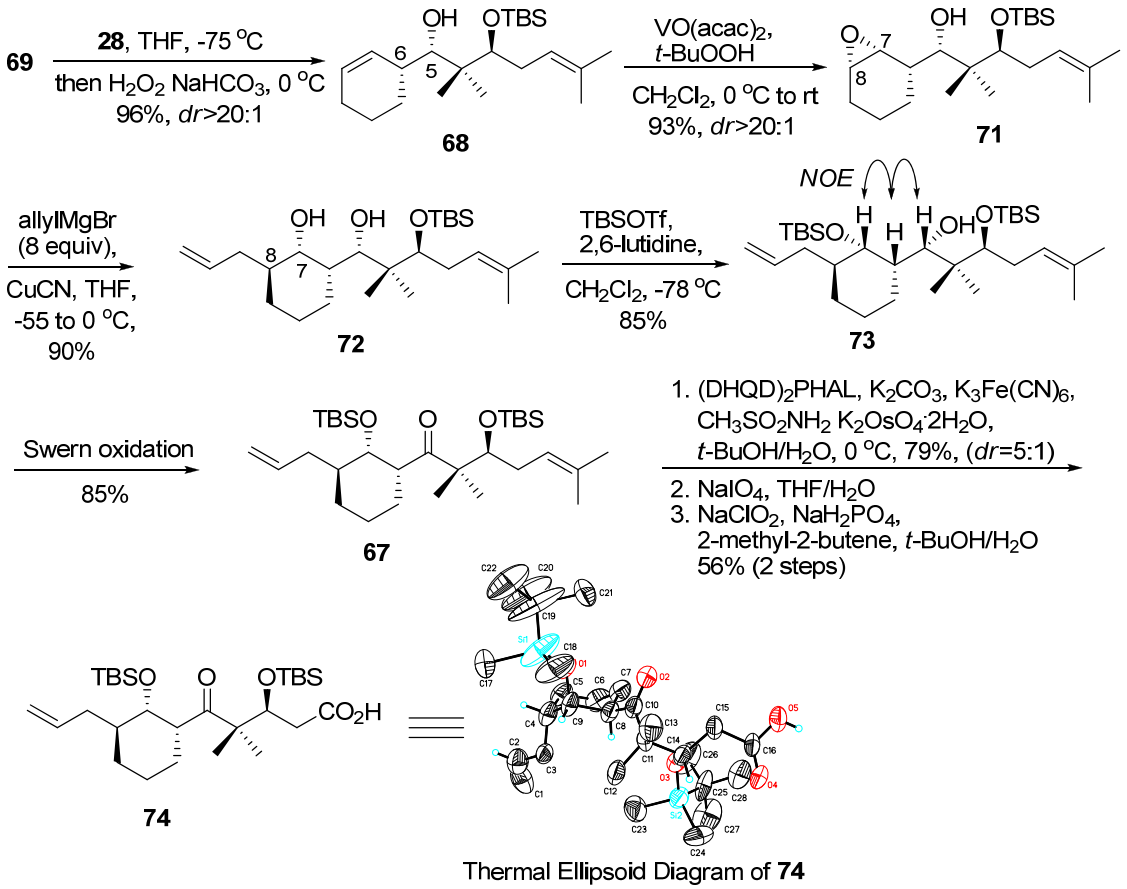
Scheme 13. Synthesis of Aldehyde **69**



The construction of Suzuki coupling precursor **67** proceeded through a sequence of steps as shown in Scheme 14. Allylboration of aldehyde **69** with freshly prepared *B*-2-cyclohexen-1-yldiisopinocampheylborane **28** gave homoallylic alcohol **68** in 96% yield (*dr*>20:1 by ^{1}H NMR). Not surprisingly, this allylboration was again unexpectedly sluggish, however, with satisfactory yield and selectivity. Stereochemistry at C5 and C6 was assigned on the basis of Brown's model study[64] and would be further confirmed later by NOESY and X-ray crystallography of compounds derived from **68**. Thus, using previously proved vanadium-catalysis strategy, alcohol **68** was converted to epoxy alcohol **71** in 93% yield (*dr*>20:1 by ^{1}H NMR). Reaction of epoxide **71** with allylmagnesium bromide in copper catalyzed fashion furnished epoxide-opened product **72** (90%

yield) along with a trace of C7-alkylated isomer and bromohydrin. The sterically less hindered hydroxyl group from **72** was selectively converted to TBS silyl ether **73** in 85% yield. At this point, a NOESY analysis was executed to confirm the relative stereochemistry (Scheme 14). Finally, the sterically hindered secondary alcohol in diene **73** was transformed to dienyl ketone **67** by Swern oxidation in 85% yield.

Scheme 14. Synthesis of Suzuki Coupling Partner **67**.



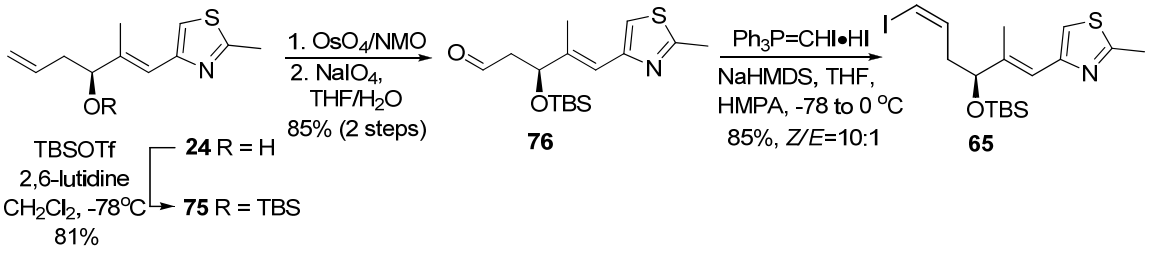
Thermal Ellipsoid Diagram of **74**

To further confirm the absolute configuration, olefin **67** was converted to carboxylic acid **74** which was fortunately isolated as a white solid. Thus, the trisubstituted olefin was selectively dihydroxylated under Sharpless asymmetric dihydroxylation conditions,[93] leading to a mixture of diastereomeric diols (79%

yield, ca. 5:1 ratio by ^{1}H NMR). Without separation, the resulting diol mixture was exposed to $NaIO_4$ mediated glycol cleavage and subsequent Pinnick oxidation[78] to furnish the corresponding carboxylic acid **74** in 56% yield over two steps. Single crystals of **74** were obtained from hexanes. X-ray crystallography confirmed that the desired stereochemistry had been maintained (Scheme 14).

The pursuit of Suzuki cross coupling required the synthesis of another coupling partner, vinyl iodide **65**. The chemistry to prepare **65** is illustrated in Scheme 15. In accordance with the literature procedure,[34] previously described alcohol **24** was converted to aldehyde **76** in 69% yield (3 steps) by exposure of **24** to TBSOTf and 2,6-lutidine, followed by as osmium tetraoxide (OsO_4) catalyzed chemoselective dihydroxylation and $NaIO_4$ mediated cleavage of the resultant diols. The conversion of aldehyde **76** into vinyl iodide **65** was performed under Stork and Zhao olefination protocol[94] in 85% yield (*Z/E*=10/1; the minor isomer (*E*) was removed in subsequent steps). The coupling constant observed from ^{1}H NMR (^3J = 7.5 Hz) supported the assignment of *cis* geometry of resultant double bond.[94]

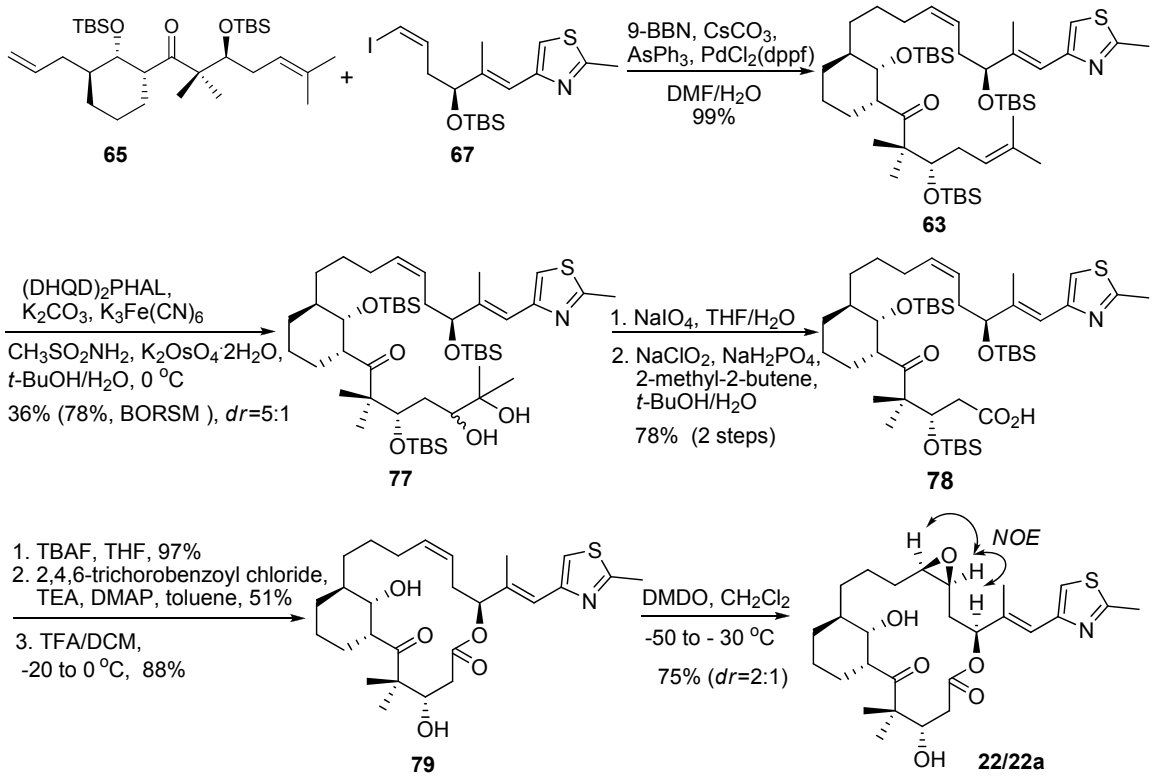
Scheme 15. Synthesis of Vinyl Iodide **65**.



With the requisite coupling precursors in hand, the final steps in the synthesis of bridged epothilone **22** were carried out as depicted in Scheme 16. After

regioselective hydroboration with 9-BBN, olefin **67** was coupled with vinyl iodide **65** following an approach reported by Danishefsky *et al.*[36] to furnish *cis*-olefin **63** (*J*=10.8 Hz) in 92% yield. A crucial regioselective dihydroxylation of triene **63** was proceeded under Sharpless conditions to convert the *gem*-dimethyl olefin to diol **77** as a mixture of diastereomers (36% yield, 78% BORSM, ca. 5:1 ratio by ^{1}H NMR). The stereochemistry of the hydroxyl group was undefined. Cleavage of the diols to carboxylic acid **78** (78%, 2 steps) was conducted via a similar sequence utilized in the preparation of carboxylic acid **74** (Scheme 16).

Scheme 16. Complete Synthesis of C6-C8 Bridged Epothilone **22**.

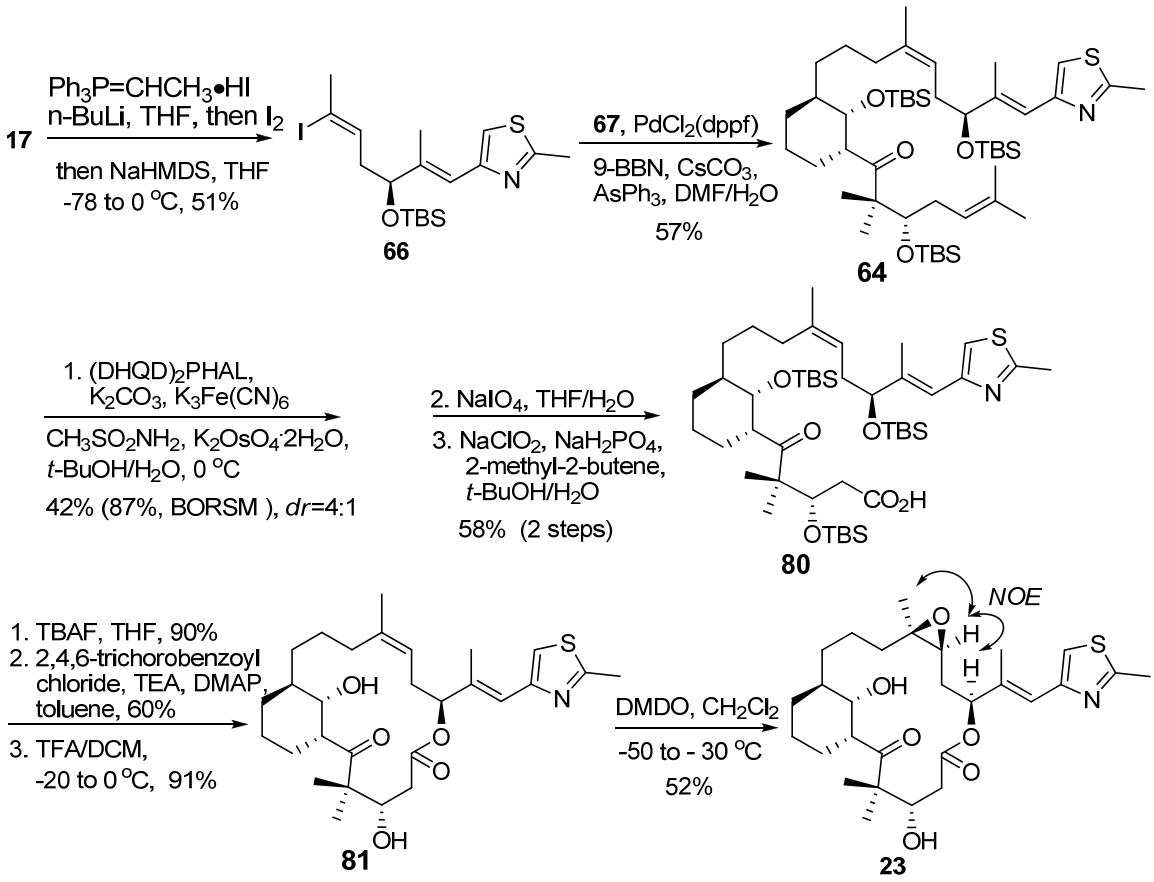


To finish the synthesis of **22**, keto acid **78** was converted to dihydroxy lactone **79** by employing a procedure utilized by Nicolaou *et al.* in the total synthesis of epothilone A/B.[34] Selective desilylation with tetra-*n*-butylammonium fluoride

(TBAF), followed by Yamaguchi lactonization and global desilylation in the presence of freshly prepared trifluoroacetic acid solution in CH_2Cl_2 (v/v, 1/4) gave dihydroxy macrolactone **20** in 44% overall yield, which is an EpoC analog.[23-26] Finally, we were pleased to obtain the C6-C8 bridged epothilone **22** as a mixture of **22** and its *cis*-epoxide diastereomer **22a** (75% total yield, ca. 2:1 ratio, ^{1}H NMR) by treatment with 3,3-dimethyldioxirane (DMDO) as described by Danishefsky.[36] Fortunately, these two diastereomers were separable by preparative thin-layer chromatography. The stereochemistry of the epoxide was determined by 1D and 2 D NOE analysis (Scheme 16).

Having demonstrated the route to C6-C8 bridged EpoA analogue **22**, we turned to the synthesis of the EpoB analogue **23**. To this end, a literature reported Wittig reaction of aldehyde **17** generated vinyl iodide **66**,[90, 95] which in turn was subjected to Suzuki cross-coupling with fragment **67** to give triene **64** in 57% yield following the conditions described above for **63** (Scheme 17). Exposure of triene **64** to Sharpless asymmetric dihydroxylation condition furnished a regioselectively dihydroxylated intermediate (42% yield, 87% yield BORSM, *dr*=4:1). The later diols were cleaved with $NaIO_4$ to give aldehyde which underwent Pinnick oxidation to give keto acid **82** (58% yield, two steps). After selective desilylation of the allylic silyl ether in the presence of TBAF (90% yield), the hydroxy keto acid was exposed to Yamaguchi lactonization (60% yield) and desilylation (91% yield), leading to dihydroxy keto lactone **81** which is a C6-C8 bridged EpoD analogue. Finally, EpoB analogue **23** was achieved as a single epoxide isomer by treatment with DMDO in 52 % yield.

Scheme 17. Synthesis of C6-C8 Bridged Epothilone **23**.



1.3. Biological Evaluation of Analogs

All the C6-C8 bridged epothilone analogs (Figure 11) were subjected to the preliminary cytotoxicity studies using an assay against A2780 human ovarian cancer cell line,[96, 97] and Taxol® (**5**) was used as a control instead of natural epothilones because of their commercial availability and similar toxicity. The cytotoxicity data is shown in Table 4, and leads to the following primary conclusions:

1. Basically, C6-C8 bridged epothilones exhibit 55-500 fold less potency against A2780 human cancer cell line in comparison with the Taxol® **5** (Entry 1, Table 4), while compound **22a** and **79** loss their potency around 1000 fold. In contrast with EpoD (Entry 2, Table 4), these bridged epothilones exhibited 30-250 fold less potency.

2. Comparing the potency of compounds **22** (bridged EpoA), **23** (bridged EpoB), **79** (bridged EpoC) and **80** (bridged EpoD), it's clear that they possess such a potency sequence: **23**>**80**>**22**>**79**. This sequence matches well with that from the natural epothilones:[39] EpoB>EpoD≈EpoA>EpoC. In addition, the fact that compound **22a** showed much less potency than **22** also agrees with the previous conclusion that the α-epoxide isomers are less potent than the natural EpoA/B with a β-epoxide.[40]

3. Compound **57** with a *trans*-double bond at C12-C13 showed better cytotoxicity than compound **70** which is a bridged EpoC. This

phenomenon further confirmed SAR property of epothilones that the nonnatural 12,13-*trans* epothilone analogs would retain the biological activity.[21c]

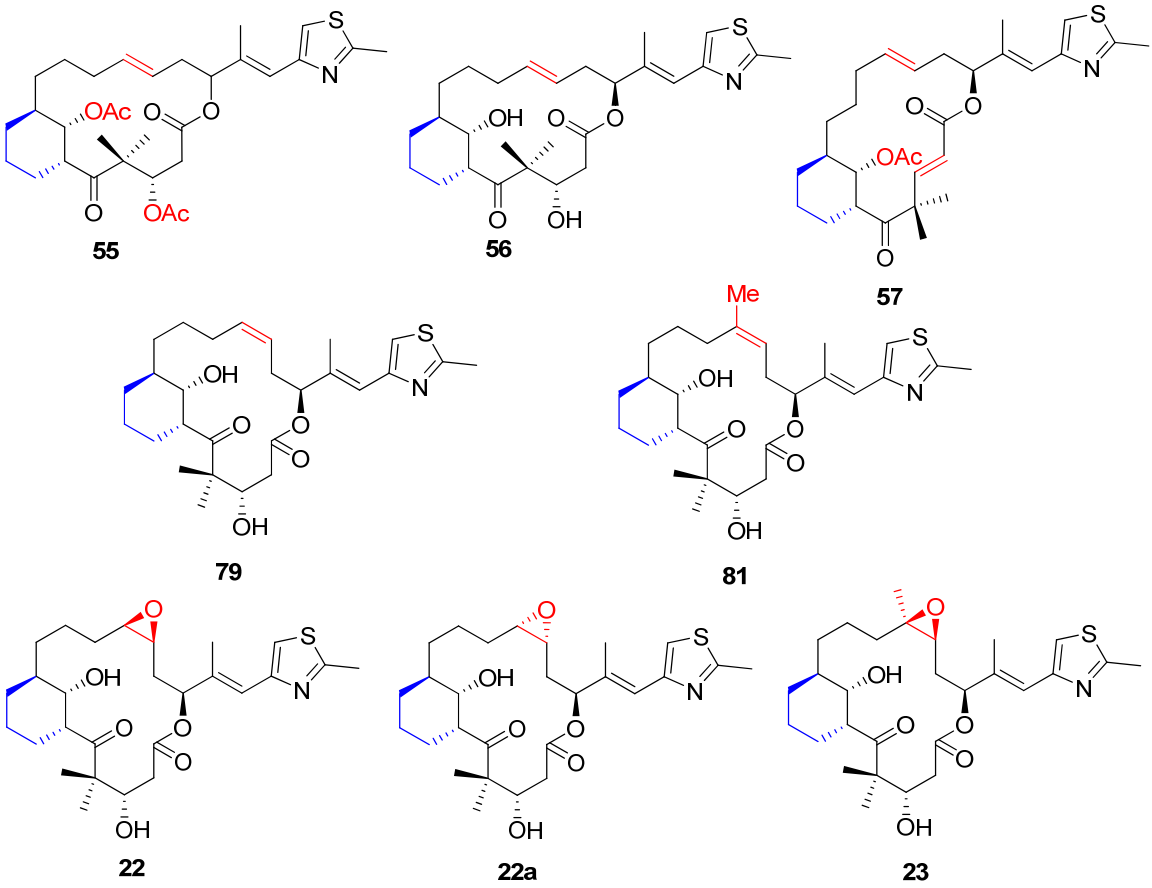


Figure 11. Synthesized C6-C8 bridged epothilone analogs

4. Surprisingly, compounds **55** and **56** with acyl protections showed similar or higher potency. These data could provide new insight into the roles of the two hydroxy groups at C3 and C8. It has been suggested that the C3-OH could be not necessary to maintain the potency and introduction of *E* olefin at C2-C3 maintain considerable activity, which is in agreement with the potency from compound **56** (Entry 7, Table 4).

However, how about the C8-OH? This hydroxy with a 8*S*-configuration has been recognized to be essential to bioactivity.[40c] Considering these new data, further study would be encouraged to probe the property of C8-OH in SAR profiles of epothilone family.

Table 4. Biological activity of Taxol and C3-C6 bridged epothilones against A2780 cancer cell line

Entry	Compd.	Cytoxicity (μM)		Entry	Compd.	Cytoxicity (μM)
1	**5** (Taxol®)	0.02		6	**55**	5.6
2	**12** (EpoD)	0.04		7	**56**	1.1
3	**22**	8.5		8	**57**	9.6
4	**22a**	24.3		9	**79**	19.0
5	**23**	3.6		10	**80**	5.1

To more precisely understand the contribution of the C6-C8 bridge, further experiments including cell line assays and tubulin assays with natural EpoA/EpoB as controls are necessary. Efforts along these lines are currently being pursued.

1.4. Conclusion

In conclusion, a series of conformationally restrained epothilone analogs with a short bridge between methyl groups at C6 and C8 were designed to mimic the binding pose determined for our recently reported EpoA-microtubule binding model. A versatile synthetic route to these bridged epothilone analogs has been successfully devised and implemented. The key stereochemistry within the bridged C6-C8 sector was controlled by asymmetric allyboration followed by hydroxy- directed epoxidation and regiocontrolled opening of the resultant epoxide.

These bridged epothilones were evaluated for their biological activity against the A2780 human ovarian cancer cell line. Unfortunately, the cytotoxicity data suggested these epothilone analogs were considerably less potent than taxol. In order to fully understand the conformational importance of C6-C8 section, additional bioactivity data of these bridged epothilones and the synthesis of novel C6-C8 conformational modified epothilone analogs are required. Also the computational model for epothilone binding must be refined to be a better predictor.

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 ($CDCl_3$) 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 ($CDCl_3$). High resolution mass spectra (HRMS) were obtained on a JEOL JMS-SX102/SX102A/E or Thermo Finnigan LTQ-FTMS instrument.

Preparation of Alcohol 29. To a stirred suspension of (-)-Ipc_2BH (1431.5 mg, 5.0 mmol, 1.0 equiv) in THF (20 mL) at -25 ^{o}C was added cyclohexa-1,3-dinene (440.7 mg, 5.5 mmol, 1.1 equiv). [The stored (-)-Ipc_2BH was prepared based on the reported procedure by Brown[98, 99] and Paterson.[100] To a stirred solution of (+)-α-pinene (20 mL, 125 mmol) in dry THF (15 mL) under argon, borane-methyl sulphide complex (5 mL, 50 mmol, 10 M in DMS) was added quickly at 0 ^{o}C. After

stirring for 5 minutes at that temperature, stirring was ceased and the clear solution allowed to stand at room temperature for >16 h, during which time crystallisation occurred. The reaction mixture was then cooled to 0 ^{o}C for 2 h and the supernatant liquid removed *via* cannula. The white crystalline mass of (-)-Ipc_2BH was broken up with a needle, washed with ice-cold pentane (3 x 20 mL), and dried under a stream of argon to give an 80-90% yield.] After being stirred overnight at -25 ^{o}C, the solid (-)-Ipc_2BH disappeared to give a clean solution of borane **28** in THF which was cooled to -100 ^{o}C and treated with pivalaldehyde (430.7 mg, 5.0 mmol, 1.0 equiv). The contents were stirred at -100 ^{o}C for 2 h, then warmed to -78 ^{o}C until the disappearance of the aldehyde from TLC (ca. 10 h). Methanol (0.5 mL) was added slowly at -78 °C, and the reaction mixture was allowed to warm to 0 ^{o}C, followed with slow addition of saturated aqueous $NaHCO_3$ solution (7.5 mL) and H_2O_2 (2 mL of 30% solution in H_2O) consequently. The resulting mixture was heated to 45 ^{o}C and was stirred for 36 h at that temperature. After cooling to room temperature, the mixture was extracted with hexanes (2 x 20 mL), and the combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (gradient elution, hexanes →10/1, hexanes/ethyl acetate) to provide the product **29** (592.7 mg, 70%) as a colorless oil: R_f = 0.63 (Hexanes/ethyl acetate, 4/1); $[\alpha]^{22}_{D}$ –3.4 (*c* 1.0, $CHCl_3$), Lit.[64b] + 6.83 *l* 0.5, neat; IR (thin film) ν_{max} 3470 (br), 3015, 2953, 2872, 1706, 1652, 1478, 1401, 1363, 1297, 1254, 1193, 1173, 1139, 1081, 1054, 984, 961, 938, 895, 860, 718 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91-5.86 (m, 1H, C*H*=CH), 5.48-5.36 (m, 1H, CH=C*H*),

3.29(dd, *J* = 3.8, 3.2 Hz, 1H, C*H*OH), 2.52-2.44 (m, 1H, C*H*CHOH), 1.99-1.94 (m, 2H), 1.82-1.74 (m, 2H), 1.62-1.44 (m, 2H), 1.39 (d, *J* = 3.8 Hz, 1H, OH), 0.98 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.79, 130.66, 82.24, 38.83, 35.52, 27.41, 24.92, 23.05, 22.18; HRMS calcd for $C_{11}H_{19}O$ 167.14359 $[M - H]^+$, found 167.14252. The analytical data are in agreement with those reported in the literature but not the $[\alpha]_D$.[64b]

Preparation of Epoxy Alcohol 30. Procedure A: To a solution of olefin **29** (33.7 mg, 0.2 mmol, 1.0 equiv) in CH_2Cl_2 (3 mL) was added *m*-CPBA (51.77 mg, 0.3 mmol, 1.5 equiv) at 0 ^oC. The resultant mixture was warmed to room temperature and stirred for 12 h. The solvent was removed under reduced pressure, and the residue was subjected to flash column chromatography (hexanes/ethyl acetate, 4/1) to afford the epoxy alcohol **30** (30.8 mg, 84%) as a colorless oil. ^1H NMR spectroscopy suggested it was a single isomer. **Procedure B:** To a blue-green suspension of $VO(acac)_2$ (2.65 mg, 0.01 mmol, 5 mol%) in anhydrous CH_2Cl_2 (3 mL) at 0 ^oC was added a solution of olefin **29** (33.7 mg, 0.2 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL). After being stirred for 10 min, anhydrous *tert*-butyl hydroperoxide (0.6 mL, ca. 5.0 M in decane, 3.0 mmol, 1.5 equiv) was added quickly at 0 ^oC. After vigorous stirred for 1 h at 0 ^oC, the resulting dark solution was warmed to room temperature and stirred overnight. Aqueous $NaSO_3$ solution (10 mL, 5%) was added to quench the reaction. After stirring for 10 minutes, the organic phase was separated, and the aqueous phases was further extracted with CH_2Cl_2 (2 x 10 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was

purified with flash column chromatography (hexanes/ethyl acetate, 4/1) to provide hydroxyl epoxide **29** (32.4 mg, 88%) as a colorless oil. ^{1}H NMR spectroscopy suggested it was a single isomer: R_f = 0.41 (Hexanes/ethyl acetate, 4/1); $[\alpha]^{22}_{D}$ +11.9 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 3489 (br), 2953, 2868, 1706, 1640, 1482, 1451, 1363, 1309, 1270, 1243, 1189, 1127, 1089, 1054, 988, 950, 899, 857, 834, 741 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.64 (t, *J* = 2.3, 2.3 Hz, 1H, C*H*OH), 3.17 (t, *J* = 4.3, 4.3 Hz, 1H, CH_2C*H*O(epoxide)CH), 3.11-3.08 (m, 1H, CH_2CHO(epoxide)C*H*), 2.27 (d, *J* = 2.4 Hz, 1H, OH), 2.12 (tdd, *J* = 8.8, 6.3, 2.4, 2.4 Hz, 1H, C*H*CHOH), 1.92-1.83 (m, 1H), 1.82-1.71 (m, 1H), 1.60-1.39 (m, 3H), 1.27-1.16 (m, 1H), 0.98 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 81.90, 57.82, 52.72, 36.38, 35.60, 27.21, 23.64, 20.53, 19.81; HRMS calcd for $C_{11}H_{21}O_2$ 185.15415 $[M + H]^+$, found 185.15304.

Preparation of Diol 31. A freshly prepared 4-pentenylmagnesium bromide (2 mL, ca.0.6 M in Et_2O, 1.2 mmol, 6 equiv) was added dropwise to a suspension of hydroxy epoxide **30** (37 mg, 0.2 mmol, 1.0 equiv), CuCN (1.72 mg, 0.02 mmol, 10 mol%) in THF (0.5 mL) at -55 °C with vigorous stirring. [4-pentenylmagnesium bromide solution in Et_2O was prepared according to a modified literature procedure: [101] To a vigorous stirred suspension of magnesium turnings (199.3 mg, 8.2 mmol) in Et_2O (8 mL) with trace of I_2 as an activator was added drops of 5-bromo-1-pentene. After the reaction being initiated, the rest of 5-bromo-1-pentene (1192.2 mg, 8.0 mmol) was added dropwise to keep the mixture refluxing. After being stirred for 1 h at room temperature, the corresponding Grignard reagent was produced as a 0.6 M diethyl ether solution].

The solution was warmed to -10 °C over 1 h and stirred another 2.5 h at this temperature. Saturated aqueous NH_4Cl was added with vigorous stirring to quench the reaction. The mixture was extracted with Et_2O (3 x 10 mL). The combined extracts were dried over $MgSO_4$ and concentrated. The resultant residue was purified by flash column chromatography (gradient elution, hexanes →2/1, hexanes/ethyl acetate) to furnish the diol **31** (45.3 mg, 89%) as a colorless oil: R_f = 0.42 (hexanes/ethyl acetate, 2/1); $[\alpha]^{22}{}_D$ -17.3 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 3389 (br), 3080, 2934, 2864, 1826, 1702, 1640, 1459, 1366, 1320, 1285, 1243, 1204, 1166, 1096, 980, 911, 706 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.78 (tdd, *J* = 16.9, 10.2, 6.6, 6.6 Hz, 1H, C*H*=CH_2), 5.01-4.91 (m, 2H, CH=C*H*$_2$), 3.65 (s, 1H), 3.35 (s, 1H), 2.88 (bs, 1H, OH), 2.63 (bs, 1H, OH), 2.03 (q, *J* = 6.8, 6.8, 6.7 Hz, 2H, C*H*$_2$CH=CH_2), 1.80-1.59 (m, 4H), 1.51-1.22 (m, 8H), 0.93 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.99, 114.69, 84.21, 78.39, 41.21, 36.91, 35.97, 34.04, 29.74, 27.41, 27.11, 23.44, 20.43, 20.33; HRMS calcd for $C_{16}H_{31}O_2$ 255.23241 $[M + H]^+$, found 255.23156.

Preparation of Silyl Ether 32. A mixture of alcohol **31** (22 mg, 0.0865 mmol, 1.0 equiv) and 2,6-lutidine (14 mg, 0.13 mmol, 2.0 equiv) in CH_2Cl_2 (2 mL) was treated with TBSOTf (23 mg, 0.0865 mmol, 1.5 equiv) dropwise at -78 °C. The reaction mixture was stirred at -78 °C until all starting material disappeared from TLC (cat. 1 h). After being quenched with saturated aqueous NH_4Cl, the reaction mixture was allowed to warm to room temperature. The organic phase was separated, and the aqueous layer was further extracted with CH_2Cl_2 (2 x 3 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated

under reduced pressure. Purification by flash column chromatography (hexanes/ethyl acetate, 20/1) afforded product **32** (31.4 mg, 85%) as a colorless oil: R_f = 0.32 (hexanes/ethyl acetate, 20/1); $[\alpha]^{22}{}_{D}$ +6.8 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 3578, 3080, 2934, 2860, 1640, 1463, 1409, 1386, 1363, 1305, 1254, 1119, 1069, 1015, 938, 911, 884, 834, 776, 676 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.80 (tdd, *J* = 16.9, 10.2, 6.6, 6.6 Hz, 1H, C*H*=CH_2), 5.04-4.92 (m, 2H, CH=C*H*$_2$), 3.59 (s, 1H, CHOSi), 3.16 (s, 1H, C*H*OH), 2.50 (d, *J* = 1.2 Hz, 1H, OH), 2.05 (q, *J* = 6.6, 6.6, 6.4 Hz, 2H, C*H*$_2$CH=CH_2), 1.79-1.61 (m, 4H), 1.51-1.20 (m, 8H), 0.923 (s, 9H, CH(OH)C(CH_3)$_3$), 0.917 (s, 9H, Si(CH_3)$_3$), 0.11 (s, 3H, Si(CH_3)$_2$), 0.09 (s, 3H, Si(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.95, 114.78, 83.39, 79.84, 41.30, 37.23, 36.65, 34.13, 30.06, 27.51, 27.11, 26.10, 23.89, 21.27, 20.46, 18.21, -3.99, -4.65; HRMS calcd for $C_{22}H_{45}O_2Si$ 369.31888 $[M + H]^+$, found 369.31821.

Preparation of Ketone Olefin 33. To a solution of DMSO (11.6 µL, 0.16275 mmol, 2.4 equiv) in dry CH_2Cl_2 (1.5 mL) was added dropwise oxalyl chloride (13.9 mg, 0.0814 mmol, 1.2 equiv) at -78 °C. After stirring for 30 min at that temperature, a solution of alcohol **32** (25 mg, 0.0678 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (1 mL) was added dropwise. The mixture was stirred for 1.5 h and was carefully treated with triethylamine (38 µL, 0.2712 mmol, 4.0 equiv) at -78 °C. After stirred for another 1.5 h, the reaction was allowed to warm to room temperature, and then saturated aqueous $NaHCO_3$ was added to dissolve the salts. After separation, and the aqueous layer was further extracted with dichloromethane (2 x 2 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution, dried with $MgSO_4$, filtered, and concentrated by rotary

evaporation to afford the crude a yellow oil residue which was purified by flash column chromatography (hexanes/ethyl acetate, 20/1) to provide ketone **33** (24.6 mg, quant) as a colorless oil: R_f = 0.32 (hexanes/ethyl acetate, 20/1); $[\alpha]^{22}{}_D$ -32.7 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 3080, 2953, 2930, 2860, 1706, 1640, 1463, 1444, 1393, 1363, 1309, 1251, 1123, 1085, 1031, 1004, 911, 834, 772, 672 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.81 (tdd, *J* = 16.9, 10.2, 6.7, 6.7 Hz, 1H, C*H*=CH_2), 5.04-4.94 (m, 2H, CH=CH_2), 3.78 (s, 1H, C*H*OH), 3.10 (td, *J* =10.2, 2.8, 2.8 Hz, 1H, CHC(O)), 2.10-1.96 (m, 3H), 1.90-1.75 (m, 2H), 1.52-1.18 (m, 8H), 1.13 (s, 9H, C(O)$C(CH_3)_3$), 0.89 (s, 9H, $SiC(CH_3)_3$), -0.02 (s, 3H, $Si(CH_3)_2$), -0.05 (s, 3H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.52, 139.00, 114.79, 72.24, 45.15, 44.85, 41.19, 34.22, 30.44, 27.44, 26.88, 26.08, 24.41, 24.12, 20.18, 18.26, -4.18; HRMS calcd for $C_{22}H_{43}O_2Si$ 367.30323 $[M + H]^+$, found 367.30228.

Preparation of Compound 34. A mixture of hydroxy epoxide **29** (36.8 mg, 0.2 mmol, 1.0 equiv), *p*-nitrobenzoyl chloride (40.8 mg, 0.22 mmol, 1.1 equiv), DMAP (29.4 mg, 0.24 mmol, 1.2 equiv) and pyridine (0.02 mL) in THF (4.0 mL) was stirred for 5 h at room temperature. The reaction mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography to afford **34** (12 mg, 16%) as a white solid. A needle shape crystal was developed from its solution in hexane for the X-ray crystallography: R_f = 0.52 (Hexanes/ethyl acetate, 4/1); $[\alpha]^{22}{}_D$ +18.7 (*c* 0.48, $CHCl_3$); IR (thin film) ν_{max} 3459 (br), 2957, 2922, 2872, 1702, 1610, 1532, 1467, 1343, 1285, 1243, 1123, 1104, 1015, 992, 953, 872, 842, 718 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.33-8.21 (m, 4H), 4.66 (d, *J* = 3.5 Hz, 1H, C*H*OCOAr), 4.27-4.22 (m, 1H, CHCl),

3.88 (bs, 2H, C*H*O*H*), 2.70-2.65 (m, 1H, C*H*CHOH), 2.14-2.04 (m, 1H), 1.78-1.69 (m, 2H), 1.54-1.44 (m, 2H), 1.34-1.22(m, 1H), 1.06 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.38, 151.05, 135.18, 131.08, 123.99, 84.09, 74.04, 60.43, 36.96, 36.58, 27.59, 26.04, 25.80, 21.62, 19.97; HRMS calcd for $C_{18}H_{25}ClNO_5$ 370.14213 $[M + H]^+$, found 370.14139.

Preparation of Aldehyde 36. A solution of TBSCl (22.6 g, 150 mmol, 1.0 equiv) in anhydrous THF (50 mL) was added at 0 °C over 2 h to a solution of neopentyl glycol (31.2 g, 300 mmol, 2.0 equiv) and *N*,*N*-diisopropylethylamine (52 mL, 300 mmol, 2.0 equiv) in anhydrous THF (200 mL). The resultant mixture was allowed to warm to room temperature. After stirring 12h, the solvent was removed under reduced pressure The residue was diluted with CH_2Cl_2 (150 mL) and washed with saturated aqueous NH_4Cl (2 x 50 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexanes/ethyl acetate, 10/1) to give alcohol intermediate (31.7g, 97%) as a colorless oil; R_f = 0.28 (hexanes/ethyl acetate, 10/1); ^1H NMR (400 MHz, $CDCl_3$) δ 3.47 (d, *J* = 5.6 Hz, 2 H, CC*H*$_2$OH), 3.46 (s, 2 H, $SiOCH_2C$), 2.85 (t, *J* = 5.6 Hz, 1 H, CCH_2O*H*), 0.90 (s, 9 H, $SiC(CH_3)_3$), 0.89 (s, 6 H, $C(CH_3)_2$), 0.06 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 72.65, 72.10, 36.59, 25.99, 21.57, 18.30, -5.52. The analytical data are in agreement with those reported in the literature[71].

Next, the alcohol prepared above was oxidized to aldehyde 36 by two procedures. **Procedure A:** Oxalyl chloride (6.1 g, 4.2 mL, 48 mmol, 1.2 equiv) was added at -78 °C to a solution of DMSO (7.5 g, 6.82 mL, 96 mmol, 2.4 equiv)

in dry CH_2Cl_2 (100 mL) and the mixture was stirred for 1 h at that temperature. A solution of alcohol (8.7 g, 40 mmol, 1 equiv) prepared above in anhydrous CH_2Cl_2 (20 mL) was added slowly (ca. 20 min) and the mixture was stirred for 1 h. After that, the mixture was carefully treated with triethylamine (23 mL, 160 mmol, 4 equiv) at -78 °C. After stirred for 1 h, the reaction was allowed to warm to room temperature, and then 1N HCl was added to dissolve the salts. After being separation, the aqueous layer was further extracted with CH_2Cl_2 (2x50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried with $MgSO_4$, filtered, and concentrated by rotary evaporation to afford the crude aldehyde which was purified by flash column chromatography (hexanes/ethyl acetate, 10/1) to provide aldehyde **36** (8.65 g, 99%) as a colorless oil. **Procedure B:** Solid *tetra*-n-propylammonium perruthenate (VII) (TPAP) (1.23 g, 3.5 mmol, 5 mol%) was added in one portion to a stirred mixture of alcohol (15.3 g, 70 mmol, 1 equiv) prepared above, 4-methylmorpholine *N*-oxide (NMO) (12.3 g, 105 mmol, 1.5 equiv) and 4 Å molecular sieve powder (35.0 g, 500 mg/ mmol) in CH_2Cl_2 (140 mL, 2 mL/mmol) at 0 ^oC under argon atmosphere. The reaction progress was monitored by TLC. After the alcohol disappeared from TLC (ca. 20 min), the reaction was diluted with Et_2O (300 mL) and filtered through a short pad of silica, eluting with diethyl ether. The filtrate was evaporated and flash column chromatography furnished aldehyde **36** (13.6 g, 90%) as a colorless oil: R_f = 0.59 (hexanes/ethyl acetate, 10/1); ^1H NMR (400 MHz, $CDCl_3$) δ 9.57 (s, 1 H, CHO), 3.59 (s, 2 H, $SiOCH_2C$), 1.04 (s, 6 H, $C(CH_3)_2$), 0.87 (s, 9 H, $SiC(CH_3)_3$), 0.03 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.42, 68.56, 48.29, 25.96, 18.74,

18.40, -5.42. The analytical data are in agreement with those reported in the literature[71].

Preparation of Homoallylic Alcohol 37. Aldehyde **36** (19.0 g, 87.8 mmol, 1.0 equiv.) was dissolved in dry Et_2O (500 mL) and cooled to -100 °C. To this solution was added (+)-diisopinocampheylallylborane (210 mL, ca. 0.63 M in pentane, 132.0 mol, 1.5 equiv) by cannulation during 1 h at -100 ^oC. [(+)-Diisopinocampheylallylborane (1.5 equiv) in pentane was typically prepared by the adaptation of the original method reported by Brown [102]. Allylmagnesium bromide (131.7 mL, 1 M solution in Et_2O, 131.7 mmol) was added dropwise over 1h to a well-stirred solution of (−)-*B*-chlorodiisopinocampheylborane (45.1 g, 140.5 mmol, 1.6 equiv) in Et_2O (120 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 (3 x 70 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 the addition was complete, the mixture was stirred at the same temperature for 30 min. Methanol (40 mL) was added at -100 °C, and the reaction mixture was allowed to reach room temperature. The solution was condensed to about 150 mL, followed addition of saturated aqueous $NaHCO_3$ solution (220 mL) and H_2O_2 (100 mL of 50% solution in H_2O) at 0 ^oC. After stirred for 30 min at 0 ^oC, the reaction mixture was allowed to stir at room temperature 24 h. The reaction mixture was extracted with Et_2O (3 x 200 mL), and the organic

extracts were combined, washed with saturated aqueous NH_4Cl solution (100 m_L), and dried over $MgSO_4$. Evaporation of the solvents followed by flash column chromatography (gradient elution, hexanes →10/1, hexanes/ethyl acetate) resulted in pure alcohol **37** (22.4 g, 98%) as a colorless oil: R_f = 0.54 (hexanes/ethyl acetate, 10/1); $[\alpha]^{22}{}_D$ -20.5 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 3501, 3076, 2957, 2860, 1640, 1475, 1393, 1363, 1254, 1007, 911, 837, 775 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ 6.00-5.89 (m, 1 H, C*H*=CH_2), 5.14-5.07 (m, 2 H, CH=C*H*$_2$), 3.56 (t, *J* = 2.6 Hz, 1 H), 3.53 (t, *J* = 3.0 Hz, 1 H), 3.48 (s, 2H, $SiOCH_2C$), 2.30-2.24 (m, 1 H, CH(OH)C*H*$_2$), 2.13-2.06 (m, 1 H, CH(OH)C*H*$_2$), 0.91 (s, 3 H, $C(CH_3)_2$), 0.90 (s, 9H, $C(CH_3)_3$), 0.84 (s, 3 H, $C(CH_3)_2$), 0.07 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.04, 116.58, 78.49, 73.46, 38.53, 36.91, 26.00, 22.40, 19.00, 18.32, -5.50, -5.52; HRMS calcd for $C_{14}H_{31}O_2Si$ 259.20933 $[M + H]^+$, found 259.20879.

Preparation of Silyl Ether 38. Alcohol **37** (11.6 g, 45.0 mmol, 1.0 equiv) was dissolved in anhydrous CH_2Cl_2 (150 mL), and the solution was cooled at -78 °C, followed with the addition of 2,6-lutidine (7.3 mL, 63.0 mmol, 1.4 equiv). After being stirred for 5 min at that temperature, TBSOTf (13.4 mL, 58.5 mmol, 1.3 equiv) was added dropwise. The resultant mixture was stirred at -78 ^oC until all starting material disappeared from TLC (cat. 1 h). Saturated aqueous NH_4Cl solution (25 mL) was added, and the reaction mixture was allowed to warm to room temperature. After separation, the aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification by flash column

chromatography (hexanes) gave product **38** (16.5 g, 99%) as a colorless oil: R_f = 0.57 (hexanes, 100%); $[\alpha]^{22}_{D}$ +6.4 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 2957, 2934, 2860, 1640, 1475, 1390, 1363, 1254, 1085, 1004, 911, 833, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.94-5.84 (m, 1 H, C*H*=CH_2), 5.04-4.96 (m, 2 H, CH=C*H*$_2$), 3.65 (dd, *J* = 6.0, 4.5 Hz, 1 H, CHOSi), 3.32 (dd, *J* = 26.0, 9.5 Hz, 1 H, OC*H*$_2$C), 2.41-2.34(m, 1 H, C*H*$_2$CH=CH_2), 2.19-2.12 (m, 1 H, C*H*$_2$CH=CH_2), 0.90 (s, 18 H, $SiC(CH_3)_3$), 0.84 (s, 3 H, $C(CH_3)_2$), 0.81 (s, 3 H, $C(CH_3)_2$), 0.041 (s, 3 H, $Si(CH_3)_2$), 0.037 (s, 3 H, $Si(CH_3)_2$), 0.02 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.99, 115.71, 75.79, 69.89, 41.21, 38.21, 26.35, 26.17, 21.43, 20.70, 18.53, 18.49, -3.16, -4.17, -5.16, -5.31; HRMS calcd for $C_{20}H_{45}O_2Si_2$ 373.29581 $[M + H]^+$, found 373.29483.

Preparation of alcohol 39. To a cooled (-78 ^oC) solution of olefin **38** (373.4 mg, 1.0 mmol, 1 equiv) in CH_2Cl_2 (20 mL) was bubbled a stream of ozone until reaction mixture a blue color appeared. The solution was then purged with oxygen for 25 minutes at -75 ^oC , at which time the blue color disappeared and Ph_3P (314.9 g,1.2 mmol, 1.2 equiv) was added. The reaction mixture was allowed to reach room temperature and stirred for additional 1 h. The solution was concentrated under reduced pressure, diluted with 20 mL of hexanes and the resulting triphenylphosphine oxide was filtered through celite. The filtrate was concentrated to give colorless oil which is used crude in the following reaction unless a mall portion was purified by column chromatography for characterization. R_f = 0.19 (CH_2Cl_2/ hexanes, 1/4); $[\alpha]^{22}_{D}$ +4.8 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 2957, 2934, 2887, 2860, 2714, 1729, 1471, 1390, 1363, 1254, 1085, 1004, 938,

849, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.82 (dd, *J* = 3.0, 1.8 Hz, 1H, CHO), 4.19 (t, *J* = 5.3 Hz, 1 H, SiOCH), 3.33 (dd, *J* = 24.3, 9.8 Hz, 2H, OCH_2C), 2.68 (ddd, *J* = 16.7, 5.1, 1.8 Hz, 1H, C*H*$_2$CHO), 2.49 (ddd, *J* = 16.7, 5.5, 3.1 Hz, 1H, C*H*$_2$CHO), 0.89 (s, 9 H, $SiC(CH_3)_3$), 0.88 (s, 9 H, $SiC(CH_3)_3$), 0.85 (s, 3 H, $C(CH_3)_2$), 0.79 (s, 3 H, $C(CH_3)_2$), 0.08 (s, 3 H, $Si(CH_3)_2$), 0.02 (s, 9 H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.91, 71.40, 69.34, 48.35, 40.80, 26.14, 21.18, 20.82, -3.82, -4.45, -5.22, -5.35; HRMS calcd for $C_{19}H_{43}O_3Si_2$ 375.27507 $[M + H]^+$, found 375.27504.

A mixture of aldehyde obtained from olefin **38** as described above with *p*-toluenesulfonic acid monohydrate (5.7 mg, 3 mol%) in anhydrous benzene (15 mL) was refluxed overnight with a Dean-Stark receiver. After cooled to room temperature, the mixture was quenched with saturated aqueous $NaHCO_3$. After separation, the organics were dried over $MgSO_4$, filtered, and concentrated. The residue was subjected to following step without further purification until a small portion was purified by flash column chromatography (hexanes/ethyl acetate, 4/1) for characterization: R_f = 0.44 (CH_2Cl_2/Hexane, 1/1); $[\alpha]^{22}{}_D$ -14.3 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 2957, 2934, 2887, 2860, 1475, 1409, 1390, 1363, 1254, 1143, 1085, 1046, 1007, 834, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.93 (dd, *J* = 6.5, 4.1 Hz, 1H, CHO_2), 4.00-3.90 (m, 2H, OCH_2CH_2O), 3.85-3.80 (m, 2H, OCH_2CH_2O), 3.78 (dd, *J* = 7.2, 4.0 Hz, 1H, CHOSi), 3.32 (d, *J* = 4.1 Hz, 2H, CH_2OSi), 1.93-1.69 (m, 2H, C*H*$_2$CHO), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.83 (s, 3H, $C(CH_3)_2$), 0.80 (s, 3H, $C(CH_3)_2$), 0.06 (d, *J* = 2.6 Hz, 6H, $Si(CH_3)_2$), 0.01 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 103.23, 73.01,

69.57, 64.85, 64.80, 40.75, 37.81, 26.39, 26.15, 21.35, 20.17, 18.63, 18.49, -3.92, -3.96, -5.18, -5.30; HRMS calcd for $C_{21}H_{47}O_4Si_2$ 419.30129 $[M + H]^+$, found 419.30060.

Next, to a stirred solution of the crude acetal obtained above in THF (5 mL) in a Nalgene bottle was added freshly prepared pyridinium hydrofluoride buffer (20mL, stock solution prepared from 40 mL of Adrich pyridinium hydrofluoride, 100 mL of pyridine, and 160 m of THF) in 30 min at 0 ^oC. The reaction was allowed to warm to room temperature and stirred for 25 h, at which time all starting material disappeared from TLC. The reaction mixture was poured into saturated aqueous $NaHCO_3$, and extracted with hexanes (3 x 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (hexanes/ethyl acetate, 10/1) furnished **39** (161.4 mg, 53%, three steps) as a colorless oil: R_f = 0.24 (Hexane/ethylacetate, 4/1); $[\alpha]^{22}{}_D$ -18.7 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 3451 (br), 2957, 2934, 2887, 2860, 1475, 1409, 1390, 1363, 1254, 1143, 1085, 1042, 1011, 961, 942, 857, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.95 (dd, *J* = 6.8, 3.6 Hz, 1H, CHO_2), 3.99-3.95 (m, 2H, OCH_2CH_2O), 3.89-3.81 (m, 2H, OCH_2CH_2O), 3.77 (dd, *J* = 6.5, 3.7 Hz, 1H, CHOSi), 3.58 (dd, *J* = 11.2, 4.3 Hz, 1H, CH_2CHOH), 3.31 (dd, *J* = 11.1, 6.9 Hz, 1H, CH_2CHOH), 2.78 (dd, *J* = 6.8, 4.7 Hz, 1H, OH), 2.06-1.77 (m, 2H, CH_2CHO_2), 0.97 (s, 3H, $C(CH_3)_2$), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.83 (s, 3H, $C(CH_3)_2$), 0.10 (s, 3H, $Si(CH_3)_2$), 0.09 (s, 3H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 103.02, 75.68, 70.08, 64.97, 64.93, 39.80, 38.16, 26.25, 22.17, 18.42, -3.99, -4.14; HRMS calcd for $C_{15}H_{33}O_4Si$ 305.21481 $[M + H]^+$, found

305.21496.

Preparation of Aldehyde 27. Aldehyde **27** was prepared from **39** (80 mg, 0.26 mmol) via Swern oxidation following a same procedure described above to prepare aldehyde **36**, to obtain **27** (80 mg, quant) as a colorless oil: R_f = 0.47 (Hexane/ethylacetate, 4/1); $[\alpha]^{22}{}_D$ -17.9 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 2957, 2934, 2887, 2860, 1729, 1471, 1409, 1366, 1254, 1143, 1089, 1042, 965, 838, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.56 (s, 1H, CHO), 4.92 (dd, *J* = 7.1, 3.4 Hz, 1H, CHO_2), 4.07 (dd, *J* = 7.8, 3.3 Hz, 1H, CHOSi), 4.01-3.92 (m, 2H, OCH_2CH_2O), 3.89-3.81 (m, 2H, OCH_2CH_2O), 1.85 (ddd, *J* = 14.3, 7.8, 3.4 Hz, 1H, C*H*$_2$CHO), 1.74 (ddd, *J* = 14.3, 7.1, 3.3 Hz, 1H, C*H*$_2$CHO), 1.06 (s, 3H, $C(CH_3)_2$), 1.00 (s, 3H, $C(CH_3)_2$), 0.86 (s, 9H, $SiC(CH_3)_3$), 0.08 (s, 3H, $Si(CH_3)_2$), 0.05 (s, 3H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.22, 102.26, 72.59, 64.96, 64.92, 51.55, 38.05, 26.14, 19.04, 18.42, 17.36, -3.93, -4.09; HRMS calcd for $C_{15}H_{31}O_4Si$ 303.19916 $[M + H]^+$, found 303.19841.

Preparation of Aldehyde 40. To a stirred solution of silyl ether **38** (7.45 g, 20 mmol) in THF (100 mL) in a Nalgene bottle was added freshly prepared pyridinium hydrofluoride buffer (stock solution prepared from 40 mL of Adrich pyridinium hydrofluoride, 100 mL of pyridine, and 160 m of THF) in 30 min at 0 ^oC. The reaction was allowed to warm to room temperature and stirred for 25 h, at which time all starting material disappeared from TLC. The reaction mixture was poured into saturated aqueous $NaHCO_3$, and extracted with hexanes (3 x 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (hexanes/ethyl

acetate, 10/1) furnished a primary alcohol (4.57 g, 88%) as a colorless oil. R_f = 0.27 (hexanes/ethyl acetate, 10/1); $[\alpha]^{22}{}_D$ +9.2 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 3424, 3076, 2957, 2860, 1802, 1640, 1471, 1432, 1390, 1363, 1254, 1805, 1038, 1004, 907, 833, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.95-5.85 (m, 1 H, C*H*=CH_2), 5.10-5.01 (m, 2 H, CH=C*H*$_2$), 3.75 (dd, *J* = 10.8, 3.2 Hz, 1 H, OCH_2C), 3.61 (t, *J* = 5.3 Hz, 1 H, SiOCH), 3.26 (dd, *J* = 10.8, 7.6 Hz, 1 H, OCH_2C), 2.83 (dd, *J* = 7.6, 3.2 Hz, 1 H, OH), 2.51-2.43 (m, 1 H, C*H*$_2$CH=CH_2), 2.32-2.24 (m, 1 H, C*H*$_2$CH=CH_2), 1.04 (s, 3 H, $C(CH_3)_2$), 0.90 (s, 9 H, $SiC(CH_3)_3$), 0.81 (s, 3 H, $C(CH_3)_2$), 0.09 (s, 3 H, $Si(CH_3)_2$), 0.08 (s, 3 H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.70, 116.69, 80.16, 70.38, 39.88, 38.36, 26.20, 23.93, 21.99, 18.30, -3.40, -4.26; HRMS calcd for $C_{14}H_{31}O_2Si$ 259.20933 $[M + H]^+$, found 259.20849.

To a stirred mixture of the alcohol (4.4 g, 17 mmol, 1 equiv) as described above, NMO (2.99 g, 25.5 mmol, 1.5 equiv) and 4 Å molecular sieve powder (8.5 g, 500 mg/ mmol) in CH_2Cl_2 (34 mL, 2 mL/mmol), solid TPAP (298 g, 0.85 mmol, 5 mol%) was added in one portion at 0 ^oC under argon atmosphere. The reaction progress was monitored by TLC. After the alcohol disappeared from TLC (ca. 10 min), the reaction was diluted with Et_2O (60 mL) and is filtered through a short pad of silica, eluting with Et_2O. The filtrate was evaporated and flash column chromatography furnished aldehyde **40** (4.1 g, 94%) as a colorless oil. R_f = 0.56 (hexanes/ethyl acetate, 10/1); $[\alpha]^{22}{}_D$ +11.5 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 3080, 2957, 2934, 2860, 2706, 1725, 1644, 1471, 1397, 1363, 1254, 1089, 1004, 911, 834, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.60 (s, 1H, CHO), 5.84-5.74 (m, 1 H, C*H*=CH_2), 5.09-5.03 (m, 2 H, CH=C*H*$_2$), 3.85 (t, *J* = 5.4 Hz, 1 H, SiOCH),

2.37-2.30 (m, 1 H, C*H*$_2$CH=CH$_2$), 2.27-2.20 (m, 1 H, C*H*$_2$CH=CH$_2$), 1.06 (s, 3 H, C(CH$_3$)$_2$), 1.03 (s, 3 H, C(CH$_3$)$_2$), 0.88 (s, 9 H, SiC(CH$_3$)$_3$), 0.07 (s, 3 H, Si(CH$_3$)$_2$), 0.04 (s, 3 H, Si(CH$_3$)$_2$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 206.54, 135.45, 117.83, 76.35, 51.63, 38.60, 26.10, 19.55, 18.36, 18.31, -3.33, -4.31; HRMS calcd for $C_{14}H_{29}O_2Si$ 257.19368 $[M + H]^+$, found 257.19304.

Preparation of Homoallylic Alcohol 41. The solution of borane **28** in THF (60 mL) at -25 °C was prepared from (-)-Ipc$_2$BH (8.59 g, 36 mmol, 2.4 equiv) and cyclohexa-1,3-dinene (2.88 g, 30 mmol, 2.0 equiv) according to the method described for the synthesis of alcohol **29**. After being cooled to -78 °C, the borane solution was treated with aldehyde **40** (3.85 g, 15.0 mmol, 1.0 equiv). The contents were stirred at -78 °C until the disappearance of the aldehyde from TLC (ca. 4-5 days). Methanol (10 mL) was added slowly at -78 °C, and the reaction mixture was allowed to warm to 0 °C, followed with slow addition of saturated aqueous NaHCO$_3$ (30 mL) and H_2O_2 (20 mL of 50% solution in H_2O) consequently. The resulting mixture was heated to 45 °C and stirred for 10-12 days at that temperature. After cooling to room temperature, the mixture was extracted with hexanes (3 x 40 mL), and the combined organic layers were dried over MgSO$_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (gradient elution, hexanes →20/1, hexanes/ethyl acetate) to provide product **41** (4.67 g, 92%) as a colorless oil: R_f = 0.58 (hexanes/ethyl acetate, 10/1); $[\alpha]^{22}_D$ +17.6 (*c* 1.0, CHCl$_3$); IR (thin film) ν_{max} 3486, 2953, 2934, 2887, 2860, 1826, 1741, 1640, 1471, 1432, 1390, 1363, 1254, 1065, 1004, 911, 838, 811, 776, 718 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.94-5.83 (m,

1H, C*H*=CH_2) 5.82-5.76 (m, 1H, CH_2C*H*=CHCH), 5.55-5.50 (m, 1H, CH_2CH=C*H*CH), 5.09-45.01 (m, 2H, CH=CH_2), 3.84 (d, *J* = 2.9 Hz, 1H, C*H*OH), 3.79 (s, 1H, OH), 3.48 (dd, *J* = 5.9, 4.5 Hz, 1H, SiOCH), 2.56-2.49 (m, 1H), 2.37-2.28 (m, 2H), 2.09-1.85 (m, 2H), 1.84-1.70 (m, 3H), 1.55-1.43 (m, 1H), 1.07 (s, 3H, C(CH_3)$_2$), 0.90 (s, 9H, SiC(CH_3)$_3$), 0.85 (s, 3H, C(CH_3)$_2$), 0.10 (s, 3H, Si(CH_3)$_2$), 0.08 (s, 3H, Si(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.92, 132.37, 128.89, 116.79, 84.73, 77.47, 42.29, 38.55, 38.12, 26.29, 24.91, 23.69, 23.58, 22.59, 22.20, 18.36,-3.43,-4.09; HRMS calcd for $C_{20}H_{39}O_2Si$ 339.27193 $[M + H]^+$, found 339.27117.

Preparation of Compounds 42, 43, 44. To a solution of olefin **41** (1.089 g, 3.2 mmol, 1 equiv) and VO(acac)$_2$ (17 mg, 0.064 mmol, 2 mol%) in anhydrous CH_2Cl_2 (32 mL, 0.1M) was added anhydrous *tert*-butyl hydroperoxide (0.87 mL, ca. 5.5 M in decane, 4.8 mmol, 1.5 equiv) at 0 ^{o}C. After being vigorous stirred for 1 h at 0 ^{o}C, the resulting dark solution was allowed to warm to room temperature and stirred overnight at which time all starting material disappeared from TLC. Aqueous $NaSO_3$ solution (10 mL, 5%) was added to quench the reaction. Vigorous stirred for 10 minutes, the organic phase was separated, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to give light yellow oil. ^{1}H NMR suggested the crude epoxide was pure enough to go following step. A small portion of the crude was purified for characterization with flash column chromatography (hexanes/ethyl acetate, 10/1) to give pure epoxide **42** as a colorless oil: R_f = 0.29 (hexanes/ethyl acetate, 10/1); $[\alpha]^{22}{}_D$ +12.6 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 3567, 3474(br), 3076, 2953, 2934, 2887, 2860, 1918, 1822,

1714, 1640, 1471, 1436, 1390, 1363, 1301, 1254, 1200, 1065, 1034, 1004, 938, 911, 838, 811, 776, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.93-5.82 (m, 1H, C*H*=CH_2), 5.10-5.01 (m, 2H, CH=C*H*$_2$), 4.04-4.01 (m, 2H, CHOH), 3.57 (dd, *J* = 6.5, 4.2 Hz, 1H, SiOCH), 3.15 (m, 1H, CH_2C*H*O(epoxide)CH), 3.10-3.05 (m, 1H, CHO(epoxide)C*H*CH), 2.59-2.52 (m, 1H, C*H*$_2$CH=CH_2), 2.38-2.28 (m, 1H, C*H*$_2$CH=CH_2), 2.04-1.98 (m, 1H, C*H*(CHOH)CH_2), 1.85-1.80 (m, 2H), 1.62-1.46 (m, 2H), 1.43-1.36 (m, 1H), 1.26-1.16 (m, 1H), 1.05 (s, 3H, C(CH_3)$_2$), 0.94 (s, 3H, C(CH_3)$_2$), 0.90 (s, 9H, SiC(CH_3)$_3$), 0.10 (s, 3H, Si(CH_3)$_2$), 0.08 (s, 3H, Si(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.01, 116.84, 83.44, 76.27, 56.10, 53.08, 42.32, 37.98, 37.60, 26.28, 24.10, 23.33, 21.38, 21.34, 20.09, 18.39, -3.38, -4.04; HRMS calcd for $C_{20}H_{39}O_3Si$ 355.26685 $[M + H]^+$, found 355.26606.

The crude epoxide **42** was dissolved in THF (10 mL) with CuCN (28.65 mg, 0.32 mmol, 0.1 equiv). After cooled to -55 °C, a freshly prepared 4-pentenylmagnesium bromide (15 mL, ca.1.28 M in Et_2O, 19.2 mmol, 6 equiv) was added dropwise with vigorous stirring. [4-pentenylmagnesium bromide solution in Et_2O was prepared according to the procedure described above to prepare compound **31**.] The solution was warmed to -10 °C over 1 h and stirred another 2.5 h at this temperature. Saturated aqueous NH_4Cl was added with vigorous stirring to quench the reaction. The mixture was extracted with Et_2O (3 x 20 mL). The combined extracts were dried over $MgSO_4$ and concentrated to furnish the crude diol **43**. ^1H NMR indicated the crude was pure enough for further reaction. A small portion of pure **43** was furnished for characterization by column chromatography (gradient elution, hexanes →4/1, hexanes/ethyl acetate) as a

colorless oil: R_f = 0.27 (hexanes/ethyl acetate, 10/1); $[\alpha]^{22}_{D}$ -19.9 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 3412(br), 3076, 2930, 2860, 1741, 1640, 1471, 1432, 1390, 1363, 1254, 1216, 1069, 1004, 911, 834, 811, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.90-5.75 (m, 2H, 2 x C*H*=CH_2), 5.09-4.92 (m, 4H, 2 x CH=C*H*$_2$), 4.32 (s, 1H), 4.05 (s, 1H), 3.97 (s, 1H), 3.69 (s, 1H), 3.47 (dd, *J* = 5.9, 4.5 Hz, 1H, CHOSi), 2.50 (m, 1H, C*H*$_2$CH=CH_2), 2.35-2.26 (m, 1H, C*H*$_2$CH=CH_2), 2.09-2.00 (m, 2H, C*H*$_2$CH=CH_2), 1.87-1.68 (m, 3H), 1.60 (d, *J* = 12.8 Hz, 1H), 1.50-1.21 (m, 8H), 1.07 (s, 3H, $C(CH_3)_2$), 0.90 (s, 9H, $SiC(CH_3)_3$), 0.81 (s, 3H, $C(CH_3)_2$), 0.10 (s, 3H, $Si(CH_3)_2$), 0.09 (s, 3H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.18, 136.60, 117.05, 114.55, 85.22, 79.39, 78.19, 42.26, 40.26, 38.16, 37.48, 34.09, 29.75, 27.45, 26.22, 23.43, 23.33, 23.12, 20.85, 20.62, 18.33, -3.40, -4.18; HRMS calcd for $C_{25}H_{49}O_3Si$ 425.34510 $[M + H]^+$, found 425.34424.

A mixture of the crude diol **43** prepared above and 1,6-lutidine (0.75 mL, 6.4 mmol, 2.0 equiv) in CH_2Cl_2 (25 mL) was treated with TBSOTf (1.10 mL, 4.8 mmol, 1.5equiv) dropwise at -78 °C. The reaction mixture was stirred at -78 ^oC until all starting material disappeared from TLC (cat. 1.5 h). After quenched with saturated aqueous NH_4Cl, the mixture was warmed to room temperature. The organic phase was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification by flash column chromatography (hexanes/ethyl acetate, 20/1) afforded compound **44** (1.48 g, 93%, 3 steps) as a colorless oil: R_f = 0.56 (hexanes/ethyl acetate, 20/1); $[\alpha]^{22}_{D}$ +2.5 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 3505, 3080, 2930, 2899, 2860, 1826, 1741,

1640, 1471, 1444, 1049, 1390, 1363, 1254, 1069, 1004, 911, 834, 811, 776, 672 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.90-5.72 (m, 2H, 2 x C*H*=CH_2), 5.02-4.91 (m, 4H, 2 x CH=C*H*$_2$), 3.61-3.57 (m, 3H, 2 x C*H*OSi, C*H*OH), 3.23 (s, 1H, OH), 2.45-2.37 (m, 1H, C*H*$_2$CH=CH_2), 2.22-2.14 (m, 1H, C*H*$_2$CH=CH_2), 2.02 (q, *J* = Hz, 2H, 2 x C*H*$_2$CH=CH_2), 1.76-1.59 (m, 4H), 1.53-1.43 (m, 2H), 1.42-1.21 (m, 6H), 0.90 (s, 3H, C(CH_3)$_2$), 0.89 (s, 9H, SiC(CH_3)$_3$), 0.87 (s, 9H, SiC(CH_3)$_3$), 0.79 (s, 3H, C(CH_3)$_2$), 0.07 (s, 3H, Si(CH_3)$_2$), 0.06 (s, 3H, Si(CH_3)$_2$), 0.05 (s, 3H, Si(CH_3)$_2$), 0.04 (s, 3H, Si(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.96, 137.64, 116.19, 114.77, 79.61, 78.76, 77.42, 43.53, 41.35, 38.32, 37.74, 34.20, 30.18, 27.57, 26.38, 26.18, 24.08, 21.77, 21.66, 20.85, 20.45, 18.52, 18.33, -3.05, -3.63, -3.96, -4.47; HRMS calcd for $C_{31}H_{63}O_3Si_2$ 539.43157 $[M + H]^+$, found 539.43070.

Preparation of Ketone 45. To a solution of DMSO (0.3 mL, 4.12 mmol, 2.4 equiv) in dry CH_2Cl_2 (8 mL) was added dropwise oxalyl chloride (260.5 mg, 2.05 mmol, 1.2 equiv) at -78 °C. After stirring for 1 h at that temperature, a solution of alcohol **44** (0.926 g, 1.71 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (10 mL) was added slowly (ca. 20 min). The mixture was stirred for 3 h and carefully treated with triethylamine (0.96 mL, 6.87 mmol, 4 equiv) at -78 °C. After stirred for another 3 h, the reaction was warmed to room temperature, and then saturated aqueous $NaHCO_3$ was added to dissolve the salts. After separation, the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution, filtered and concentrated by rotary evaporation to afford the crude as a yellow oil residue, which was purified by flash column chromatography (gradient elution, hexanes/CH_2Cl_2, 10/1→ 4/1) to afford

product **45** (909 mg, 99%) as a colorless oil: R_f = 0.41 (hexanes/ethyl acetate, 20/1); $[\alpha]^{22}_{D}$ -41.6 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 3080, 2953, 2930, 2895, 2860, 1830, 1698, 1640, 1471, 1444, 1390, 1363, 1254, 1085, 1027, 1004, 938, 911, 838, 811,776, 672 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.87-5.66 (m, 2H, 2 x C*H*=CH_2), 5.04-4.93 (m, 4H, 2 x CH=C*H*$_2$), 3.86 (bs, 1H, CHC*H*OSi), 3.71 (t, *J* = 4.8 Hz, 1H, $C(CH_3)_2$C*H*OSi), 3.14 (d, *J* = 10.5 Hz, 1H, CHC(O)), 2.21-2.14 (m, 1H), 2.10-1.93 (m, 4H), 1.87-1.71 (m, 2H), 1.50-1.43 (m, 2H), 1.41-1.29 (m, 4H), 1.27-1.19 (m, 5H), 1.03 (s, 3H, $C(CH_3)_2$), 0.90 (s, 9H, $SiC(CH_3)_3$), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.08 (s, 3H, $Si(CH_3)_2$), 0.05 (s, 3H, $Si(CH_3)_2$), 0.01 (s, 3H, $Si(CH_3)_2$), -0.04 (s, 3H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.55, 138.95, 136.84, 116.57, 114.83, 78.99, 72.18, 53.50, 47.58, 41.38, 39.88, 34.26, 30.34, 27.62, 26.35, 26.06, 25.08, 23.01, 20.10, 18.45, 18.29, -3.46, -3.62, -3.80, -4.34; HRMS calcd for $C_{31}H_{61}O_3Si_2$ 537.41592 $[M + H]^+$, found 537.41533.

Preparation of Dihydroxy Ketone 46. A solution of ketone **45** (909 mg, 1.69 mmol) in CH_2Cl_2 (1 mL) was treated with a freshly prepared 20% (v/v) CF_3CO_2H solution in CH_2Cl_2 (12 mL) at -20 °C. The reaction mixture was allowed to reach 0 °C in 20 min and stirred for additional 1.5 h at that temperature at which time all silyl ether disappeared from TLC plate. The mixture was diluted with CH_2Cl_2 (10 mL) and carefully neutralized by saturated aqueous $NaHCO_3$. After separation, the aqueous phase was further extracted with CH_2Cl_2 (2 x 10 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by preparative chromatography (hexanes/ethyl acetate, 4/1) to afford hydroxy ketone **46** (408 mg, 78%) as a colorless oil: R_f = 0.28 (hexanes/ethyl

acetate, 4/1); $[\alpha]^{22}_{D}$ -16.6 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 3440(br), 3075, 2976, 2931, 2861, 1678, 1640, 1465, 1413, 1364, 1125, 1072, 986, 912, 872 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.90-5.75 (m, 2H, 2 x C*H*=CH_2), 5.18-5.13 (m 2H, CH=C*H*$_2$), 5.04-4.93 (m, 2H, CH=C*H*$_2$), 3.79 (ddd, *J* = 10.4, 3.4, 2.2 Hz, 1H, CHC*H*OH), 3.71 (s, 1H), 3.63 (s, 1H), 3.18 (ddd, *J* = 11.4, 3.4, 2.2 Hz, 1H, CHC(O)), 2.33-2.24 (m, 2H), 2.09-2.00 (m, 3H), 1.94-1.75 (m, 3H), 1.54-1.27 (m, 8H), 1.21 (s, 3H, C(CH_3)$_2$), 1.13 (s, 3H, C(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 222.12, 138.94, 135.46, 118.63, 114.78, 75.33, 70.96, 52.65, 44.18, 38.93, 36.61, 34.03, 29.72, 27.23, 24.45, 23.68, 21.65, 20.15, 18.78; HRMS calcd for $C_{19}H_{33}O_3$ 309.24297 $[M + H]^+$, found 309.24225.

Preparation of Hydroxy Epoxide 47. To a solution of olefin **46** (555 mg, 1.80 mmol, 1 equiv) and $VO(acac)_2$ (9.6 mg, 0.036 mmol, 2 mol%) in anhydrous CH_2Cl_2 (18 mL, 0.1M) was added anhydrous *tert*-butyl hydroperoxide (0.66 mL, ca. 5.5 M in decane, 3.6 mmol, 1.5 equiv) at -5 ^oC. The mixture was stirred at -5-0 ^oC until all starting material disappeared from TLC plate (ca. 72 h). Aqueous Na_2SO_3 solution (5 mL, 5%) was added slowly to quench the reaction. The organic phase was separated, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified with flash column chromatography (hexanes/ethyl acetate, 1/1) to give a mixture of diastereomeric hydroxy epoxide **47** (519 mg, 89%, ca. 10:1 ratio by ^1H NMR) as a colorless oil: R_f = 0.40 (hexanes/ethyl acetate, 1/1); $[\alpha]^{22}_{D}$ -24.6 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 3463(br), 2928, 2860, 1680, 1640, 1468, 1444, 1410, 1366, 1261, 1067, 984, 912, 831 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.80 (tdd, *J* = 16.9, 10.2, 6.6, 6.6 Hz, 1H,

C*H*=CH_2), 5.04-4.93 (m, 2H, CH=CH_2), 4.03 (ddd, *J* = 10.3, 3.8, 1.8 Hz, 1H, $C(CH_3)_2$C*H*OH), 3.71 (s, 1H), 3.56 (s, 1H), 3.22-3.11 (m, 2H, CHC(O), C*H*O(epoxide)CH_2), 2.94 (d, *J* = 3.9 Hz, 1H, CH_2CHO*H*), 2.80 (t, *J* = 4.8 Hz, 1H, CHO(epoxide)CH_2), 2.51 (dd, *J* = 4.8, 2.7 Hz, 1H, CHO(epoxide)CH_2), 2.08-2.03 (m, 2H, CH_2CH=CH_2), 1.93-1.74 (m, 4H), 1.55-1.25 (m, 9H), 1.20 (s, 3H, $C(CH_3)_2$), 1.12 (s, 3H, $C(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 222.01, 138.93, 114.80, 75.50, 71.05, 52.61, 51.53, 46.84, 44.36, 38.97, 34.52, 34.03, 29.78, 27.19, 24.43, 23.77, 21.55, 20.10, 18.91; HRMS calcd for $C_{19}H_{33}O_4$ 325.23788 $[M + H]^+$, found 325.23673.

Preparation of Acetate 48. To a mixture of diol **47** (496 mg, 1.53 mmol, 1.0 equiv), *N*,*N*'-diisopropylethylamine (1.6 mL, 9.18 mmol, 6.0 equiv), and 4-(dimethylamino)pyridine (DMAP) (18.7 mg, 0.153 mmol, 10 mol%) in CH_2Cl_2 (15 mL) was added acetic anhydride (624.8 mg, 6.12 mmol, 4.0 equiv) at 0 ^oC. After being stirred for 1 h at 0 ^oC , the reaction mixture was allowed to warm to room temperature and stirred for another 1 h.. Saturated aqueous NH_4Cl was added to quench the reaction. After separation, the aqueous phase was further extracted with CH_2Cl_2 (2 x 10 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash chromatography (hexanes/ethyl acetate, 4/1) to afford pure **48** (580 mg, 93%) as a colorless oil: R_f = 0.65 (hexanes/ethyl acetate, 1/1); $[\alpha]^{22}_D$ -31.5 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 2930, 2861, 1735, 1700, 1640, 1444, 1370, 1233, 1020, 911, 840, 802, 643, 604 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83-5.73 (m, 1H, C*H*=CH_2), 5.44 (dd, *J* = 10.4, 2.1 Hz, 1H, CHC*H*OAc), 5.03-4.92 (m, 2H, CH=CH_2), 4.82 (dd,

J = 7.2, 3.8 Hz, 1H, CH_2CHOA_C), 3.46-3.30 (m, 1H, CHC(O)), 2.93 (td, *J* = 4.8, 2.7, 2.7 Hz, 1H, C*H*O(epoxide)CH_2), 2.71 (t, *J* = 4.8 Hz, 1H, CHO(epoxide)CH_2), 2.43 (dd, *J* = 4.8, 2.7 Hz, 1H, CHO(epoxide)CH_2), 2.12-2.00 (m, 9H), 1.89-1.79 (m, 2H), 1.75 (ddd, *J* = 14.6, 4.4, 2.2 Hz, 1H), 1.56-1.24 (m, 7H), 1.24-1.12 (m, 5H), 1.05 (s, 3H, $C(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.84, 170.90, 170.81, 138.83, 114.84, 75.20, 74.89, 52.11, 50.49, 46.32, 43.24, 37.21, 34.53, 34.05, 31.02, 27.11, 26.41, 25.53, 21.43, 21.27, 19.75, 19.52; HRMS calcd for $C_{23}H_{37}O_6$ 409.25901 $[M + H]^+$, found 409.25821.

Preparation of Keto Acid 49. A mixture of epoxide **48** (122.6 mg, 0.3 mmol, 1.0 equiv) and *n*-Bu_4NHSO_4 (10.2 mg, 0.03 mmol, 10 mol%) in CH_3CN/H_2O (3 mL, v/v, 1/1) was stirred for 10 h at 50 ^oC. After cooled down to room temperature, the mixture was diluted with Et_2O (10 mL), washed with brine, dried over $MgSO_4$, filtered and concentrated to give desired crude intermediate diol (119 mg) as a light yellow oil.

The crude diol was dissolved in THF (5 mL), and treated dropwise at 0 °C with a solution of $NaIO_4$ (128.3 mg, 0.6 mmol, 2.0 equiv) in H_2O (5 mL). The resultant biphasic mixture was stirred at 0 °C for 2 h at which time all starting material disappeared from TLC plate. The reaction mixture was diluted with Et_2O (15 mL), washed with brine, dried over $MgSO_4$, filtered and concentrated to give desired crude aldehyde (115 mg). The aldehyde was unstable on silica gel column and went following step without further purification.

The crude aldehyde obtained above was dissolved in *t*-BuOH (1.5 mL, 0.2 M),

2-methyl-2-butene (0.6 mL, 2 M solution in THF, 1.2 mmol, 4.0 equiv), H_2O (0.3 mL). The resultant mixture was treated with $NaClO_2$ (81.4 mg, 0.9 mmol, 3.0 equiv), and NaH_2PO_4 (62 mg, 0.45 mmol, 1.5 equiv). After stirring for 6 h, the reaction mixture wad concentrated under reduced pressure, and the residue was subjected to flash column chromatography (gradient elution, hexanes/ethyl acetate, 5/1→ 1/1, then 1/1 with 1% HCO_2H) to furnish carboxylic acid **49** (57.5 mg, 45%, 3 steps) as a colorless oil: R_f = 0.33 (hexanes/ethyl acetate, 1/1 with 1% HOAC); $[\alpha]^{22}{}_D$ -34.5 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 3075(br), 2932, 2862, 1735, 1702, 1640, 1444, 1371, 1234, 1079, 1026, 989, 913, 804, 643, 605 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.78 (tdd, *J* = 16.9, 10.2, 6.7, 6.7 Hz, 1H, C*H*=CH_2), 5.56 (dd, *J* = 9.4, 2.8 Hz, 1H, CHC*H*OAc), 5.02-4.93 (m, 2H, CH=C*H*$_2$), 4.84 (dd, *J* = 6.9, 3.7 Hz, 1H, CH_2CHOA_C), 3.39-3.35 (m, 1H, CHC(O)), 2.61 (dd, *J* = 16.1, 2.8 Hz, 1H, CH_2CO_2), 2.44 (dd, *J* = 16.1, 9.4 Hz, 1H, CH_2CO_2), 2.12-1.98 (m, 9H), 1.90-1.76 (m, 2H), 1.57-1.28 (m, 6H), 1.22- 1.15 (m, 6H), 1.07 (s, 3H, $C(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.61, 176.18, 171.02, 170.32, 138.84, 114.85, 74.68, 73.25, 52.16, 43.39, 37.26, 36.22, 34.05, 30.89, 26.88, 26.44, 25.55, 21.42, 21.35, 21.06, 19.81, 19.73; HRMS calcd for $C_{22}H_{34}O_7Na$ 433.22022 $[M + Na]^+$, found 433.21902.

Preparation of Thiazole 51. To a solution of thioacetamide (19.2 g, 255 mol, 1.02 equiv) in absolute ethanol (150 mL), ethyl bromopyruvate **50** (90%, 48.8 g, 250 mol, 1.00 equiv) was added dropwise in 30 min. After being stirred for 12 h at room temperature, the reaction mixture was poured onto 2.5 *N* HCl (150 mL), stirred 30 min, and extracted with diethyl ether (3 x 100 mL). The aqueous

solution was cautiously neutralized with excess, solid $NaHCO_3$ and extracted with diethyl ether (3 x 100 mL). The combined extracts were washed with brine, dried over MgSO4, and concentrated under reduced pressure to give a yellow solid, which was purified by flash chromatography (hexanes/ethyl acetate, 2/1) to give product **51** (40.92 g, 96%) as a white solid: R_f = 0.31 (hexanes/ethyl acetate, 2/1); mp. 55-56 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H, C=CHS), 4.42 (q, *J* = 7.2 Hz, 2H, CH_3CH_2O), 2.77 (s, 3 H, $N=C(S)CH_3$), 1.40 (t, *J* = 7.2 Hz, 3 H, CH_3CH_2O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.82, 161.43, 146.89, 127.34, 61.44, 19.43, 14.43. The analytical data are in agreement with those reported in the literature. [79, 103]

Preparation of Aromatic Aldehyde 52. To a solution of thiazole ester **51** (20.6 g, 120 mmol, 1.00 equiv) in dry CH_2Cl_2 (1 L) was added DIBAL-H (1.00 M in CH_2Cl_2, 180 mL, 180 mmol, 1.50 equiv) via syringe pump over 1 h at –78 °C. After being stirred for 2 h at that temperature, an additional portion of DIBAL-H (1.00 M in CH_2Cl_2, 45.0 mL, 45.0 mmol) was added over 30 min and the clear solution stirred until its completion was verified by ^{1}H NMR (ca. 1h). After addition of methanol (5 mL) at -78 °C to quench the reaction, the mixture was warmed to room temperature and saturated aqueous Rochelle salt (700 mL) was added. The biphasic mixture was rapidly stirred overnight whereupon two clear, colorless layers formed. The aqueous layer was withdrawn and extracted with CH_2Cl_2 (2 x 200 mL). The combined organic solutions were washed with brine (500 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Flash column chromatography provided the aldehyde **52** (14.2 g, 93 %) as a yellow solid. R_f =

0.40 (hexanes/ethyl acetate, 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) ẟ 9.96 (s, 1H, CHO), 8.04 (s, 1H, C=CHS), 2.77 (s, 3 H, N=C(S)CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.52, 167.79, 154.95, 128.40, 19.44. The analytical data are in agreement with those reported in the literature[34, 79].

Preparation of Aldehyde 53. To a solution of aromatic aldehyde **52** (12.7 g, 100 mmol, 1.0 equiv) in benzene (300 mL), was added 2-(triphenylphosphoranilidenyl)-propionaldehyde (36.6 g, 115 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, 1/1) produced the desired aldehyde **53** (40.08 g, 98%) as a white solid: R_f = 0.35 (hexanes/ethyl acetate, 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.56 (s, 1 H, CHO), 7.45 (s, 1 H, CCH=C), 7.25 (d, *J* = 1.2 Hz, 1 H, SCH=C), 2.76 (d, *J* = 1.2 Hz, 3 H, N=C(S)CH_3), 2.20 (s, 3 H, CH=C(CHO)C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.45, 166.03, 151.64, 141.21, 138.44, 123.05, 19.40, 11.13. The analytical data are in agreement with those reported in the literature.[34, 104]

Peparation of Secondary Alcohol 24. To a solution of aldehyde **53** (836.5 mg, 5.0 mmol, 1.0 equiv) in anhydrous ether (25 mL) was added freshly prepared (+)-diisopinocampheylallylborane (20 mL, 0.3 M in pentane, 6.0 mmol, 1.2 equiv) at -100 °C. [(+)-Diisopinocampheylallylborane in pentane was prepared from (−)-*B*-chlorodiisopinocampheylborane (2.57 g, 8.0 mol) and allylmagnesium

bromide (7.5 mL, 1 M solution in ether, 7.5 mmol) according to the method described for the synthesis of **37**.] After the addition was complete, the mixture was stirred at the same temperature for 1 h. Methanol (1 mL) was added at -100 °C, and the reaction mixture was allowed to warm to room temperature. Aminoethanol (0.91 mL, 15.0 mmol, 3.0 equiv) was added. After being stirred overnight, saturated aqueous NH_4Cl solution (20 mL) was added. The mixture was extracted with EtOAc (3 x 20 mL), and the combined organics were dried over $MgSO_4$, and concentrated under reduced pressure followed by flash column chromatography (gradient elution, 10/1 →1/1, hexanes/ethyl acetate) provided allylic alcohol **24** (1.02 g, 97%) as a colorless oil: R_f = 0.43 (hexanes/ethyl acetate, 1/1); $[\alpha]^{22}_{D}$ -19.4 (*c* 1.0, $CHCl_3$), lit.[34] -20.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (s, 1 H, SCH=C), 6.56 (s, 1 H, C*H*=CCH_3), 5.77-5.88 (m, 1 H, C*H*=CH_2), 5.11-5.19 (m, 2 H, CH=CH_2), 4.22 (t, *J* = 7.4 Hz, 1 H, C*H*OH), 2.71 (s, 3H, N=C(S)CH_3), 2.35-2.47 (m, 2 H, CH_2=CHCH_2), 2.05 (d, *J* = 1.2 Hz, 3 H, CH=CCH_3), 1.90 (d, *J* = 2.8 Hz, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.80, 152.89, 141.70, 134.82, 119.17, 117.94, 115.62, 76.61, 40.15, 19.28, 14.51. The analytical data are in agreement with those reported in the literature.[34]

Preparation of Keto Ester 54. Procedure A: To a stirred solution of keto acid **49** (205.25 mg, 0.5 mmol, 1.0 equiv), alcohol **24** (115 mg, 0.55 mmol, 1.1 equiv), and triethylamine (0.42 mL, 3.0 mmol, 6.0 equiv) in toluene (15 mL) were subsequently added at -78 ^{o}C a solution of DMAP (6 mg, 0.05 mmol, 10 mol%) in toluene (0.5 mL) and 2,4,6-trichlorobenzoyl chloride (0.39 mL, 2.5 mmol, 5.0 equiv). The reaction was warmed to 0 ^{o}C in 30 min, and the resulted white slurry

was stirred at 0 ^{o}C for 20 min before being quenched with saturated aqueous $NaHCO_3$. After separation, the aqueous phase was further extracted with ethyl EtOAc (2 x 10 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated. The resultant residue was purified by flash chromatography (hexanes/ethyl acetate, 2/1) to afford keto ester **54** (258.5 mg, 86%) as a colorless oil: **Procedure B:** A solution of keto acid **49** (39 mg, 0.095 mmol, 1.0 equiv), alcohol **24** (22 mg, 0.105 mmol, 1.1 equiv), and DMAP (1.2 mg, 0.0096 mmol, 10 mol %) in CH_2Cl_2 (0.5 mL) was cooled to 0 ^{o}C, and treated with 1-ethyl-3-((dimethylamino)propyl)carbodiimide hydrochloride (EDCI, 20 mg, 0.105 mmol, 1.1 equiv). The solution was concentrated to dryness in vacuo, and the residue was subjected to flash column chromatography for furnish the keto ester **54** (33 mg, 58%) as a colorless oil: R_f = 0.47 (hexanes/ethyl acetate, 2/1); $[\alpha]^{22}_{D}$ -53.1 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 3076, 2930, 2860, 1733, 1701, 1641, 1505, 1443, 1370, 1298, 1234, 1177, 1025, 989, 913, 875, 733, 645, 603 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.96 (s, 1H, SCH=C), 6.49 (s, 1H, C*H*=CCH_3), 5.77 (tdd, *J* = 17.0, 10.3, 6.6, 6.6 Hz, 1H, C*H*=CH_2), 5.70 (tdd, *J* = 13.9, 10.2, 7.0, 7.0 Hz, 1H, C*H*=CH_2), 5.58 (dd, *J* = 9.4, 2.6 Hz, 1H, CHC*H*OAc), 5.31 (t, *J* = 6.8, 6.8 Hz, 1H, C*H*OC(O)CH_2), 5.11-4.93 (m, 4H, 2 x CH=CH_2), 4.84 (dd, *J* = 6.4, 3.5 Hz, 1H, CH_2C*H*OA_C), 3.38-3.34 (m, 1H, CHC(O)), 2.69 (s, 3H, N=C(S)CH_3), 2.58 (dd, *J* = 16.1, 2.8 Hz, 1H, CH_2CO_2), 2.52-2.41 (m, 3H), 2.10-1.98 (m, 11H), 1.88-1.79 (m, 2H), 1.55-1.29 (m, 6H), 1.24-1.12 (m, 6H), 1.05 (s, 3H, $C(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.63, 170.89, 169.96, 169.91, 164.78, 152.66, 138.82, 136.82, 133.50, 121.51, 117.97, 116.71, 114.82, 79.10, 74.66, 73.31, 52.18, 43.48, 37.56,

37.29, 36.52, 34.03, 30.85, 26.78, 26.45, 25.42, 21.40, 21.09, 19.97, 19.74, 19.44, 14.78; HRMS calcd for $C_{33}H_{48}NO_7S$ 602.31515 $[M + H]^+$, found 602.31448.

Preparation of Lactone 55. Procedure A: To a solution of diene **54** (7.5 mg, 0.0125 mmol, 1.0 equiv) in CH_2Cl_2 (12.5 mL, 0.001 M) was added Grubbs catalyst I (1.1 mg, 0.00125 mol, 10 mol %), and the reaction mixture was allowed to stir at 25 ^oC for 12 h. After the completion of the reaction as established by TLC, the solvent was removed under reduced pressure and the crude product was purified by preparative thin-layer chromatography (Hexanes/ethyl acetate, 3/1) to afford the *trans*-lactone **55** (6.0 mg, 84%) as a white foam. **Procedure B**: To a solution of diene **54** (15 mg, 0.0249 mmol, 1.0 equiv) in toluene (25 mL) was added with Grubbs catalyst I (2.1 mg, 0.00249 mol, 10 mol %), and the reaction mixture was allowed to stir at 80 ^oC for 12 h. After the reaction is complete, the mixture was worked up according to the procedure described in procedure A to furnish **55** (10.9 mg, 76%). **Procedure C**: Diene **54** (13 mg, 0.0216 mmol, 1.0 equiv) was converted to **55** (12.2 mg, 100%) in accordance with the procedure described in procedure A except for the use of Grubbs catalyst II (1.8 mg, 0.0022 mol, 10 mol %). **Procedure D**: Diene **54** (13 mg, 0.0216 mmol, 1.0 equiv) was converted to **55** (10.1 mg, 100%) in accordance with the procedure described in procedure B except for the use of Grubbs catalyst II (1.8 mg, 0.0022 mol, 10 mol %). **Procedure E**: Diene **54** (12 mg, 0.02 mmol, 1.0 equiv) was converted to **55** (10.8 mg, 95%) in accordance with the procedure described in procedure A except for the use of Hoveyda-Grubbs catalyst II (0.6 mg, 0.002 mol, 5 mol %). The crude reaction mixtures in procedures A, B, C, D and E were determined to be >20:1

ratio of diastereomeric *trans*-olefin by ^{1}H NMR spectroscopy. R_f = 0.37 (hexanes/ethyl acetate, 2/1); $[\alpha]^{22}_{D}$ -47.8 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 2926, 2862, 1731, 1707, 1504, 1443, 1371, 1239, 1180, 1029, 972, 916, 731 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 6.97 (s, 1H, SCH=C), 6.50 (s, 1H, C*H*=CCH_3), 5.87 (dd, *J* = 7.2, 5.2 Hz, 1H, CH_2C*H*OAc), 5.57 (ddd, *J* =14.4, 7.2, 7.2 Hz, 1H, C*H*=CH), 5.47 (ddd, *J* =14.4, 7.2, 7.2 Hz,, 1H, CH=C*H*), 5.31 (dd, *J* = 9.4, 1.9 Hz, 1H, C*H*OC(O)CH_2), 5.07 (s, 1H, CHC*H*OAc), 3.29-3.23 (m, 1H, CHC(O)), 2.69 (s, 3H, N=C(S)CH_3), 2.71-2.68 (m, 1H, CH_2CO_2), 2.62-2.56 (m, 2H), 2.41 (dd, *J* = 15.3, 4.9 Hz, 1H), 2.21-2.15 (m, 1H), 2.10 (s, 3H, ArCH=CC*H*$_3$), 2.05 (s, 3H, CH_3CO_2), 2.03 (s, 3H, CH_3CO_2), 1.98-1.89 (m, 2H), 1.86-1.76 (m, 1H), 1.72-1.67 (m, 2H), 1.57-1.493 (m, 3H), 1.40-1.35 (m, 2H), 1.33-1.21 (m, 2H), 1.14 (s, 3H, C(CH_3)$_2$), 1.07 (s, 3H, C(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.62, 170.71, 170.27, 169.21, 164.79, 152.88, 137.68, 132.67, 126.91, 119.64, 116.73, 79.62, 71.33, 70.48, 53.62, 41.94, 37.83, 37.71, 36.50, 31.30, 28.82, 26.94, 24.99, 24.09, 21.42, 21.24, 20.00, 19.89, 19.50, 18.87, 15.39; HRMS calcd for $C_{31}H_{44}NO_7S$ 574.28385 $[M + H]^+$, found 574.28292.

Preparation of *trans*-2,3-keto lactone 57. A mixture of lactone **55** (21 mg, 0.0366 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (2 mL) was treated with 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (55.7 mg, 0.366 mmol, 10.0 equiv) at room temperature. After being stirred for 3 h, no more **55** was detected from TLC. The solvent was removed under reduced pressure without further workup. The resultant residue was purified by preparative thin-layer chromatography (Hexanes/ethyl acetate, 4/1) to furnish product **57** (18.4 mg, 96%) as a colorless

oil: R_f = 0.51 (hexanes/ethyl acetate, 2/1); $[\alpha]^{22}{}_D$ +17.4 (*c* 1.68, $CHCl_3$); IR (thin film) ν_{max} 2929, 2861, 1713, 1645, 1503, 1444, 1379, 1362, 1294, 1242, 1177, 1048, 1017, 992, 970, 913, 879, 731 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.40 (d, *J* = 16.0 Hz, 1H, C*H*=CHC(O)), 6.96 (s, 1H, SCH=C), 6.61 (s, 1H, C*H*=CCH_3), 6.07 (d, *J* = 16.0 Hz, 1H, CH=C*H*C(O)), 5.56 (dd, *J* = 10.3, 2.2 Hz, 1H, C*H*OC(O)CH_2), 5.53-5.37 (m, 2H, CH_2C*H*=C*H*), 4.86 (s, 1H, CHC*H*OAc), 3.01-2.98 (m, 1H, CHC(O)), 2.71 (s, 3H, N=C(S)CH_3), 2.52-2.49 (m, 1H), 2.44-2.39 (m, 1H), 2.19-2.14 (m, 1H), 2.11 (s, 3H, ArCH=CC*H*$_3$), 2.00 (s, 3H, CH_3CO_2), 2.04-1.95 (m, 1H), 1.93-1.85 (m, 1H), 1.69-1.62 (m, 2H), 1.58-1.52 (m 1H), 1.50-1.37 (m, 3H), 1.26-1.12 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.45, 170.59, 165.38, 164.88, 152.72, 152.39, 138.22, 132.55, 127.20, 121.98, 112.00, 116.39, 77.77, 71.34, 51.91, 43.51, 39.24, 36.58, 33.09, 28.54, 26.72, 23.64, 23.29, 23.00, 22.79, 21.38, 19.46, 15.61; HRMS calcd for $C_{29}H_{40}NO_5S$ 514.26272 $[M + H]^+$, found 574.26186.

Preparation of Chloroacetyl Keto Acid 62. To a mixture of diol **47** (476.4 mg, 1.47 mmol, 1.0 equiv), pyridine (0.70 mL, 8.82 mmol, 6.0 equiv), and DMAP (18 mg, 0.147 mmol, 10 mol %) in CH_2Cl_2 (15 mL) was added chloroacetic anhydride (754 mg, 4.41 mmol, 3.0 equiv) at 0 ^oC. After being stirred for 2.5 h at 0 ^oC, the reaction mixture was quenched with saturated aqueous NH_4Cl. The organic phase was separated, and the aqueous phase was further extracted with CH_2Cl_2 (2 x 10 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash chromatography (hexanes/ethyl acetate, 2/1) to afford pure chloroacetyl epoxide intermediate (700

mg, 100%) as a colorless oil: R_f = 0.47 (hexanes/ethyl acetate, 2/1); $[\alpha]^{22}{}_D$ -32.9 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 3055, 2932, 2864, 1757, 1702, 1640, 1412, 1308, 1264, 1185, 1070, 992, 916, 896, 846, 782, 732, 703, 573 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.79 (tdd, *J* = 16.9, 10.2, 6.7, 6.7 Hz, 1H, C*H*=CH_2), 5.49 (dd, *J* = 10.6, 2.1 Hz, 1H, CHC*H*OAcCl), 5.04-4.96 (m, 3H, CH=C*H*$_2$, CH_2C*H*OAcCl), 4.13 (d, *J* = 1.0 Hz, 2H, $ClCH_2CO_2$), 4.05 (d, *J* = 2.8 Hz, 2H, $ClCH_2CO_2$), 3.41-3.36 (m, 1H, CHC(O)), 2.94 (m, 1H, C*H*O(epoxide)CH_2), 2.74-2.69 (t, *J* = 4.2 Hz, 1H, CHO(epoxide)C*H*$_2$), 2.41 (dd, *J* = 4.8, 2.7 Hz, 1H, CHO(epoxide)C*H*$_2$), 2.11-2.01 (m, 3H), 1.93-1.80 (m, 3H), 1.56-1.20 (m, 12H), 1.13 (s, 3H, $C(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.32, 167.25, 138.63, 115.08, 75.84, 52.06, 50.25, 46.17, 43.17, 41.28, 37.50, 34.24, 33.94, 30.41, 26.58, 25.86, 25.05, 21.02, 20.05, 19.55; HRMS calcd for $C_{23}H_{35}Cl_2O_6$ 477.18107 $[M + H]^+$, found 477.17990.

Epoxide as prepared above (360 mg, 0.754 mmol, 1.0 equiv) was taken up in THF/H_2O (16.5 mL, v/v, 10/1,) and treated sequentially at 0 °C with $NaIO_4$ (161.3 mg, 0.754 mmol, 1.0 equiv) and HIO_4•$2H_2O$ (343.8 mg, 1.508 mmol, 2.0 equiv). The resultant biphasic mixture was stirred at 0 °C for 10 min and then warmed to 25 °C. After 24 h, the reaction contents were quenched by the addition of saturated aqueous $NaHCO_3$, diluted with EtOAc (20 mL) and H_2O (10 mL). The organic phase was separated, and the aqueous phase was further extracted with EtOAc (2 x 10 mL). The combined organic layers were then washed with brine, dried over $MgSO_4$, and concentrated to give the desired crude intermediate aldehyde, which was unstable and went to following step without further purification.

The crude aldehyde obtained above was dissolved in *t*-BuOH (4 mL, 0.2 M), 2-methyl-2-butene (1.5 mL, 2 M solution in THF, 3.02 mmol, 4.0 equiv), H_2O (0.75 mL). The resultant mixture was treated with $NaClO_2$ (204.6 mg, 2.26 mmol, 3.0 equiv), and NaH_2PO_4 (156.1 mg, 1.13 mmol, 1.5 equiv). After stirring for 5 h, the reaction mixture wad concentrated under reduced pressure, and the residue was subjected to flash column chromatography (gradient elution, hexanes/ethyl acetate, 5/1→ 2/1, then 1/1 with 1% HCO_2H) to furnish keto acid **62** (266.1 mg, 72%, 2 steps) as a colorless oil: R_f = 0.41 (hexanes/ethyl acetate, 1/1 with 1% HOAC); $[\alpha]^{22}{}_D$ -41.6 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 3076(br), 2933, 2864, 1744, 1710, 1640, 1411, 1306, 1287, 1259, 1182, 1163, 984, 914, 751, 700, 667, cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.78 (tdd, *J* = 16.9, 10.2, 6.6, 6.6 Hz, 1H, C*H*=CH_2), 5.56 (dd, *J* = 9.6, 2.4 Hz, 1H, CHC*H*OAcCl), 5.02-4.95 (m, 3H, CH_2C*H*OAcCl, CH=CH_2), 4.06 (d, *J* = 2.4 Hz, 2H, $ClCH_2CO_2$), 4.05 (d, *J* = 3.6 Hz, 2H, $ClCH_2CO_2$), 3.39-3.36 (m, 1H, CHC(O)), 2.65 (dd, *J* = 16.4, 2.8 Hz, 1H, CH_2CO_2), 2.45 (dd, *J* = 16.4, 9.3 Hz, 1H, CH_2CO_2), 2.07-2.02 (m, 3H), 1.86-1.82 (m, 2H), 1.57-1.51 (m, 1H), 1.50-1.43 (m, 6H), 1.28 (bs, 2H), 1.26 (s, 3H, $C(CH_3)_2$), 1.13 (s, 3H, $C(CH_3)_2$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 212.08, 176.12, 167.31, 166.68, 138.62, 115.05, 75.76, 75.12, 52.14, 43.33, 41.25, 40.94, 37.48, 35.82, 33.91, 30.33, 26.54, 25.79, 25.10, 21.16, 19.95, 19.51; HRMS calcd for $C_{22}H_{32}Cl_2O_7Na$ 501.14228 $[M + Na]^+$, found 501.14136.

Chloroacetyl Keto Ester 63. To a stirred solution of keto acid **62** (95 mg, 0.20 mmol, 1.0 equiv), alcohol **24** (46 mg, 0.22 mmol, 1.1 equiv), and triethylamine (110.2 mg, 1.1 mmol, 5.5 equiv) in toluene (10 mL) were

subsequently added at -78 °C a solution of 4-dimethylaminopyridine (2.4 mg, 0.02 mmol, 10 mol%) in toluene (0.5 mL) and 2,4,6-trichlorobenzoyl chloride (241.5 mg, 1.0 mmol, 5.0 equiv). The reaction was warmed to -35 °C in 1 h, and the resulted white slurry was stirred at -35 °C for 2 h before being quenched with saturated aqueous NH_4Cl at -35 °C. After separation, the aqueous phase was further extracted with ethyl EtOAc (2 x 10 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated. The resultant residue was purified by flash chromatography (hexanes/ethyl acetate, 2/1) to afford pure **63** (65 mg, 49%) as a colorless oil: R_f = 0.46 (hexanes/ethyl acetate, 2/1); $[\alpha]^{22}_{D}$ -11.5 (*c* 0.9, $CHCl_3$); IR (thin film) ν_{max} 3076, 2930, 2862, 1735, 1701, 1641, 1505, 1444, 1412, 1370, 1290, 1179, 990, 916, 877, 784, 732 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.96 (s, 1H, SCH=C), 6.47 (s, 1H, C*H*=CCH_3), 5.82-5.75 (m, 1H, C*H*=CH_2), 5.74-5.67 (m, 1H, C*H*=CH_2), 5.63 (dd, *J* = 9.9, 2.7 Hz, 1H, CHC*H*OAcCl), 5.29 (t, *J* = 6.2, 6.2 Hz, 1H, C*H*OC(O)CH_2), 5.11-4.95 (m, 5H, 2 x CH=CH_2, CH_2C*H*OA_CCl), 4.05 (d, *J* = 2.1 Hz, 2H, $ClCH_2CO_2$), 4.00 (d, *J* = 2.0 Hz, 2H, $ClCH_2CO_2$), 3.40-3.37 (m, 1H, CHC(O)), 2.70 (s, 3H, N=C(S)CH_3), 2.62 (dd, *J* = 16.2, 2.7 Hz, 1H, CH_2CO_2), 2.49-2.42 (m, 3H), 2.09-1.99 (m, 6H), 1.88-1.80 (m, 2H); 1.58-1.34 (m, 6H), 1.31-1.24 (m, 5H), 1.11 (s, 3H, C(CH_3)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.17, 169.60, 167.25, 166.52, 164.93, 152.53, 138.64, 136.86, 133.35, 121.25, 118.12, 116.72, 115.04, 79.16, 75.80, 75.41, 52.16, 43.46, 41.27, 41.03, 37.53, 37.46, 36.17, 33.93, 30.32, 26.59, 25.76, 24.99, 21.30, 20.09, 19.52, 19.44, 14.92; HRMS calcd for $C_{33}H_{46}Cl_2NO_7S$ 670.23720 $[M + H]^+$, found 670.23669.

Preparation of Compound 64. To a solution of diene **63** (60 mg, 0.089mmol,

1.0 equiv) in CH_2Cl_2 (89 mL, 0.001 M) was added Hoveyda-Grubbs catalyst II (11 mg, 0.018 mol, 20 mol %), and the reaction mixture was allowed to stir at 25 ^oC for 24 h. After the completion of the reaction as established by TLC, the solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (gradient elution, hexanes/ethyl acetate, 10/1→ 2/1,) to afford the *trans*-lactone **64** (44.4 mg, 77%) as a white foam. R_f = 0.41 (hexanes/ethyl acetate, 2/1); $[\alpha]^{22}_D$ +36.9 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 2928, 2863, 1732, 1707, 1504, 1445, 1410, 1289, 1263, 1182, 1075, 1048, 1010, 975, 900, 785, 733, 702, 572 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.98 (s, 1H, SCH=C), 6.49 (s, 1H, C*H*=CCH_3), 5.94 (dd, *J* = 9.6, 1.2 Hz, 1H, CHC*H*OAcCl), 5.60 (ddd, *J* = 14.6, 7.2, 7.2 Hz, 1H, C*H*=CH), 5.48 (ddd, *J* = 14.8, 7.4, 7.4 Hz, 1H, C*H*=CH), 5.43 (t, *J* = 5.7, 5.7 Hz, 1H, C*H*OC(O)CH_2), 5.18 (s, 1H, CH_2C*H*OA_CCl), 4.15 (d, *J* = 7.2 Hz, 2H, $ClCH_2CO_2$), 4.08 (d, *J* = 3.6 Hz, 2H, $ClCH_2CO_2$), 3.10 (dd, *J* = 10.8, 1.8 Hz, 1H, CHC(O)), 2.70 (s, 3H, N=C(S)CH_3), 2.64 (dd, *J* = 15.6, 1.2 Hz, 1H, CH_2CO_2), 2.56 (dd, *J* = 15.6, 11.4 Hz, 1H, CH_2CO_2), 2.50-2.45 (m, 2H), 2.18-2.13 (m, 1H), 2.08 (s, 3H, CH=CC*H*$_3$), 2.97-1.90 (m, 2H), 1.83-1.74 (m, 2H), 1.63-1.50 (m, 4H), 1.46-1.39 (m, 2H), 1.37-1.31 (m, 2H), 1.10 (s, 3H, C(CH_3)), 1.09 (s, 3H, C(CH_3)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.52, 169.49, 167.27, 167.02, 164.83, 152.84, 137.20, 133.11, 126.35, 119.27, 116.61, 78.18, 74.60, 73.04, 53.46, 42.05, 41.51, 40.95, 37.00, 36.93, 35.16, 31.26, 28.21, 27.12, 24.49, 23.78, 21.53, 19.86, 19.49, 19.11, 15.91; HRMS calcd for $C_{31}H_{42}Cl_2NO_7S$ 642.20590 $[M + H]^+$, found 642.20502.

Preparation of Hydroxy Lactone 56. A solution of chlorolactone **64** (60 mg,

0.093 mmol) in methanol (10 mL) at 0 ^{o}C was treated with ammonium hydroxide (0.5 mL), and stirred at that temperature until the reaction was complete (ca. 12 h). The solvent was removed under reduced pressure to give white foam. Next, the white foam was dissolved in methanol (10 mL), and treated with amino methanol (1mL, 7N in methanol) at 0 ^{o}C. After being stirred for 48 h, ^{1}H NMR suggested the reaction was complete. The solvent was removed under reduced pressure and the residue was purified by preparative thin-layer chromatography (Hexanes/ethyl acetate, 15/4) to afford hydroxy lactone **56** (26 mg, 57%) as a white foam: R_f = 0.38 (CH_2Cl_2/MeOH, 15:1); $[\alpha]^{22}{}_{D}$ –11.6 (*c* 0.85, $CHCl_3$); IR (thin film) ν_{max} 3486 (br), 2930, 2860, 1729, 1679, 1505, 1444, 1405, 1374, 1336, 1297, 1247, 1177, 1123, 1085, 1046, 984, 915, 865, 726, 676 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.96 (s, 1H, SCH=C), 6.52 (s, 1H, C*H*=CCH_3), 5.48 (dd, *J* = 9.8, 3.7 Hz, 1H, C*H*OC(O)), 5.45-5.40 (m, 1H, C*H*=CH), 5.37-5.32 (m, 1H, C*H*=CH), 4.41 (dd, *J* = 10.5, 1.8 Hz, 1H, C*H*OHC$(CH_3)_2$), 4.16 (s, 1H, CHCHO*H*), 3.67 (d, *J* = 1.5 Hz, 1H, CHO*H*C$(CH_3)_2$), 3.65 (d, *J* = 2.5 Hz, 1H, CHC*H*OH), 2.81 (d, *J* = 10.4 Hz, 1H, CHC(O)), 2.70 (s, 3H, N=C(S)CH_3), 2.50-2.42 (m, 3H), 2.24-2.19 (m, 1H), 2.17 (d, *J* = 17.0 Hz, 1H, CH_2CO_2), 2.07 (s, 3H, CH=CC*H*$_3$), 1.93-1.83 (m, 3H), 1.73 (bs, 1H), 1.59-1.52 (m, 3H), 1.51-1.43 (m, 1H), 1.34-1.22 (m, 5H), 1.21-1.12 (m, 2H), 1.02 (s, 3H, C$(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 221.27, 173.30, 165.04, 152.42, 137.41, 134.02, 126.68, 120.60, 116.80, 79.52, 71.59, 71.53, 53.85, 43.83, 38.41, 37.97, 36.69, 31.70, 28.14, 27.45, 24.84, 24.27, 22.49, 20.64, 19.46, 16.05, 15.12; HRMS calcd for $C_{27}H_{40}NO_5S$ 490.26272 $[M + H]^+$, found 490.26064.

Preparation of *gem*-Dimethyl Olefin 79. First a crude aldehyde was

prepared from olefin **38** (11.18 g, 30.0 mmol, 1 equiv) by ozonolysis according to the same procedure described above to prepare **39**.

Next Isopropyltriphenylphosphonium iodide (19.45 g, 45 mmol, 1.5 equiv) was suspended in 100 mL THF, cooled to 0 °C, and to this mixture was added slowly *n*-BuLi (18 mL, 2.5 M in hexane, 45 mmol, 1.5 equiv). The solution was stirred for 30 min at 0 °C and the above crude aldehyde was added slowly to form a red solution. After 3h, the reaction was quenched with 5 mL water, extracted with diethyl either (50 mL x 3), dried over $MgSO_4$. After filtration, the filtrate was condensed and the residue was diluted by hexane (100 mL). The resulting triphenylphosphine oxide was filtered through celite, and the filtrate was concentrated under reduced pressure. The residues were purified by column chromatography using hexane as eluent to afford **70** (9.61 g, 80 %, 2 steps) as a colorless oil. R_f = 0.71 (hexanes); $[\alpha]^{22}{}_D$ -3.7 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 2957, 2930, 2887, 2860, 1471, 1390, 1363, 1254, 1081, 1007, 938, 833, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.19 (m, 1H, CH=C), 3.60 (dd, *J* = 6.9, 4.1 Hz, 1H, SiOCH), 3.31 (q, *J* = 9.5 Hz, 2H, OCH_2C), 2.30-2.18 (m, 1H, CH_2CH), 2.07 (td, *J* = 15.2, 7.7 Hz, 1H, CH_2CH), 1.68 (s, 3H, CH=C(CH_3)$_2$), 1.59 (s, 3H, CH=C(CH_3)$_2$), 0.89 (s, 9H, SiC(CH_3)$_3$), 0.88 (s, 9H, SiC(CH_3)$_3$), 0.84 (s, 3H, C(CH_3)$_2$), 0.80 (s, 3H, C(CH_3)$_2$), 0.02 (s, 3H, Si(CH_3)$_2$), 0.02 (s, 6H, Si(CH_3)$_2$), 0.00 (s, 3H, Si(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.27, 123.97, 76.60, 69.93, 41.08, 31.98, 26.34, 26.16, 26.07, 21.44, 20.72, 18.55, 18.49, 18.11, -3.49, -4.16, -5.18, -5.31; HRMS calcd for $C_{22}H_{49}O_2Si_2$ 401.32711 $[M + H]^+$, found 401.32745.

Preparation of Aldehyde 69. To a stirred solution of silyl either **70** (9.61 g,

24 mmol) in THF (100 mL) in a Nalgene bottle was added freshly prepared pyridinium hydrofluoride buffer (stock solution prepared from 40 mL of Adrich pyridinium hydrofluoride, 100 mL of pyridine, and 160 m of THF) in 30 min at 0 ^{o}C. The reaction was allowed to warm to room temperature and stirred for 24 h, at which time all starting material disappeared from TLC. The reaction mixture was poured into saturated aqueous $NaHCO_3$, and extracted with hexanes (3x100 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (hexanes/ethyl acetate, 10/1) furnished primary alcohol intermediate (4.97 g, 72%) as a colorless oil. R_f = 0.39 (hexanes/ethyl acetate, 10/1); $[\alpha]^{22}{}_{D}$ -0.8 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 3459, 2961, 2930, 2887, 2860,1475, 1386, 1363, 1254, 1085, 1054, 938, 833, 810, 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.24-5.16 (m, 1 H, C*H*=C), 3.74 (dd, *J* = 10.8, 3.0 Hz, 1 H, OCH_2C), 3.56 (t, *J* = 5.4 Hz, 1 H, SiOCH), 3.25 (dd, *J* = 10.8, 7.8 Hz, 1 H, OCH_2C), 2.96 (dd, *J* = 7.8, 3.0 Hz, 1 H, OH), 2.39-2.33 (m, 1 H, CH_2CH=C), 2.21 (td, *J* = 15.6, 6.8 Hz, 1H, CH_2CH=C), 1.69 (s, 3 H, CH=C(CH_3)$_2$), 1.60 (s, 3 H, CH=C(CH_3)$_2$), 1.04 (s, 3H, C(OH)C(CH_3)$_2$), 0.89 (s, 9 H, SiC(CH_3)$_3$), 0.79 (s, 3 H, C(OH)C(CH_3)$_2$), 0.08 (s, 3 H, Si(CH_3)$_2$), 0.05 (s, 3 H, Si(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.35, 122.71, 81.27, 70.49, 39.66, 32.32, 26.20, 26.06, 24.11, 22.20, 18.33, 18.17, -3.71, -4.23; HRMS calcd for $C_{16}H_{35}O_2Si$ 287.24063 $[M + H]^+$, found 287.23999.

Next, oxalyl chloride (2.6 g, 20.5 mmol, 1.2 equiv) was added at -78 °C to a solution of DMSO (3.2 g, 2.9 mL, 41.0 mmol, 2.4 equiv) in dry CH_2Cl_2 (70 mL) and the mixture stirred for 1 h at that temperature. A solution of alcohol intermediate

(4.9 g, 17.1 mmol, 1 equiv) as described above in anhydrous CH_2Cl_2 (10 mL) was added slowly (ca. 30 min) and the mixture was stirred for 1 h at -78 ^oC. After that, the mixture was carefully treated with triethylamine (9.6 mL, 68.8 mmol, 4 equiv) at -78 °C. After stirred for another 1 h, the reaction was allowed to warm to room temperature, and then saturated $NaHCO_3$ was added to dissolve the salts. After separation, the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organics were washed with saturated aqueous $NaHCO_3$, dried with $MgSO_4$, filtered, and concentrated by rotary evaporation. The residue wad diluted by hexanes (100 mL) and washed with sat. aqueous $NaHCO_3$ solution (100 mL x 3), dried over $MgSO_4$, filtered and concentrated to provide crude aldehyde as light yellow oil which was purified by flash column chromatography to provide **69** as a colorless oil (4.9 g, 100%) which was pure enough as suggested by ^1H NMR and was used as crude in following step unless a small portion was purified by column chromatography (hexanes/ethyl acetate, 10/1) for characterization: R_f = 0.53 (hexanes/ethyl acetate, 10/1); $[\alpha]^{22}_{D}$ +6.5 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 2957, 2930, 2887, 2860,1729, 1467, 1378, 1254, 1085, 1023, 934, 833, 810, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.54 (s, 1H, CHO), 5.12-5.06 (m, 1 H, C*H*=$C(CH_3)_2$), 3.81 (t, *J* = 5.8 Hz, 1 H, SiOCH), 2.20-2.17 (m, 2 H, CH_2CH=C), 1.67 (s, 3 H, CH=C(CH_3)$_2$), 1.58 (s, 3 H, CH=C(CH_3)$_2$), 1.04 (s, 3H, C(O)$C(CH_3)_2$), 1.02 (s, 3 H, C(O)$C(CH_3)_2$), 0.88 (s, 9 H, $SiC(CH_3)_3$), 0.05 (s, 3 H, $Si(CH_3)_2$), 0.04 (s, 3 H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.0, 134.02, 121.24, 76.96, 51.61, 32.77, 26.11, 26.04, 18.96, 18.67, 18.37, 18.28, -3.61, -4.35; HRMS calcd for $C_{16}H_{33}O_2Si$ 285.22498 $[M + H]^+$, found 285.22425.

Preparation of Alcohol 68. Alcohol **68** was prepared from aldehyde **69** (4.27 g, 15.0 mmol) by treatment with borane **28** according to the same procedure described above for the preparation of **41**, to obtain pure alcohol **68** (5.26 g, 96%) as a colorless oil: R_f = 0.53 (hexanes/ethyl acetate, 20/1); $[\alpha]^{22}{}_D$ +17.5 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 3483, 2954, 2927, 2856, 1471, 1388, 1361, 1252, 1061, 1004, 931, 811, 772, 718 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.82-5.77 (m, 1H, CH_2CH=CHCH), 5.63-5.49 (m, 1H, CH_2CH=C*H*CH), 5.26-5.09 (m, 1H, C*H*=$C(CH_3)_2$), 3.94 (s, 1H, OH), 3.85 (d, *J* = 3.1 Hz, 1H, C*H*OH), 3.43 (dd, *J* = 6.8, 4.0 Hz, 1H, SiOCH), 2.40 (m, 1H, CH_2CH=$C(CH_3)_2$), 2.34-2.19 (m, 2H), 2.14-1.85 (m, 2H), 1.84-1.70 (m, 3H), 1.69 (s, 3H, CH=$C(CH_3)_2$), 1.60 (s, 3H, CH=$C(CH_3)_2$), 1.56-1.41 (m, 1H), 1.07 (s, 3H, $C(OH)C(CH_3)_2$), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.84 (s, 3H, $C(OH)C(CH_3)_2$), 0.09 (s, 3H, $Si(CH_3)_2$), 0.05 (s, 3H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.52, 132.44, 128.70, 123.07, 85.92, 77.68, 42.12, 38.54, 32.07, 26.28, 26.04, 24.93, 23.86, 23.71, 22.75, 22.23, 18.40, 18.23, -3.82, -4.08; HRMS calcd for $C_{22}H_{43}O_2Si$ 367.30323 $[M + H]^+$, found 367.30261.

Preparation of Hydroxy Epoxide 71. Homoallylic alcohol **68** (1.47 g, 4.0 mmol) was converted into epoxide **71** (1.42 g, 93%) according to the procedure described above for **42**, as a colorless oil: R_f = 0.38 (hexanes/ethyl acetate, 10/1); $[\alpha]^{22}{}_D$ +8.5 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 3474, 2954, 2928, 2884, 2856, 1471, 1360, 1251, 1063, 1003, 983, 935, 833, 809, 773, 773, 737, 666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.24-5.09 (m, 1H, C*H*=$C(CH_3)_2$), 4.16 (s, 1H, OH), 4.03 (d, *J* = 5.2 Hz, 1H, C*H*OH), 3.50 (dd, *J* = 7.3, 3.6 Hz, 1H, SiOCH), 3.14 (td, *J* = 5.4, 2.8 Hz, 1H, CH_2CHO(epoxide)CH), 3.08 (dd, *J* = 4.0, 2.8 Hz, 1H,

CHO(epoxide)C*H*CH), 2.51-2.35 (m, 1H, C*H*$_2$CH=C(CH$_3$)$_2$), 2.28 (td, *J* = 15.3, 7.6 Hz, 1H, C*H*$_2$CH=C(CH$_3$)$_2$), 2.01 (m, 1H, C*H*(CHOH)CH$_2$), 1.82 (m, 2H), 1.68 (s, 3H, CH=C(C*H*$_3$)$_2$), 1.60 (s, 3H, CH=C(C*H*$_3$)$_2$), 1.65-1.47 (m, 2H), 1.46-1.32 (m, 1H), 1.27-1.11 (m, 1H), 1.05 (s, 3H, C(OH)C(C*H*$_3$)$_2$), 0.93 (s, 3H, C(OH)C(C*H*$_3$)$_2$), 0.88 (s, 9H, SiC(CH$_3$)$_3$), 0.09 (s, 3H, Si(CH$_3$)$_2$), 0.04 (s, 3H, Si(CH$_3$)$_2$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 132.54, 123.22, 84.89, 76.37, 56.00, 53.09, 42.11, 37.72, 31.91, 26.25, 26.03, 24.14, 23.70, 21.48, 20.09, 18.40, 18.21, -3.80, -4.03; HRMS calcd for $C_{22}H_{43}O_3Si$ 383.29815 $[M + H]^+$, found 383.29770.

Preparation of Diol 72. To a mixture of hydroxy epoxide **71** (1.42 g, 3.71 mmol, 1.0 equiv), CuCN (33.2 mg, 0.37 mmol, 0.1 equiv) in dry THF (10 mL) was added allylmagnesium bromide (29.7 mL, 1.0 M in Et$_2$O, 29.7 mmol, 8.0 equiv) dropwise at -78 °C. The solution was warmed to 0 °C over 2 h and quenched by saturated NH$_4$Cl with vigorous stirring. The mixture was extracted with diethyl ether (3 x 20 mL). The combined extracts were dried over MgSO$_4$ and concentrated to furnish a residue, which was purified by chromatography (gradient elution, hexanes →4/1, hexanes/ethyl acetate) to afford diol **72** (1.34 g, 85%) as a colorless oil: R_f = 0.58 (hexanes/ethyl acetate, 4/1); $[\alpha]^{22}_{D}$ -31.9 (*c* 1.0, CHCl$_3$); IR (thin film) ν_{max} 3417(br), 2928, 2856, 1640, 1471, 1442, 1388, 1360, 1251, 1064, 1002, 983, 929, 909, 834, 809, 774, cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.83-5.71 (m, 1H, CH$_2$=C*H*CH$_2$), 5.16 (t, *J* = 6.4 Hz, 1H, C*H*=C(CH$_3$)$_2$), 4.98 (d, *J* = 6.9 Hz, 1H, C*H*$_2$=CH), 4.96 (s, 1H, C*H*$_2$=CH), 4.40 (s, 1H, OH), 4.05 (s, 1H, C*H*OH), 3.97 (s, 1H, C*H*OH), 3.71 (s, 1H, OH), 3.43 (t, *J* = 5.4 Hz, 1H, CHOSi), 2.44-2.32 (m, 1H, C*H*$_2$CH=C(CH$_3$)$_2$), 2.27-2.20 (m, 1H, C*H*$_2$CH=C(CH$_3$)$_2$),

2.12-2.04 (m, 2H, CH_2CH=CH_2), 1.90-1.76 (m, 3H), 1.69 (s, 3H, CH=C(CH_3)$_2$), 1.61 (s, 1H), 1.59 (s, 3H, CH=C(CH_3)$_2$), 1.51 (s, 1H), 1.49 (s, 1H), 1.38 (tt, *J* = 12.78, 3.25 Hz, 1H), 1.30 (d, *J* = 13.11 Hz, 1H), 1.07 (s, 3H, C(OH)C(CH_3)$_2$), 0.88 (s, 9H, SiC(CH_3)$_3$), 0.79 (s, 3H, C(OH)C(CH_3)$_2$), 0.08 (s, 3H, Si(CH_3)$_2$), 0.05 (s, 3H, Si(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.00, 132.67, 122.65, 115.54, 86.26, 79.49, 77.36, 42.04, 39.77, 37.20, 35.22, 32.13, 26.20, 26.03, 23.63, 23.27, 23.22, 20.74, 20.55, 18.35, 18.24, -3.80, -4.22; HRMS calcd for $C_{25}H_{49}O_3Si$ 425.34510 $[M + H]^+$, found 425.34453.

Preparation of Silyl Ether 73. A mixture of alcohol **72** (1.52 g, 3.58 mmol, 1.0 equiv) and 2,6-lutidine (0.83 mL, 7.16 mmol, 2.0 equiv) in CH_2Cl_2 (40 mL) was treated with *tert*-butyldimethylsilyl triflate (1.42 g, 5.37 mmol, 1.5 equiv) dropwise at -78 °C. The reaction mixture was stirred at -78 °C until all starting material disappeared from TLC (cat. 1 h). After quenching with saturated aqueous NH_4Cl solution, the reaction mixture was allowed to warm to room temperature. The organic phase was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification by flash column chromatography (hexanes/ethyl acetate, 20/1) afforded **73** (1.88 g, 97%) as a colorless oil: R_f = 0.45 (hexanes/ethyl acetate, 20/1); $[\alpha]^{22}_D$ -3.0 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 3493, 2928, 2856, 1640, 1471, 1387, 1361, 1251, 1064, 1003, 931, 911, 833, 811, 772, 669 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.74 (tdd, *J* = 17.0, 10.0, 7.0 Hz, 1H, CH_2=C*H*CH_2), 5.16 (t, *J* = 6.3 Hz, 1H, C*H*=C(CH_3)$_2$), 5.01 (d, *J* = 10.3 Hz, 1H, CH_2=CH), 4.98 (s, 1H, CH_2=CH), 3.69 (s, 1H, C*H*OH), 3.61 (s, 1H,

CHC*H*OSi), 3.56 (dd, *J* = 7.0, 3.33 Hz, 1H, SiOC*H*CH_2), 3.44 (s, 1H, OH), 2.38-2.26 (m, 1H, C*H*$_2$CH=C$(CH_3)_2$), 2.19 (td, *J* = 15.2, 7.5 Hz, 1H, C*H*$_2$CH=C$(CH_3)_2$), 2.09 (t, *J* = 7.1 Hz, 2H, C*H*$_2$CH=CH_2), 1.84-1.72 (m, 1H), 1.70 (m, 2H), 1.68 (s, 3H, CH=C(C*H*$_3)_2$), 1.59 (s, 3H, CH=C(C*H*$_3)_2$), 1.52 (m, 2H), 1.46-1.32 (m, 1H), 1.32-1.23 (m, 2H), 0.94 (s, 3H, C(OH)C(C*H*$_3)_2$), 0.93 (s, 9H, SiC$(CH_3)_3$), 0.88 (s, 9H, SiC$(CH_3)_3$), 0.81 (s, 3H, C(OH)C(C*H*$_3)_2$), 0.10 (s, 3H, Si$(CH_3)_2$), 0.08 (s, 3H, Si$(CH_3)_2$), 0.07 (s, 3H, Si$(CH_3)_2$), 0.03 (s, 3H, Si$(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.68, 131.98, 123.75, 116.00, 81.55, 77.26, 76.81, 43.16, 41.22, 37.73, 35.68, 32.11, 26.37, 26.16, 26.07, 24.27, 22.41, 21.83, 20.94, 20.58, 18.49, 18.33, 18.19, -3.47, -3.70, -3.90, -4.23; HRMS calcd for $C_{31}H_{63}O_3Si_2$ 539.43517 $[M + H]^+$, found 539.43103. NOESY (600 MHz, $CDCl_3$) confirmed the relative configuration between the protons at C5, C6 and C7.

Preparation of Ketone 67. To a solution of dimethylsulfoxide (0.46 mL, 6.48 mmol, 2.4 equiv) in dry dichloromethane (15 mL) was added dropwise oxalyl chloride (411.2 mg, 3.24 mmol, 1.2 equiv) at -78 °C. After stirring for 1 h at that temperature, a solution of alcohol **73** (1.46 g, 2.7 mmol, 1.0 equiv) in anhydrous dichloromethane (15 mL) was added slowly (ca. 20 min). The mixture was stirred for 12 h and was carefully treated with triethylamine (1.51 mL, 10.8 mmol, 4 equiv) at -78 °C. After being stirred for another 12 h, the reaction was allowed to warm to room temperature, followed with quench with saturated aqueous $NaHCO_3$ to dissolve the salts. The organic phase was separated, and the aqueous layer was further extracted with dichloromethane (2 x 20 mL). The combined organics were washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and

concentrated by rotary evaporation to afford the crude ketone as a yellow oil residue which was purified by flash column chromatography (gradient elution, hexanes/CH_2Cl_2, 10/1→ 4/1) to provide **67** (1.24 g, 85%) as a colorless oil: R_f = 0.49 (hexanes/ethyl acetate, 20/1); $[\alpha]^{22}{}_D$ -50.3 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 2952, 2927, 2856, 1698, 1640, 1471, 1462, 1360, 1250, 1080, 1024, 1005, 934, 911, 810, 771, 671 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.77 (tdd, *J* = 17.0, 10.0, 6.9 Hz, 1H, CH_2=C*H*CH_2), 5.04 (m, 3H, C*H*=C$(CH_3)_2$, CH_2=CH), 3.88 (s, 1H, SiOCH), 3.68 (s, 1H, SiOCH), 3.15 (d, *J* = 10.3 Hz, 1H, CHC(O)), 2.31-2.15 (m, 1H), 2.11-1.96 (m, 3H), 1.96-1.86 (m, 2H), 1.83 (tt, *J* = 12.9, 4.4 Hz, 1H), 1.65 (s, 3H, CH=C(C$H_3)_2$), 1.54 (s, 3H, CH=C(C$H_3)_2$), 1.52-1.42 (m, 1H), 1.41-1.13 (m, 6H), 1.03 (s, 3H, C(O)C$(CH_3)_2$), 0.90 (s, 9H, SiC$(CH_3)_3$), 0.88 (s, 9H, SiC$(CH_3)_3$), 0.07 (s, 3H, Si$(CH_3)_2$), 0.02 (s, 3H, Si$(CH_3)_2$), 0.01 (s, 3H, Si$(CH_3)_2$), -0.03 (s, 3H, Si$(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.56, 137.64, 132.50, 123.04, 116.17, 79.61, 71.81, 53.46, 47.37, 41.15, 35.78, 33.80, 26.32, 26.07, 25.15, 23.10, 20.10, 19.90, 18.46, 18.28, 18.13, -3.57, -3.77, -3.83, -4.26; HRMS calcd for $C_{31}H_{61}O_3Si_2$ 537.41592 $[M + H]^+$, found 537.41814.

Preparation of Keto Acid 74. To a solution of diene **67** (215 mg, 0.4 mmol, 1.0 equiv) in *t*-BuOH (4 mL) and H_2O (2 mL) was added $(DHQD)_2PHAL$ (15.6 mg, 0.02 mmol, 5 mol %), and the reaction was cooled to 0 °C. Then to the reaction was consequently added K_2CO_3 (165.9 mg, 1.2 mmol, 3.0 equiv), $K_3Fe(CN)_6$ (395.1 mg, 1.2 mmol, 3.0 equiv), $CH_3SO_2NH_2$ (57 mg, 0.6 mmol, 1.5 equiv) and K_2OsO_4•2 H_2O (1.5 mg, 0.004 mmol, 1 mol%). The yellow/orange slurry was stirred for 24 h at 0 °C at which time the reaction was quenched with solid

$Na_2S_2O_3$ (600 mg). After being stirred for 20 min at room temperature, ethyl acetate (10 mL) and water (10 mL) were added to the reaction mixture. After separation, the aqueous phase was further extracted with the ethyl acetate (2 x 10 mL). The combined organics were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. Purification by flash chromatography (gradient elution, hexanes/ethyl acetate, 10/1→ 4/1) yielded 36.9 mg of starting diene **67** and 181.5 mg (79% yield, 96% BORSM) of selectively dihydroxylated intermediate as a ca. 5:1 mixture of diastereisomers by ^{1}H NMR. The mixture underwent the following step without further separation unless a small portion of the mixtures was isolated by preparative thin-layer chromatography (hexanes/ethyl acetate, 6:1) for characterization, major isomer: R_f = 0.34 (hexanes/ethyl acetate, 4/1); $[\alpha]^{22}{}_D$ -4.0 (*c* 0.33, $CHCl_3$); IR (thin film) ν_{max} 3489 (br), 2953, 2930, 2895, 2860, 1695, 1640, 1471, 1444, 1386, 1363, 1289, 1251, 1162, 1085, 1027, 1004, 977, 938, 911, 838, 776, 672 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.76 (tdd, *J* = 17.0, 10.1, 6.9, 6.9 Hz, 1H, C*H*=CH_2), 5.07-5.03 (m, 2H, CH=C*H*$_2$), 4.11 (s, 1H), 3.85 (bs, 1H), 3.20 (s, 1H), 3.03 (d, *J* = 11.2 Hz, 1H, CHC(O)), 2.76 (s, 1H), 2.32 (s, 1H), 2.29 (bs, 1H), 2.04-1.94 (m, 2H), 1.88-1.79 (m, 1H), 1.68-1.56 (m, 2H), 1.45-1.33 (m, 3H), 1.31-1.78 (m, 5H), 1.14 (s, 3H, C(C*H*$_3$)$_2$OH), 1.10 (s, 3H, C(O)C(CH_3)), 1.07 (s, 3H, C(O)C(CH_3)), 0.91 (s, 9H, SiC(CH_3)$_3$), 0.88 (s, 9H, SiC(CH_3)$_3$), 0.13 (s, 3H, Si(CH_3)$_2$), 0.10 (s, 3H, Si(CH_3)$_2$), 0.04 (s, 3H, Si(CH_3)$_2$), 0.00 (s, 3H, Si(CH_3)$_2$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 216.70, 137.50, 116.29, 75.36, 72.70, 53.07, 47.27, 40.82, 37.20, 36.11, 26.28, 26.25, 26.09, 25.55, 23.66, 20.03, 18.89, 18.35, 18.30, -3.77, -3.79, -4.08; HRMS

calcd for $C_{31}H_{62}O_5Si_2Na$ 593.40335 $[M + Na]^+$, found 593.40265. Minor isomer: R_f = 0.26 (hexanes/ethyl acetate, 4/1); $[\alpha]^{22}{}_D$ +30.3 (*c* 1.41, $CHCl_3$); IR (thin film) ν_{max} 3489 (br), 2957, 2930, 2899, 2860, 1698, 1640, 1471, 1444, 1363, 1254, 1162, 1081, 1027, 1007, 973, 934, 915, 838, 776, 672 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.76 (tdd, *J* = 17.0, 10.2, 6.9, 6.9 Hz, 1H, C*H*=CH_2), 5.06-5.02 (m, 2H, CH=C*H*$_2$), 4.00 (d, *J* = 6.8 Hz, 1H), 3.77 (bs, 1H), 3.53 (ddd, *J* = 11.5, 4.1, 1.6 Hz, 1H, C*H*OH), 3.18 (d, *J* = 8.1 Hz, 1H, CHC(O)), 2.98 (s, 1H), 2.29 (bs, 1H), 2.14 (s, 1H), 2.09-1.89 (m, 2H), 1.90-1.81 (m, 1H), 1.50-1.19 (m, 10H), 1.16 (s, 3H, C(C*H*$_3$)$_2$OH), 1.09 (s, 3H, C(CH_3)$_2$), 1.06 (s, 3H, C(CH_3)$_2$), 0.92 (s, 9H, SiC(CH_3)$_3$), 0.89 (s, 9H, SiC(CH_3)$_3$), 0.14 (s, 3H, Si(CH_3)$_2$), 0.11 (s, 3H, Si(CH_3)$_2$), 0.02 (s, 3H, Si(CH_3)$_2$), -0.01 (s, 3H, Si(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.54, 137.57, 116.21, 75.17, 72.92, 53.86, 46.97, 40.77, 37.82, 36.14, 26.50, 26.38, 26.08, 24.76, 23.61, 19.94, 18.86, 18.52, 18.25,-3.41, -3.64, -3.92, -4.04; HRMS calcd for $C_{31}H_{62}O_5Si_2Na$ 593.40335 $[M + Na]^+$, found 593.40424.

To a solution of diol mixture (145 mg, 0.254 mmol, 1.0 equiv) as prepared above in THF/H_2O (10 mL, v/v, 4:1) was added $NaIO_4$ (217.4 mg, 1.02 mmol, 4.0 equiv) in one portion at 0 ^oC. After stirring for 4 h at room temperature, the reaction was diluted with diethyl ether (20 mL) and washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford crude aldehyde, which went to next step without further purification.

The crude aldehyde obtained as described above was dissolved in *t*-BuOH (1.3 mL, 0.2 M), 2-methyl-2-butene (0.51 mL, 2 M solution in THF, 1.02 mmol, 4.0 equiv), H_2O (0.25 mL). The resulting mixture was treated with $NaClO_2$ (68.9 mg,

0.76 mmol, 3.0 equiv), and NaH_2PO_4 (52.6 mg, 0.38 mmol, 1.5 equiv). After stirring for 5 h, the reaction mixture was diluted with diethyl ether (10 mL), washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was subjected to flash column chromatography (gradient elution, hexanes/ethyl acetate, 20/1→ 6/1, then 5/1 with 1% HCO_2H) to furnish keto acid **74** (272.3 mg, 56%, 2 steps) as a white solid. R_f = 0.39 (hexanes/ethyl acetate, 4/1 with 1% HOAc); $[\alpha]^{22}{}_D$ -71.9 (*c* 1.32, $CHCl_3$); IR (thin film) ν_{max} 2928, 2857, 1709, 1472, 1463, 1389, 1361, 1302, 1251, 1081, 1024, 975, 939, 907, 833, 810, 774, 731, 672 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.76 (tdd, *J* = 17.0, 10.1, 6.9, 6.9 Hz, 1H, C*H*=CH_2), 5.06-5.02 (m, 2H, CH=CH_2), 4.13 (s, 1H), 3.84 (s, 1H), 3.20 (d, *J* = 10.6 Hz, 1H, CHC(O)), 2.63 (dd, *J* = 16.9, 2.9 Hz, 1H), 2.30-2.14 (m, 2H), 2.02-1.96 (m, 2H), 1.89 (bs, 1H), 1.84 (tt, *J* = 12.8, 4.3 Hz, 1H), 1.48-1.42 (m, 1H), 1.38-1.20 (m, 6H), 1.16-1.06 (m, 1H), 1.03 (s, 3H, $C(CH_3)_2$), 0.90 (s, 9H, $SiC(CH_3)_3$), 0.88 (s, , 9H, $SiC(CH_3)_3$), 0.13 (s, 3H, $Si(CH_3)_2$), 0.04 (s, 3H, $Si(CH_3)_2$), 0.00 (s, 3H, $Si(CH_3)_2$), -0.05 (s, 3H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.05, 177.97, 137.56, 116.19, 76.17, 71.50, 52.95, 47.35, 41.13, 39.99, 35.72, 29.92, 26.18, 26.03, 24.37, 23.43, 23.21, 21.09, 19.92, 18.33, 18.23, -4.01, -4.27, -4.38; HRMS calcd for $C_{28}H_{55}O_5Si_2$ 527.35880 $[M + H]^+$, found 527.35803. A flat single crystal of **74** was developed from its solution in hexanes, which was qualified for X-ray crystallography.

Preparation of Silyl Ether 75. To a solution of alcohol **24** (1.28 g, 6.1mmol, 1.0 equiv), imidazole (0.63g, 9.2 mmol, 1.5 equiv) in DMF (6 mL, 1.0 M) was added portionwise *tert*-butyldimethylsilyl chloride (1.10 g, 7.3 mmol, 1.2 equiv) at

0 ^{o}C and the reaction mixture was allowed to stir for 45 min at that temperature, and then at room temperature for overnight, after which time no starting alcohol was detected by TLC. The reaction was quenched by methanol (0.5 mL) at 0 °C, and the solvent was removed under reduced pressure. Diethyl ether (20 mL) was added followed by saturated aqueous NH_4Cl (10 mL). After separation, the aqueous phase was further extracted with diethyl ether (2 x 20 mL). The combined organics were dried over $MgSO_4$, and the solvents were removed under reduced pressure. Flash column chromatography (hexanes/ethyl acetate, 2/1) provided pure silyl ether **75** (1.25 g, 81%): R_f =0.66 (hexanes/ethyl acetate, 2/1); $[\alpha]^{22}{}_{D}$ +1.20 (*c* 1.0, $CHCl_3$), lit.[34] +1.39 (*c* 3.0, $CHCl_3$); IR (thin film) ν_{max} 2954, 2928, 2856, 2358, 1471, 1252, 1182, 1074, 913, 835, 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (s, 1 H, SCH=C), 6.46 (s, 1 H, C*H*=CCH_3), 5.83-5.73 (m, 1 H, C*H*=CH_2), 5.07-4.99 (m, 2H, CH_2=CH), 4.15 (t, *J* = 6.4 Hz, 1 H, C*H*OSi), 2.71 (s, 3 H, N=C(S)CH_3), 2.40-2.26 (m, 2 H, CH_2=CHCH_2), 2.00 (d, 3 H, *J* = 1.2 Hz, CH=CCH_3), 0.89 (s, 9 H, $SiC(CH_3)_3$), 0.06 (s, 3 H, $Si(CH_3)_2$), 0.01 (s, 3 H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.60, 153.33, 142.27, 135.56, 119.06, 116.77, 115.32, 78.67, 41.63, 26.06, 19.45, 18.45, 14.13, -4.41, -4.74; HRMS calcd for $C_{17}H_{30}NOSSi$ 324.18174 $[M + H]^+$, found 324.18124. The analytical data are in agreement with those reported in the literature[34].

Preparation of Aldehyde 76. To a solution of olefin **75** (160.0 mg, 0.5 mmol) in THF/*t*-BuOH (1:1, 5.0 mL) and H_2O (0.5 mL) was added NMO (70.3 mg, 0.6 mmol, 1.2 equiv) at 0 °C, followed by OsO_4 (0.052 mL, solution in *t*BuOH 1.0 mol %, 2.5% by weight). After being stirred for 3 h at 0 ^{o}C, the reaction was quenched

by addition of Na_2SO_3 solution (50 mg in 1 mL H_2O). Stirring was continued for another 10 min, and then diethyl ether (10 mL) was added, followed by brine solution (2x10 mL). The organic phase was separated, and the aqueous phase was extracted with diethyl ether (2 x10 mL). The combined organic extracts were dried over $MgSO_4$ and filtered, and the solvents were removed under reduced pressure to give the diol product (222.3 mg) as a light yellow oil, R_f = 0.57 (ethyl acetate), which was immediately used in the following step without further purification and characterization.

$NaIO_4$ (257 mg, 1.2 mmol, 2.4 equiv) was added in one portion at 0 ^oC to a solution of this diol in THF/H_2O (10 mL, v/v, 1/1). After stirring for 45 min, the reaction was allowed to warm to room temperature and stirred until the diol disappeared from TLC (ca. 30 min), at which point the mixture was extracted with diethyl ether (3 x 10 mL). The organic extracts were washed with brine, dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The crude oil product was purified by flash column chromatography (hexanes/ethyl acetate, 4/1) to give pure aldehyde **76** (137.5 mg, 85% two steps) as a colorless oil: R_f = 0.39 (hexanes/ethyl acetate, 4/1); $[\alpha]^{22}{}_D$ -20.2 (*c* 1.0, $CHCl_3$), lit.[34] -20.3 (*c* 1.4, $CHCl_3$); IR (thin film) ν_{max} 2953, 2927, 2855, 1724, 1504, 1471, 1388, 1251, 1182, 1076, 995, 834, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.79 (dd, *J* = 2.8, 2.0 Hz, 1 H, CHO), 6.94 (s, 1 H, SCH=C), 6.56 (s, 1 H, C*H*=CCH_3), 4.69 (dd, *J* = 8.0, 3.6 Hz, 1 H, CHOSi), 2.75 (ddd, *J* = 15.2, 8.4, 2.8 Hz, 1 H, CHOCH_2), 2.71 (s, 3 H, N=C(S)CH_3), 2.38 (ddd, *J* = 15.2, 4.4, 2.0 Hz, 1 H, CHOCH_2), 2.04 (d, *J* = 1.2 Hz, 3 H, CH=CCH_3), 0.88 (s, 9 H, $SiC(CH_3)_3$), 0.08 (s, 3 H, $Si(CH_3)_2$), 0.03 (s, 3 H,

$Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.81, 164.92, 152.88, 140.67, 119.54, 116.16, 74.19, 50.35, 25.94, 19.47, 18.32, 14.29, -4.37, -5.00; HRMS calcd for $C_{16}H_{28}NO_2SSi$ 326.16100 $[M + H]^+$, found 326.16049. The analytical data are in agreement with those reported in the literature.[34, 105]

Preparation of Vinyl Iodide 65. To a suspension of iodomethyl)triphenylphosphonium iodide (328.6 mg, 0.62 mmol, 1.5 equiv) in THF (15 mL) was slowly added NaHMDS in THF(0.62mL, 1 M in THF, 1.5 equiv). The iodomethyl)triphenylphosphonium iodide was prepared following the reported procedure.[106, 107] After being stirred for 5 min at ambient temperature, the dark red mixture was cooled to -78 ^oC, and HMPA (0.35 mL) was added, followed by a solution of aldehyde **76** (136 mg, 0.41 mmol, 1.0 equiv) in THF (5 mL). The solution was stirred for 30 min at -78^oC, and then warmed to room temperature to stir for another 1 hour before being diluted with hexanes. The triphenylphosphine oxide was filtered off through a celite pad, and the filtrate was concentrated under reduced pressure. Purification by column chromatography (gradient elution, hexanes/ethyl acetate, 20/1 →4/1) provided vinyl iodide **65** (156.1 mg, 85%) as brown oil. ^1H NMR indicated it is a *Z/E* mixture as a 10:1 ratio. The mixture went to following step without separation: R_f = 0.47 (hexanes/ethyl acetate, 4/1); $[\alpha]^{22}_D$ + 9.8 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 2953, 2930, 2856, 1610, 1505, 1471, 1440, 1390, 1363, 1289, 1254, 1181, 1077, 938, 883, 837, 775 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) *δ* 6.94 (s, 1 H, SCH=C), 6.49 (s, 1 H, C*H*=CCH_3), 6.26 (d, *J* = 7.2 Hz, 1H, C*H*I=CH), 6.22 (dd, *J* = 7.5, 6.6 Hz, 1H, CHI=C*H*), 4.25 (t, *J* = 6.3 Hz, 1 H, CHOSi), 2.71 (s, 3 H, N=C(S)CH_3), 2.48-2.38 (m, 2 H, CHCH_2CH), 2.03 (s, 3H, CH=CCH_3),

0.90 (s, 9 H, $SiC(CH_3)_3$), 0.07 (s, 3 H, $Si(CH_3)_2$), 0.02 (s, 3 H, $Si(CH_3)_2$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.70, 153.16, 141.67, 138.18, 119.29, 115.60, 84.04, 77.06, 42.06, 26.05, 19.46, 18.42, 14.31, -4.43, -4.76; HRMS calcd for $C_{17}H_{29}INOSSi$ 450.07838 $[M + H]^+$, found 450.07761.

Preparation of Triene 63. To a solution of olefin **67** (900 mg, 1.63 mmol, 1.2 equiv) in THF (3 mL) was added dropwise 9-BBN (3.54 mL, 1.77 mmol, 0.5 M solution in THF, 1.3 equiv). In a separate flask, the vinyl iodide **65** (611.8 mg, 1.36 mmol) was dissolved in DMF (5.0 mL). Cs_2CO_3 (655.2 mg, 2.04 mmol, 1.5 equiv) was then added with vigorous stirring followed by sequential addition of Ph_3As (83.4 mg, 0.33 mmol, 0.2 equiv), $PdCl_2(dppf)_2$ (222.3 g, 0.33 mmol, 0.2 equiv), and H_2O (0.98 mL, 65.32 mmol, 40 equiv). The resulting red suspension was purged with a stream of argon gas 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 and slowly became pale yellow after 2 h. The reaction was then poured into saturated aqueous NH_4Cl (10.0 mL) and extracted with diethyl ether (3 x 20 mL). The combined organics were washed with brine, dried over anhydrous $MgSO_4$, and concentrated. Purification by flash chromatography (gradient elution, hexanes/ethyl acetate, 40/1→ 10/1) to provide **64** (1.08 g, 92%) as a colorless oil: R_f = 0.5 (hexanes/ethyl acetate, 10/1); $[\alpha]^{22}_{D}$ -33.3 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 2952, 2927, 2856, 1698, 1471, 1462, 1386, 1360, 1250, 1183, 1079, 1004, 936, 833, 810, 772, 670 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.91 (s, 1 H, SCH=C), 6.46 (s, 1 H, C*H*=CCH_3), 5.43 (ddd, *J* = 10.8, 7.8, 7.2 Hz, 1H, C*H*=CH), 5.38 (ddd, *J* = 10.8, 7.2, 6.6 Hz, 1H, CH=C*H*), 5.04 (t, *J* = 10.0 Hz,

1H, C*H*=C(CH_3)$_2$), 4.13 (t, *J* = 6.4 Hz, 1H, C(CH_3)C*H*(CH_2)OSi), 3.88 (s, 1H, SiOCH), 3.65 (s, 1H, SiOCH), 3.13 (d, *J* = 10.7 Hz, 1H, CHC(O)), 2.70 (s, 3H, N=C(S)CH_3), 2.37-2.25 (m, 2H), 2.04-1.98 (m, 7H), 1.91-1.86 (m, 1H), 1.84-1.77 (m, 1H), 1.64 (s, 3H, CH=C(C*H*$_3$)$_2$), 1.53 (s, 3H, CH=C(C*H*$_3$)$_2$), 1.47-1.31 (m, 5H), 1.27 (s, 3H, C(CH_3)$_2$), 1.25-1.21 (m, 2H), 1.03 (s, 3H, C(O)C(CH_3)$_2$), 0.89 (s, 9H, SiC(CH_3)$_3$), 0.88 (s, 9H, SiC(CH_3)$_3$), 0.87 (s, 9H, SiC(CH_3)$_3$), 0.063 (s, 3H, Si(CH_3)$_2$), 0.059 (s, 3H, Si(CH_3)$_2$), 0.01 (s, 3H, Si(CH_3)$_2$), 0.007 (s, 3H, Si(CH_3)$_2$), -0.002 (s, 3H, Si(CH_3)$_2$), -0.05 (s, 3H, Si(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.56, 164.56, 153.33, 142.35, 132.52, 131.27, 126.34, 123.02, 119.13, 115.24, 79.82, 78.84, 71.93, 53.43, 47.60, 41.54, 34.90, 33.77, 30.67, 28.51, 28.00, 26.34, 26.06, 25.11, 22.82, 20.15, 19.43, 18.46, 18.44, 18.28, 18.13, 14.06, -3.53, -3.77, -3.83, -4.42, -4.71; HRMS calcd for $C_{48}H_{90}NO_4SSi_3$ 860.58984 $[M + H]^+$, found 860.59040.

Preparation of Compound 77. To a solution of triene **63** (570 mg, 0.66 mmol, 1.0 equiv) in *t*-BuOH (7.6 mL) and H_2O (3.8 mL) was added $(DHQD)_2PHAL$ (25.8 mg, 0.033 mmol, 5 mol %) and the reaction was placed at 0 °C. Then to the reaction was consequently added K_2CO_3 (274.8 mg, 1.98 mmol, 3.0 equiv), $K_3Fe(CN)_6$ (750.4 mg, 1.98 mmol, 3.0 equiv), $CH_3SO_2NH_2$ (94.5 mg, 0.99 mmol, 1.5 equiv) and K_2OsO_4•2 H_2O (2.5 mg, 0.0066 mmol, 1 mol%). The yellow/orange slurry was stirred for 24 h at 0 °C at which time the reaction was quenched with solid $Na_2S_2O_3$ (990 mg). After being stirred for 20 min at room temperature, ethyl acetate (10 mL) and water (10 mL) were added to the reaction mixture, and the layers separated. The aqueous phase was further extracted with the ethyl acetate

(2 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. Purification by flash chromatography (gradient elution, hexanes/ethyl acetate, 10/1→ 4/1) yielded 290.8 mg of starting triene **63** and 248.6 mg (42% yield, 86% BORSM) of selectively dihydroxylated product **77** as a ca. 5:1 mixture of diastereomers by ^{1}H NMR. The mixture underwent the following step without further separation unless a small portion of the major diastereomer was isolated by preparative thin-layer chromatography (hexanes/ethyl acetate, 4:1) for characterization: R_f = 0.34 (hexanes/ethyl acetate, 4/1); $[\alpha]^{22}{}_D$ -14.2 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 3466 (br), 2952, 2928, 2856, 1695, 1471, 1462, 1386, 1361, 1250, 1083, 1026, 835, 775, 670 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.92 (s, 1H, SCH=C), 6.46 (s, 1H, C*H*=CCH_3), 5.59-5.27 (m, 2H, CH=CH), 4.13 (t, *J* = 6.4 Hz, 1H, $C(CH_3)CH(CH_2)OSi$), 4.08 (s, 1H), 3.87 (s, 1H), 3.17 (s, 1H), 3.03 (d, *J* = 11.1 Hz, 1H, CHC(O)), 2.81-2.65 (br s, 1H, OH), 2.71 (s, 3H, $N=C(S)CH_3$), 2.44-2.21 (m, 3H), 2.09-2.01 (m, 2H), 2.00 (d, *J* = 1.1 Hz, 3H, $CH=CCH_3$), 1.99-1.94 (m, 1H), 1.83-1.78 (m, 2H), 1.70-1.55 (m, 2H), 1.49-1.25 (m, 11H), 1.14 (s, 3H, $C(CH_3)_2OH$), 1.10 (s, 3H, $C(CH_3)_2OH$), 1.08 (s, 3H, $C(O)C(CH_3)_2$), 0.90 (s, 9H, $SiC(CH_3)_3$), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.87 (s, 9H, $SiC(CH_3)_3$), 0.12 (s, 3H, $Si(CH_3)_2$), 0.10 (s, 3H, $Si(CH_3)_2$), 0.06 (s, 3H, $Si(CH_3)_2$), 0.02 (s, 3H, $Si(CH_3)_2$), 0.01 (s, 3H, $Si(CH_3)_2$), -0.02 (s, 3H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.83, 164.62, 153.30, 142.39, 131.25, 126.38, 119.13, 115.25, 78.84, 75.56, 75.39, 72.70, 53.04, 47.56, 41.21, 37.18, 34.92, 30.76, 28.35, 27.98, 26.32, 26.27, 26.09, 26.07, 25.64, 23.65, 20.08, 19.43, 19.00, 18.45, 18.36, 18.32, 14.08, -3.66,

-3.80, -4.05, -4.42, -4.71; HRMS calcd for $C_{48}H_{92}NO_6SSi_3$ 894.59531 $[M + H]^+$, found 894.59423.

Preparation of Keto Acid 78. To a solution of diol **77** (365 mg, 0.41 mmol, 1.0 equiv) in THF/H_2O (10 mL, v/v, 4:1) was added $NaIO_4$ (349.5 mg, 1.64 mmol, 4.0 equiv) in one portion at 0 ^oC. After stirring for 12 h at room temperature, the reaction was diluted with diethyl ether (20 mL) and washed with brine, dried over $MgSO_4$, filtered and condensed under reduced pressure to afford crude aldehyde as yellow oil which was unstable and went to next step without further purification.

The crude aldehyde obtained from **77** as described above was dissolved in *t*-BuOH (2 mL, 0.2 M), 2-methyl-2-butene (0.82 mL, 2 M solution in THF, 1.64 mmol, 4.0 equiv), H_2O (0.4 mL). The resulting mixture was treated with $NaClO_2$ (110.6 mg, 1.23 mmol, 3.0 equiv), and NaH_2PO_4 (84.5 mg, 0.62 mmol, 1.5 equiv). After stirring for 6 h, the reaction mixture was diluted with diethyl ether (10 mL), washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was subjected to flash column chromatography (gradient elution, hexanes/ethyl acetate, 20/1→ 6/1, then 5/1 with 1% HCO_2H) to furnish keto acid **78** (272.3 mg, 78%, 2 steps) as a pale white foam: R_f = 0.4 (hexanes/ethyl acetate, 4/1 with 1% HCO_2H); $[\alpha]^{22}_D$ -34.5 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 2951, 2917, 2886, 2856, 1710, 1698, 1471, 1462, 1250, 1187, 1080, 1024, 810,773, 733, 670 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.93 (s, 1H, SCH=C), 6.52 (s, 1H, C*H*=CCH_3), 5.53-5.31 (m, 2H, CH=CH), 4.19 (s, 1H, SiOCH), 4.14 (t, *J* = 6.5 Hz, 1H, $C(CH_3)CH(CH_2)OSi$), 3.86 (s, 1H, SiOCH), 3.17 (d, *J* = 11.2 Hz, 1H, CHC(O)), 2.71 (s, 3H, $N=C(S)CH_3$), 2.60 (dd, *J* = 17.0, 2.8 Hz,

1H, CH_2CO_2), 2.38-2.26 (m, 2H), 2.18 (dd, *J* = 17.0, 6.5 Hz, 1H, CH_2CO_2), 2.09-1.99 (m, 3H), 1.98 (d, *J* = 0.8 Hz, 3H, CH=CC*H*$_3$), 1.85-1.77 (m, 1H), 1.71 (bs, 1H), 1.49-1.17 (m, 12H), 1.03 (s, 3H, $C(CH_3)_2$), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.87 (s, 9H, $SiC(CH_3)_3$), 0.12 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H), 0.01 (s, 3H, $Si(CH_3)_2$), -0.02 (s, 3H, $Si(CH_3)_2$), -0.07 (s, 3H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.88, 177.05, 165.05, 153.04, 142.71, 131.32, 126.35, 118.97, 115.07, 78.81, 75.94, 71.62, 53.13, 47.27, 41.54, 39.90, 34.90, 30.60, 28.42, 27.94, 26.19, 26.07, 26.02, 23.01, 21.21, 20.05, 19.15, 18.43, 18.34, 18.24, 14.06, -3.94, -4.01, -4.29, -4.38, -4.43, -4.71; HRMS calcd for $C_{45}H_{84}NO_6SSi_3$ 850.53271 $[M + H]^+$, found 850.53180.

Preparation of Dihydroxy Lactone 79. A solution of tri(silyl ether) **78** (307.7 mg, 0.362 mmol, 1.0 equiv) in THF (7.0 mL) was treated with TBAF (2.17 mL, 1 M solution in THF, 2.2 mmol, 6.0 equiv) at 25 ^{o}C. The reaction was complete in 8 h as indicated from TLC analysis. The reaction mixture was diluted with ethyl acetate (10 mL) and saturated aqueous NH_4Cl (10 mL). The resulting solution was extracted with ethyl acetate (2 x 10 mL), and the combined organics were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (CH_2Cl_2/MeOH, 10/1) to afford hydroxy acid (252.4 mg, 95%) as a yellow oil or white foam: R_f = 0.44 (CH_2Cl_2/MeOH, 10/1); $[\alpha]^{22}_{D}$ -37.9 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 2927, 2856, 1698, 1471, 1463, 1388, 1361, 1257, 1189, 1086, 1023, 835, 811, 776 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.95 (s, 1H, SCH=C), 6.66 (s, 1H, C*H*=CCH_3), 5.58 (dt, *J* = 10.8, 7.3 Hz, 1H, C*H*=CH), 5.44 (dt, *J* = 10.8, 7.3 Hz, 1H, CH=C*H*), 4.32 (dd, *J*

= 6.2, 3.5 Hz, 1H, CH_2CHOSi), 4.21 (t, *J* = 6.4 Hz, 1H, C*H*OH), 3.89 (s, 1H, CHC*H*OSi), 3.16 (d, *J* = 10.9 Hz, 1H, CHC(O)), 2.71 (s, 3H, $N=C(S)CH_3$), 2.55 (dd, *J* = 16.9, 3.5 Hz, 1H, CH_2CO_2), 2.44 (m, 2H), 2.25 (dd, *J* = 16.9, 6.3 Hz, 1H, CH_2CO_2), 2.12 (m, 2H), 2.08-1.98 (m, 4H), 1.85 (tt, *J* = 13.0, 4.4, Hz, 1H), 1.74 (s, 1H), 1.55-1.44 (m, 3H), 1.42-1.31 (m, 3H), 1.31-1.21 (m, 7H), 1.07 (s, 3H, $C(CH_3)_2$), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.13 (s, 3H, $Si(CH_3)_2$), 0.07 (s, 3H, $Si(CH_3)_2$), 0.01 (s, 3H, $Si(CH_3)_2$), -0.04 (s, 3H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.69, 175.68, 165.30, 152.69, 141.83, 133.42, 125.30, 119.15, 115.49, 77.15, 75.19, 71.70, 53.57, 46.76, 41.61, 39.88, 33.50, 30.48, 29.92, 28.45, 27.92, 26.20, 26.04, 23.20,22.69, 20.56, 20.12, 19.07, 18.36, 18.27, 14.86, -3.90, -4.11, -4.37; HRMS calcd for $C_{39}H_{70}NO_6SSi_2$ 736.44624 $[M + H]^+$, found 736.44516.

To a solution of hydroxyl acid (240 mg, 0.326 mmol, 1.0 equiv) prepared from **78** in THF (5 mL) were added triethylamine (0.27 mL, 1.96 mmol, 6.0 equiv) and 2,4,6-trichlorobenzoyl chloride (397.5 mg, 1.63 mmol, 5.0 equiv). The mixture was stirred at room temperature for 1.0 h, diluted with toluene (10 mL), and added dropwise over a period of 3 h to a prepared, stirred solution of DMAP (600 mg, 4.89 mmol, 15 equiv) in toluene (250 mL). After the addition is complete, the reaction mixture was stirred for additional 1.0 h and concentrated under reduced pressure. The residue was dissolved in diethyl ether (5 mL) and filtered through a celite pad. After being concentrated, the residue was purified by flash chromatography (Hexanes/ethyl acetate, 4/1) to afford the desired macrolactone (119.3 mg, 51%) as a colorless oil: R_f = 0.54 (Hexanes/ethyl acetate, 4/1); $[\alpha]^{22}_D$

–91.5 (*c* 1.42, $CHCl_3$); IR (thin film) ν_{max} 2926, 2855, 1736, 1709, 1505, 1471, 1462, 1387, 1361, 1248, 1163, 1086, 1061, 1006, 834, 813, 774, 734, 670 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.95 (s, 1H, SCH=C), 6.54 (s, 1H, C*H*=CCH_3), 5.50 (ddd, *J* = 10.2, 9.9, 5.4 Hz, 1H, C*H*=CH), 5.47-5.42 (m, 1H, CH=C*H*), 5.34 (d, *J* = 7.0 Hz, 1H, C*H*OC(O)), 4.46 (t, *J* = 5.6 Hz, 1H, C*H*$C(CH_3)_2$), 4.02 (s, 1H, CHC*H*OSi), 3.03 (d, *J* = 11.2 Hz, 1H, CHC(O)), 2.82-2.72 (m, 2H), 2.71 (s, 3H, N=C(S)CH_3), 2.64 (dd, *J* = 15.9, 5.6 Hz, 1H, CH_2CO_2), 2.35 (d, *J* = 15.8 Hz, 1H), 2.19-2.09 (m, 4H), 2.10-1.99 (m, 2H), 1.94 (tt, *J* = 13.5, 4.7 Hz, 1H), 1.64 (s, 1H), 1.58-1.50 (m, 2H), 1.48-1.22 (m, 6H), 1.11 (s, 3H, $C(CH_3)_2$), 1.04 (s, 3H, $C(CH_3)_2$), 0.90 (s, 9H, $SiC(CH_3)_3$), 0.82 (s, 9H, $SiC(CH_3)_3$), 0.09 (s, 3H, $Si(CH_3)_2$), 0.08 (s, 3H, $Si(CH_3)_2$), 0.00 (s, 3H, $Si(CH_3)_2$), -0.01 (s, 3H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.51, 170.66, 164.88, 152.60, 137.91, 133.14, 125.06, 119.88, 116.44, 78.78, 74.62, 69.94, 54.66, 45.09, 42.16, 40.68, 31.60, 31.06, 28.37, 28.09, 26.33, 26.04, 24.81, 23.65, 22.61, 20.99, 20.03, 19.45, 18.47, 18.34, 15.81, -3.71, -4.02, -4.08, -4.17; HRMS calcd for $C_{39}H_{68}NO_5SSi_2$ 718.43567 $[M + H]^+$, found 718.43439.

A solution of Yamaguchi lactonization product (89 mg, 0.124 mmol) in CH_2Cl_2 (0.1 mL) was treated with a freshly prepared CF_3CO_2H/CH_2Cl_2(0.73 mL, v/v, 1:4) at -20 °C. The reaction mixture was allowed to reach 0 °C in 20 min and was stirred for additional 1 h at that temperature at which time all silyl ether disappeared from TLC plate. The mixture was diluted with CH_2Cl_2 (5 mL) and carefully neutralized by saturated aqueous $NaHCO_3$. After separation, the aqueous phase was further extracted with CH_2Cl_2 (2 x 5 mL). The combined

organics were dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by preparative thin-layer chromatography (CH_2Cl_2/MeOH, 20/1) to afford pure desired epothilone C analog **79** (53.4 mg, 88%) as a colorless oil: R_f = 0.36 (CH_2Cl_2/MeOH, 15:1); $[\alpha]^{22}{}_D$ –86.8 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 3478 (br), 2928, 2860, 1736, 1678, 1507, 1443, 1409, 1291, 1248, 1187, 1084, 1046, 982, 913, 731 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.97 (s, 1H, SCH=C), 6.62 (s, 1H, C*H*=CCH_3), 5.50 (ddd, *J* = 10.5, 10.5, 5.0 Hz, 1H, C*H*=CH), 5.40 (ddd, *J* = 10.5, 10.5, 5.0 Hz, 1H, C*H*=CH), 5.22 (d, *J* = 8.3 Hz, 1H, C*H*OC(O)), 4.42 (dd, *J* = 11.5, 1.8 Hz, 1H, C*H*OHC$(CH_3)_2$), 4.20 (s, 1H, CHC*H*OH), 3.89 (s, 1H, OH), 3.49 (s, 1H, OH), 2.98 (d, *J* = 10.8 Hz, 1H, CHC(O)), 2.76-2.63 (m, 4H), 2.50 (dd, *J* = 14.7, 11.6 Hz, 1H, CH_2CO_2), 2.32 (dd, *J* = 14.7, 2.3 Hz, 1H, CH_2CO_2), 2.30-2.24 (m, 1H), 2.18 (tt, *J* = 10.7, 7.6 Hz, 1H), 2.08 (s, 3H, CH=CC*H*$_3$), 2.04-1.85 (m, 3H), 1.84-1.74 (m, 1H), 1.66-1.43 (m, 4H), 1.36-1.29 (m, 2H), 1.28 (s, 3H, $C(CH_3)_2$), 1.26-1.16 (m, 2H), 1.06 (s, 3H, $C(CH_3)_2$)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 220.74, 170.52, 165.35, 152.04, 139.43, 133.17, 125.23, 119.44, 115.82, 78.76, 73.05, 69.62, 54.22, 43.97, 39.79, 39.54, 31.91, 30.05, 28.83, 28.10, 25.17, 23.92, 23.58, 20.85, 19.25, 17.77, 16.26; HRMS calcd for $C_{27}H_{40}NO_5S$ 490.26272 $[M + H]^+$, found 490.26144.

Preparation of Bridged EpothiloneA (22) and (22a). To a solution of bridged epothilone C (**79**) (23 mg, 0.047 mmol, 1.0 equiv) in dry CH_2Cl_2 (2mL) at -50 °C was added a freshly prepared dry solution of 3,3-dimethyldioxirane [108] (1.18 mL, ca. 0.094 mmol, 0.08 M in acetone, 2.0 equiv). The resulting solution was allowed to warm to -30 °C for 2 h. A stream of argon was then bubbled

through the solution to remove excess dimethyldioxirane. The crude mixture was determined to be a mixture of diastereomeric *cis*-epoxides (ca. 5:2 ratio by ^{1}H NMR).Preparative thin-layer chromatography (CH_2Cl_2/MeOH, 20/1) to afford bridged epothilone A (**22**) (13.0 mg, 55%) as a white foam and the *cis*-epoxide diastereomer **22a** (7.0 mg, 29%) as a white solid. **22**: R_f = 0.34 (CH_2Cl_2/MeOH, 15:1); $[\alpha]^{22}{}_D$ –26.9 (*c* 0.87, $CHCl_3$); IR (thin film) ν_{max} 3462 (br), 2930, 2864, 1731, 1679, 1509, 1444, 1413, 1390, 1293, 1258, 1181, 1154, 1085, 1046, 980, 919, 725 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.98 (s, 1H, SCH=C), 6.61 (s, 1H, C*H*=CCH_3), 5.35 (dd, *J* = 9.9, 1.5 Hz, 1H, C*H*OC(O)), 4.38 (d, *J* = 10.3 Hz, 1H, C*H*OHC$(CH_3)_2$), 4.31 (s, 1H, CHC*H*OH), 4.00 (s, 1H, OH), 3.83 (bs, 1H, CHC*H*OH), 3.03 (ddd, *J* = 9.6, 3.0, 3.0 Hz, 1H, CH_2CH-O(epoxide)C*H*), 2.98 (d, *J* = 10.6 Hz, 1H, CHC(O)), 2.96-2.93 (ddd, *J* = 9.6, 3.0, 3.0 Hz, 1H, CH_2C*H*-O(epoxide)CH), 2.68 (s, 3H, N=C(S)CH_3), 2.52 (dd, *J* = 14.5, 11.3 Hz, 1H, CH_2CO_2), 2.30 (dd, *J* = 14.5, 2.5 Hz, 1H, CH_2CO_2), 2.24 -2.18 (m, 1H), 2.09 (s, 3H, CH=CC*H*$_3$), 2.08-2.02 (m, 1H), 1.95-1.84 (m, 3H), 1.80 (ddd, *J* = 15.0, 9.9, 9.9 Hz, 1H), 1.68 (ddd, *J* = 25.4, 12.1, 5.3 Hz, 1H), 1.63-1.56 (m, 2H), 1.56-1.46 (m, 2H), 1.44-1.39 (m, 1H), 1.38-1.22 (m, 6H), 1.08 (s, 3H, C$(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 220.87, 170.45, 165.54, 151.68, 138.84, 120.16, 116.19, 76.96, 72.93, 68.08, 57.70, 55.75, 54.11, 43.80, 39.82, 39.65, 31.89, 30.90, 27.98, 25.34, 25.26, 24.74, 23.36, 21.04, 19.25, 17.96, 16.07; HRMS calcd for $C_{27}H_{40}NO_6S$ 506.25763 [M + H] $^+$, found 506.25654. *cis*-Epoxide diastereomer **22a:** R_f = 0.34 (CH_2Cl_2/MeOH, 15:1); $[\alpha]^{22}{}_D$ –58.9 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 3466 (br), 2926, 2860, 1737, 1679, 1556, 1509, 1447, 1413, 1390, 1324, 1297, 1254, 1189,

1150, 1085, 1042, 1004, 984, 953, 919 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.99 (s, 1H, SCH=C), 6.65 (s, 1H, C*H*=CCH_3), 5.60 (t, *J* =3.9 Hz, 1H, C*H*OC(O)), 4.36 (dd, *J* = 11.1, 1.9 Hz, 1H, C*H*OH$C(CH_3)_2$), 4.16 (s, 1H, CHC*H*OH), 3.99 (s, 1H, OH), 3.80 (bs, 1H, OH), 3.24 (ddd, *J* = 7.4, 4.4, 4.4 Hz, 1H, CH_2CH-O(epoxide)C*H*), 3.11 (dd, *J* = 12.3, 1.7 Hz, 1H, CHC(O)), 3.05-3.02 (m, 1H, CH_2C*H*-O(epoxide)CH), 2.69 (s, 3H, N=C(S)CH_3), 2.56 (dd, *J* = 14.7, 11.2 Hz, 1H, CH_2CO_2), 2.37 (dd, *J* = 14.6, 2.6 Hz, 1H, CH_2CO_2), 2.10 (s, 3H, CH=CC*H*$_3$), 2.09-1.96 (m, 3H), 1.93-1.82 (m, 3H), 1.66-1.46 (m, 6H), 1.39-1.18 (m, 6H), 1.08 (s, 3H, $C(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 221.01, 169.96, 165.32, 151.91, 136.90, 119.81, 116.12, 75.86, 72.88, 68.25, 57.23, 54.24, 53.79. 44.18, 39.78, 39.59, 30.83, 29.01, 28.28, 25.42, 25.06, 24.51, 22.20, 21.08, 19.27, 18.82, 16.31; HRMS calcd for $C_{27}H_{40}NO_6S$ 506.25763 $[M + H]^+$, found 506.25659. The direction of the epoxide was further determined by 1D and 2D NOE.

Preparation of Vinyl Iodide 66. 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 ^oC. 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 ^oC. After warming to -30 ^oC, 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 ^oC again, to which was added aldehyde **17** (0.651 g, 2.0 mmol, 1.0 equiv) in THF (10 mL) dropwise within 10 min. The mixture was warmed to -30 ^oC gradually, stirred for 10 min at -30 ^oC, 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 **66** (0.472 g, 51%) as a pale yellow oil: R_f = 0.47 (hexanes/ethyl acetate, 4/1); $[\alpha]^{22}_{D}$ + 14.1 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 2953, 2927, 2855, 1653, 1504, 1471, 1250, 1183, 1065, 1030, 938, 833, 774, 730, 666, 573 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.94 (s, 1H, SCH=C), 6.49 (s, 1H, C*H*=CCH_3), 5.46 (td, *J* =6.8, 1.6 Hz, 1H, C*H*=CI(CH_3)), 4.21 (t, *J* = 6.3 Hz, 1H, CHOSi), 2.71 (s, 3H, N=C(S)CH_3), 2.48 (d, *J* = 1.3 Hz, 3H, $ClCH_3$), 2.45-2.29 (m, 2H, CHCH_2CH), 2.02 (d, *J* = 1.2 Hz, 3H, CH=CCH_3), 0.90 (s, 9 H, $SiC(CH_3)_3$), 0.06 (s, 3 H, $Si(CH_3)_2$), 0.01 (s, 3 H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.65, 153.23, 141.95, 132.33, 119.09, 115.48, 102.59, 77.49, 43.89, 33.88, 26.03, 19.45, 18.42, 14.31, -4.45, -4.79; HRMS calcd for $C_{18}H_{31}INOSSi$ 464.09403 $[M + H]^+$, found 464.09278. The analytical data are in agreement with those reported in the literature.[90, 95]

Preparation of Triene 64. Triene **64** was prepared from olefin **67** (900 mg, 1.63 mmol, 1.2 equiv) and vinyl iodide **66** (630.4 mg, 1.36 mmol) according to the same procedure described above for the preparation of **63**, to obtain pure triene **64** (678 mg, 57%) as a colorless oil: R_f = 0.49 (hexanes/ethyl acetate, 10/1); $[\alpha]^{22}_{D}$ -49.4 (*c* 1.9, $CHCl_3$); IR (thin film) ν_{max} 2952, 2927, 2856, 1697, 1462, 1471, 1386, 1360, 1250, 1184, 1079, 1004, 937, 908, 833, 809, 772, 732, 670 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.91 (s, 1H, SCH=C), 6.46 (s, 1H, ArC*H*=CCH_3), 5.15 (t,

J = 6.9 Hz, 1H, C*H*=CCH$_3$), 5.04 (t, *J* = 6.7 Hz, 1H, C*H*=C(CH$_3$)$_2$), 4.08 (t, *J* = 6.8 Hz, 1H, C(CH$_3$)C*H*(CH$_2$)OSi), 3.89 (bs, 1H, SiOCH), 3.65 (s, 1H, SiOCH), 3.13 (d, *J* = 10.5 Hz, 1H, CHC(O)), 2.71 (s, 3H, N=C(S)CH$_3$), 2.32-2.20 (m, 2H), 2.03-1.97 (m, 7H), 1.89 (ddd, *J* = 15.0, 7.5, 7.5 Hz, 1H), 1.86-1.78 (m, 1H), 1.68 (s, 3H, CH=CC*H*$_3$CH$_2$), 1.64 (s, 3H, CH=C(C*H*$_3$)$_2$), 1.53 (s, 3H, CH=C(C*H*$_3$)$_2$), 1.50-1.30 (m, 6H), 1.27 (s, 3H, C(CH$_3$)$_2$), 1.26-1.19 (m, 3H), 1.03 (s, 3H, C(O)C(CH$_3$)$_2$), 0.90 (s, 9H, SiC(CH$_3$)$_3$), 0.89 (s, 9H, SiC(CH$_3$)$_3$), 0.88 (s, 9H, SiC(CH$_3$)$_3$), 0.07 (s, 3H, Si(CH$_3$)$_2$), 0.05 (s, 3H, Si(CH$_3$)$_2$), 0.01 (s, 3H, Si(CH$_3$)$_2$), 0.003 (s, 3H, Si(CH$_3$)$_2$), 0.000 (s, 3H, Si(CH$_3$)$_2$), -0.04 (s, 3H, Si(CH$_3$)$_2$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 214.62, 164.54, 153.42, 142.68, 136.87, 132.52, 123.02, 121.89, 118.93, 115.17, 79.85, 79.21, 72.18, 53.41, 47.63, 41.57, 35.57, 33.79, 32.63, 31.05, 26.89, 26.35, 26.06, 25.16, 23.83, 22.81, 20.15, 19.44, 18.46, 18.29, 18.13, 14.14, -3.52, -3.74, -3.82, -4.35, -4.43, -4.72; HRMS calcd for $C_{49}H_{92}NO_4SSi_3$ 874.60549 $[M + H]^+$, found 874.60610.

Preparation of Keto Acid 80. To prepare the keto acid 80, an dihydroxy intermediate was firstly prepared from triene **64** (540 mg, 0.617 mmol, 1.0 equiv) according to a same procedure to prepare compound **77**. Purification of the crude by flash chromatography (gradient elution, hexanes/ethyl acetate, 10/1→ 4/1) yielded 279.5 mg of starting triene **64** and 236.6 mg (42% yield, 87% BORSM) of selectively dihydroxylated intermediate as a ca. 4:1 mixture of diastereisomers by ^{1}H NMR. The mixture underwent the following step without further separation unless a small portion of the major diasteroisomer was isolated by preparative thin-layer chromatography (hexanes/ethyl acetate, 4:1) for characterization: R_f =

0.33 (hexanes/ethyl acetate, 4/1); $[\alpha]^{22}_{D}$ -5.7 (*c* 0.44, $CHCl_3$); IR (thin film) ν_{max} 3470 (br), 2953, 2930,2887, 2856, 1695, 1505, 1463, 1386, 1363, 1251, 1185, 1085, 1031, 1007, 965, 938, 911, 838, 776, 726, 672 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.91 (s, 1H, SCH=C), 6.46 (s, 1H, ArC*H*=CCH_3), 5.15 (t, *J* = 7.1 Hz, 1H, C*H*=CCH_3CH_2), 4.08 (m, 2H), 3.88 (bs, 1H), 3.17 (bs, 1H, OH), 3.03 (d, *J* = 11.1 Hz, 1H, CHC(O)), 2.74 (bs, 1H, OH), 2.70 (s, 3H, N=C(S)CH_3), 2.34 (s, 1H), 2.30-2.19 (m, 2H), 2.10-1.89 (m, 7H), 1.81 (m, 2H), 1.67 (s, 3H, CH=CC*H*$_3CH_2$), 1.61 (dd, *J* = 15.0, 7.2 Hz, 1H), 1.44-1.30 (m, 7H), 1.28-1.16 (m, 4H), 1.14 (s, 3H, C(C*H*$_3)_2$OH), 1.09 (s, 3H, C(C*H*$_3)_2$OH), 1.07 (s, 3H, C(O)C($CH_3)_2$), 0.90 (s, 9H, SiC($CH_3)_3$), 0.88 (s, 9H, SiC($CH_3)_3$), 0.87 (s, 9H, SiC($CH_3)_3$), 0.12 (s, 3H, Si($CH_3)_2$), 0.09 (s, 3H, Si($CH_3)_2$), 0.04 (s, 3H, Si($CH_3)_2$), 0.02 (s, 3H, Si($CH_3)_2$), 0.00 (s, 3H, Si($CH_3)_2$), -0.01 (s, 3H, Si($CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.82, 164.57, 153.39, 142.68, 136.81, 121.93, 118.92, 115.76, 79.20, 75.68, 75.36, 72.68, 53.02, 47.57, 41.23, 37.17, 35.58, 32.57, 31.19, 26.70, 26.32, 26.26, 26.08, 26.05, 25.64, 23.79, 23.64, 20.06, 19.44, 18.97, 18.45, 18.35, 14.15, -3.65, -3.81, -4.06, -4.43, -4.72; HRMS calcd for $C_{49}H_{94}NO_6SSi_3$ 908.61097 $[M + H]^+$, found 908.61022.

The diol mixture (232 mg, 0.255 mmol, 1.0 equiv) prepared as described above was converted to keto acid **80** (129 mg, 58%, 2 steps) following a same procedure to prepare compound **78** to obtain **80** (129 mg, 58%, 2 steps) as a pale white foam: R_f = 0.44 (hexanes/ethyl acetate, 4/1 with 1% HOAc); $[\alpha]^{22}_{D}$ -35.3 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 3103 (br), 2953, 2930, 2895, 2856, 1710, 1698, 1509, 1471, 1463, 1444, 1390, 1363, 1297, 1251, 1189, 1081, 1031, 1007, 942,

911, 834, 776, 730, 676 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.92 (s, 1H, SCH=C), 6.52 (s, 1H, ArC*H*=CCH_3), 5.16 (t, *J* = 7.1 Hz, 1H, C*H*=CCH_3CH_2), 4.22 (bs, 1H, SiOCH), 4.11 (dd, *J* = 7.6, 5.4 Hz, 1H, $C(CH_3)CH(CH_2)OSi$), 3.86 (bs, 1H, SiOCH), 3.17 (d, *J* = 10.9 Hz, 1H, CHC(O)), 2.71 (s, 3H, $N=C(S)CH_3$), 2.58 (dd, *J* = 17.1, 2.7 Hz, 1H, CH_2CO_2), 2.33-2.12 (m, 3H), 2.04-1.99 (m, 3H), 1.98 (s, 3H, ArCH=CC*H*$_3$), 1.91-1.76 (m, 1H), 1.71 (bs, 1H), 1.68 (s, 3H, CH=CC*H*$_3CH_2$), 1.53-1.18 (m, 12H), 1.04 (s, 3H, $C(CH_3)_2$), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.12 (s, 3H, $Si(CH_3)_2$), 0.05 (s, 6H, $Si(CH_3)_2$), 0.00 (s, 3H, $Si(CH_3)_2$), -0.01 (s, 3H, $Si(CH_3)_2$), -0.06 (s, 3H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.87, 176.52, 165.05, 153.13, 143.14, 136.84, 121.97, 118.68, 115.00, 79.17, 75.76, 71.62, 53.23, 47.18, 41.52, 39.88, 35.54, 32.52, 30.90, 26.78, 26.20, 26.05, 26.03, 23.72, 23.00, 21.02, 20.08, 19.13, 18.46, 18.34, 18.25, 14.20, -3.91, -4.26, -4.30, -4.45, -4.73; HRMS calcd for $C_{46}H_{86}NO_6SSi_3$ 864.54836 $[M + H]^+$, found 864.54673.

Preparation of Dihydroxy Keto Ester 81. To prepare the keto ester **81**, selective desilylation of **80** (292 mg, 0.338 mmol) according to the procedure described above for the intermediate of **79** give hydroxy acid intermediate (228 mg, 90%)as a yellow oil: R_f = 0.45 (CH_2Cl_2/MeOH, 10/1); $[\alpha]^{22}{}_D$ -12.2 (*c* 0.35, $CHCl_3$); IR (thin film) ν_{max} 3190(br), 2953, 2930, 2899, 2860, 1710, 1698, 1513, 1463, 1444, 1390, 1363, 1297, 1251, 1189, 1085, 1027, 1007, 942, 911, 837, 776, 718, 671 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.94 (s, 1H, SCH=C), 6.61 (s, 1H, ArC*H*=CCH_3), 5.18 (t, *J* = 6.7 Hz, 1H, CH_2CH=CCH_3), 4.22 (s, 1H, SiOC*H*CH_2), 4.16 (t, *J* = 6.5 Hz, 1H, C*H*OH), 3.85 (s, 1H, CHC*H*OSi), 3.16 (d, *J* = 10.7 Hz, 1H,

CHC(O)), 2.70 (s, 3H, N=C(S)CH_3), 2.56 (dd, *J* = 16.8, 4.8 Hz, 1H, CH_2CO_2), 2.36 (t, *J* = 6.8 Hz, 2H), 2.18 (dd, *J* = 16.8, 6.4 Hz, 1H, CH_2CO_2), 2.11-1.94 (m, 6H), 1.86-1.54 (m, 5H), 1.52-1.16 (m, 13H), 1.03 (s, 3H, $C(CH_3)_2$), 0.87 (s, 9H, $SiC(CH_3)_3$), 0.86 (s, 9H, $SiC(CH_3)_3$), 0.11 (s, 3H, $SiC(CH_3)_3$), 0.03 (s, 3H, $Si(CH_3)_2$), -0.02 (s, 3H, $Si(CH_3)_2$), -0.07 (s, 3H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.75, 176.55, 165.21, 152.75, 142.04, 139.14, 120.64, 119.04, 115.48, 77.42, 75.62, 74.35, 53.32, 47.04, 41.62, 39.98, 34.19, 32.48, 30.78, 26.81, 26.19, 26.02, 23.81, 23.18, 22.89, 20.82, 20.06, 19.09, 18.33, 18.24, 14.81, -3.93, -4.23, -4.34; HRMS calcd for $C_{40}H_{72}NO_6SSi_2$ 750.46189 $[M + H]^+$, found 750.46170.

Next, this hydroxy acid intermediate (320 mg, 0.426 mmol, 1.0 equiv) obtained from **80** was converted to macrolactone intermediate following the previously described Yamaguchi condition for the preparation of keto ester **79**, affording the desired macrolactone (195 mg, 60%) as a colorless oil or white foam: R_f = 0.63 (Hexanes/ethyl acetate, 4/1); $[\alpha]^{22}{}_D$ –75.9 (*c* 1.24, $CHCl_3$); IR (thin film) ν_{max} 2930, 2895, 2856, 1737, 1710, 1664, 1505, 1471, 1386, 1363, 1301, 1251, 1185, 1166, 1089, 1065, 1007, 942, 911, 834, 772, 722, 672 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.95 (s, 1H, SCH=C), 6.53 (s, 1H, ArC*H*=CCH_3), 5.35 (dd, *J* = 8.1, 2.2 Hz, 1H, C*H*OC(O)), 5,21 (t, *J* = 5.7 Hz, 1H, CH_2CH=CCH_3), 4.48 (t, *J* = 5.4 Hz, 1H, $C(CH_3)_2CH$OSi), 3.99 (s, 1H, CHC*H*OSi), 3.08 (d, *J* = 11.1 Hz, 1H, CHC(O)), 2.75-2.67 (m, 5H), 2.61 (dd, *J* = 15.8, 5.1 Hz, 1H, CH_2CO_2), 2.35 (d, *J* = 16.1 Hz, 1H), 2.26-2.20 (m, 1H), 2.12 (d, *J* = 1.1 Hz, 3H, ArCH=CCH_3), 2.10-2.00 (m, 1H), 1.99-1.87 (m, 2H), 1.67 (s, 3H, CH=CCH_3CH_2), 1.66-1.57 (m, 2H), 1.58-1.26 (m, 8H), 1.11 (s, 3H, $C(CH_3)_2$), 1.04 (s, 3H, $C(CH_3)_2$), 0.90 (s, 9H, $SiC(CH_3)_3$), 0.82 (s,

9H, $SiC(CH_3)_3$), 0.09 (s, 3H, $SiC(CH_3)_2$), 0.07 (s, 3H, $Si(CH_3)_2$), 0.00 (s, 3H, $Si(CH_3)_2$), -0.02 (s, 1H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.60, 170.616, 164.89, 152.66, 138.30, 137.99, 120.90, 119.86, 116.44, 79.11, 74.44, 70.16, 54.70, 45.13, 42.39, 40.69, 32.32, 32.00, 30.94, 26.54, 26.28, 26.04, 24.79, 23.55, 23.15, 21.94, 21.05, 19.81, 19.47, 18.42, 18.33, 15.73, -3.69, -4.08, -4.18, -4.21; HRMS calcd for $C_{40}H_{70}NO_5SSi_2$ 732.45132 $[M + H]^+$, found 732.45108.

Finally, dihydroxy lactone **81** was prepared from bis(silyl ether) lactone intermediate (205 mg, 0.28 mmol) by treatment with CF_3COOH according to the same procedure described above for the preparation of **79**, to obtain pure lactone **81** (137 mg, 91%) as a colorless oil or white foam: R_f = 0.46 (CH_2Cl_2/MeOH, 15:1); $[\alpha]^{22}{}_D$ –109.9 (*c* 1.35, $CHCl_3$); IR (thin film) ν_{max} 3435 (br), 2934, 2864, 1733, 1679, 1509, 1447, 1413, 1378, 1336, 1293, 1251, 1185, 1143, 1081, 1046, 984, 938, 914, 849, 714, 683 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.95 (s, 1H, SCH=C), 6.60 (s, 1H, ArC*H*=CCH_3), 5.13 (m, 2H, C*H*OC(O), CH_2C*H*=CCH_3), 4.62-4.39 (m, 1H, C*H*OHC(CH_3)), 4.28 (s, 1H, CHC*H*OH), 3.87 (s, 1H, OH), 3.69 (d, *J* = 5.9 Hz, 1H, OH), 2.98 (dd, *J* = 12.4, 2.2 Hz, 1H, CHC(O)), 2.67 (s, 3H, N=C(S)CH_3), 2.62 (ddd, *J* = 15.2, 10.1, 10.1 Hz, 1H), 2.44 (dd, *J* = 14.2, 11.4 Hz, 1H, CH_2CO_2), 2.35-2.30 (m, 1H), 2.26-2.21 (m, 2H), 2.06 (d, *J* = 1.1 Hz, 3H, ArCH=CC*H*$_3$), 2.02-1.85 (m, 2H), 1.81-1.74 (m, 2H), 1.67 (s, 3H, CH=CC*H*$_3$$CH_2$), 1.62-1.44 (m, 5H), 1.38-1.19 (m, 6H), 1.04 (s, 3H, $C(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 221.06, 170.48, 165.33, 151.94, 140.02, 138.48, 121.17, 119.17, 115.61, 79.13, 73.02, 69.77, 54.28, 43.81, 40.03, 39.82, 32.89, 32.13, 29.93, 27.03, 25.26, 23.91, 23.88, 23.39, 20.89, 19.18, 17.02, 16.28; HRMS calcd for $C_{28}H_{42}NO_5S$ 504.27837 $[M + H]^+$,

found 504.27762.

Preparation of C6-C8 bridged epothilone B (23). To a solution of bridged desoxyepothilone B (**81**) (0.20 mg, 0.04 mmol, 1.0 equiv) in CH_2Cl_2 (0.4 mL) at -78 ^oC was added freshly prepared 3,3-dimethyldioxirane [108] (1.0 mL, ca. 0.08 mmol,ca. 0.08 M in acetone, 2.0 equiv) dropwise. The resulting solution was warmed to -50 ^oC for 1 h, and another portion of dimethyldioxirane (0.4 mL, 0.032 mmol) was added. After stirring at -50 ^oC for additional 2.5 h, A stream of argon was then bubbled through the solution at -50 ^oC to remove excess dimethyldioxirane and solvent. The crude reaction mixture was determined to be >20:1 ratio of diastereomeric *cis*-epoxides by ^1H NMR spectroscopy. The resulting residue was purified by preparative thin-layer chromatography (CH_2Cl_2/MeOH, 30/1) to afford bridged epothilone B (**23**) (10.8 mg, 52%) as a white foam: R_f = 0.39 (CH_2Cl_2/MeOH, 15:1); $[\alpha]^{22}_D$ –57.8 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 3470 (br), 2934, 2864, 1737, 1679, 1505, 1467, 1444, 1413, 1382, 1324, 1293, 1251, 1177,1154, 1073, 1042, 984, 941, 880, 760 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.98 (s, 1H, SCH=C), 6.61 (s, 1H, ArC*H*=CCH_3), 5.33 (dd, *J* = 8.9, 2.7 Hz, 1H, C*H*OC(O)), 4.43 (d, *J* = 10.0 Hz, 1H, C*H*OHC$(CH_3)_2$), 4.37 (s, 1H, CHC*H*OH), 4.13 (s, 1H, OH), 4.00 (s, 1H, OH), 3.01 (dd, *J* = 12.1, 1.8 Hz, 1H, CHC(O)), 2.79 (dd, *J* = 9.1, 2.8 Hz, 1H, CH_2C*H*-O(epoxide)C), 2.68 (s, 3H, N=C(S)CH_3), 2.50 (dd, *J* = 14.2, 10.7 Hz, 1H, CH_2CO_2), 2.24 (dd, *J* = 14.3, 2.6 Hz, 1H, CH_2CO_2), 2.16 (ddd, *J* = 15.1, 2.8, 2.8 Hz, 1H), 2.08 (s, 3H, CH=CC*H*$_3$), 2.07-2.00 (m, 1H), 1.97-1.72 (m, 5H), 1.72-1.47 (m, 5H), 1.41-1.20 (m, 9H), 1.07 (s, 3H, C$(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 221.45, 170.43, 165.59, 151.62,

138.88, 120.07, 116.10, 77.02, 72.99, 68.27, 62.51, 61.72, 53.94, 43.76, 40.21, 39.76, 33.06, 32.68, 30.92, 25.47, 25.33, 24.77, 23.50, 23.00, 21.14, 19.23, 17.70, 16.18; HRMS calcd for $C_{28}H_{42}NO_6S$ 520.27328 $[M + H]^+$, found 520.27228.

1.5.2. Molecular Modeling and Docking

The 3-D structures of bridged epothilones **22/23** were constructed based on the electron crystallographic (EC) pose of EpoA bound to tubulin.[60] The resulting structures of **22/23** was then fully optimized with the MMFF/GBSA/H_2O force field to provide the nearest local minimum. The latter was flexibly Glide-docked [109] into the electron crystallographic structure of EpoA-tubulin.[60] The best docking pose was chosen on the basis of the Emodel scoring function together with visualization to ensure a reasonable binding mode and match with the EC complex.

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 $2.5x10^5$ 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 IC_{50} 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.

1.5.4. X-ray Crystallography data

Chloride 34.

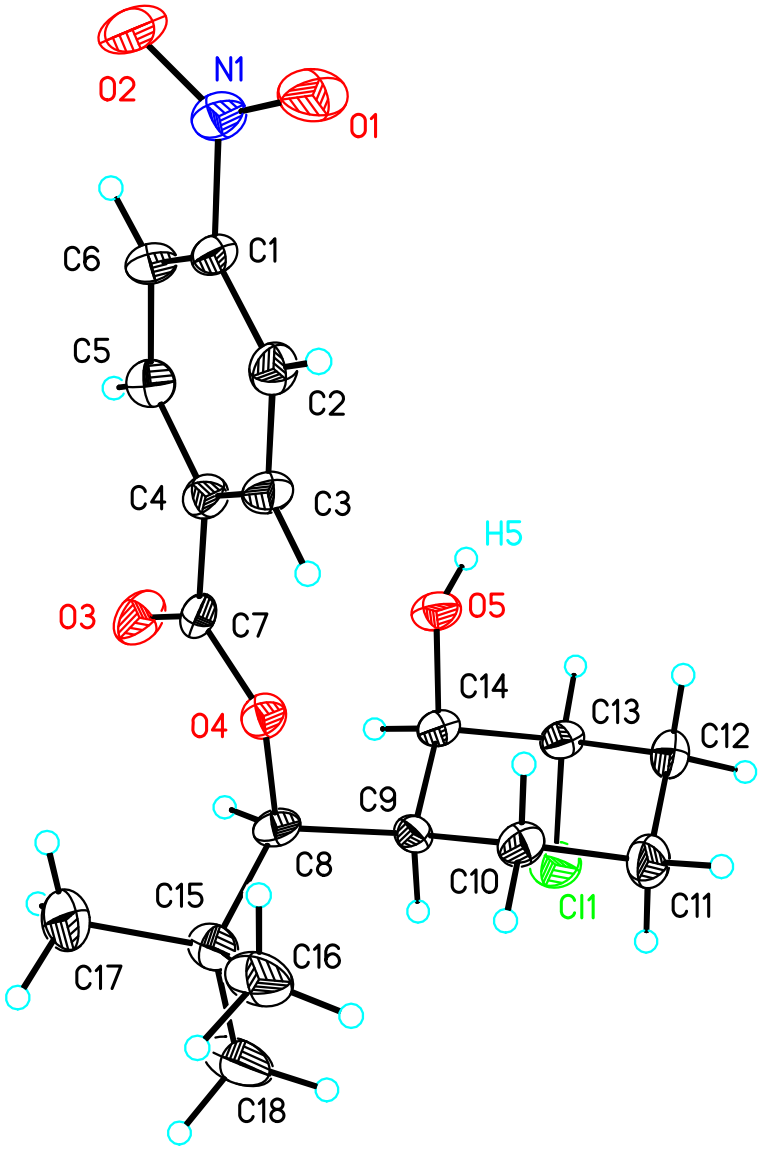


Figure S1. Thermal ellipsoid diagram of **34** with 50% displacement ellipsoids

Table S1. Crystal data and structure refinement for **34**.

Identification code	34	
Empirical formula	C18 H26 Cl N O6	
Formula weight	387.85	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 12.041(3) Å	= 90°.
	b = 6.3544(15) Å	= 114.682(5)°.
	c = 13.675(3) Å	= 90°.
Volume	950.7(4) $Å^3$	
Z	2	
Density (calculated)	1.355 Mg/m^3	
Absorption coefficient	0.235 mm^{-1}	
F(000)	412	
Crystal size	0.29 x 0.06 x 0.04 mm^3	
Theta range for data collection	1.64 to 28.34°.	
Index ranges	-16<=h<=16, -8<=k<=8, -18<=l<=18	
Reflections collected	14089	
Independent reflections	4706 [R(int) = 0.0811]	
Completeness to theta = 28.34°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9907 and 0.9350	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4706 / 1 / 234	
Goodness-of-fit on F2	1.105	
Final R indices [I>2sigma(I)]	R1 = 0.0811, wR2 = 0.1497	
R indices (all data)	R1 = 0.1063, wR2 = 0.1604	
Absolute structure parameter	0.11(11)	
Largest diff. peak and hole	0.479 and -0.372 $e.Å^{-3}$	

Table S2. Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($Å^2 x\ 10^3$) for **34**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
Cl(1)	2967(1)	-452(2)	3686(1)	32(1)
N(1)	-948(3)	5125(6)	9003(3)	25(1)
O(1)	-863(3)	7020(5)	8957(3)	35(1)
O(2)	-1653(3)	4209(6)	9282(3)	38(1)
O(3)	1917(3)	-1775(5)	7554(3)	32(1)
O(4)	3091(2)	1049(5)	7714(2)	22(1)
O(5)	1419(2)	1377(5)	5611(2)	25(1)
C(1)	-135(3)	3842(7)	8684(3)	22(1)
C(2)	936(3)	4734(7)	8735(3)	24(1)
C(3)	1696(4)	3521(7)	8435(3)	25(1)
C(4)	1378(4)	1454(7)	8096(3)	22(1)
C(5)	289(4)	612(7)	8061(3)	25(1)
C(6)	-463(4)	1797(7)	8377(3)	24(1)
C(7)	2143(4)	55(6)	7752(3)	22(1)
C(8)	3817(3)	-97(7)	7241(3)	21(1)
C(9)	3581(3)	893(7)	6154(3)	19(1)
C(10)	3837(4)	3244(7)	6153(3)	25(1)
C(11)	3668(4)	3969(7)	5032(3)	30(1)
C(12)	2388(4)	3492(7)	4192(3)	29(1)
C(13)	2069(4)	1151(7)	4189(3)	25(1)
C(14)	2298(3)	387(7)	5322(3)	21(1)
C(15)	5132(4)	-282(8)	8120(3)	27(1)
C(16)	5687(4)	1784(9)	8664(4)	38(1)
C(17)	5082(5)	-1760(10)	8985(4)	46(1)
C(18)	5934(4)	-1255(10)	7625(4)	48(2)
O(1S)	9149(3)	505(6)	4231(3)	40(1)

Table S3. Bond lengths [Å] and angles [°] for **34**.

Cl(1)-C(13)	1.818(4)	C(2)-C(1)-N(1)	118.6(4)
N(1)-O(1)	1.212(4)	C(3)-C(2)-C(1)	118.4(4)
N(1)-O(2)	1.215(4)	C(2)-C(3)-C(4)	120.0(4)
N(1)-C(1)	1.473(5)	C(3)-C(4)-C(5)	119.7(4)
O(3)-C(7)	1.199(5)	C(3)-C(4)-C(7)	123.2(4)
O(4)-C(7)	1.325(5)	C(5)-C(4)-C(7)	117.1(4)
O(4)-C(8)	1.478(4)	C(6)-C(5)-C(4)	120.6(4)
O(5)-C(14)	1.422(4)	C(1)-C(6)-C(5)	118.0(4)
C(1)-C(6)	1.372(6)	O(3)-C(7)-O(4)	124.9(4)
C(1)-C(2)	1.383(5)	O(3)-C(7)-C(4)	122.5(4)
C(2)-C(3)	1.383(6)	O(4)-C(7)-C(4)	112.6(3)
C(3)-C(4)	1.392(6)	O(4)-C(8)-C(9)	108.6(3)
C(4)-C(5)	1.399(5)	O(4)-C(8)-C(15)	107.4(3)
C(4)-C(7)	1.491(5)	C(9)-C(8)-C(15)	120.2(3)
C(5)-C(6)	1.379(5)	C(14)-C(9)-C(10)	110.4(3)
C(8)-C(9)	1.528(5)	C(14)-C(9)-C(8)	111.0(3)
C(8)-C(15)	1.542(5)	C(10)-C(9)-C(8)	116.6(3)
C(9)-C(14)	1.522(5)	C(9)-C(10)-C(11)	110.7(4)
C(9)-C(10)	1.526(6)	C(12)-C(11)-C(10)	111.5(3)
C(10)-C(11)	1.530(6)	C(11)-C(12)-C(13)	111.6(4)
C(11)-C(12)	1.519(6)	C(14)-C(13)-C(12)	111.4(4)
C(12)-C(13)	1.537(6)	C(14)-C(13)-Cl(1)	108.7(3)
C(13)-C(14)	1.534(5)	C(12)-C(13)-Cl(1)	110.8(3)
C(15)-C(16)	1.519(7)	O(5)-C(14)-C(9)	109.9(3)
C(15)-C(18)	1.522(6)	O(5)-C(14)-C(13)	107.4(3)
C(15)-C(17)	1.532(6)	C(9)-C(14)-C(13)	112.7(3)
O(1)-N(1)-O(2)	125.2(4)	C(16)-C(15)-C(18)	109.8(4)
O(1)-N(1)-C(1)	117.0(3)	C(16)-C(15)-C(17)	107.6(4)
O(2)-N(1)-C(1)	117.8(4)	C(18)-C(15)-C(17)	109.4(4)
C(7)-O(4)-C(8)	117.3(3)	C(16)-C(15)-C(8)	114.5(4)
C(6)-C(1)-C(2)	123.1(4)	C(18)-C(15)-C(8)	108.6(3)
C(6)-C(1)-N(1)	118.2(3)	C(17)-C(15)-C(8)	106.9(4)

Table S4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **34**. 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}
Cl(1)	31(1)	45(1)	24(1)	-1(1)	14(1)	4(1)
N(1)	21(2)	29(2)	25(2)	-3(2)	10(2)	-3(2)
O(1)	35(2)	24(2)	51(2)	-7(2)	24(2)	2(2)
O(2)	36(2)	39(2)	56(2)	-1(2)	34(2)	0(2)
O(3)	43(2)	21(2)	43(2)	-3(2)	28(2)	-4(2)
O(4)	25(2)	23(2)	21(1)	-1(1)	12(1)	2(1)
O(5)	17(1)	33(2)	24(2)	-2(1)	9(1)	-2(1)
C(1)	17(2)	27(2)	23(2)	3(2)	10(2)	0(2)
C(2)	24(2)	23(2)	25(2)	1(2)	9(2)	-4(2)
C(3)	15(2)	31(3)	28(2)	2(2)	9(2)	-3(2)
C(4)	22(2)	25(2)	20(2)	-1(2)	10(2)	-1(2)
C(5)	24(2)	26(2)	23(2)	-2(2)	9(2)	-1(2)
C(6)	17(2)	28(3)	28(2)	-1(2)	10(2)	-2(2)
C(7)	25(2)	22(2)	24(2)	7(2)	15(2)	1(2)
C(8)	20(2)	25(3)	22(2)	-4(2)	12(2)	0(2)
C(9)	17(2)	23(2)	17(2)	3(2)	7(2)	4(2)
C(10)	21(2)	25(2)	28(2)	1(2)	10(2)	-4(2)
C(11)	30(2)	24(2)	33(2)	6(2)	10(2)	-4(2)
C(12)	29(2)	31(3)	28(2)	11(2)	13(2)	1(2)
C(13)	21(2)	31(2)	26(2)	3(2)	13(2)	2(2)
C(14)	18(2)	22(2)	23(2)	-1(2)	11(2)	-1(2)
C(15)	25(2)	39(3)	15(2)	-1(2)	8(2)	7(2)
C(16)	24(2)	53(3)	27(2)	-5(2)	0(2)	-1(2)
C(17)	38(3)	66(4)	30(3)	19(3)	10(2)	3(3)
C(18)	31(3)	81(5)	29(3)	1(3)	10(2)	23(3)

Table S5. Hydrogen coordinates ($x10^4$) and isotropic displacement parameters ($Å^2 x\ 10^3$) for **34**.

	x	y	z	U(eq)
H(5)	731	1340	5086	37
H(2)	1144	6145	8969	29
H(3)	2435	4099	8460	30
H(5A)	66	-791	7817	30
H(6)	-1188	1215	8382	29
H(8)	3481	-1559	7089	25
H(9)	4153	179	5900	23
H(10A)	4684	3542	6677	30
H(10B)	3274	4038	6377	30
H(11A)	3819	5502	5046	36
H(11B)	4273	3250	4833	36
H(12A)	2330	3888	3472	35
H(12B)	1790	4350	4340	35
H(13)	1183	954	3707	30
H(14)	2173	-1171	5302	25
H(16A)	6431	1500	9314	57
H(16B)	5098	2534	8859	57
H(16C)	5890	2652	8169	57
H(17A)	4751	-3125	8662	69
H(17B)	4555	-1147	9296	69
H(17C)	5908	-1952	9552	69
H(18A)	6702	-1740	8199	72
H(18B)	6109	-200	7186	72
H(18C)	5507	-2452	7172	72
H(1S)	8771	-1129	4081	60
H(2S)	8643	1546	3554	60

Table S6. Torsion angles [°] for **34**.

O(1)-N(1)-C(1)-C(6)	-158.4(4)	C(15)-C(8)-C(9)-C(14)	164.6(4)
O(2)-N(1)-C(1)-C(6)	21.1(6)	O(4)-C(8)-C(9)-C(10)	56.4(4)
O(1)-N(1)-C(1)-C(2)	23.3(6)	C(15)-C(8)-C(9)-C(10)	-67.8(5)
O(2)-N(1)-C(1)-C(2)	-157.3(4)	C(14)-C(9)-C(10)-C(11)	-57.0(4)
C(6)-C(1)-C(2)-C(3)	1.7(6)	C(8)-C(9)-C(10)-C(11)	175.0(3)
N(1)-C(1)-C(2)-C(3)	180.0(4)	C(9)-C(10)-C(11)-C(12)	57.7(5)
C(1)-C(2)-C(3)-C(4)	-0.2(6)	C(10)-C(11)-C(12)-C(13)	-55.0(5)
C(2)-C(3)-C(4)-C(5)	-0.1(6)	C(11)-C(12)-C(13)-C(14)	51.9(5)
C(2)-C(3)-C(4)-C(7)	179.5(4)	C(11)-C(12)-C(13)-Cl(1)	-69.2(4)
C(3)-C(4)-C(5)-C(6)	-1.1(6)	C(10)-C(9)-C(14)-O(5)	-64.6(4)
C(7)-C(4)-C(5)-C(6)	179.3(4)	C(8)-C(9)-C(14)-O(5)	66.3(4)
C(2)-C(1)-C(6)-C(5)	-2.8(6)	C(10)-C(9)-C(14)-C(13)	55.1(4)
N(1)-C(1)-C(6)-C(5)	178.9(4)	C(8)-C(9)-C(14)-C(13)	-173.9(3)
C(4)-C(5)-C(6)-C(1)	2.5(6)	C(12)-C(13)-C(14)-O(5)	68.7(4)
C(8)-O(4)-C(7)-O(3)	9.4(6)	Cl(1)-C(13)-C(14)-O(5)	-169.0(3)
C(8)-O(4)-C(7)-C(4)	-171.8(3)	C(12)-C(13)-C(14)-C(9)	-52.5(4)
C(3)-C(4)-C(7)-O(3)	173.2(4)	Cl(1)-C(13)-C(14)-C(9)	69.8(4)
C(5)-C(4)-C(7)-O(3)	-7.2(6)	O(4)-C(8)-C(15)-C(16)	-51.2(4)
C(3)-C(4)-C(7)-O(4)	-5.7(6)	C(9)-C(8)-C(15)-C(16)	73.5(5)
C(5)-C(4)-C(7)-O(4)	173.9(3)	O(4)-C(8)-C(15)-C(18)	-174.2(4)
C(7)-O(4)-C(8)-C(9)	109.1(4)	C(9)-C(8)-C(15)-C(18)	-49.5(6)
C(7)-O(4)-C(8)-C(15)	-119.5(4)	O(4)-C(8)-C(15)-C(17)	67.9(4)
O(4)-C(8)-C(9)-C(14)	-71.3(4)	C(9)-C(8)-C(15)-C(17)	-167.4(4)

Symmetry transformations used to generate equivalent atoms:

Table S7. Hydrogen bonds for 34 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(5)-H(5)...O(1S)#1	0.84	1.85	2.652(4)	159.5
O(1S)-H(1S)...O(5)#2	1.12	1.68	2.743(5)	156.7
O(1S)-H(2S)...O(3)#3	1.09	1.74	2.824(5)	169.5

Symmetry transformations used to generate equivalent atoms:

#1 x-1,y,z #2 -x+1,y-1/2,-z+1 #3 -x+1,y+1/2,-z+1

Keto Acid 74.

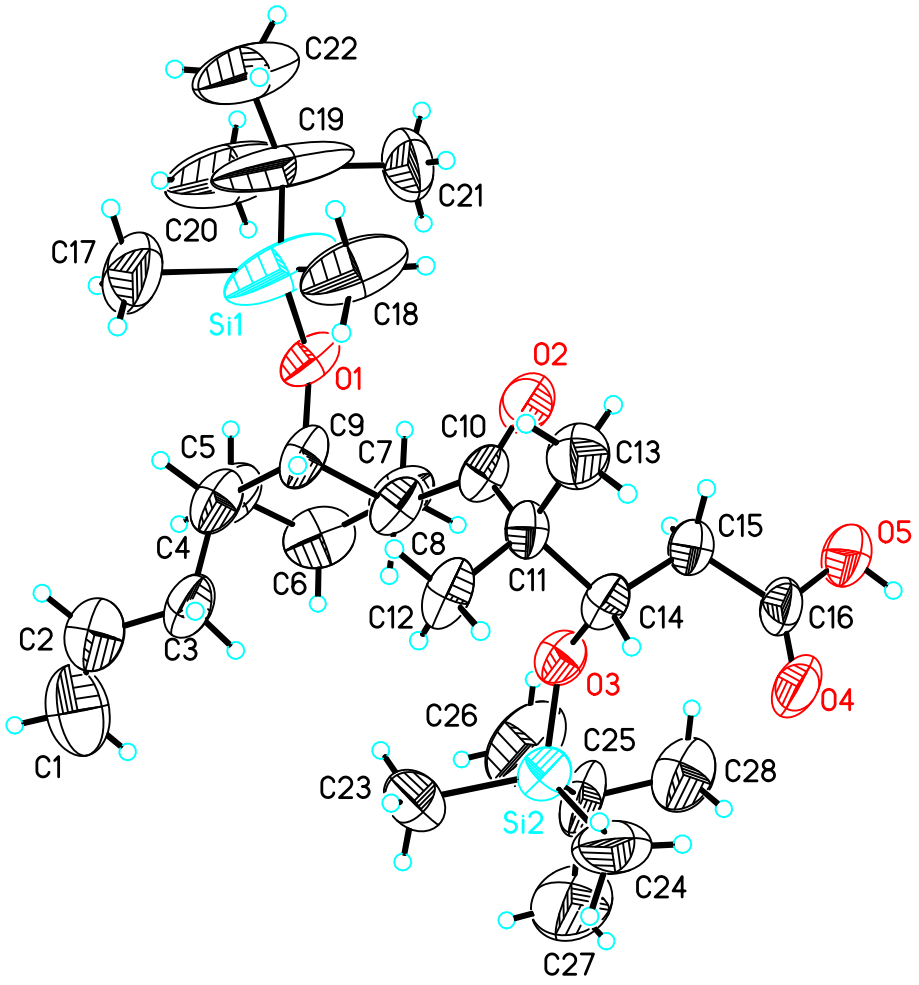


Figure S2. Thermal ellipsoid diagram of **74** with 50% displacement ellipsoids

Table S8. Crystal data and structure refinement for **74**.

Identification code	**74**	
Empirical formula	C28 H54 O5 Si2	
Formula weight	526.89	
Temperature	173(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	C2	
Unit cell dimensions	a = 36.7236(13) Å	α= 90°.
	b = 7.3663(4) Å	β= 105.935(2)°.
	c = 25.1062(9) Å	γ = 90°.
Volume	6530.7(5) Å^3	

Z	8
Density (calculated)	1.072 Mg/m^3
Absorption coefficient	1.227 mm^{-1}
F(000)	2320
Crystal size	0.27 x 0.19 x 0.02 mm^3
Theta range for data collection	1.83 to 66.82°.
Index ranges	-42<=h<=38, -7<=k<=7, -28<=l<=29
Reflections collected	12095
Independent reflections	7460 [R(int) = 0.0481]
Completeness to theta = 66.82°	81.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9759 and 0.7330
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7460 / 1 / 633
Goodness-of-fit on F^2	1.049
Final R indices [I>2sigma(I)]	R1 = 0.0745, wR2 = 0.1975
R indices (all data)	R1 = 0.1341, wR2 = 0.2331
Absolute structure parameter	0.06(6)
Largest diff. peak and hole	0.807 and -0.689 $e.Å^{-3}$

Table **S9**. Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($Å^2 x\ 10^3$) for Keto acid **74**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	52(4)	-4540(20)	8381(6)	116(5)
C(2)	202(3)	-3770(17)	8833(5)	90(3)
C(3)	565(2)	-2896(13)	8959(4)	68(2)
C(4)	570(2)	-911(15)	9205(4)	73(3)
C(5)	367(2)	474(16)	8786(4)	80(3)
C(6)	588(3)	976(16)	8376(4)	86(3)
C(7)	979(2)	1665(14)	8683(3)	74(3)
C(8)	1192(2)	264(12)	9083(3)	60(2)
C(9)	966(2)	-187(14)	9503(3)	66(2)
C(10)	1593(2)	730(14)	9365(3)	57(2)
C(11)	1911(2)	-701(11)	9473(3)	52(2)

C(12)	1769(2)	-2652(13)	9509(4)	69(3)
C(13)	2217(2)	-262(15)	10014(3)	75(3)
C(14)	2091(2)	-630(11)	8975(3)	54(2)
C(15)	2292(2)	1174(14)	8948(4)	74(3)
C(16)	2586(2)	1075(14)	8637(3)	59(2)
C(17)	628(4)	-114(19)	10719(5)	119(4)
C(18)	1501(3)	610(20)	10850(4)	121(5)
C(19)	905(4)	3440(30)	10691(5)	215(12)
C(20)	498(4)	4110(30)	10348(5)	206(11)
C(21)	1253(3)	4773(16)	10489(4)	95(3)
C(22)	925(4)	3620(30)	11306(5)	163(8)
C(23)	1308(3)	-3804(18)	8001(5)	108(4)
C(24)	2144(3)	-3948(16)	8092(4)	98(3)
C(25)	1622(2)	-1226(19)	7311(4)	92(4)
C(26)	1264(3)	-70(20)	7230(5)	136(6)
C(27)	1561(4)	-2640(30)	6832(5)	151(7)
C(28)	1951(3)	-5(19)	7279(4)	100(4)
C(1A)	3676(4)	7170(20)	4306(4)	119(5)
C(2A)	3981(3)	6705(17)	4690(4)	87(3)
C(3A)	3987(2)	5857(13)	5220(3)	62(2)
C(4A)	4219(2)	4040(13)	5315(3)	63(2)
C(5A)	4015(2)	2486(14)	4958(3)	70(3)
C(6A)	3668(2)	1832(16)	5107(4)	80(3)
C(7A)	3770(2)	1227(14)	5727(4)	75(3)
C(8A)	3956(2)	2858(12)	6087(3)	58(2)
C(9A)	4320(2)	3462(12)	5928(3)	52(2)
C(10A)	4049(2)	2414(15)	6704(4)	67(3)
C(11A)	3999(2)	3876(17)	7119(3)	73(3)
C(12A)	4014(3)	5760(17)	6936(4)	90(3)
C(13A)	4293(3)	3510(20)	7681(4)	117(5)
C(14A)	3599(2)	3488(14)	7201(3)	63(2)
C(15A)	3549(3)	1554(15)	7399(4)	83(3)
C(16A)	3294(3)	1450(20)	7779(4)	85(3)
C(17A)	5293(2)	3121(15)	5885(4)	82(3)
C(18A)	5143(2)	2856(15)	7011(3)	75(3)
C(19A)	5135(2)	-590(16)	6325(4)	84(3)

C(20A)	5012(4)	-1380(20)	5732(6)	138(6)
C(21A)	5554(3)	-1002(19)	6560(6)	127(5)
C(22A)	4912(3)	-1571(16)	6671(6)	117(4)
C(23A)	2543(4)	2530(30)	6510(12)	303(19)
C(24A)	2826(6)	5850(30)	7144(6)	253(14)
C(25A)	2699(6)	5190(70)	5957(8)	430(40)
C(26A)	2773(6)	4180(60)	5494(7)	380(30)
C(27A)	3039(6)	7260(30)	6011(11)	268(16)
C(28A)	2291(4)	5850(50)	5794(8)	310(20)
O(1)	942(1)	1377(9)	9811(2)	64(2)
O(2)	1682(2)	2297(10)	9500(3)	76(2)
O(3)	1800(1)	-874(8)	8472(2)	57(1)
O(4)	2697(2)	-258(10)	8464(3)	74(2)
O(5)	2737(2)	2686(10)	8626(3)	84(2)
O(1A)	4572(1)	1933(8)	6006(2)	56(1)
O(2A)	4173(2)	910(12)	6871(3)	95(2)
O(3A)	3321(1)	3782(9)	6694(2)	63(2)
O(4A)	3239(2)	2663(14)	8049(3)	109(3)
O(5A)	3140(2)	-176(13)	7780(3)	103(2)
Si(1)	1015(1)	1450(7)	10480(1)	142(2)
Si(2)	1730(1)	-2444(4)	7986(1)	69(1)
Si(1A)	5026(1)	1865(3)	6303(1)	54(1)
Si(2A)	2898(1)	4656(7)	6564(2)	125(2)

Table **S10**. Bond lengths [Å] and angles [°] for **74**.

C(1)-C(2)	1.252(16)	C(13)-H(13B)	0.9800
C(1)-H(1A)	0.9500	C(13)-H(13C)	0.9800
C(1)-H(1B)	0.9500	C(14)-O(3)	1.426(9)
C(2)-C(3)	1.435(13)	C(14)-C(15)	1.531(12)
C(2)-H(2)	0.9500	C(14)-H(14)	1.0000
C(3)-C(4)	1.585(14)	C(15)-C(16)	1.496(11)
C(3)-H(3A)	0.9900	C(15)-H(15A)	0.9900
C(3)-H(3B)	0.9900	C(15)-H(15B)	0.9900
C(4)-C(5)	1.508(13)	C(16)-O(4)	1.190(10)
C(4)-C(9)	1.538(12)	C(16)-O(5)	1.314(11)
C(4)-H(4)	1.0000	C(17)-Si(1)	2.045(12)
C(5)-C(6)	1.522(13)	C(17)-H(17A)	0.9800
C(5)-H(5A)	0.9900	C(17)-H(17B)	0.9800
C(5)-H(5B)	0.9900	C(17)-H(17C)	0.9800
C(6)-C(7)	1.521(13)	C(18)-Si(1)	1.876(10)
C(6)-H(6A)	0.9900	C(18)-H(18A)	0.9800
C(6)-H(6B)	0.9900	C(18)-H(18B)	0.9800
C(7)-C(8)	1.501(11)	C(18)-H(18C)	0.9800
C(7)-H(7A)	0.9900	C(19)-C(22)	1.533(16)
C(7)-H(7B)	0.9900	C(19)-C(20)	1.587(15)
C(8)-C(10)	1.490(11)	C(19)-Si(1)	1.644(16)
C(8)-C(9)	1.544(10)	C(19)-C(21)	1.79(3)
C(8)-H(8)	1.0000	C(20)-H(20A)	0.9800
C(9)-O(1)	1.404(11)	C(20)-H(20B)	0.9800
C(9)-H(9)	1.0000	C(20)-H(20C)	0.9800
C(10)-O(2)	1.222(11)	C(21)-H(21A)	0.9800
C(10)-C(11)	1.540(11)	C(21)-H(21B)	0.9800
C(11)-C(13)	1.541(11)	C(21)-H(21C)	0.9800
C(11)-C(12)	1.541(12)	C(22)-H(22A)	0.9800
C(11)-C(14)	1.566(9)	C(22)-H(22B)	0.9800
C(12)-H(12A)	0.9800	C(22)-H(22C)	0.9800
C(12)-H(12B)	0.9800	C(23)-Si(2)	1.856(10)
C(12)-H(12C)	0.9800	C(23)-H(23A)	0.9800
C(13)-H(13A)	0.9800	C(23)-H(23B)	0.9800

C(23)-H(23C)	0.9800	C(7A)-H(7A1)	0.9900
C(24)-Si(2)	1.839(10)	C(7A)-H(7A2)	0.9900
C(24)-H(24A)	0.9800	C(8A)-C(10A)	1.526(11)
C(24)-H(24B)	0.9800	C(8A)-C(9A)	1.561(10)
C(24)-H(24C)	0.9800	C(8A)-H(8A)	1.0000
C(25)-C(28)	1.526(15)	C(9A)-O(1A)	1.437(10)
C(25)-C(26)	1.532(15)	C(9A)-H(9A)	1.0000
C(25)-C(27)	1.560(17)	C(10A)-O(2A)	1.227(11)
C(25)-Si(2)	1.863(10)	C(10A)-C(11A)	1.545(13)
C(26)-H(26A)	0.9800	C(11A)-C(12A)	1.467(15)
C(26)-H(26B)	0.9800	C(11A)-C(13A)	1.548(12)
C(26)-H(26C)	0.9800	C(11A)-C(14A)	1.564(11)
C(27)-H(27A)	0.9800	C(12A)-H(12D)	0.9800
C(27)-H(27B)	0.9800	C(12A)-H(12E)	0.9800
C(27)-H(27C)	0.9800	C(12A)-H(12F)	0.9800
C(28)-H(28A)	0.9800	C(13A)-H(13D)	0.9800
C(28)-H(28B)	0.9800	C(13A)-H(13E)	0.9800
C(28)-H(28C)	0.9800	C(13A)-H(13F)	0.9800
C(1A)-C(2A)	1.307(14)	C(14A)-O(3A)	1.413(9)
C(1A)-H(1A1)	0.9500	C(14A)-C(15A)	1.537(13)
C(1A)-H(1A2)	0.9500	C(14A)-H(14A)	1.0000
C(2A)-C(3A)	1.466(12)	C(15A)-C(16A)	1.510(12)
C(2A)-H(2A)	0.9500	C(15A)-H(15C)	0.9900
C(3A)-C(4A)	1.569(13)	C(15A)-H(15D)	0.9900
C(3A)-H(3A1)	0.9900	C(16A)-O(4A)	1.171(14)
C(3A)-H(3A2)	0.9900	C(16A)-O(5A)	1.326(15)
C(4A)-C(5A)	1.518(12)	C(17A)-Si(1A)	1.866(9)
C(4A)-C(9A)	1.541(11)	C(17A)-H(17D)	0.9800
C(4A)-H(4A)	1.0000	C(17A)-H(17E)	0.9800
C(5A)-C(6A)	1.500(12)	C(17A)-H(17F)	0.9800
C(5A)-H(5A1)	0.9900	C(18A)-Si(1A)	1.860(8)
C(5A)-H(5A2)	0.9900	C(18A)-H(18D)	0.9800
C(6A)-C(7A)	1.563(12)	C(18A)-H(18E)	0.9800
C(6A)-H(6A1)	0.9900	C(18A)-H(18F)	0.9800
C(6A)-H(6A2)	0.9900	C(19A)-C(21A)	1.521(12)
C(7A)-C(8A)	1.545(12)	C(19A)-C(22A)	1.527(14)

C(19A)-C(20A)	1.547(15)	O(3A)-Si(2A)	1.631(5)
C(19A)-Si(1A)	1.849(11)	O(5A)-H(5A3)	0.8400
C(20A)-H(20D)	0.9800		
C(20A)-H(20E)	0.9799	C(2)-C(1)-H(1A)	120.0
C(20A)-H(20F)	0.9800	C(2)-C(1)-H(1B)	120.0
C(21A)-H(21D)	0.9800	H(1A)-C(1)-H(1B)	120.0
C(21A)-H(21E)	0.9800	C(1)-C(2)-C(3)	123.5(11)
C(21A)-H(21F)	0.9800	C(1)-C(2)-H(2)	118.2
C(22A)-H(22D)	0.9800	C(3)-C(2)-H(2)	118.2
C(22A)-H(22E)	0.9800	C(2)-C(3)-C(4)	114.2(7)
C(22A)-H(22F)	0.9800	C(2)-C(3)-H(3A)	108.7
C(23A)-Si(2A)	2.018(17)	C(4)-C(3)-H(3A)	108.7
C(23A)-H(23D)	0.9800	C(2)-C(3)-H(3B)	108.7
C(23A)-H(23E)	0.9800	C(4)-C(3)-H(3B)	108.7
C(23A)-H(23F)	0.9800	H(3A)-C(3)-H(3B)	107.6
C(24A)-Si(2A)	1.781(13)	C(5)-C(4)-C(9)	109.0(8)
C(24A)-H(24D)	0.9800	C(5)-C(4)-C(3)	113.7(8)
C(24A)-H(24E)	0.9800	C(9)-C(4)-C(3)	114.7(7)
C(24A)-H(24F)	0.9800	C(5)-C(4)-H(4)	106.2
C(25A)-C(26A)	1.47(3)	C(9)-C(4)-H(4)	106.2
C(25A)-C(28A)	1.520(18)	C(3)-C(4)-H(4)	106.2
C(25A)-Si(2A)	1.550(19)	C(4)-C(5)-C(6)	112.5(7)
C(25A)-C(27A)	1.95(5)	C(4)-C(5)-H(5A)	109.1
C(26A)-H(26D)	0.9800	C(6)-C(5)-H(5A)	109.1
C(26A)-H(26E)	0.9800	C(4)-C(5)-H(5B)	109.1
C(26A)-H(26F)	0.9800	C(6)-C(5)-H(5B)	109.1
C(27A)-H(27D)	0.9800	H(5A)-C(5)-H(5B)	107.8
C(27A)-H(27E)	0.9800	C(7)-C(6)-C(5)	110.1(7)
C(27A)-H(27F)	0.9800	C(7)-C(6)-H(6A)	109.6
C(28A)-H(28D)	0.9800	C(5)-C(6)-H(6A)	109.6
C(28A)-H(28E)	0.9800	C(7)-C(6)-H(6B)	109.6
C(28A)-H(28F)	0.9800	C(5)-C(6)-H(6B)	109.6
O(1)-Si(1)	1.628(6)	H(6A)-C(6)-H(6B)	108.2
O(3)-Si(2)	1.649(6)	C(8)-C(7)-C(6)	110.8(8)
O(5)-H(5)	0.8400	C(8)-C(7)-H(7A)	109.5
O(1A)-Si(1A)	1.630(5)	C(6)-C(7)-H(7A)	109.5

C(8)-C(7)-H(7B)	109.5	O(3)-C(14)-C(15)	108.9(7)
C(6)-C(7)-H(7B)	109.5	O(3)-C(14)-C(11)	108.9(5)
H(7A)-C(7)-H(7B)	108.1	C(15)-C(14)-C(11)	112.3(7)
C(10)-C(8)-C(7)	115.0(8)	O(3)-C(14)-H(14)	108.9
C(10)-C(8)-C(9)	111.9(6)	C(15)-C(14)-H(14)	108.9
C(7)-C(8)-C(9)	109.1(6)	C(11)-C(14)-H(14)	108.9
C(10)-C(8)-H(8)	106.8	C(16)-C(15)-C(14)	114.0(8)
C(7)-C(8)-H(8)	106.8	C(16)-C(15)-H(15A)	108.7
C(9)-C(8)-H(8)	106.8	C(14)-C(15)-H(15A)	108.7
O(1)-C(9)-C(4)	111.0(6)	C(16)-C(15)-H(15B)	108.7
O(1)-C(9)-C(8)	109.0(8)	C(14)-C(15)-H(15B)	108.7
C(4)-C(9)-C(8)	110.8(7)	H(15A)-C(15)-H(15B)	107.6
O(1)-C(9)-H(9)	108.7	O(4)-C(16)-O(5)	123.2(7)
C(4)-C(9)-H(9)	108.7	O(4)-C(16)-C(15)	126.8(9)
C(8)-C(9)-H(9)	108.7	O(5)-C(16)-C(15)	109.7(8)
O(2)-C(10)-C(8)	120.2(8)	Si(1)-C(17)-H(17A)	109.6
O(2)-C(10)-C(11)	117.9(7)	Si(1)-C(17)-H(17B)	109.0
C(8)-C(10)-C(11)	121.9(8)	H(17A)-C(17)-H(17B)	109.5
C(10)-C(11)-C(13)	110.2(7)	Si(1)-C(17)-H(17C)	109.8
C(10)-C(11)-C(12)	113.3(6)	H(17A)-C(17)-H(17C)	109.5
C(13)-C(11)-C(12)	108.7(7)	H(17B)-C(17)-H(17C)	109.5
C(10)-C(11)-C(14)	107.5(6)	Si(1)-C(18)-H(18A)	110.4
C(13)-C(11)-C(14)	109.4(6)	Si(1)-C(18)-H(18B)	109.7
C(12)-C(11)-C(14)	107.6(7)	H(18A)-C(18)-H(18B)	109.5
C(11)-C(12)-H(12A)	109.5	Si(1)-C(18)-H(18C)	108.3
C(11)-C(12)-H(12B)	109.3	H(18A)-C(18)-H(18C)	109.5
H(12A)-C(12)-H(12B)	109.5	H(18B)-C(18)-H(18C)	109.5
C(11)-C(12)-H(12C)	109.7	C(22)-C(19)-C(20)	107.2(10)
H(12A)-C(12)-H(12C)	109.5	C(22)-C(19)-Si(1)	117.2(15)
H(12B)-C(12)-H(12C)	109.5	C(20)-C(19)-Si(1)	112.6(11)
C(11)-C(13)-H(13A)	109.6	C(22)-C(19)-C(21)	113.2(14)
C(11)-C(13)-H(13B)	109.7	C(20)-C(19)-C(21)	108.2(16)
H(13A)-C(13)-H(13B)	109.5	Si(1)-C(19)-C(21)	98.1(8)
C(11)-C(13)-H(13C)	109.2	C(19)-C(20)-H(20A)	107.1
H(13A)-C(13)-H(13C)	109.5	C(19)-C(20)-H(20B)	110.4
H(13B)-C(13)-H(13C)	109.5	H(20A)-C(20)-H(20B)	109.5

C(19)-C(20)-H(20C)	110.9	C(25)-C(26)-H(26C)	109.7
H(20A)-C(20)-H(20C)	109.5	H(26A)-C(26)-H(26C)	109.5
H(20B)-C(20)-H(20C)	109.5	H(26B)-C(26)-H(26C)	109.5
C(19)-C(21)-H(21A)	109.0	C(25)-C(27)-H(27A)	110.0
C(19)-C(21)-H(21B)	108.8	C(25)-C(27)-H(27B)	109.4
H(21A)-C(21)-H(21B)	109.5	H(27A)-C(27)-H(27B)	109.5
C(19)-C(21)-H(21C)	110.6	C(25)-C(27)-H(27C)	109.1
H(21A)-C(21)-H(21C)	109.5	H(27A)-C(27)-H(27C)	109.5
H(21B)-C(21)-H(21C)	109.5	H(27B)-C(27)-H(27C)	109.5
C(19)-C(22)-H(22A)	112.3	C(25)-C(28)-H(28A)	109.5
C(19)-C(22)-H(22B)	108.5	C(25)-C(28)-H(28B)	110.0
H(22A)-C(22)-H(22B)	109.5	H(28A)-C(28)-H(28B)	109.5
C(19)-C(22)-H(22C)	107.6	C(25)-C(28)-H(28C)	108.9
H(22A)-C(22)-H(22C)	109.5	H(28A)-C(28)-H(28C)	109.5
H(22B)-C(22)-H(22C)	109.5	H(28B)-C(28)-H(28C)	109.5
Si(2)-C(23)-H(23A)	110.1	C(2A)-C(1A)-H(1A1)	120.0
Si(2)-C(23)-H(23B)	109.4	C(2A)-C(1A)-H(1A2)	120.0
H(23A)-C(23)-H(23B)	109.5	H(1A1)-C(1A)-H(1A2)	120.0
Si(2)-C(23)-H(23C)	108.9	C(1A)-C(2A)-C(3A)	125.3(10)
H(23A)-C(23)-H(23C)	109.5	C(1A)-C(2A)-H(2A)	117.3
H(23B)-C(23)-H(23C)	109.5	C(3A)-C(2A)-H(2A)	117.3
Si(2)-C(24)-H(24A)	109.9	C(2A)-C(3A)-C(4A)	111.9(7)
Si(2)-C(24)-H(24B)	109.1	C(2A)-C(3A)-H(3A1)	109.2
H(24A)-C(24)-H(24B)	109.5	C(4A)-C(3A)-H(3A1)	109.2
Si(2)-C(24)-H(24C)	109.4	C(2A)-C(3A)-H(3A2)	109.2
H(24A)-C(24)-H(24C)	109.5	C(4A)-C(3A)-H(3A2)	109.2
H(24B)-C(24)-H(24C)	109.5	H(3A1)-C(3A)-H(3A2)	107.9
C(28)-C(25)-C(26)	109.1(12)	C(5A)-C(4A)-C(9A)	109.0(8)
C(28)-C(25)-C(27)	107.4(8)	C(5A)-C(4A)-C(3A)	113.2(6)
C(26)-C(25)-C(27)	109.6(9)	C(9A)-C(4A)-C(3A)	111.0(7)
C(28)-C(25)-Si(2)	110.9(6)	C(5A)-C(4A)-H(4A)	107.8
C(26)-C(25)-Si(2)	110.6(6)	C(9A)-C(4A)-H(4A)	107.8
C(27)-C(25)-Si(2)	109.2(10)	C(3A)-C(4A)-H(4A)	107.8
C(25)-C(26)-H(26A)	108.9	C(6A)-C(5A)-C(4A)	114.3(7)
C(25)-C(26)-H(26B)	109.9	C(6A)-C(5A)-H(5A1)	108.7
H(26A)-C(26)-H(26B)	109.5	C(4A)-C(5A)-H(5A1)	108.7

C(6A)-C(5A)-H(5A2)	108.7	C(11A)-C(12A)-H(12D)	109.2
C(4A)-C(5A)-H(5A2)	108.7	C(11A)-C(12A)-H(12E)	109.9
H(5A1)-C(5A)-H(5A2)	107.6	H(12D)-C(12A)-H(12E)	109.5
C(5A)-C(6A)-C(7A)	110.6(7)	C(11A)-C(12A)-H(12F)	109.3
C(5A)-C(6A)-H(6A1)	109.5	H(12D)-C(12A)-H(12F)	109.5
C(7A)-C(6A)-H(6A1)	109.5	H(12E)-C(12A)-H(12F)	109.5
C(5A)-C(6A)-H(6A2)	109.5	C(11A)-C(13A)-H(13D)	109.7
C(7A)-C(6A)-H(6A2)	109.5	C(11A)-C(13A)-H(13E)	109.8
H(6A1)-C(6A)-H(6A2)	108.1	H(13D)-C(13A)-H(13E)	109.5
C(8A)-C(7A)-C(6A)	107.9(8)	C(11A)-C(13A)-H(13F)	109.0
C(8A)-C(7A)-H(7A1)	110.1	H(13D)-C(13A)-H(13F)	109.5
C(6A)-C(7A)-H(7A1)	110.1	H(13E)-C(13A)-H(13F)	109.5
C(8A)-C(7A)-H(7A2)	110.1	O(3A)-C(14A)-C(15A)	108.2(8)
C(6A)-C(7A)-H(7A2)	110.1	O(3A)-C(14A)-C(11A)	108.9(6)
H(7A1)-C(7A)-H(7A2)	108.4	C(15A)-C(14A)-C(11A)	114.4(8)
C(10A)-C(8A)-C(7A)	111.5(8)	O(3A)-C(14A)-H(14A)	108.4
C(10A)-C(8A)-C(9A)	110.6(6)	C(15A)-C(14A)-H(14A)	108.4
C(7A)-C(8A)-C(9A)	110.1(6)	C(11A)-C(14A)-H(14A)	108.4
C(10A)-C(8A)-H(8A)	108.2	C(16A)-C(15A)-C(14A)	113.6(9)
C(7A)-C(8A)-H(8A)	108.2	C(16A)-C(15A)-H(15C)	108.8
C(9A)-C(8A)-H(8A)	108.2	C(14A)-C(15A)-H(15C)	108.8
O(1A)-C(9A)-C(4A)	108.8(6)	C(16A)-C(15A)-H(15D)	108.8
O(1A)-C(9A)-C(8A)	107.8(7)	C(14A)-C(15A)-H(15D)	108.8
C(4A)-C(9A)-C(8A)	110.3(6)	H(15C)-C(15A)-H(15D)	107.7
O(1A)-C(9A)-H(9A)	110.0	O(4A)-C(16A)-O(5A)	123.1(9)
C(4A)-C(9A)-H(9A)	110.0	O(4A)-C(16A)-C(15A)	124.3(12)
C(8A)-C(9A)-H(9A)	110.0	O(5A)-C(16A)-C(15A)	112.6(12)
O(2A)-C(10A)-C(8A)	119.9(9)	Si(1A)-C(17A)-H(17D)	109.8
O(2A)-C(10A)-C(11A)	120.1(8)	Si(1A)-C(17A)-H(17E)	109.6
C(8A)-C(10A)-C(11A)	120.0(9)	H(17D)-C(17A)-H(17E)	109.5
C(12A)-C(11A)-C(10A)	115.3(8)	Si(1A)-C(17A)-H(17F)	109.0
C(12A)-C(11A)-C(13A)	112.1(10)	H(17D)-C(17A)-H(17F)	109.5
C(10A)-C(11A)-C(13A)	108.0(9)	H(17E)-C(17A)-H(17F)	109.5
C(12A)-C(11A)-C(14A)	109.4(8)	Si(1A)-C(18A)-H(18D)	109.5
C(10A)-C(11A)-C(14A)	104.7(8)	Si(1A)-C(18A)-H(18E)	109.4
C(13A)-C(11A)-C(14A)	107.0(7)	H(18D)-C(18A)-H(18E)	109.5

Si(1A)-C(18A)-H(18F)	109.5	Si(2A)-C(24A)-H(24F)	108.9
H(18D)-C(18A)-H(18F)	109.5	H(24D)-C(24A)-H(24F)	109.5
H(18E)-C(18A)-H(18F)	109.5	H(24E)-C(24A)-H(24F)	109.5
C(21A)-C(19A)-C(22A)	109.2(10)	C(26A)-C(25A)-C(28A)	109(2)
C(21A)-C(19A)-C(20A)	107.1(9)	C(26A)-C(25A)-Si(2A)	121(3)
C(22A)-C(19A)-C(20A)	107.9(11)	C(28A)-C(25A)-Si(2A)	120.6(15)
C(21A)-C(19A)-Si(1A)	113.1(8)	C(26A)-C(25A)-C(27A)	101(3)
C(22A)-C(19A)-Si(1A)	109.6(7)	C(28A)-C(25A)-C(27A)	110(3)
C(20A)-C(19A)-Si(1A)	109.7(8)	Si(2A)-C(25A)-C(27A)	91(2)
C(19A)-C(20A)-H(20D)	109.8	C(25A)-C(26A)-H(26D)	110.1
C(19A)-C(20A)-H(20E)	109.5	C(25A)-C(26A)-H(26E)	109.3
H(20D)-C(20A)-H(20E)	109.5	H(26D)-C(26A)-H(26E)	109.5
C(19A)-C(20A)-H(20F)	109.1	C(25A)-C(26A)-H(26F)	109.1
H(20D)-C(20A)-H(20F)	109.5	H(26D)-C(26A)-H(26F)	109.5
H(20E)-C(20A)-H(20F)	109.5	H(26E)-C(26A)-H(26F)	109.5
C(19A)-C(21A)-H(21D)	109.6	C(25A)-C(27A)-H(27D)	108.4
C(19A)-C(21A)-H(21E)	109.4	C(25A)-C(27A)-H(27E)	110.5
H(21D)-C(21A)-H(21E)	109.5	H(27D)-C(27A)-H(27E)	109.5
C(19A)-C(21A)-H(21F)	109.4	C(25A)-C(27A)-H(27F)	109.5
H(21D)-C(21A)-H(21F)	109.5	H(27D)-C(27A)-H(27F)	109.5
H(21E)-C(21A)-H(21F)	109.5	H(27E)-C(27A)-H(27F)	109.5
C(19A)-C(22A)-H(22D)	110.0	C(25A)-C(28A)-H(28D)	110.0
C(19A)-C(22A)-H(22E)	109.3	C(25A)-C(28A)-H(28E)	110.4
H(22D)-C(22A)-H(22E)	109.5	H(28D)-C(28A)-H(28E)	109.5
C(19A)-C(22A)-H(22F)	109.2	C(25A)-C(28A)-H(28F)	108.0
H(22D)-C(22A)-H(22F)	109.5	H(28D)-C(28A)-H(28F)	109.5
H(22E)-C(22A)-H(22F)	109.5	H(28E)-C(28A)-H(28F)	109.5
Si(2A)-C(23A)-H(23D)	110.2	C(9)-O(1)-Si(1)	125.3(6)
Si(2A)-C(23A)-H(23E)	109.3	C(14)-O(3)-Si(2)	132.0(5)
H(23D)-C(23A)-H(23E)	109.5	C(16)-O(5)-H(5)	109.5
Si(2A)-C(23A)-H(23F)	108.9	C(9A)-O(1A)-Si(1A)	128.8(5)
H(23D)-C(23A)-H(23F)	109.5	C(14A)-O(3A)-Si(2A)	130.8(5)
H(23E)-C(23A)-H(23F)	109.5	C(16A)-O(5A)-H(5A3)	109.5
Si(2A)-C(24A)-H(24D)	109.0	O(1)-Si(1)-C(19)	112.1(7)
Si(2A)-C(24A)-H(24E)	110.6	O(1)-Si(1)-C(18)	111.4(4)
H(24D)-C(24A)-H(24E)	109.5	C(19)-Si(1)-C(18)	114.8(7)

O(1)-Si(1)-C(17)	110.7(5)	C(19A)-Si(1A)-C(18A)	111.3(5)
C(19)-Si(1)-C(17)	98.9(10)	O(1A)-Si(1A)-C(17A)	110.8(4)
C(18)-Si(1)-C(17)	108.1(7)	C(19A)-Si(1A)-C(17A)	111.2(5)
O(3)-Si(2)-C(24)	111.2(4)	C(18A)-Si(1A)-C(17A)	109.0(4)
O(3)-Si(2)-C(23)	108.9(4)	C(25A)-Si(2A)-O(3A)	117.6(7)
C(24)-Si(2)-C(23)	109.5(6)	C(25A)-Si(2A)-C(24A)	122.8(14)
O(3)-Si(2)-C(25)	106.6(5)	O(3A)-Si(2A)-C(24A)	112.3(6)
C(24)-Si(2)-C(25)	112.6(5)	C(25A)-Si(2A)-C(23A)	91(2)
C(23)-Si(2)-C(25)	107.9(5)	O(3A)-Si(2A)-C(23A)	105.6(6)
O(1A)-Si(1A)-C(19A)	103.2(4)	C(24A)-Si(2A)-C(23A)	101.5(12)
O(1A)-Si(1A)-C(18A)	111.3(3)		

Symmetry transformations used to generate equivalent atoms:

Table **S12**. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **74**.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)	102(8)	110(12)	128(11)	50(9)	19(8)	-10(8)
C(2)	75(6)	106(10)	92(8)	14(7)	27(6)	1(6)
C(3)	63(5)	66(7)	89(6)	18(5)	44(4)	16(4)
C(4)	53(4)	100(9)	73(6)	8(5)	29(4)	10(5)
C(5)	61(5)	103(9)	78(6)	6(5)	24(5)	26(5)
C(6)	89(6)	99(9)	60(6)	13(5)	5(5)	30(6)
C(7)	93(6)	78(7)	57(5)	21(5)	32(5)	29(5)
C(8)	59(4)	73(7)	55(5)	14(4)	28(4)	15(4)
C(9)	46(4)	92(7)	66(5)	10(5)	28(4)	9(4)
C(10)	56(5)	66(7)	57(5)	9(4)	29(4)	5(4)
C(11)	47(4)	56(6)	56(5)	8(3)	21(3)	-7(3)
C(12)	56(4)	83(8)	79(6)	21(5)	37(4)	13(4)
C(13)	73(5)	92(8)	59(5)	3(5)	17(4)	-4(5)
C(14)	49(4)	59(6)	61(5)	7(4)	28(4)	8(3)
C(15)	75(5)	77(7)	86(6)	-18(5)	51(5)	-28(5)
C(16)	50(4)	72(7)	61(5)	2(4)	30(4)	-12(4)
C(17)	146(10)	96(10)	151(11)	12(9)	100(9)	-18(8)
C(18)	143(10)	146(13)	71(7)	8(7)	23(6)	93(10)

C(19)	161(13)	340(30)	103(10)	-127(13)	-35(9)	168(17)
C(20)	125(10)	330(30)	128(11)	-100(15)	-21(9)	129(15)
C(21)	87(6)	80(8)	125(9)	3(7)	44(6)	-27(6)
C(22)	131(10)	260(20)	90(9)	-72(11)	18(8)	47(12)
C(23)	120(8)	104(11)	112(8)	-40(7)	51(7)	-51(8)
C(24)	104(7)	82(9)	106(8)	-30(6)	27(6)	20(6)
C(25)	40(4)	173(12)	69(6)	1(6)	23(4)	-5(5)
C(26)	102(8)	213(18)	92(8)	31(10)	24(7)	59(10)
C(27)	136(11)	240(20)	73(8)	-55(10)	24(7)	-23(12)
C(28)	82(6)	142(12)	75(6)	15(7)	22(5)	11(7)
C(1A)	137(10)	142(14)	69(7)	20(7)	17(7)	24(9)
C(2A)	91(6)	105(9)	73(6)	7(6)	35(5)	19(6)
C(3A)	58(5)	76(7)	56(5)	-4(4)	22(4)	8(4)
C(4A)	49(4)	88(8)	54(5)	-4(4)	17(4)	-3(4)
C(5A)	61(5)	91(8)	57(5)	-20(5)	13(4)	9(5)
C(6A)	58(5)	100(8)	79(6)	-23(6)	12(4)	-6(5)
C(7A)	54(5)	70(7)	111(8)	-7(5)	39(5)	-15(4)
C(8A)	41(4)	72(6)	64(5)	-9(4)	22(3)	6(4)
C(9A)	45(4)	63(6)	51(5)	-4(4)	18(3)	-10(3)
C(10A)	41(4)	97(8)	73(6)	10(5)	34(4)	3(4)
C(11A)	46(4)	130(10)	47(5)	-11(5)	17(4)	4(5)
C(12A)	82(6)	103(10)	99(7)	-37(7)	48(6)	-25(6)
C(13A)	65(6)	219(16)	61(6)	-11(7)	6(5)	6(7)
C(14A)	55(4)	83(7)	58(5)	4(4)	25(4)	6(4)
C(15A)	77(6)	98(9)	93(7)	18(6)	55(5)	2(5)
C(16A)	62(5)	129(12)	75(7)	24(7)	39(5)	0(6)
C(17A)	57(5)	104(9)	97(7)	-3(6)	40(5)	-14(5)
C(18A)	55(4)	87(8)	79(6)	-14(5)	12(4)	-1(4)
C(19A)	60(5)	85(9)	105(7)	-15(6)	17(5)	14(5)
C(20A)	128(10)	112(12)	156(11)	-68(10)	9(9)	33(9)
C(21A)	58(6)	113(12)	195(13)	-15(10)	12(7)	30(6)
C(22A)	100(8)	49(8)	206(14)	29(8)	48(8)	-3(6)
C(23A)	81(9)	210(20)	570(50)	240(30)	11(16)	-34(12)
C(24A)	290(20)	330(30)	163(14)	-14(17)	104(16)	230(20)
C(25A)	150(17)	1010(100)	115(15)	30(30)	4(12)	320(40)
C(26A)	189(19)	820(80)	101(13)	-100(30)	-34(12)	240(40)

C(27A)	149(16)	210(30)	410(40)	140(30)	10(20)	-42(17)
C(28A)	93(10)	640(60)	211(18)	120(30)	43(11)	170(20)
O(1)	65(3)	85(5)	48(3)	3(3)	26(2)	19(3)
O(2)	79(4)	66(5)	96(4)	1(4)	48(3)	2(3)
O(3)	50(3)	66(4)	56(3)	4(2)	17(2)	7(2)
O(4)	63(3)	81(5)	93(4)	0(4)	50(3)	2(3)
O(5)	86(4)	89(5)	99(5)	-9(4)	61(4)	-24(4)
O(1A)	40(2)	68(4)	61(3)	-8(3)	16(2)	0(2)
O(2A)	102(5)	102(6)	103(5)	35(4)	65(4)	41(5)
O(3A)	45(3)	86(5)	62(3)	-5(3)	20(3)	5(3)
O(4A)	109(5)	143(8)	100(6)	-37(5)	72(5)	-45(5)
O(5A)	97(5)	119(7)	118(6)	15(5)	73(4)	18(5)
Si(1)	158(3)	215(5)	52(2)	7(2)	28(2)	117(3)
Si(2)	63(1)	78(2)	72(2)	-13(1)	28(1)	-4(1)
Si(1A)	41(1)	60(2)	66(1)	-4(1)	21(1)	-4(1)
Si(2A)	83(2)	165(4)	119(3)	-23(3)	16(2)	62(2)

Table S12. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for **74**.

	x	y	z	U(eq)
H(1A)	179	-4557	8099	139
H(1B)	-189	-5094	8320	139
H(2)	69	-3768	9108	108
H(3A)	648	-2830	8616	82
H(3B)	751	-3652	9228	82
H(4)	427	-982	9491	88
H(5A)	323	1583	8983	96
H(5B)	116	-15	8581	96
H(6A)	612	-102	8152	103
H(6B)	450	1928	8121	103
H(7A)	1123	1963	8413	89
H(7B)	955	2789	8887	89
H(8)	1196	-866	8865	72
H(9)	1106	-1145	9762	79
H(12A)	1651	-2734	9814	103

H(12B)	1983	-3495	9575	103
H(12C)	1582	-2970	9160	103
H(13A)	2132	-678	10331	112
H(13B)	2261	1051	10042	112
H(13C)	2452	-884	10013	112
H(14)	2278	-1640	9015	65
H(15A)	2100	2092	8769	88
H(15B)	2414	1592	9330	88
H(17A)	373	141	10481	179
H(17B)	638	174	11104	179
H(17C)	687	-1402	10690	179
H(18A)	1532	-655	10746	182
H(18B)	1538	681	11251	182
H(18C)	1687	1375	10745	182
H(20A)	312	3311	10442	310
H(20B)	472	4039	9950	310
H(20C)	454	5367	10446	310
H(21A)	1221	4613	10092	142
H(21B)	1505	4356	10696	142
H(21C)	1224	6061	10569	142
H(22A)	980	4868	11441	244
H(22B)	1123	2809	11519	244
H(22C)	680	3246	11352	244
H(23A)	1374	-4677	8307	162
H(23B)	1215	-4456	7650	162
H(23C)	1110	-2984	8053	162
H(24A)	2353	-3297	8005	147
H(24B)	2075	-5006	7849	147
H(24C)	2223	-4350	8479	147
H(26A)	1307	833	7529	204
H(26B)	1049	-840	7241	204
H(26C)	1209	558	6872	204
H(27A)	1337	-3377	6816	227
H(27B)	1784	-3429	6898	227
H(27C)	1527	-1995	6480	227
H(28A)	1893	569	6913	149

H(28B)	2183	-724	7339	149
H(28C)	1986	934	7565	149
H(1A1)	3433	6965	4360	142
H(1A2)	3697	7715	3973	142
H(2A)	4218	6934	4619	104
H(3A1)	3724	5605	5230	74
H(3A2)	4101	6711	5525	74
H(4A)	4461	4261	5216	76
H(5A1)	3940	2883	4566	85
H(5A2)	4193	1458	4990	85
H(6A1)	3556	797	4866	96
H(6A2)	3478	2818	5044	96
H(7A1)	3539	849	5827	90
H(7A2)	3948	187	5789	90
H(8A)	3773	3891	6010	69
H(9A)	4445	4491	6169	62
H(12D)	4248	5945	6829	135
H(12E)	4007	6594	7238	135
H(12F)	3796	5996	6617	135
H(13D)	4532	4104	7689	176
H(13E)	4334	2195	7732	176
H(13F)	4196	3988	7980	176
H(14A)	3554	4366	7481	76
H(15C)	3442	777	7071	100
H(15D)	3800	1059	7595	100
H(17D)	5225	2649	5505	123
H(17E)	5565	2972	6052	123
H(17F)	5227	4412	5879	123
H(18D)	5120	4181	6985	112
H(18E)	5403	2527	7213	112
H(18F)	4967	2382	7209	112
H(20D)	5144	-750	5497	207
H(20E)	4738	-1229	5578	207
H(20F)	5075	-2677	5747	207
H(21D)	5592	-2319	6588	190
H(21E)	5645	-456	6929	190

H(21F)	5695	-494	6315	190
H(22D)	4940	-2887	6641	176
H(22E)	4644	-1243	6535	176
H(22F)	5009	-1202	7059	176
H(23D)	2574	1675	6227	454
H(23E)	2281	2969	6412	454
H(23F)	2601	1914	6870	454
H(24D)	3071	6269	7377	380
H(24E)	2706	5057	7361	380
H(24F)	2662	6896	7010	380
H(26D)	2771	2875	5564	575
H(26E)	3021	4536	5451	575
H(26F)	2576	4475	5153	575
H(27D)	3267	6852	5913	402
H(27E)	3111	7751	6388	402
H(27F)	2913	8210	5751	402
H(28D)	2219	6254	5407	469
H(28E)	2259	6851	6034	469
H(28F)	2129	4829	5836	469
H(5)	2882	2656	8418	126
H(5A3)	3017	-200	8017	154

Table S13. Torsion angles [°] for **74**.

C(1)-C(2)-C(3)-C(4)	130.8(13)
C(2)-C(3)-C(4)-C(5)	-71.4(10)
C(2)-C(3)-C(4)-C(9)	162.2(8)
C(9)-C(4)-C(5)-C(6)	56.0(11)
C(3)-C(4)-C(5)-C(6)	-73.3(10)
C(4)-C(5)-C(6)-C(7)	-56.7(12)
C(5)-C(6)-C(7)-C(8)	57.9(11)
C(6)-C(7)-C(8)-C(10)	174.1(7)
C(6)-C(7)-C(8)-C(9)	-59.3(10)
C(5)-C(4)-C(9)-O(1)	64.3(9)
C(3)-C(4)-C(9)-O(1)	-166.9(7)
C(5)-C(4)-C(9)-C(8)	-57.0(10)

C(3)-C(4)-C(9)-C(8)	71.8(10)
C(10)-C(8)-C(9)-O(1)	65.3(9)
C(7)-C(8)-C(9)-O(1)	-63.2(9)
C(10)-C(8)-C(9)-C(4)	-172.3(8)
C(7)-C(8)-C(9)-C(4)	59.2(10)
C(7)-C(8)-C(10)-O(2)	36.9(11)
C(9)-C(8)-C(10)-O(2)	-88.3(10)
C(7)-C(8)-C(10)-C(11)	-140.6(7)
C(9)-C(8)-C(10)-C(11)	94.2(9)
O(2)-C(10)-C(11)-C(13)	35.1(9)
C(8)-C(10)-C(11)-C(13)	-147.3(7)
O(2)-C(10)-C(11)-C(12)	157.2(7)
C(8)-C(10)-C(11)-C(12)	-25.3(10)
O(2)-C(10)-C(11)-C(14)	-84.0(8)
C(8)-C(10)-C(11)-C(14)	93.5(8)
C(10)-C(11)-C(14)-O(3)	-55.1(8)
C(13)-C(11)-C(14)-O(3)	-174.8(7)
C(12)-C(11)-C(14)-O(3)	67.3(8)
C(10)-C(11)-C(14)-C(15)	65.5(9)
C(13)-C(11)-C(14)-C(15)	-54.1(10)
C(12)-C(11)-C(14)-C(15)	-172.0(7)
O(3)-C(14)-C(15)-C(16)	-81.6(9)
C(11)-C(14)-C(15)-C(16)	157.7(7)
C(14)-C(15)-C(16)-O(4)	-7.5(14)
C(14)-C(15)-C(16)-O(5)	178.8(8)
C(1A)-C(2A)-C(3A)-C(4A)	125.5(13)
C(2A)-C(3A)-C(4A)-C(5A)	-73.4(10)
C(2A)-C(3A)-C(4A)-C(9A)	163.7(7)
C(9A)-C(4A)-C(5A)-C(6A)	55.9(10)
C(3A)-C(4A)-C(5A)-C(6A)	-68.1(10)
C(4A)-C(5A)-C(6A)-C(7A)	-57.3(11)
C(5A)-C(6A)-C(7A)-C(8A)	57.3(10)
C(6A)-C(7A)-C(8A)-C(10A)	177.4(6)
C(6A)-C(7A)-C(8A)-C(9A)	-59.4(8)
C(5A)-C(4A)-C(9A)-O(1A)	62.1(7)
C(3A)-C(4A)-C(9A)-O(1A)	-172.6(6)

C(5A)-C(4A)-C(9A)-C(8A)	-56.0(9)
C(3A)-C(4A)-C(9A)-C(8A)	69.3(9)
C(10A)-C(8A)-C(9A)-O(1A)	65.4(9)
C(7A)-C(8A)-C(9A)-O(1A)	-58.3(8)
C(10A)-C(8A)-C(9A)-C(4A)	-175.9(8)
C(7A)-C(8A)-C(9A)-C(4A)	60.4(9)
C(7A)-C(8A)-C(10A)-O(2A)	39.5(10)
C(9A)-C(8A)-C(10A)-O(2A)	-83.4(10)
C(7A)-C(8A)-C(10A)-C(11A)	-142.3(7)
C(9A)-C(8A)-C(10A)-C(11A)	94.8(8)
O(2A)-C(10A)-C(11A)-C(12A)	154.2(8)
C(8A)-C(10A)-C(11A)-C(12A)	-24.0(11)
O(2A)-C(10A)-C(11A)-C(13A)	28.1(12)
C(8A)-C(10A)-C(11A)-C(13A)	-150.1(8)
O(2A)-C(10A)-C(11A)-C(14A)	-85.6(9)
C(8A)-C(10A)-C(11A)-C(14A)	96.2(9)
C(12A)-C(11A)-C(14A)-O(3A)	59.4(10)
C(10A)-C(11A)-C(14A)-O(3A)	-64.7(10)
C(13A)-C(11A)-C(14A)-O(3A)	-179.1(9)
C(12A)-C(11A)-C(14A)-C(15A)	-179.5(8)
C(10A)-C(11A)-C(14A)-C(15A)	56.5(10)
C(13A)-C(11A)-C(14A)-C(15A)	-57.9(12)
O(3A)-C(14A)-C(15A)-C(16A)	-92.2(9)
C(11A)-C(14A)-C(15A)-C(16A)	146.3(8)
C(14A)-C(15A)-C(16A)-O(4A)	-24.4(15)
C(14A)-C(15A)-C(16A)-O(5A)	156.3(9)
C(4)-C(9)-O(1)-Si(1)	103.1(7)
C(8)-C(9)-O(1)-Si(1)	-134.5(6)
C(15)-C(14)-O(3)-Si(2)	118.7(7)
C(11)-C(14)-O(3)-Si(2)	-118.6(6)
C(4A)-C(9A)-O(1A)-Si(1A)	105.7(6)
C(8A)-C(9A)-O(1A)-Si(1A)	-134.7(5)
C(15A)-C(14A)-O(3A)-Si(2A)	92.7(9)
C(11A)-C(14A)-O(3A)-Si(2A)	-142.4(7)
C(9)-O(1)-Si(1)-C(19)	-172.0(10)
C(9)-O(1)-Si(1)-C(18)	57.7(9)

C(9)-O(1)-Si(1)-C(17)	-62.7(7)
C(22)-C(19)-Si(1)-O(1)	174.3(12)
C(20)-C(19)-Si(1)-O(1)	49.3(19)
C(21)-C(19)-Si(1)-O(1)	-64.3(8)
C(22)-C(19)-Si(1)-C(18)	-57.2(18)
C(20)-C(19)-Si(1)-C(18)	177.8(13)
C(21)-C(19)-Si(1)-C(18)	64.2(10)
C(22)-C(19)-Si(1)-C(17)	57.6(15)
C(20)-C(19)-Si(1)-C(17)	-67.4(16)
C(21)-C(19)-Si(1)-C(17)	179.0(7)
C(14)-O(3)-Si(2)-C(24)	-8.9(8)
C(14)-O(3)-Si(2)-C(23)	111.9(8)
C(14)-O(3)-Si(2)-C(25)	-132.0(6)
C(28)-C(25)-Si(2)-O(3)	60.6(8)
C(26)-C(25)-Si(2)-O(3)	-60.5(10)
C(27)-C(25)-Si(2)-O(3)	178.8(6)
C(28)-C(25)-Si(2)-C(24)	-61.7(10)
C(26)-C(25)-Si(2)-C(24)	177.2(9)
C(27)-C(25)-Si(2)-C(24)	56.5(8)
C(28)-C(25)-Si(2)-C(23)	177.4(8)
C(26)-C(25)-Si(2)-C(23)	56.3(11)
C(27)-C(25)-Si(2)-C(23)	-64.4(8)
C(9A)-O(1A)-Si(1A)-C(19A)	172.8(6)
C(9A)-O(1A)-Si(1A)-C(18A)	53.2(7)
C(9A)-O(1A)-Si(1A)-C(17A)	-68.2(7)
C(21A)-C(19A)-Si(1A)-O(1A)	176.7(8)
C(22A)-C(19A)-Si(1A)-O(1A)	-61.2(8)
C(20A)-C(19A)-Si(1A)-O(1A)	57.2(8)
C(21A)-C(19A)-Si(1A)-C(18A)	-63.8(9)
C(22A)-C(19A)-Si(1A)-C(18A)	58.3(8)
C(20A)-C(19A)-Si(1A)-C(18A)	176.7(7)
C(21A)-C(19A)-Si(1A)-C(17A)	57.9(9)
C(22A)-C(19A)-Si(1A)-C(17A)	-180.0(7)
C(20A)-C(19A)-Si(1A)-C(17A)	-61.7(8)
C(26A)-C(25A)-Si(2A)-O(3A)	31(5)
C(28A)-C(25A)-Si(2A)-O(3A)	174(3)

C(27A)-C(25A)-Si(2A)-O(3A)	-72(2)
C(26A)-C(25A)-Si(2A)-C(24A)	179(3)
C(28A)-C(25A)-Si(2A)-C(24A)	-38(5)
C(27A)-C(25A)-Si(2A)-C(24A)	75.4(16)
C(26A)-C(25A)-Si(2A)-C(23A)	-77(4)
C(28A)-C(25A)-Si(2A)-C(23A)	66(4)
C(27A)-C(25A)-Si(2A)-C(23A)	179.6(15)
C(14A)-O(3A)-Si(2A)-C(25A)	166(2)
C(14A)-O(3A)-Si(2A)-C(24A)	15.2(13)
C(14A)-O(3A)-Si(2A)-C(23A)	-94.6(12)

Symmetry transformations used to generate equivalent atoms:

Table S14. Hydrogen bonds for **74** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(5A)-H(5A3)...O(4)	0.84	1.84	2.671(8)	173.0
O(5)-H(5)...O(4A)	0.84	1.80	2.638(8)	172.8

Symmetry transformations used to generate equivalent atoms:

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Part II: Discovery of Small Molecule CXCR4 Antagonists

2.1. Introduction and Background

2.1.1. CXCR4 Chemokine Receptor and Its Ligand SDF-1

The CXC chemokine receptor-4 (CXCR4) is a seven-transmembrane G-protein coupled receptor (GPCR) classified as a member of the class I GPCR or rhodopsin-like GPCR family.[1-3] The chemokine stromal cell-derived factor-1 (SDF-1 or CXCL12) is an 8-kDa, 67-residue CXC chemokine peptide,[4] originally isolated from a bone marrow stromal cell line and is the natural ligand for CXCR4.[5] The two proteins are rather unique among chemokines and their receptors, in that SDF-1 interacts specifically with CXCR4 [6] while recently SDF-1 was found to bind with an alternative receptor CXCR7. [7] This fact already suggests that the SDF-1/CXCR4 axis may play an important and unique biological role in various pathophysiological processes meditated by CXCR4.

CXCR4 first drew attention as a major coreceptor for the infection of T cell line-tropic (X4) strains of human immunodeficiency virus 1 (HIV-1).[8, 9] As shown in Figure 1, CXCR4 is one of the major coreceptors for the entry of HIV-1 virus. Following with the interaction between viral envelope (Env) glycoprotein gp120 and CD4 receptor at the cell membrane, the gp120/CD4 complex and a coreceptor, such as CXCR4 or CCR5, triggers conformational changes in the viral envelope that lead to membrane fusion and entry of the viral genome into the host cell cytoplasm.[10, 11] Importantly, the CXCR4 receptor is expressed much more broadly than chemokine receptors in general, i.e., not only on a wide variety of

leukocytes, but also on cells outside the immune system. Compelling evidence is accumulating that the CXCR4 is far more than a coreceptor for HIV, playing an important role in cancer metastasis, regulation of stem cell trafficking, and neovascularization.[12-15] Consequently, therapeutic strategies to block the interaction between CXCR4 and SDF-1 hold promise for a variety of clinical applications.

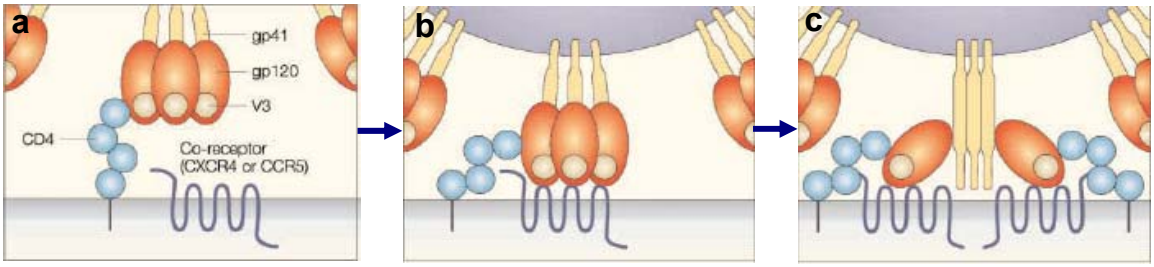


Figure 1. CXCR4 involved in HIV-1 entry process (Adapted from ref.8).

2.1.2. AMD3100: A Potent CXCR4 Antagonist

Since the identification of HIV as the causative agent of the acquired immune deficiency syndrome (AIDS) and the disclosure of CXCR4 as a coreceptor for HIV entry, tremendous efforts have been involved in developping potent CXCR4 antagonists. Generally, the CXCR4 antagonists can be divided into three categories: peptide CXCR4 antagonists, pseudo-peptide CXCR4 antagonists and non-peptide (small molecular) CXCR4 antagonists. Peptide CXCR4 antagonists initially were designed to mimic the action mechanism of SDF-1, including T22, T140, ALX40-4C.[9, 16] Due to the poor pharmacokinetic (PK) profile of peptide antagonists, *pseudo*-peptide CXCR4 antagonists have provoked scientist's interest to improve the PK properties while maintaining the potency.[17, 18] The

disclosure of nonpeptidic small molecule CXCR4 antagonists has been limited in comparison with peptide mimic CXCR4 antagonist.[19-21] To our best knowledge, non-peptide CXCR4 antagonists mainly focus on the cyclam-containing heterocyclic compounds,[22] as shown in Figure 2, such as AMD3100 (**3**),[8] AMD3451 (**4**),[23] and AMD3465 (**5**).[24, 25]

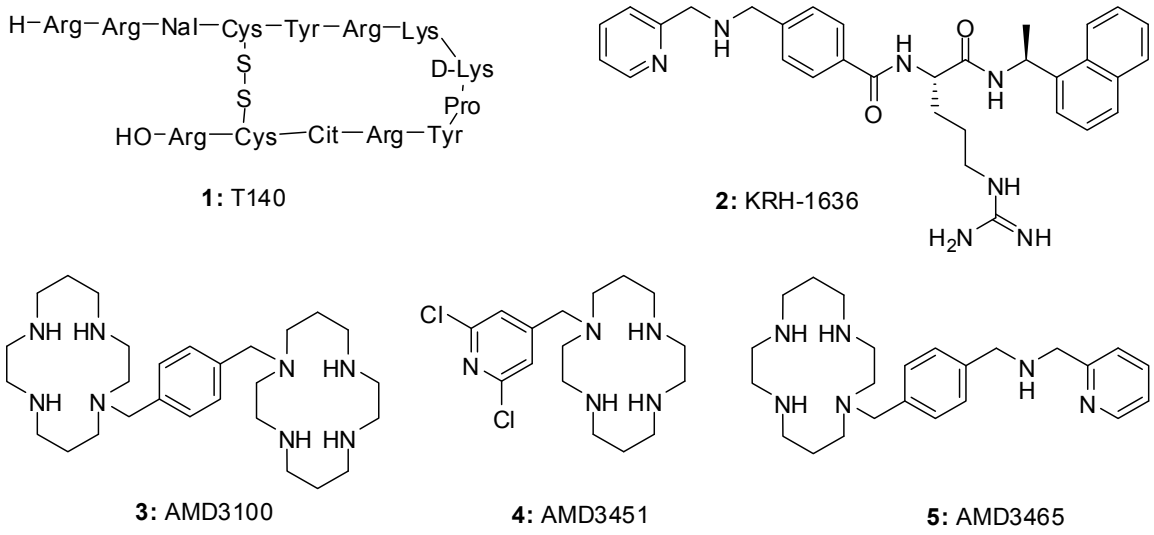


Figure 2. Structures of selected CXCR4 antagonists.

Bicyclam containing small molecule CXCR4 antagonist AMD3100 was the first CXCR4 antagonist to enter clinical trials for treatment of HIV infection, and was discovered as an anti-HIV agent long before it was understood that it functions by specific blockade of the CXCR4 receptor.[8, 19] At physiological pH, the cyclam ring is doubly charged carrying an overall charge of 2^+ and can adopt a stable *trans*-Ⅲ *R,R,S,S* type conformation with respect to the four nitrogen atoms.[21] The protonated cyclam has the propensity to form a direct, hydrogen-bonded complex with a carboxylic acid group in a putative interaction model between AMD3100 and CXCR4.[2, 3, 21] The latter model suggests that one

cyclam ring might be “sandwiched” between Asp262 and Glu318 residues in the receptor, while the disposition of the other ring is compatible with binding to Asp171 at the other end of the main ligand-binding pocket (Figure 3).[2]

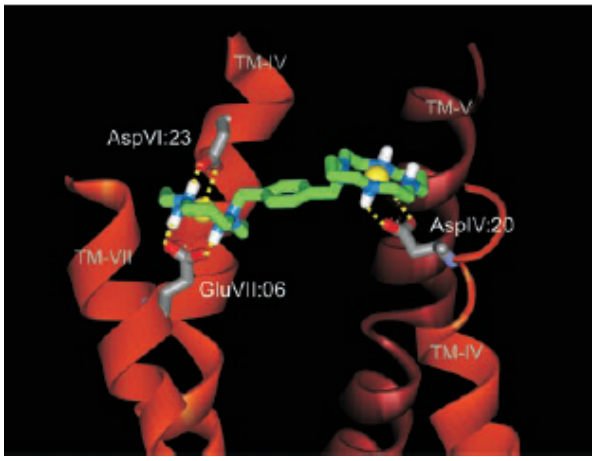


Figure 3. Presumed binding mode of AMD3100(Zn_2) in CXCR4.

Mutation of Asp171 and Asp262 to alanines in the CXCR4 chemokine receptor also suggests that the negatively charged aspartate residues at positions 171 and 262, located in transmembrane domains IV and VII, respectively, may represent crucial sites for electrostatic interaction of the positively charged bicyclam rings. The highly basic V3 loop of the gp120 envelope protein of certain HIV-1 strains conceivably operates in a similar fashion.[23]

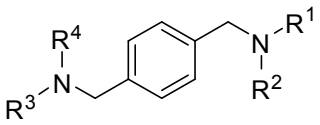
Although antagonist AMD3100 binds specifically to CXCR4 and is effective as an anti-HIV agent, AMD3100 was withdrawn from phase II clinic trials in May 2001 due to cardiotoxicity.[26, 27] In addition, a specific pharmacokinetic deficit of AMD3100 is its lack of oral bioavailability.[26, 28] Another orally bioavailable compound, AMD070, is currently recruiting patients for a Phase I/II trial for HIV patients.[29, 30]

2.2. Discovery of Small Molecule CXCR4 Antagonists

2.2.1 Design Rationale

The discovery and development of effective, small molecule peptide mimics remains a major focus for many medicinal chemistry programs. However, because peptides oftentimes exhibit poor drug-like properties, we sought to identify a novel series of potent, small molecule antagonists that might prove to be practical for preclinical advancement and progression into clinical evaluation.

From the precedent modeling study, it is clear that the two basic centers which are protonated under physiological conditions and form hydrogen bonding with the CXCR4 residue are crucial to maintain the potency. However, the cyclam possessing high affinity to coordinate with metal ions could be responsible for the side effects.[31-34] With this scenario in mind, a series of small molecular compounds with the general structure **6** (Figure 4) were proposed on the basis of overlapping structural features with cyclam containing **3**, presumably resulting in a similar binding mode to the CXCR4 receptor.[2, 3, 35] The cyclam moieties in AMD3100 (**3**) were replaced by *N*-containing basic centers which are not only capable of binding to acidic residues in CXCR4, but also eliminate potential toxicity originating from the possible coordination of the cyclam rings with metal ions. The central 1,4-biphenyllene bridge is proposed to keep the distance of the two basic centers.

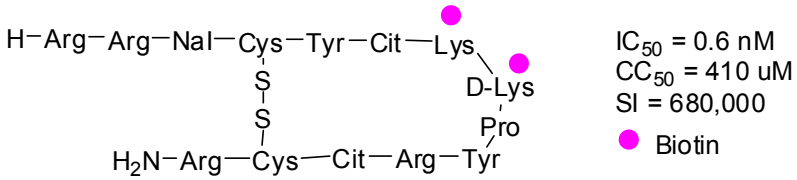


6

Figure 4. Potential CXCR4 antagonist template **6**.

2.2.2 Initial Screening to Identify the G1 Lead WZ13

TN14003, a synthetic 14-mer peptide (**7**, Figure 5), has been previously reported to block both CXCR4/SDF-1 mediated invasion *in vitro* and metastasis *in vivo* with a high specificity by binding competitively with its ligand, SDF-1.[14] The anti-invasion and anti-metastasis activity of this peptide correlates well with its inhibitory activity in preventing the binding of SDF-1 to CXCR4.[14] We therefore created a competitive binding assay using biotin-labeled TN14003 and streptavidin-conjugated rhodamine to determine the binding efficiency of new chemical entities to the SDF-1 binding domain of CXCR4. Cells incubated with high affinity compounds show only blue nuclear staining, whereas compounds with low affinity resulted in staining CXCR4 (red; rhodamine) as well as the nuclei (blue; sytox blue) (Figure 6).



7: T14003

Figure 5. Structure of biotin-labeled peptide CXCR4 antagonist TN14003 (**7**).

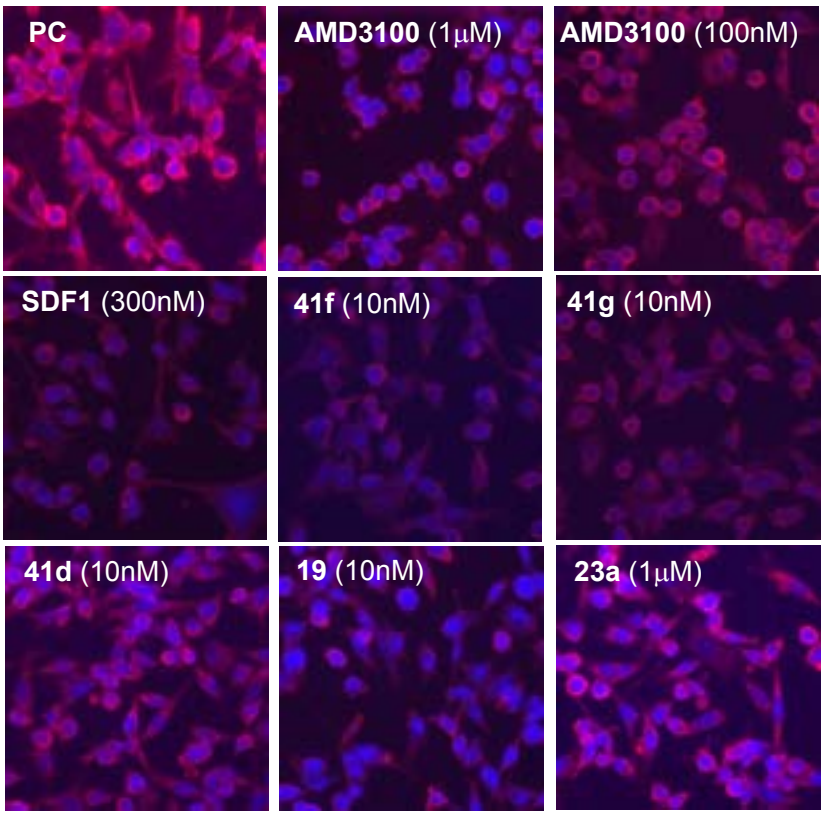
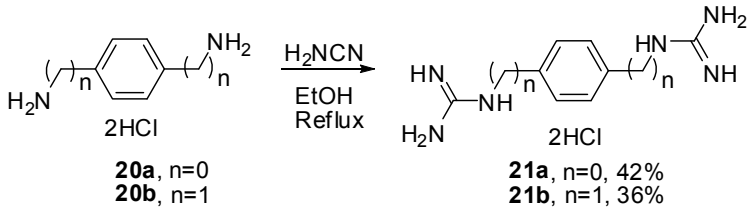


Figure 6. Selected data from competitive biding assay.

Following our lead design rationale, screening was initiated with various compounds in which two strong basic centers were connected by a phenyl-containing bridge (Table 1). Compounds **8-19** are commercially available and were subjected to competitive affinity assay without further purification. Guanidine derivatives **21a/b** were prepared by allowing cyanamide to react with the corresponding ammonium hydrochloride salts **20a/b** (Scheme 1).[36] Hydrazone derivatives **23a/b** were obtained by condensation of aldehyde **22** and amino guanidines (Scheme 2).[37, 38] Dihydroimidazole **25** was prepared by an addition-elimination reaction involving *p*-xylylenediamine **24** and 2-(methylmercapto)-2-imidazoline (Scheme 3).[38] Amine **26** was synthesized by one-pot reductive amination of aldehyde **22** and amine in the presence of the

reducing reagent $NaBH(OAc)_3$ (Scheme 4).[39]

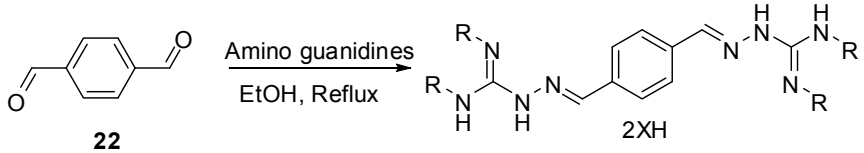
Scheme 1. Synthesis of Guanidine **21a** and **21b**.



20a, n=0
20b, n=1

21a, n=0, 42%
21b, n=1, 36%

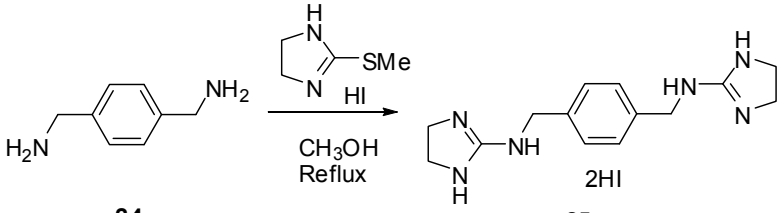
Scheme 2. Synthesis of Hydrazone **22** and **23**.



22

23a, R=H, X=Cl, 36%
23b, R= -CH_2CH_2-, X=Br, 42%

Scheme 3. Synthesis of Dihydroimidazol **25**.

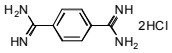
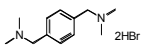
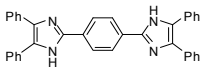
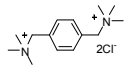
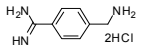
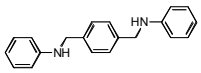
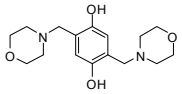
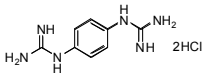
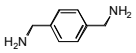
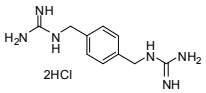
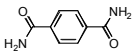
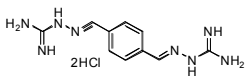
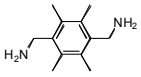
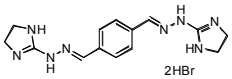
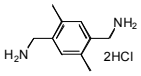
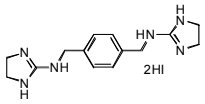
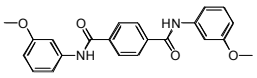
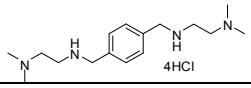


24

25, 53%

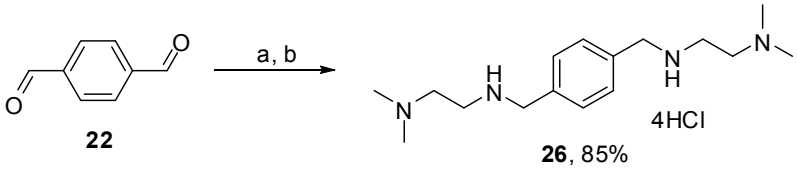
From the initial screening results, *N*,*N*'-diphenyl-*p*-xylylenediamine **WZ13** (**19**) and guanylhydrazone **23a** were found to be active in the competitive affinity assay with effective concentrations (EC) of approximately 10 and 100 nM, respectively (Table 1). Since the amine **19** was more active than **22**, it became our de facto G1 lead around which we further pursued potential CXCR4 antagonists.

Table 1. Structures and Activity of Selected Compounds for Initial Screening.

Compd.	Structure	ECa(nM)	Compd.	Structure	ECa(nM)
8		>1000	**17**		>1000
9		>1000	**18**		>1000
10		>1000	**19**		10
11		>1000	**21a**		>1000
12		>1000	**21b**		>1000
13		>1000	**23a**		100
14		>1000	**23b**		>1000
15		>1000	**25**		>1000
16		>1000	**26**		>1000

[a] EC (effective concentration) is defined as the concentration at which the compound still elicits a positive response in the peptidic CXCR4 antagonist **7** competition assay.

Scheme 4. Synthesis of Compound **26**.[a]



[a] Reagents and conditions: (a) *N,N'*-Dimethylethanediamine, $NaBH(OAc)_3$, $ClCH_2CH_2Cl$; (b) HCl/EtOH, Et_2O

2.2.3 SAR Study of WZ13 to Discover of G2 Lead WZ811

Although the initial screening yielded **19** as a lead, the compound was shown to possess a poor pharmacokinetic profile (data not shown). Accordingly, an SAR was developed by manipulation of the three sectors of structure **19** as illustrated in Figure 7, namely, the central aromatic ring A, the intermediate linkers B, and the distal phenyl rings C.

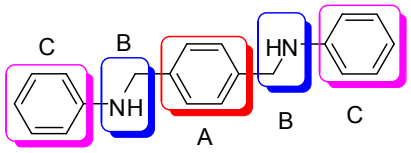
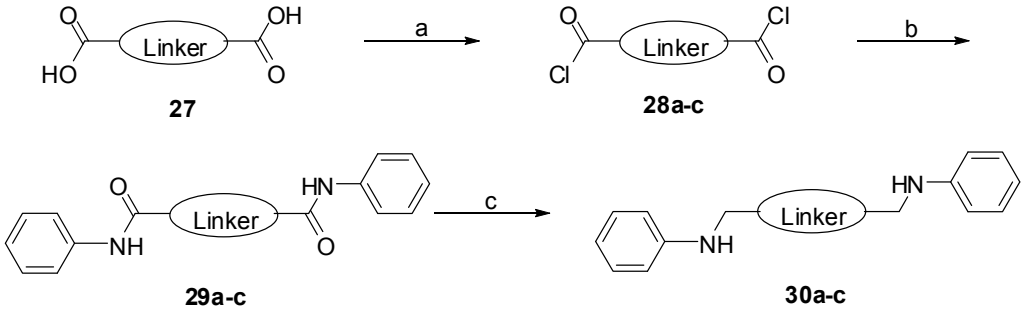


Figure 7. The three sectors of **19** subjected to synthetic modification as an approach to potential CXCR4 antagonists.

Sector A: Central Aromatic Ring. In order to probe the spatial influence of the flat central phenyl ring, a saturated cyclohexane ring replacement, **30a,** was prepared (Scheme 5). Combining the precursor dicarboxylic acid **27** with SO_2Cl_2 gave the corresponding acid chloride **28a** that was subsequently allowed to react with aniline to provide amide **29a**. The latter was easily reduced by $LiAlH_4$ to deliver the target amine **30a** with a central cyclohexane linker (Scheme 5).[40] Surprisingly, **30a** proved to be completely inactive (Table 2) suggesting that a central linker with a planar or near planar geometry is crucial for maintaining activity. To further study the importance of the central aromatic ring on activity, compounds **30b**, **33a-b** and **35a** were also subjected to the competition assay. Compound **30b** was prepared as shown in Scheme 5, while compounds **33a-b** were prepared by a general procedure A (Scheme 6), a reductive amination procedure similar to that used for compound **25**. Compound **35a** was obtained by

S_N2 displacement (Scheme 7). Compound **33b** was included because many anthracene-containing compounds with at least one basic center have proven to be effective antitumor agents by intercalating to DNA.[37] The competition binding assay indicated no significant difference between **30b**, **33b** and **35a**, while **33a** proved to be 10-fold more active.

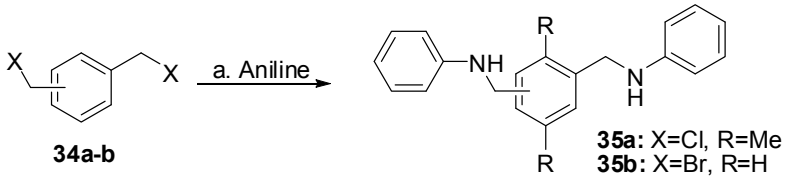
Scheme 5. Preparation of Compounds **30a-c**.[a]



[a] Reagents and conditions: a) SO_2Cl_2, reflux; b) aniline, pyridine, CH_2Cl_2; c) $LiAlH_4$, THF, reflux.

Scheme 6. General Procedure A to Potential CXCR4 Antagonists.

Scheme 7. Synthesis of Compounds **35a**-**b**.[a]

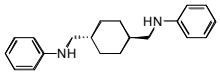
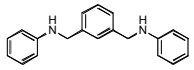
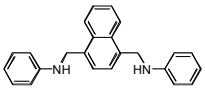
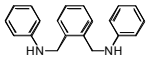
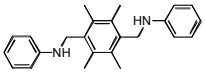
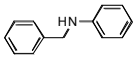
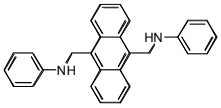
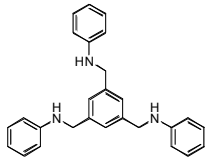
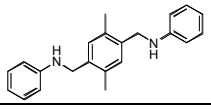


[a] Reagents and conditions: a)**35a**, pyridine, EtOH, reflux; **35b**, pyridine, EtOH, -20 °C.

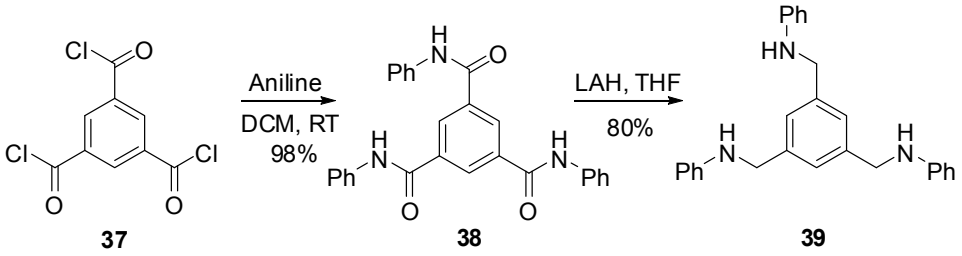
In subsequent experiments, the position and number of anilinomethyl substituents on the central phenyl ring were varied (Table 2). Compound **36** was

obtained from commercial sources, while trisubstituted **39** was prepared by a two-step sequence (Scheme 8). The results show that analogs with one or three $PhNHCH_2$ moieties (**36,** and **39**) were unable to block the CXCR4 receptor. The *meta*-disubstituted analogue **33c** exhibits CXCR4 affinity similar to *para*-disubstituted **19**, while the affinity of *ortho*-disubstituted **35b** decreases by10-fold.

Table 2. SAR Studies around the Central Ring (Sector A).

Compd	Structure	EC(nM)	Compd	Structure	EC(nM)
30a		>1000	**33c**		10
30b		100	**35b**		100
33a		10	**36**		>1000
33b		100	**39**		>1000
35a		200			

Scheme 8. Preparation of Compound **39**.

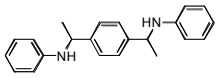
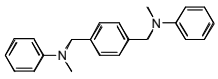
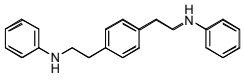
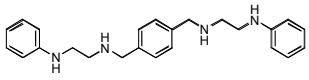
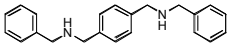


37 **38** **39**

Sector B: Amine linker. The initial modifications involved introduction of methyl groups to the linkages between aromatic rings as depicted by **40a** and **40b**,

which were prepared according to general procedure A (Scheme 6). The methyl groups on the benzylic carbons were expected to exert a conformational bias on the terminal rings relative to **19**, while those on nitrogen were intended to increase the hydrophobicity and basicity of the heteroatom. Both substitutions reduced the affinity to about 50-100 nM. Thus, it would appear that an NH group is necessary to retain the high affinity shown by **19**. Secondly, one or more carbon or nitrogen atoms were inserted between the central and terminal phenyl rings (**30c, 40c-d**). In **30c** (Scheme 5), the CH_2CH_2NH-moiety caused complete loss of activity even though the extra N is potentially available for binding to the aspartic acid residue in CXCR4. In **40c** and **40d**, prepared from general procedure A (Scheme 6), the extra carbon also reduced the potency. In summary, modification of sector B illustrates that a terminal phenyl ring connected directly to an unalkylated nitrogen center results in the best activity of the modifications tested.

Table 3. CXCR4 Blockades with Variations in the Alkylamine (Sector B).

Compd	Structure	EC(nM)
40a		50
40b		200
30c		100
40c		>1000
40d		80

Sector C: Terminal Phenyl Rings. The modification of the terminal aromatic

ring was summarized in Table 4. Several electron-withdrawing groups were introduced onto the *para* position of the terminal phenyl rings by combining the dialdehyde with various aniline derivatives (Scheme 6, R=R_1=H, R_2=aromatic amine). The CXCR4 competition assay demonstrates that none of the compounds block the chemokine (**41a-c,** entry 1-3, and Table 4). Conversely, electron-donating substituents at the *para* position retain low EC values as illustrated by *para*-methoxy in **41d** and alkyl in **41e** and **41f**. By contrast, electron donating and withdrawing substituents at the *meta* and *ortho* positions elicit mixed effects on activity (**41g-l**, entry 7-12, and Table 4). For example, **41g** (*m*-F) exhibits an effective concentration of 100 nM, while **41k** (*o*-F), **41h** (*m*-NO_2) and **41i** (*m*-OMe) experience a 100-fold improvement by comparison (EC = 1 nM). Surprisingly, **41l** (*o*-OMe) is ten-fold less active, while **41j** (*m*-CF_3) is completely unable to block the action of peptide **7** on CXCR4.

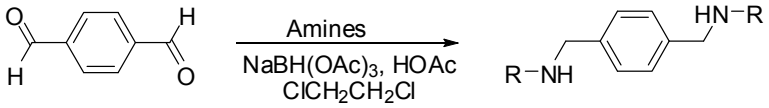
Table 4. CXCR4 Blockade with Variations in the Terminal Rings (Sector C)

Entry	Compd	R	EC(nM)	Entry	Compd	R	EC(nM)
1	**41a**	*p*-CN	1000	7	**41g**	*m*-F	100
2	**41b**	*p*-NO_2	1000	8	**41h**	*m*-NO_2	1
3	**41c**	p-F	1000	9	**41i**	*m*-OMe	1
4	**41d**	*p*-OMe	25	10	**41j**	*m*-CF_3	1000
5	**41e**	*p*-Me	10	11	**41k**	*o*-F	1
6	**41f**	*p*-Et	20	12	**41l**	*o*-OMe	10

Further SAR study: Introduction of pyridine moiety. In addition to the cyclam moiety, 2-aminomethyl-pyridine moiety also has been wildly introduced to design the CXCR4 antagonists, such as KRH1636 (**2**) and AMD3465 (**5**) (Figure

2). Thus, it's not unusual for us to incorporate this heteroaromatic moiety into our program. Firstly, aminomethyl-pyridine containing compounds **42-44** was prepared from the general procedure A (Scheme 6, R=R_1=H, R_2=pyridinemethyl). However, surprising to us, a striking loss of potency was observed when these compounds were subjected to the competitive assay against the peptide CXCR4 antagonist **7** (Table 5). This fact was in agreement with the previous SAR study around sector B of the G1 lead WZ13 (**19**), suggesting that a terminal aromatic ring connected directly to an unalkylated nitrogen center could be required to high affinity to CXCR4.

Scheme 9. General Procedure B to Potential CXCR4 Antagonists.



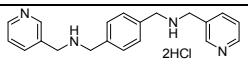
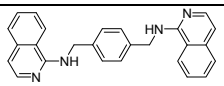
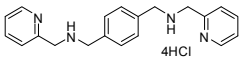
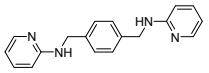
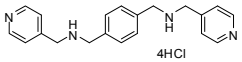
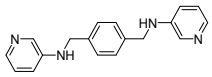
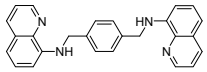
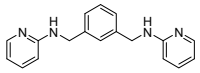
22

45-49, see table 5
51-53, see table 6

To address the above problem, we designed and synthesized compounds **45- 49** in which a heteroaromatic amine moiety was introduced to replace the side phenyl moiety in G1 lead compound **19** and its active analogue **33c**. The pyridine-containing compound was prepared by general procedure B, a one-pot reductive amination in the presence of acetic acid as shown in Scheme 9. The presence of acetic acid is important both to accelerate the reaction and to improve the yield.[39] Compound **45** and **46** with bulky quinoline and isoquinoline moieties showed poor affinity. However, the competition binding assay indicated that compounds **47-49** are able to effectively inhibit peptide **7** binding to CXCR4 in nanomolar concentrations (Table 5). Specifically, compound **47** (WZ811) whose

preparation has been previous described in a two steps sequence,[41, 42] possesses a subnanomolar potency (EC_{50}=0.3 nM) as shown in Figure 8.

Table 5. CXCR4 Blockade with Pyridine Moiety

Compd	Structures	EC(nM)	Compd	Structures	EC(nM)
42		>1000	**46**		1000
43		>1000	**47**		0.3
44		>1000	**48**		8
45		1000	**49**		6

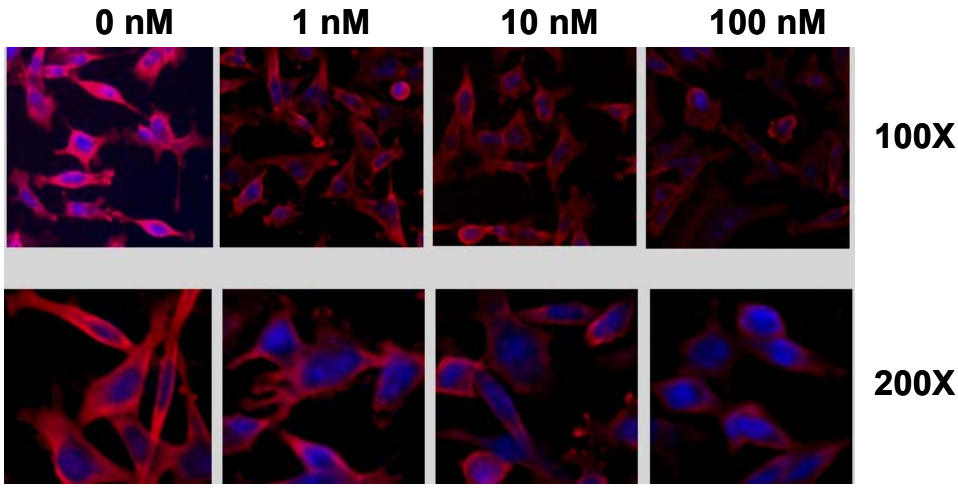


Figure 8. Inhibitory efficacy of WZ811 (**47**) against peptidic antagonist **7** binding to CXCR4. These results indicate that EC_{50} is less than 1 nM.

2.2.4 Functional Assays of WZ811

At this stage, it's timely to further evaluate the activity of WZ811 (**47**) as a potential CXCR4 antagonist. Thus, compound **47** was subjected to two functional assays with encouraging results as discussed below.

cAMP Assay. We originally planned to subject promising CXCR4 antagonists to the calcium mobilization assay utilized by Hatse *et al.* [43] to show that AMD3100 (**3**) is specific against CXCR4. However, a general consensus concerning the GPCR pathway has recently emerged that the heterotrimeric guanosine 5'-triphosphate GTP regulatory Gs proteins stimulate cAMP production, while the pertussis toxin-sensitive Gi proteins reduce cAMP.[44, 45] We determined the absorption increase at 665nm with various concentrations of SDF-1 (0 - 200ng/mL) to estimate the EC_{80} to be 150 ng/mL (data not shown). With *pre*-treatment of **47** (15 min at room temperature), the effect of 150 ng/mL of SDF-1 on cAMP reduction was significantly reduced in a dose dependent manner. Compound **47** was effective in counteracting SDF-1 function at doses as low as a few nanomolar, while AMD3100 (**3)** was only effective at approximately 1000 nM (Figure 9).

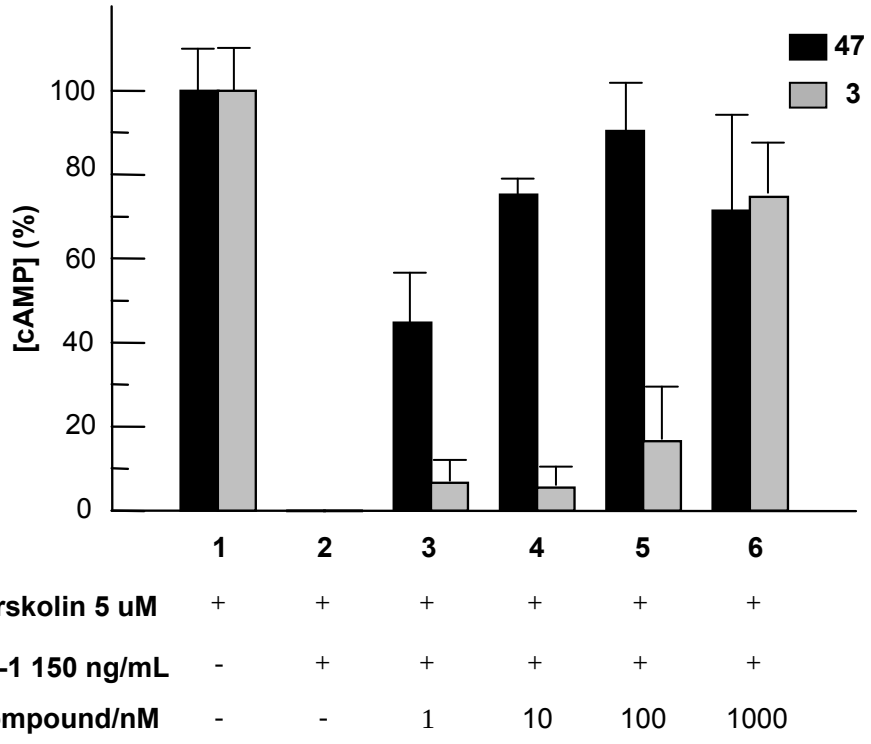


Figure 9. Comparison of inhibition of cAMP production by **47** and **3**.

Invasion Assay. We previously reported that peptidic antagonist **7** effectively blocks SDF-1-mediated Matrigel invasion in an assay using SDF-1 as a chemoattractant.[14] Thus, the compounds discussed above with a general structure **6** were examined in the same assay. As shown in Figure 10, compound **47** was effective at blocking SDF-1 induced invasion. This is consistent with the data displayed in Figure 7 in which **47** is shown to be as potent as **7** in blocking SDF-1 mediated invasion when tested at the same concentration (EC_{50} = 5.2 nM). In addition, cyclam **3** is not as effective as **47** even at a ten-fold higher concentration. Thus, this study demonstrates that **47** is an effective inhibitor of CXCR4-mediated signaling at low nM concentrations.

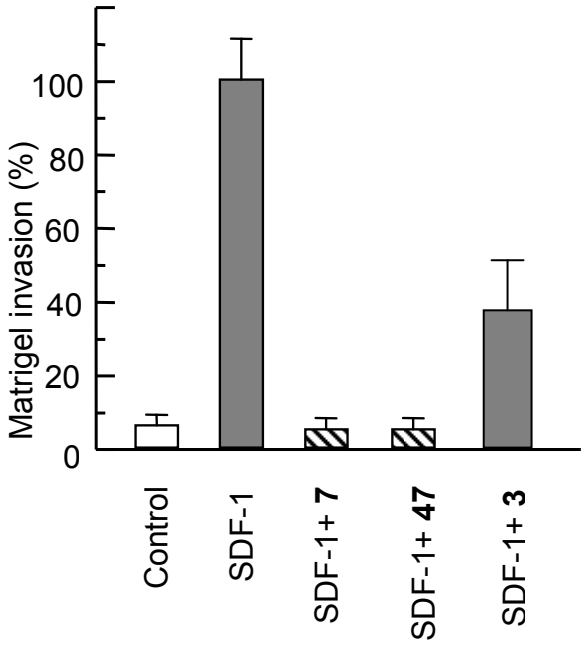


Figure 10. Inhibition of CXCR4/SDF-1 mediated invasion of MDA-MB-231 *in vitro* by **47** compared to **7** and **3**.

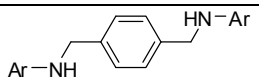
2.2.5 Discovery of MSX-122

It was in this stage that several problems with WZ811 (**47**) were realized. As described above, WZ811 has shown high potency as a potential CXCR4 antagonist both in the competition binding assay and functional assays. However, WZ811 exhibited poor pharmacokinetic properties in further *in vivo* tests. For example, it showed poor plasma stability in mice ($t_{1/2}$=5 min, table 6). As a working hypothesis, we speculated that the poor pharmacokinetic profile of WZ811 might be the result of rapid oxidative metabolism and that inclusion of a nitrogen atom in terminal aromatic rings might impede this process.

Following the above SAR profile, a series of electron-withdrawing functional groups were introduced to the side phenyl ring with a general structure **50** (Table 6). Compounds **51-53** were prepared from terephthalaldehyde **22** and various aromatic amines in accordance with general procedure B (Scheme 9), while oxide **54** was prepared by oxidizing **53** in the presence of *meta*-chloroperbenzoic acid (mCPBA) (Scheme 10). To prepare compounds **58**, pyrimidine derivative **56** was converted into **57** in 78% yield,[46] followed by reacting with amine **24** to afford desired compound **58** in 75% yield (Scheme 11). Compound **60** was prepared by reacting amine **24** with cyanuric chloride **59** in 94% yield. The plasma stability of these potential CXCR4 blockades in mice with the EC value in the previous described competition assay has been summarized in Table 6. The *in vivo* plasma stability data partly proved our previous hypothesis. Compounds **51** ($t_{1/2}$=17 min) and **52** ($t_{1/2}$=40 min) with the electron-withdrawing F possess increased plasma

stability at the cost of losing partial potency by 100 fold in comparison with the parent compound **47**. In the rat model, the plasma half life of compound **52** was much longer, $t_{1/2}$=136 min. Introduction of a second nitrogen atom into **47** led to compound **53** (MSX-122). MSX-122 is much more stable than compound **47** in mice ($t_{1/2}$=45 min) and has a plasma half life 90 min in rats. More importantly, it maintains the high potency of compound **47**. Attempts to increase its plasma stability by oxidizing pyrimidine nitrogen atoms gave ussatisfactory results with a total loss of activity. Introduction of F into **53** generated compound **58** with greatly improved plasma stability ($t_{1/2}$=220 min), while maintaining similar potency to MSX-122. However, the poor solubility of compound **58** ceased its further application in preclinical studies. The chloro-triazine moiety in compound **60** did not improve the plasma stability with a light loss of potency.

Table 6. EC values and Plasma Stability of Selected Analogs

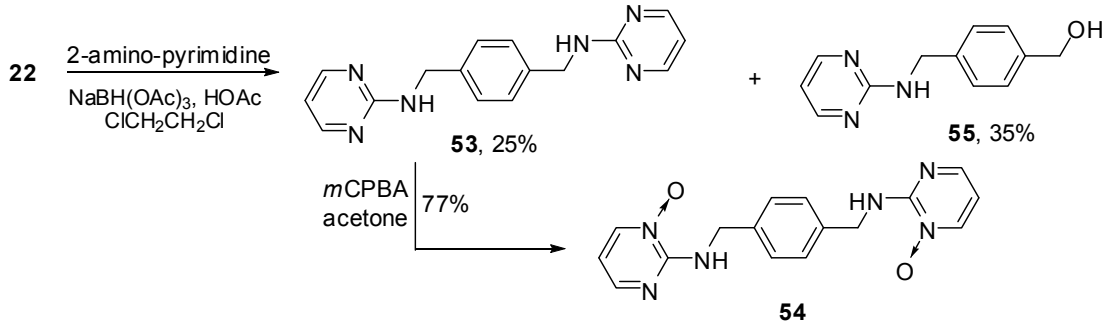


50

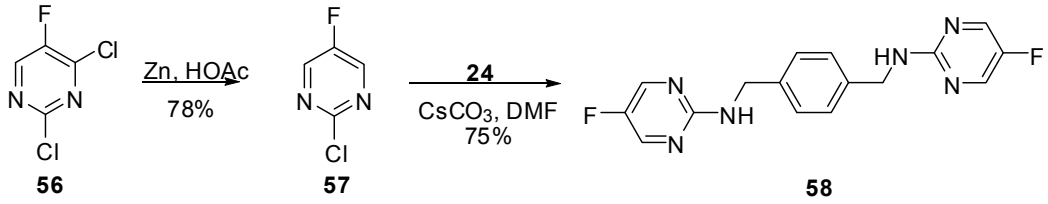
Compd	Ar	EC (nM)	$t_{1/2}$[a] (min)	Compd	Ar	EC (nM)	$t_{1/2}$[a] (min)
47		1	5	**53**		1	45(90[b])
41k		1	19	**54**		>1000	NA
51		100	17	**58**		1	220
52		100	40(136[b])	**60**		10	<5

a. Half life time in mice; b. Half life time in rats.

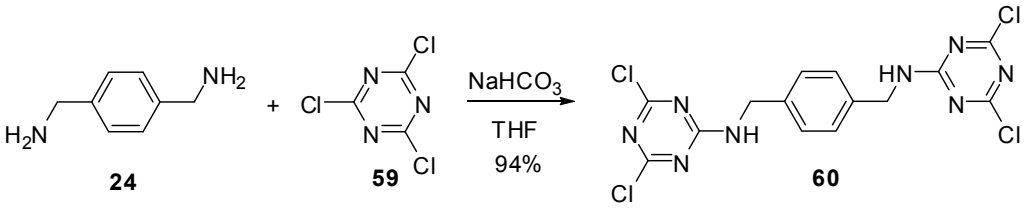
Scheme 10. Synthesis of Compounds **53** and **55**.



Scheme 11. Synthesis of Compound **58**.



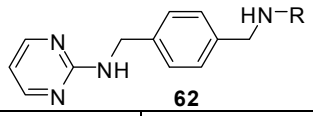
Scheme 12. Synthesis of Compound **60**.



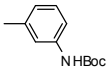
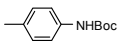
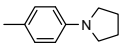
To pursuit the improved pharmacokinetic profile of the candidates, our attention was turned to introduce asymmetric moieties into pyrimidine containing CXCR4 antagonists (Table 7). Synthesis of compounds **62a-k** started from the alcohol **55** which was obtained as the major side product from the preparation of **53** (Scheme 10). Alcohol **55** was converted to aldehyde **61** by Dess-Martin oxidation in 94% yield, and subsequent exposure of **61** to reductive amination with various amines furnished the desired pyrimidine-containing CXCR4 blockades **62a-k** with asymmetric structures (Scheme 13). Scheme 14 illustrated the preparation of pyrrolidine containing analogs. Mono-protection of aminoaniline **63** with Boc_2O gave compound **64**, followed by treatment with 1,4-dibromobutane

in presence of triethylamine affording pyrrolidine **65**. Deprotection of **65**, followed by reductive amination with aldehyde **61** led to the products **62l-n**. As shown in Table 7, unfortunately, attempts to improve the PK profile by introducing asymmetric moieties were unworkable temporarily, although several of these analogs showed high potency in the competition affinity assay.

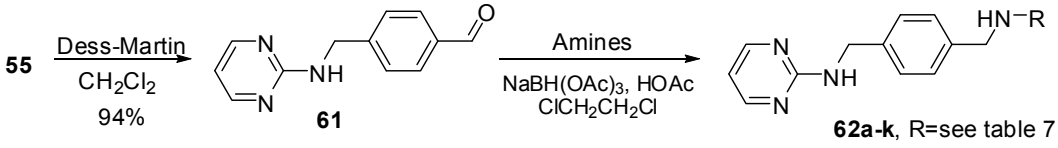
Table 7. Asymmetric Pyrimidine-containing Potential CXCR4 Antagonists



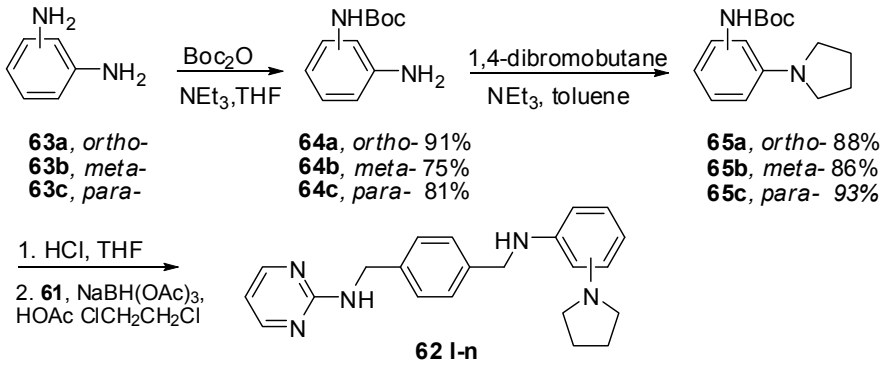
62

Compd	R	EC (nM)	$t_{1/2}$ (min)	Compd	R	EC (nM)	$t_{1/2}$ (min)
62a		10	14	**62h**		1	45
62b		100	NA	**62i**		>1000	NA
62c		10	NA	**62j**		1	16
62d		1	17	**62k**		10	15
62e		1	15	**62l**		100	<10
62f		10	NA	**62m**		10	<10
62g		1	NA	**62n**		1	<10

Scheme 13. Preparation of Pyrimidine-containing Asymmetric Analogs



Scheme 14. Preparation of Pyrrolidinyl CXCR4 Blockade



2.2.6 Preclinical Study of MSX-122

Anti-metastatic efficacy in experimental animal models for breast cancer and head and neck cancer: MSX-122 was tested in an experimental animal model of breast cancer metastasis using a total of 12 mice, 6 in each group (control and 4 mg/kg i.p.). MDA-MB-231 cells were injected intravenously as described previously.[14] The mice were treated with MSX-122 daily for 35 days by intraperitoneal injection at a dose of 4 mg/kg. All untreated control mice developed lung metastases and exhibited bubble-like lung metastases in addition to discoloration (Figure 11a top), while the group treated with MSX-122 intraperitoneally exhibited significantly fewer lung metastases (Figure 11a bottom). Lung sections from mice in control and treated groups were stained with H & E and the metastatic tumor area was calculated in five fields per section under microscope. The estimated average areas of micrometastasis on the lung surface from the control and treated groups were 47.5% and 13%, respectively (Figure 11b). The results were also confirmed by the real-time RT-PCR using primers to detect human CXCR4 (Figure 11c)

In a second study, MSX-122 was added to the daily drinking water to determine the efficacy of MSX-122 when given orally. The estimated daily water consumption was 3mL/mouse (10 mg/kg/day). Again, there were significantly fewer lung metastases in the orally treated group relative to control (Figure 11d). Thus, MSX-122 appears to possess potential as an orally available therapeutic for inhibiting cancer metastasis.

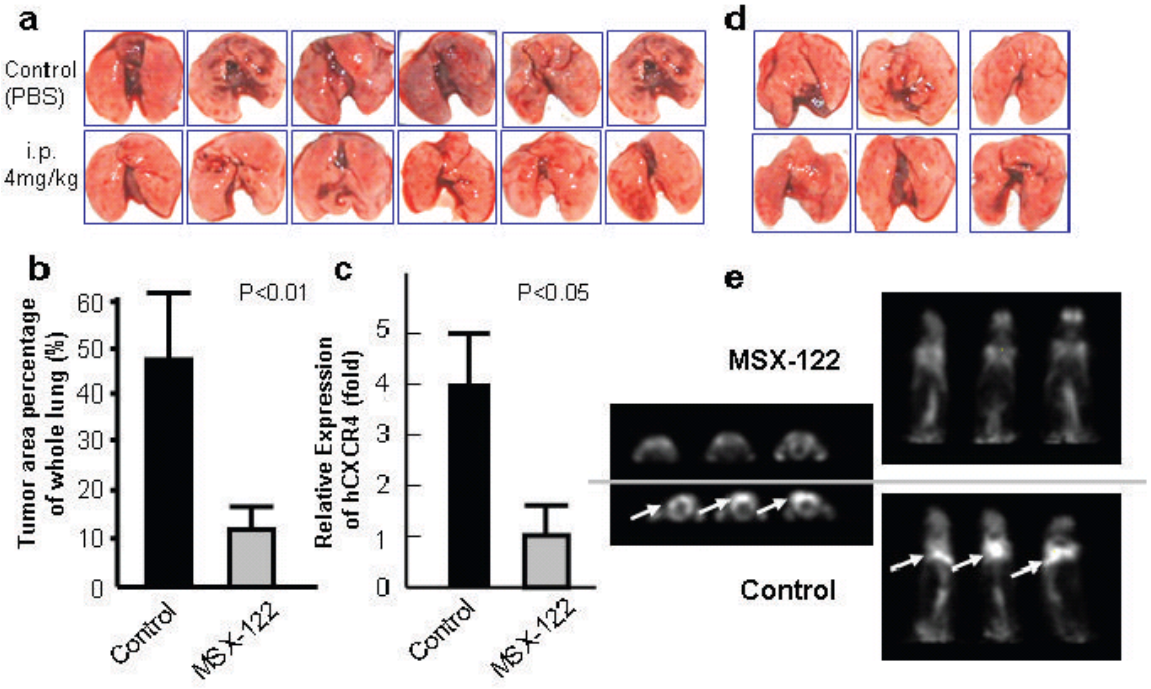


Figure 11. Anti-metastatic efficacy of MSX-122 in animal models.

To determine whether MSX-122 can inhibit metastatic progression in a different cancer type, metastatic 686LN-Ms cells were injected intravenously through the tail vein to generate experimental animal models for Head and Neck cancer metastasis. A total of 12 mice, 6 mice in each group (control and 40 mg/kg, i.p. three times weekly), were employed. We also selected TN14003 as a suitable positive control in preference to AMD3100 in view of the moderate potency and

significant toxicity that was observed in our hands. In our previous study, the use of non-invasive [^{18}F]FDG-PET to detect metastases[47] was validated. In Figure 11e (left panel) FDGPET axial images of 3 randomly selected mice from each group are shown and the lung metastases are indicated by white arrows. The mice injected with saline exhibited significant lung metastases after 30 days (bottom three mice), while the arm administered with 40 mg/kg MSX-122 showed no evidence of metastases (similar to what we observed in a group of mice treated with TN140037). The two panels on the right (Figure 11e) are the coronal images of the same mice on the left. The top three mice were treated with 40 mg/kg i.p. MSX-122, and the bottom three mice were injected with saline. The highly glycolytic tumors are indicated by white arrows. In a subsequent experiment, an arm administered with an intermediate dose (4 mg/kg, three times weekly) demonstrated lung metastases, but with much less intensity as compared to the control group, thus demonstrating a dose dependent efficacy for MSX-122 (data not shown).

***In vivo* angiogenesis assay (Matrigel plugs):** To determine the effect of CXCR4/SDF-1 interaction on angiogensis *in vivo*, matrigel plug angiogenesis experiments were performed in nude mice. A mixture of 2 x 10^5 MDA-MB-231 cells in 0.5 mL of growth factor-reduced Matrigel was injected subcutaneously. Mice were treated with either MSX-122 or AMD3100 and compared to saline control. H&E stainings of the excised plugs revealed neovasculatures and a high number of tumor cells in the control group treated with saline (Figure 12a, top), which was blocked by daily treatment of 10 mg/kg i.p. AMD3100 or MSX-122

treatment at 10 mg/kg, s.c. (Figure 12a, middle and bottom panels). In addition, the average plug weight of AMD3100 or MSX-122 for the treated group was approximately 30% or 70% less, respectively, relative to the control group (Figure 12b).

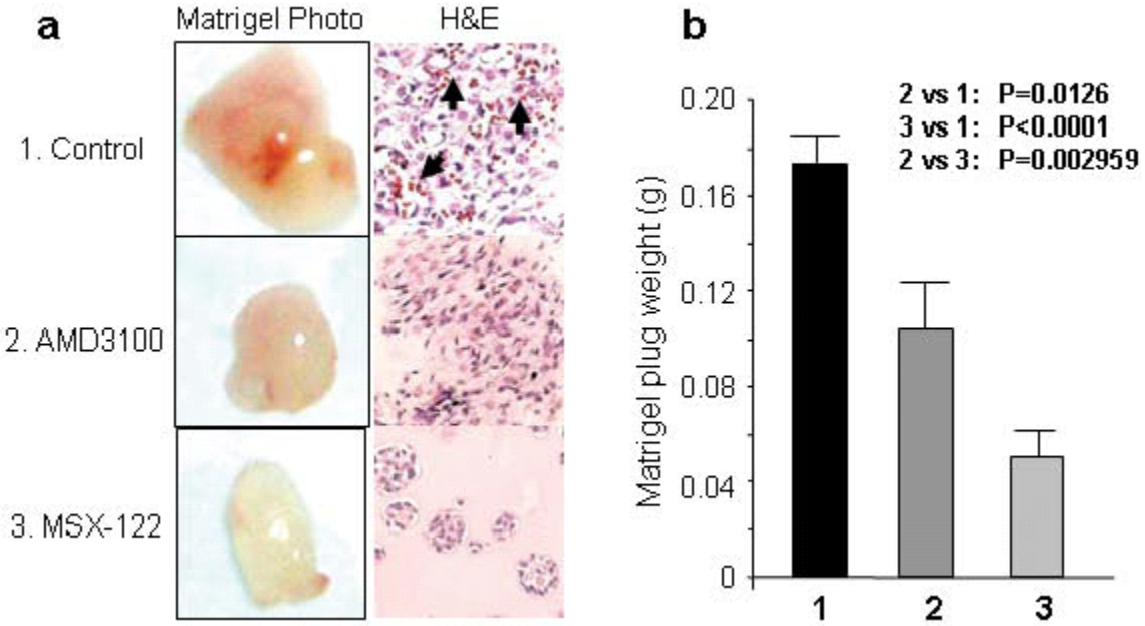


Figure 12. MSX-122 effectively blocked SDF-1/CXCR-4 mediated angiogenesis.

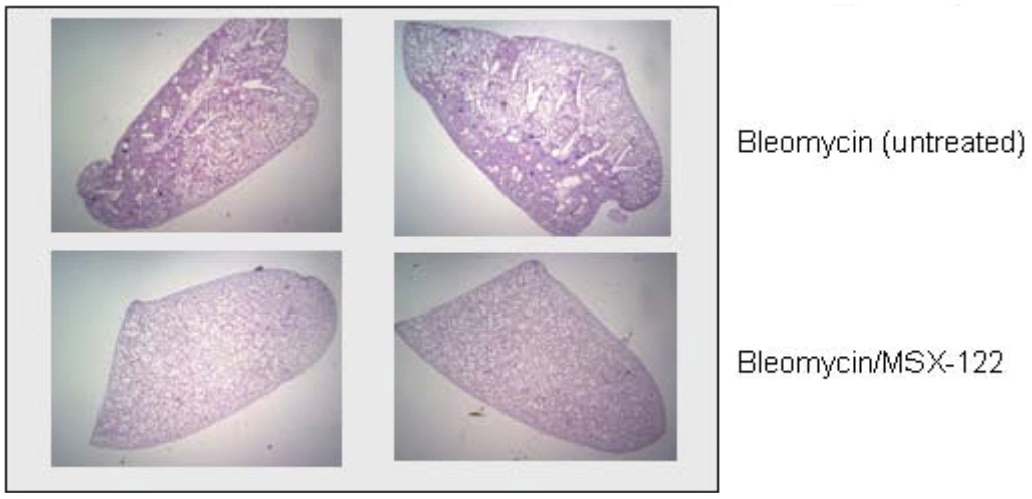


Figure 13. MSX-122 effectively prevented bleomycin-induced lung fibrosis.

A CXCR4 antagonist attenuates bleomycin-induced lung fibrosis in mice: The efficacy of MSX-122 to block bleomycin-induced lung fibrosis was performed in a previous reported animal model.[48] Mice received intraperitoneally 10 mg/kg of MSX-122 or saline one day before bleomycin treatment and daily for 20 days. Lungs harvested 20 days after bleomycin treatment were analyzed histologically. Figure 13 shows H&E tainings of lung to highlight lung fibrosis. Bleomycin causes marked increases in collagen deposition, which is completely prevented by treatment with MSX- 122.

***In vitro* genotoxicity and safety:** As an initial safety assessment, MSX-122 was tested for genotoxicity. An *in vitro* Ames test was carried out (BioReliance Corp., Rockville, MD) and demonstrated no evidence of mutagenicity. An *in vitro* chromosome aberration screening test was also conducted (BioReliance Corp., Rockville, MD) using CHO cells treated with MSX-122. The analysis showed no statistically significant increase in structural or numerical chromosome aberrations at any dose level up to the highest dose of 2 mM. Sufficiently scorable cells in the presence of S9 were available for 4 h treatment and in the absence of S9 for a 20 h treatment. It was concluded that MSX-122 does not induce chromosome aberrations. Finally, MSX-122 was tested for its potential to interfere with the rapid delayed rectifier current (I_{Kr}) in human ventricles through the cardiac potassium channel, hERG, since inhibition of I_{Kr} has been reported to be the most common cause of cardiac action potential prolongation by non-cardiac drugs.[49, 50] The resulting data indicate that MSX-122 do not exert a significant inhibitory effect on hERG channel currents (1 μM MSX-122-0.2% inhibition, n = 3).

5-day dose ranging toxicology studies in rats and monkeys: Initially, three groups of rats (5 males and 5 females per group) were dosed with 0, 250 and 600 mg/kg of MSX-122 orally once per day for 5 days. We selected 600 mg/kg since previous escalating, single dose PK studies demonstrated that additional plasma exposure was not achieved with higher doses. The pharmacokinetic data show that micromolar concentrations of MSX-122 are maintained throughout the term of the study after day 1, and C_{max} values are in the range of 2 – 4 μg/mL (6.8 – 13.6 μM). No signs or symptoms of toxicity were observed in any of the animals during the study, and no toxicity was observed upon termination from blood serum chemistry or gross necropsy.

Next, a 5-day repeat dose study was carried out in non-naïve monkeys in order to determine the maximum plasma levels that can be achieved and to identify any resulting toxicity. Accordingly, two non-naïve cynomolgus monkeys (1 male and 1 female) and two naïve cynomolgus monkeys (1 male and 1 female) were dosed with 1,000 and 2,000 mg/kg, respectively, orally once per day for 5 days. No drug related signs or symptoms of toxicity after five days of dosing were observed, and there were no abnormalities in the resulting blood serum chemistry. There were also no abnormalities or signs of toxicity observed from gross necropsy of the animals dosed at 2000 mg/kg. The only observations were loose and watery stool in a subset of the animals, which may have been caused by the excipients in the formulation. The data showed that micromolar concentrations of MSX-122 were maintained throughout the term of the study with C_{max} in the range of 5.1 μM (1.5 μg/mL) to 12 μM (3.5 μg/mL).

2.3. Conclusion

The current study presents the discovery of a new class of nonpeptide CXCR4 antagonists with low molecular weights and a novel and simple scaffold: two aromatic amine moieties connected by a para-xylylene group. The template was designed in part based on structural features imbedded in the previously reported CXCR4 antagonist AMD3100 (**3**),[2, 3, 35] and appears to incorporate the critical features necessary for blocking the complexation of CXCR4 by SDF-1, while eliminating the metal-chelating properties of a cyclic polyamine. Screening of analogs, performed using a competitive affinity binding assay employing the peptidic CXCR4 antagonist TN14003 (**7**), led to the identification of the initial lead WZ13 (**19**). Structure-activity studies around WZ13 brought to light several important structural insights: 1) the central aromatic ring is critical for high CXCR4 affinity; 2) a one-carbon separation between the central phenyl ring and the nitrogen of the acyclic linker is essential for high potency; 3) anti-CXCR4 activity is much more sensitive to *para* substitution on the terminal aromatic rings compared to *meta* and *ortho* substitution. 4) the SAR profile led to the design and synthesis of WZ811 (**47**), the second generation lead, a highly potent competitive blocker of CXCR4 action at subnanomolar and further functional assays demonstrate that WZ811 can effectively counteract SDF-1 function at low doses and block *in vitro* CXCR4/SDF-1 mediated signaling more effectively than AMD3100.

Attempts to improve the pharmacokinetic profile of WZ811 discovered MSX-122 (**47**). Preclinical study of MSX-122 proved the its compelling features as

CXCR4 antagonist, including: 1) potent inhibition of the CXCR4/SDF-1 interaction (IC_{50} ~ 10 nM); 2) undetectable toxicity in mice, rats and monkeys even at extreme doses (2000 mg/kg for 5 days); 3) a reasonable plasma exposure after oral dosing; 4) effectiveness as an anti-metastatic and anti-angiogenic agent *in vivo*; and 5) effectiveness in blocking bleomycin induced lung fibrosis. Encouraged by the preclinical results, MSX-122 is currently in phase I clinical trial.

2.4. Experimental Section

2.4.1 Biochemistry

Cell Culture/Reagents. Human breast carcinoma cell line, MDA-MB-231, and head and neck cancer cell line, 686LN-Ms, were maintained in RPMI-1640 and DMEM/Ham's F-12 50:50 (Sigma, St. Louis, MO), respectively, supplemented with 10% FBS, 100 U/mL of penicillin sodium, and 100 µg/mL of streptomycin sulfate (Pen/Strep), at 37°C in humidified air containing 5% carbon dioxide air atmosphere. Human glioma cell lines as U87CD4CXCR4 cells were obtained through the NIH AIDS Research & Reference Reagent Program and were cultured in DMEM supplemented with 15% FBS and Pen/Strep. Human umbilical vein endothelial cells (HUVECs) were cultured in M199 (Cat# 10-060-CV, Cellgro, Herndon, VA), supplemented with 20% fetal calf serum (Sigma, St. Louis, MO). The cells were incubated in 5% CO_2 in air at 37°C until confluent.

Initial screening of anti-CXCR4 small molecules based on a binding affinity assay. For compound screening based on a competition binding assay, 2 x 104 MDA-MB-231 cells in a 200 µL of medium were seeded in 8-well slide chamber two days before the experiments. Various concentration of different compounds (1, 10, 100, and 1000 nM) were added to the separate wells, incubated for 10 minutes at room temperature, and then the cells were fixed in 4% of ice-cold paraformaldehyde. The cells were rehydrated in PBS and blocked to eliminate non-specific binding (Avidin and Biotin Blocking Solution, Zymed Laboratories, Inc., San Francisco, CA). The slides were subsequently incubated

for 45 min at room temperature with 0.05 μg/mL of biotinylated **7**, washed three times with PBS and incubated in streptavidin-rhodamine (1:150 dilution) (Jackson ImmunoResearch Laboratories, West Grove, PA) for 30 min at room temperature. Finally, the slides were washed with PBS, mounted in an antifade mounting solution (Molecular Probes, Eugene, OR), and the samples were analyzed on a Nikon Eclipse E800 microscope.

Tumor Cell Invasion Assay. To model *in vitro* metastasis, a Matrigel invasion assay was performed within a Matrigel invasion chamber from BD Biocoat Cellware (San Jose, CA). SDF-1α (200 ng/mL, R & D Systems, Minneapolis, MN) was added to the bottom chamber to induce the invasion of MDA-MB-231 cells through the Matrigel. The selected compounds were added to the cells before the cells were seeded in the top chamber. The Matrigel invasion chamber was incubated for 22 h in a humidified tissue culture incubator. First, non-invading cells were removed from the top of the Matrigel with a cotton tipped swab. Invading cells at the bottom of the Matrigel were fixed in methanol and stained with hematoxylin and eosin (H&E). The invasion rate was determined by counting the H&E stained cells.

cAMP assay to measure G_i function. Perkin-Elmer's LANCE cAMP assay kit (Cat # AD0262) based on time-resolved fluorescence resonance energy transfer (TR-FRET) was utilized to determine a compound's ability to block cAMP modulation induced by the CXCR4/SDF-1 interaction. Human glioma U87 cells overexpressing CD4 and CXCR4 (U87CD4CXCR4) were seeded at 2500

cells/well in a 384-well plate in a 2% FBS, 48 h before the test. The experiment was performed according to the manufacturer's instruction using 5 μM Forskolin to induce cAMP production that is reduced by the presence of SDF-1. Results were measured in a Perkin-Elmer Envision 2102 Multilabel Reader with the following parameters: flash energy area = low, flash energy level = 239, counting cycle = 1 ms, and ex/em = 340nm/665nm.

***In vitro* angiogenesis assay.** To perform the capillary tube formation assay,[51] 250 μL of growth factor reduced Matrigel (BD Bioscience, Bedford, MA) was added to each well of a 24-well plate and was allowed to polymerize for 30 min at 37°C. After human umbilical vein endothelial cells (HUVEC) (purchased from Emory Tissue Core) were pre-incubated in M199 containing 1% FBS overnight, the cells were harvested with a non-enzymatic cell dissociation solution (ICN, Irvine,CA). AMD3100 or MSX-122 was added to the cells for 10 min at room temperature before seeding. The cells were plated onto the layer of Matrigel at a density of $1x10^5$cells in 1 mL of M199 with 1 % FBS and 200 ng/mL of SDF-1 (R&D Systems, Minneapolis, MN). After 18 hrs, the wells were photographed at 4x magnification in five randomized fields and the number of tubular networks was counted.

Animal Experiments for metastasis. Six- to eight-week-old CB-17 female nude mice (Taconic Farms, Germantown, NY) were given injections of 1.5×10^6 MDA-MB-231 breast cancer cells mixed with the compound (1 μM, less than 5 min preincubation) through the tail vein (six mice per group). From the following day, group MSX-122 mice were treated by intraperitoneal injection of 4 mg/kg of

MSX-122 daily. Control group animals were injected intraperitoneally with saline. The animals were sacrificed 35 days after the tumor cell injection. Whole lung tissues were harvested in optimum cutting temperature (OCT, Fisher Scientific, Suwanee, GA) compound and snap-frozen in liquid nitrogen. The frozen lung tissues were sectioned and subjected to real-time RT-PCR for human CXCR4 and H&E histostaining to evaluate the presence or absence of tumor. These experiments were repeated once more to confirm the results. In addition, 6 mice were treated by MSX-122 in drinking water (0.067 mg/mL, equivalent to 10 mg/kg/d based on 3 mL water consumption per mouse per day for a 20 g mouse). For the Head and Neck cancer animal model, metastatic subclones of 686LN-Ms cells were injected in the same way as MDA-MB-231 cells. Group MSX-122 mice were treated by intraperitoneal injection of 40 mg/kg of MSX-122 three times for the first week, then twice weekly thereafter; Control group animals were injected intraperitoneally with saline. These animals were imaged by FDG-PET 30 days after the tumor cell injection. MicroPET studies were performed using 3 randomly picked mice from each of the two groups: control and MSX-122-treated as described previously.[47] Data acquisition and processing, including image reconstruction, image display, and analyses were performed with the ASIPro program provided by Concorde Microsystems (Knoxville, TN). A pixel region of interest was outlined in the regions of increased FDG uptake, and after correcting for radioactive decay, the maximal standardized uptake value (SUV_{max}) was semi-quantitatively calculated according to Truong *et al.*.[52] All protocols for animal studies were reviewed and approved by the Institutional Animal Care and Use

Committee at Emory University.

***In vivo* angiogenesis assay (Matrigel plug).** 2 x 10^5 MDA-MB-231 cells were mixed with the compound in 0.5 mL of growth factor-reduced matrigel (BD Biosciences, San Jose, CA) at 1 μM concentration and implanted subcutaneously into the flanks of nude mice (two plugs per mouse, 6 mice per group). The mice in the CXCR4 antagonist-treated group received daily subcutaneous injections of AMD3100 or MSX-122 in the middle of the two plugs (two plugs per mouse) at 10 mg/kg. Ten days after matrigel injection, the animals were sacrificed, and the Matrigel plugs were excised. The excised plugs were photographed, weighed, and fixed for histological analysis.

Bleomycin-induced lung fibrosis model. Mice were anesthetized by isofluorane inhalation, the trachea exposed using sterile technique and 4 U/kg bleomycin (Sigma, ST Louis, MO) in 100 μL of PBS or PBS vehicle injected into the tracheal lumen. After inoculation, the incision was closed and the animals were allowed to recover. Ten mice per group were used to determine the effects of MSX-122 on lung fibrosis, after inflation and fixation with 3.8% paraformaldehyde for 24h, lung tissue was paraffin-embedded, sectioned, and stained with H&E staining as previously described.[48]

Toxicology studies in rats and monkeys. The test article was administered at two dose levels to two separate groups of five male and five female rats (Groups 2 and 3) by oral gavage. The vehicle alone was administered to a group of 5 male and 5 female rats (Group1). In addition there were 4 groups of 4 male

and 4 female rats that received the low and high dose of the test article and were used for collection of blood for TK analyses on Day 0 and Day 4. Group 1, 2, 3, 6 and 7 rats were dosed once daily for 5 days; Group 4 and 5 rats were dosed once, on Day 0. Observations were conducted during the study. The day after the 5th dose, blood was taken from all main study animals for clinical pathology determinations, after which the animals were terminated. Gross necropsy was performed on the animals in groups 1, 2 and 3.The first group was treated intravenously with a single, 2 mg/kg, dose of MSX-122 (bismethanesulfonic acid salt). The article was formulated (10% ethanol, 20% propylene glycol and 70% of a 10% solution of hydroxypropyl-β-cyclodextrin in 50 mM lactic acid) at a concentration of 0.5 mg/mL and injected into the tail vein with a total dose volume of 4 mL/kg. The second group was treated orally with a single, 15 mg/kg dose of MSX-122. The oral dosing formulation contained 1.5 mg/mL of MSX-122 in 5% PEG-200 and 95% of a 0.5% solution of methylcellulose and the dose volume was 10 mL/kg.

This study was carried out at MPI Research, Inc. with 2 non-naïve cynomolgus monkeys (1 male and 1 female) and 2 naïve cynomolgus monkeys (1 male and 1 female). All animals were dosed once daily for five days by oral gavage with a slurry of MSX-122 in 5 mL/kg/dose of dosing solution (10% TPGS, 40% PEG-400, 50% water). The naïve animals were dosed with 2000 mg/kg of MSX-122 and the non-naïve animals were dosed with 1000 mg/kg. Blood samples were collected at 0.25, 0.5, 1, 2, 4, 8 and 12 h post dose on day 1 and at 0.5, 1, 2, 4, 8, 12, 24, and 48 h post dose on day 5. The 24 h blood sample from

day 5 was used for serum pathology. The naive animals were sacrificed and evaluated by necropsy and the nonnative animals were returned to the colony.

2.4.2 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.

Commercial reagents and solvents were used as received unless otherwise noted. Dehydrated dichloromethane, *N*,*N*-dimethylformamide (DMF), tetrahydrofuran (THF), toluene, and 1,2-dichloroethane 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. 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 ($CDCl_3$) 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 ($CDCl_3$). High resolution mass spectra (HRMS) were obtained on a JEOL JMS-SX102/SX102A/E or Thermo Finnigan LTQ-FTMS instrument.

Compounds **1, 3, 7-19, 36, 41c-f,** and **41j** are available from commercial suppliers and were tested without further purification.

1, 4-Diguanidobenzene dihydrochloride (21a). The preparation was performed according to a modified literature procedure.[36] *p*-Phenylenediamine dihydrochloride (1.81 g, 1.0 mmol) and cyanamide (1.26 g, 3.0 mmol) in absolute ethanol (50 mL) were heated under reflux overnight. After condensation, the resulting dihydrochloride was filtered off, washed with diethyl ether and dried to give crude product which was recrystallized from hot methanol to give **21a** as white crystals (0.81g, 42% yield): mp 302-304 ^{o}C (dec.); ^{1}H NMR (600 MHz, D_2O) δ 7.40 (4H, s); ^{13}C NMR (150 MHz, D_2O) δ 159.02, 136.36, 129.98. Anal. Calcd for $C_8H_{12}N_6 \cdot 2HCl$: C, 36.24; H, 5.32; N, 31.70; Cl, 26.74; Found: C, 36.34; H, 5.34; N, 31.76; Cl, 26.70.

1,1'-(1,4-phenylenebis(methylene))diguanidine dihydrochloride (21b). The title compound was prepared according to the procedure described above for **21a** as a pale white solid in 36% yield: mp 278-311 ^{o}C (dec.). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08 (s, 2H), 7.32 (s, 4H), 6.85-7.71 (bs, 8H); 4.37 (s, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.12, 136.61, 127.53, 43.65. Anal. Calcd for $C_8H_{12}N_6 \cdot 2HCl$: C, 40.96; H, 6.19; N, 31.66; Found: C, 40.99; H, 6.23; N, 31.31.

1,4-Bis[2-(diaminomethylene)carbohydrazonoyl]benzene dihydrochloride (23a). Terephthaldicarboxaldehyde (0.67 g, 5.0 mmol) and aminoguanidine hydrochloride (1.22 g, 11.0 mmol) in ethanol (25 mL) with ethanolic HCl (2.0 mL) was heated to reflux for 2 h. After cooling to room temperature, the white precipitate was filtered off to give **23a** as a pale white solid (1.51 g, 95%). mp 316-318 ^{o}C(dec.). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.31 (s, 2H), 8.21 (s, 2H), 7.94 (s, 4H), 7.60-8.20 (bs, 8H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.52, 145.98, 135.18, 127.84. Anal. Calcd for $C_{10}H_{14}N_8 \cdot 2HCl \cdot 0.7H_2O$: C, 36.20; H, 5.29; N, 33.77; Cl, 21.37; Found: C, 36.07; H, 5.23; N, 33.42; Cl, 21.11. The analytical data are in agreement with those reported in the literature.[53]

1,4-bis((*E*)-(2-(4,5-dihydro-1*H*-imidazol-2-yl)hydrazono)methyl)benzene dihydrobromide (23b). The title compound was prepared according to the procedure described above for **23a** as a pale white solid in quantitative yield: mp 349-352 ^{o}C (dec.); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.39 (s, 2H), 8.30-9.20 (bs, 4H), 8.22 (s, 2H), 7.92 (s, 4H), 3.75 (s, 8H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.80, 147.20, 135.16, 127.81, 42.74. Anal. Calcd for $C_{14}H_{18}N_8 \cdot 2HBr$: C, 40.96; H, 6.19; N, 31.66; Found: C, 41.19; H, 6.35; N, 31.31. The analytical data are in

agreement with those reported in the literature. [37]

***N*,*N*'-Bis(4,5-dihydro-1*H*-imidazol-2-yl)-1,4-benzenedimethanamine dihydroiodide (25).** *p*-Phenylenediamine (544.8 mg, 4.0 mmol) and 2-methylmercapto-4,5-dihydroimidazole hydroiodide (2.06 g, 8.4 mmol) were dissolved in methanol (25 mL). After refluxing overnight, the solution was reduced to minimal volume under reduced pressure, and diethyl either was added, producing a white precipitate. The precipitate was collected and recrystallized in hot methanol to give **25** as a pale white solid (1.12 g, 53%): mp 294-296 ^{o}C (dec.); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (s, 2H), 7.60-8.60 (bs, 4H), 7.31 (s, 4H), 4.36 (d, J = 6.0Hz, 4H), 3.60 (s, 8H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.31, 136.50, 127.53, 45.06, 42.54. Anal. Calcd for $C_{14}H_{20}N_6 \cdot 2HI$: C, 31.84; H, 4.20; N, 15.91; Found: C, 32.06; H, 4.35; N, 15.77. The analytical data are in agreement with those reported in the literature.[38]

***N*,*N*'-Bis[2-(dimethylamino)ethyl]-1,4-benzenedimethanamine tetrahydrochloride (26).** This procedure is performed according to a modified literature procedure.[39] A mixture of terephthaldicarboxaldehyde (0.67 g, 5.0 mmol) and *N*,*N*-dimethyl-1,2-ethanediamine (0.93 g, 1.21 mL, 10.5 mmol) were treated with sodium triacetoxyborohydride (3.18 g, 15.0 mmol) in 1,2-dichloethane (20 mL). After stirring at room temperature under an argon or nitrogen atmosphere until the disappearance of the reactants from TLC plates, the reaction mixture was quenched by adding aqueous NaOH (10%), extracted with diethyl ether (2 x 30 mL). The combined organic phases were washed by brine and dried over anhydrous $MgSO_4$. The solvent was evaporated to give the crude product which

was dissolved in ethanol, following addition of ethanolic HCl dropwise to form white precipitate which was filtered off, dried, and recrystallized from hot water and ethanol to give **26** as a pale white solid (1.96 g, 85%): mp 250-252 ^{o}C (dec.); ^{1}H NMR (600 MHz, D_2O) δ 7.58 (s, 4H), 4.37 (s, 4H), 3.58 (s, 8H), 2.98 (s, 12H); ^{13}C NMR (100 MHz, D_2O) δ 131.95, 130.81, 52.45, 51.30, 43.45, 41.45. Anal. Calcd for $C_{16}H_{30}N_4 \cdot 4HCl \cdot 2H_2O$: C, 41.75; H, 8.32; N, 12.17; Found: C, 41.83; H, 8.26; N, 11.92. The analytical data are in agreement with those reported in the literature.[54]

***N,N'*-Diphenyl-*trans*-1,4-cyclohexanedimethanamine (30a).** This compound was prepared in two steps starting from commercially available *trans*-1,4-cyclohexanedicarboxylic acid.

Step 1. A mixture of *trans*-1, 4-cyclohexanedicarboxylic acid (0.69 g, 4.0 mmol) in thionyl chloride (15 mL) was refluxed for 2 h in an anhydrous system with a condenser equipped with a NaOH trap at the top. After removing the excess thionyl chloride under reduced pressure, dichloromethane (50 mL) was added into the resulting carboxylic chloride residue **22a**, following the addition of amine (0.73 mL, 8.0 mmol) and pyridine (0.97 mL, 12.0 mmol). The mixture was stirred at room temperature for 1h. The solvent was reduced to minimal volume under reduced pressure. The white precipitate was filtered off, washed through dichloromethane and water to give crude amides **29a** as a white solid in quantitative yield which was pure enough to next step: ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.86 (s, 2H), 7.61 (d, J = 7.8 Hz, 4H), 7.31 (t, J = 7.8 Hz, 4H), 7.02 (d, J = 7.8 Hz, 2H), 2.35 (bs, 2H), 1.91 (d, J = 7.2 Hz, 4H), 1.52-1.47 (m, 4H); ^{13}C

NMR (100 MHz, DMSO-d_6) δ 173.94, 139.42, 131.63, 122.93, 119.03, 44.09, 31.29. HRMS calcd for $C_{20}H_{23}N_2O_2$, 323.17595 $[M+H]^+$; Found 323.17515.

Step 2. A mixture of amide **29a** (322.4 mg, 1.0 mmol) and $LiAlH_4$ (2.0 mL, 2.0 mmol, 1N in THF) in THF (40 mL) was refluxed until the disappearance of the amide from TLC plates. After cool down to room temperature, the reaction was quenched with the addition of water and aqueous NaOH (15 %) as described in the literature,[40] and then extracted with diethyl ether (2 x 40 mL). The combined organic phases were washed by brine and dried over $MgSO_4$. Removal of the solvent gave the free amine product which was purified by the column chromatography to give **30a** (255.3 mg, 85%) as a pale yellow solid: mp140-144 ^oC; R_f = 0.48 (Hexane/ethyl acetate, 4/1); ^1H NMR (600 MHz, $CDCl_3$) δ 7.20-7.16 (m, 4H), 6.69 (tt, *J* = 7.8 Hz, 0.6 Hz, 2H), 6.60 (dd, *J* = 9.0 Hz, 0.6 Hz, 4H), 3.72 (s, 2H), 2.99 (d, *J* = 6.6 Hz, 4H), 1.92 (d, *J* = 6.6 Hz, 4H), 1.61-1.58 (m, 2H), 1.06-1.00 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.71, 129.45, 117.19, 112.82, 50.65, 37.94, 30.96. *m/z* (EI^+) calcd for $C_{20}H_{26}N_2$, 294.5; Found 294.5 M^+. Anal. Calcd for $C_{20}H_{26}N_2$: C, 81.59; H, 8.90; N, 9.51; Found: C, 81.45; H, 8.98; N, 9.27.

***N,N'*-Diphenyl-1,4-naphthalenedimethanamine (30b).** The title compound was prepared according to the two-step sequence described above for **30a** as a white solid in 61% yield (2 steps).

***N,N'*-Diphenyl-1,4-Naphthalenedicarboxamide (29b).** Starting from 1,4-naphethalenediacetic acid, **29b** was obtained in quantitative yield as a white solid: ^1H NMR (400 MHz, DMSO-d_6) δ 10.66 (s, 2H), 8.24 (dd, *J* = 6.4 Hz, 3.2 Hz,

2H), 7.84 (s, 2H), 7.82 (s, 4H), 7.67 (dd, *J* = 6.8, 3.6 Hz, 2H), 7.40 (t, *J* = 7.6 Hz, 4H), 7.15 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.84, 139.15, 136.65, 129.79, 128.78, 127.30, 125.57, 124.36, 123.88, 119.91. HRMS calcd for $C_{24}H_{19}N_2O_2$, 367.14465 $[M+H]^+$; Found 367.14381.

30b. mp 174-177 °C; R_f = 0.51 (Hexane/ethyl acetate, 4/1); ^{1}H NMR (600 MHz, $CDCl_3$), 8.15 (dd, *J* = 6.0 Hz, 3.0 Hz, 2H), 7.58 (dd, *J* = 6.0, 3.0 Hz, 2H), 7.51 (s, 2H), 7.23 (t, *J* = 7.8 Hz, 4H); 6.77 (t, *J* = 7.2 Hz, 2H), 6.71 (d, *J* = 7.2 Hz, 4H), 4.76 (s, 4H), 4.12 (bs, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ148.24, 134.54, 132.15, 129.56, 126.51, 126.02, 124.58, 117.97, 113.06, 46.75. *m/z* (EI^+) calcd for $C_{24}H_{22}N_2$, 338.5; Found 338.4 M^+. Anal. Calcd for $C_{24}H_{22}N_2$: C, 85.17; H, 6.55; N, 8.31; Found: C, 84.71; H, 6.47; N, 8.11.

***N*,*N*'-Diphenyl-1,4-benzenediethanamine (30c).** The title compound was prepared according to the two-step sequence described above for **30a** as a yellow solid in 49% yield (2 steps).

***N*,*N*'-Diphenyl-1,4-Benzenediacetamide (29c).** Starting from 1,4-phenylenediacetic acid, **29c** was obtained in quantitative yield as a white solid: ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.13 (s, 2H), 7.58 (d, *J* = 7.2 Hz, 4H), 7.28 (t, *J* = 7.2 Hz, 8H), 7.02 (d, *J* = 7.2 Hz, 2H), 3.61 (s, 4H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 169.13, 139.23, 134.29, 129.05, 128.69, 123.18, 119.10, 42.95. HRMS calcd for $C_{22}H_{21}N_2O_2$, 345.16030 $[M+H]^+$; Found 345.15948.

30c: mp 85-86 °C; R_f = 0.47 (Hexane/ethyl acetate, 4/1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.22-7.18 (m, 8H), 6.73 (t, *J* = 7.2 Hz, 2H), 6.64 (d, *J* = 7.2 Hz, 4H), 3.69

(bs, 2H); 3.42 (t, *J* = 7.2 Hz, 4H), 2.92 (t, *J* = 7.2 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.21, 137.60, 129.49, 129.22, 117.87, 113.18, 45.24, 35.32. *m/z* (EI^+) calcd for $C_{22}H_{24}N_2$, 316.5; Found 316.4 M^+. Anal. Calcd for $C_{22}H_{24}N_2$: C, 83.50; H, 7.64; N, 8.85; Found: C, 83.63; H, 7.65; N, 8.64.

2,3,5,6-Tetramethyl-*N*,*N*'-diphenyl-1,4-benzenedimethanamine (33a). **General procedure A:** This procedure is performed according to a modified literature procedure.[39] A mixture of aniline (0.11 mL, 1.05 mmol), 2,3,5,6-tetramethyl-1,4-benzenedicarboxaldehyde (95.1 mg, 0.5 mmol) in 1,2-dichloroethane (10 mL) was treated with sodium triacetoxyborohydride (317.9 mg, 1.5 mmol) at room temperature. After being stirred for overnight, the reaction was quenched by aqueous NaOH (10%), and diluted with ethyl acetate (20 mL). After separation, the organic phase was further washed with brine and the combined aqueous phase was extracted with ethyl acetate (2 x 10 mL). The combine organics were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The resultant residue was purified by flash column chromatography (Hexane/ethyl acetate, 4/1) to deliver desired product **33a** (110.9 mg, 64%) as a white solid: R_f = 0.67 (Hexane/ethyl acetate, 4/1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27-7.25 (m, 4H), 6.78 (t, *J* = 7.8 Hz, 2H), 6.71(d, *J* = 7.8 Hz, 4H); 4.31 (s, 4H), 3.48 (bs, 2H), 2.32 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.44, 134.94; 134.31; 129.53; 117.67; 112.73; 43.70, 16.52. *m/z* (EI^+) calcd for $C_{24}H_{31}N_2$, 344.7; Found 344.5 M^+. Anal. Calcd for $C_{24}H_{31}N_2$: C, 83.68; H, 8.19; N, 8.13; Found: C, 83.34; H, 8.09; N, 7.89.

***N*,*N*'-Diphenyl-9,10-anthracenedimethanamine (33b).** The title compound

was prepared according to general procedure A as a yellow solid in 98% yield: mp 262-265 ^{o}C (dec.); R_f = 0.54 (Hexane/ethyl acetate, 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (dd, *J* = 7.2, 3.2 Hz, 4H), 7.55 (dd, *J* = 7.2, 3.2 Hz, 4H), 7.32 (t, *J* = 8.0 Hz, 4H), 6.87-6.83 (m, 6H), 5.20 (s, 4H), 3.98 (bs, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 148.51, 130.86, 130.53, 129.68, 126.50, 125.13, 118.15, 112.94, 41.34. HRMS calcd for $C_{28}H_{25}N_2$ 389.20177 $[M+H]^+$; Found 389.20095. Anal. Calcd for $C_{28}H_{24}N_2$: C 86.56; H, 6.23; N, 7.21; Found: C, 86.35; H, 6.13; N, 6.82.

2,5-Dimethyl-*N*,*N*'-diphenyl-1,4-benzenedimethanamine (35a). 2,5-bis(chloromethyl)-*p*-xylene (406.2 mg, 2.0 mmol) and aniline (0.38 mL, 4.2 mmol) in absolute ethanol (15 mL) with pyridine (0.81 mL, 10 mmol) were heated to refluxing overnight. The solvent was removed to minimum volume following addition of ethyl acetate (15 mL). The resulting mixture was washed with brine, dried over $MgSO_4$. Removal of the solvent gave the crude product which was purified by the column chromatography to give **35a** (433.5 mg, 68%) as a pale yellow solid: mp 149-152 ^{o}C; R_f = 0.54 (Hexane/ethyl acetate, 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-7.17 (m, 6H), 6.76 (t, *J* = 7.2 Hz, 2H), 6.67 (d, *J* = 8.0 Hz, 4H), 4.24 (s, 4H), 3.90 (bs, 2H), 2.32 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.42, 136.25, 134.21, 130.85, 129.50, 117.82, 113.04, 46.44, 18.68. *m/z* (EI^+) calcd for $C_{22}H_{24}N_2$, 316.5; Found 316.4 M^+. Anal. Calcd for $C_{22}H_{24}N_2$: C, 83.50; H, 7.64; N, 8.85; Found: C, 83.46; H, 7.38; N, 9.01.

***N*,*N*'-Diphenyl-1,3-benzenedimethanamine (33c).** From *m*-phthalaldehyde (536.0 mg, 4.0 mmol), aniline (0.77 mL, 2.1 mmol) and sodium triacetoxyborohydride (2.54 g, 12.0 mmol), general procedure A delivered **33c**

(1.02g, 88%) as a pale yellow solid: R_f = 0.57 (Hexane/ethyl acetate, 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.38-7.34 (m, 3H), 7.24-7.21 (m, 4H), 6.78 (t, *J* = 7.8 Hz, 2H), 6.68 (d, *J* = 7.8 Hz, 4H); 4.36 (s, 4H), 4.07 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.26, 140.09, 129.44, 129.03, 126.74, 126.54, 117.77, 113.05, 48.42. *m/z* (EI^+) calcd for $C_{20}H_{20}N_2$ 318.5; Found 318.4. Anal. Calcd for $C_{20}H_{20}N_2$: C, 83.30; H, 6.99; N, 9.71; Found: C, 83.31; H, 6.95; N, 9.70. The analytical data are in agreement with those reported in the literature.[55]

***N*,*N*'-Diphenyl-1,2-benzenedimethanamine (35b)**. To a solution of aniline (1.8 mL, 20 mmol) and pyridine (1.62 mL, 20 mmol) in absolute ethanol (10 mL) was added dropwise a solution of *o*-xylylene dibromide (527.9 mg, 2.0 mmol) in ethanol (10 mL) at -20 ^{o}C. The reaction mixture was stirred at -20 ^{o}C for 24 h, at which point the solvent was removed to minimum volume following addition of ethyl acetate (15 mL). The resulting mixture was washed with brine, dried over $MgSO_4$. Removal of the solvent gave the crude product which was purified by the column chromatography to give **35b** (333.5 mg, 58%) as a white solid: mp 110-111 ^{o}C (Lit.[56] 108-109 ^{o}C); 108-109 ^{o}C; R_f = 0.53 (Hexane/ethyl acetate, 4/1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46-7.42 (m, 2H), 7.32-7.28 (m, 2H), 7.19 (tt, *J* = 6.6, 1.8 Hz, 4H), 6.77 (t, *J* = 7.8 Hz, 2H), 6.68 (d, *J* = 7.8 Hz, 4H), 4.60 (bs, 2H), 4.40 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.13, 137.44, 129.56, 129.51, 131.17, 118.21, 113.41, 46.55. HRMS calcd for $C_{20}H_{21}N_2$, 319.17047 $[M+H]^+$; Found 319.16957. Anal. Calcd for $C_{20}H_{20}N_2$: C, 83.30; H, 6.99; N, 9.71; Found: C, 83.32; H, 6.97; N, 9.72.

***N*,*N*',*N*''-Triphenyl-1,3,5-benzenetrimethanamine (39).** Starting from

trimesoyl chloride, the modified general procedure described above for **30a** provided the title compound **39** as a pale yellow solid in 80% yield (2 steps).

1,3,5-Benzenetricarboxamide (38) Starting from 1,3,5-Benzenetricarbonyl trichloride, **38** was obtained in quantitative yield as a white solid: ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.60 (s, 3H), 8.71 (s, 3H), 7.83 (t, J = 7.8 Hz, 6H), 7.40 (t, J = 7.8 Hz, 6H), 7.15 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.54, 138.94, 135.50, 129.79, 128.75, 124.00, 120.41. HRMS calcd for $C_{27}H_{22}N_3O_3$, 436.16612 $[M+H]^+$; Found 436.16254.

39: mp 113-115 °C; R_f = 0.74 (Hexane/ethyl acetate, 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31(s, 3H); 7.20-7.16 (m, 6H), 6.74 (tt, J = 7.2, 0.8 Hz, 3H), 6.65-6.61 (m, 6H), 4.32 (s, 6H), 4.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ148.24, 140.60, 129.44, 125.66, 117.84, 113.10, 48.42. *m/z* (EI^+) calcd for $C_{27}H_{27}N_3$ 393.5; Found 393.5. Anal. Calcd for $C_{27}H_{27}N_3$: C, 82.41; H, 6.92; N, 10.68; Found: C, 81.99; H, 6.86; N, 10.40.

α,α'-Ddimethyl-*N*,*N*'-diphenyl-1,4-benzenedimethanamine (40a). Starting from 1,4-diacetylbenzene (648.8 mg, 4.0 mmol), aniline (0.77 mL, 8.4 mmol) and sodium triacetoxyborohydride (2.54 g, 12.0 mmol) with HOAc (0.46 mL, 8.0 mmol), the modified general procedure A delivered **40a** (238.5 mg, 19%) as a pale white solid: R_f = 0.44 (Hexane/ethyl acetate, 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (s, 4H), 7.11 (t, J = 7.8 Hz, 4H), 6.68-6.64 (m, 2H), 6.54-6.50 (m, 4H); 4.49-4.47 (m, 2H), 4.01 (s, 2H), 1.52 (s, 3H), 1.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.51, 143.93, 143.96, 129.30, 126.35, 117.36, 117.35, 113.43, 53.31, 53.29, 25.01,

24.91. HRMS calcd for $C_{22}H_{25}N_2$, 317.20177 $[M+H]^+$; Found 317.20095. Anal. Calcd for $C_{22}H_{24}N_2$: C, 83.50; H, 7.64; N, 8.85; Found: C, 83.05; H, 7.72; N, 8.68. The analytical data are in agreement with those reported in the literature.[57]

***N*,*N*'-Dimethyl-*N*,*N*'-diphenyl-1,4-benzenedimethanamine (40b).** Starting from 1,4-benzenedialdehyde (536.0 mg, 4.0 mmol), *N*-methyl-benzenenamine (0.91 mL, 8.4 mmol) and sodium triacetoxyborohydride (2.54 g, 12.0 mmol), general procedure A delivered the title compound **40b** (1.18 g, 93%) as a pale white solid: mp 75-76 ^oC; R_f = 0.69 (Hexane/ethyl acetate, 4/1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.26-7.22 (m, 4H), 7.19 (s, 4H), 6.77-6.74 (m, 6H), 4.53 (s, 4H), 3.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.90, 137.83, 129.35, 127.16, 116.69, 112.52, 56.53, 38.69. HRMS calcd for $C_{22}H_{25}N_2$, 317.20177 $[M+H]^+$; Found 317.20085. Anal. Calcd for $C_{22}H_{24}N_2$: C, 83.50; H, 7.64; N, 8.85; Found: C, 83.36; H, 7.63; N, 8.87.

***N*,*N*'-Bis[2-(phenylamino)ethyl]-1,4-benzenedimethanamine (40c).** The title compound was prepared according to general procedure A as a pale white solid in 56% yield: mp 42-43 ^oC; R_f = 0.66 (3:1, CH_2Cl_2 /MeOH); ^1H NMR (600 MHz, $CDCl_3$) δ 7.29 (s, 4H), 7.18 (t, *J* = 5.2 Hz, 4H), 6.71 (t, *J* = 4.8 Hz, 2H), 6.64 (d, *J* = 6 Hz, 4H), 4.12 (bs, 2H), 3.81 (s, 4H), 3.23 (t, *J* = 3.6 Hz, 4H), 2.91 (t, *J* = 3.6 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.64; 139.18; 129.38; 131.36; 117.53; 113.13; 53.49; 48.17; 43.65. HRMS calcd for $C_{24}H_{31}N_4$, 375.25487 $[M+H]^+$; Found 375.25391.

***N*,*N*'-Bis(phenylmethyl)-1,4-benzenedimethanamine (40d).** Starting from

1,4-benzenedialdehyde (536.0 mg, 4.0 mmol), benzenemethanamine (0.92 mL, 8.4 mmol) and sodium triacetoxyborohydride (2.54 g, 12.0 mmol), general procedure A delivered the title compound **40d** (852.8 mg, 67%) as a pale yellow solid: R_f = 0.69 (ethyl acetate with 2% NH_4OH); ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.34-7.30 (m, 8H); 7.31 (s, 4H); 7.22 (tt, *J* = 7.2, 1.2 Hz, 2H), 3.66 (s, 4H), 3.65 (s, 4H), 2.53 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 140.44, 139.12, 131.49, 131.33, 131.26, 127.04, 53.24, 53.00. HRMS calcd for $C_{22}H_{25}N_2$, 317.20177 $[M+H]^+$; Found 317.20083. Anal. Calcd for $C_{22}H_{24}N_2$: C, 83.50; H, 7.64; N, 8.85; Found: C, 83.49; H, 7.72; N, 8.80. The analytical data are in agreement with those reported in the literature.[58]

***N*,*N*'-Bis(4-cyanylphenyl)-1,4-benzenedimethanamine (41a).** The title compound was prepared according to general procedure A as a pale white solid in 57% yield: mp 214-217 ^{o}C; R_f = 0.25 (Hexane/ethyl acetate, 1/1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.42 (d, *J* = 9.2 Hz, 4H), 7.29 (s, 4H), 7.26 (t, *J* = 6.0 Hz, 2H), 6.63 (d, *J* = 9.2 Hz, 4H); 4.30 (d, *J* = 6.0 Hz, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.04, 137.68, 133.31, 127.31, 120.54, 112.22, 95.88, 45.41. *m/z* (EI^+) calcd for $C_{22}H_{18}N_4$, 338.4; Found 338.5 M^+. Anal. Calcd for $C_{22}H_{18}N_4$: C, 78.08; H, 5.36; N, 16.56; Found: C, 77.84; H, 5.38; N, 16.17.

***N*,*N*'-Bis(4-nitrophenyl)-1,4-benzenedimethanamine (41b).** The title compound was prepared according to general procedure A as a yellow solid in 62% yield: R_f = 0.24 (Hexane/ethyl acetate, 1/1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 (d, *J* = 9.2 Hz, 4H), 7.88 (t, *J* = 5.6 Hz, 2H), 7.33 (s, 4H), 6.66 (d, *J* = 9.2 Hz, 4H), 4.39 (d, *J* = 5.6 Hz, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.40, 137.42,

135.86, 127.42, 126.14, 45.50. HRMS calcd for $C_{20}H_{19}N_4O_4$, 379.14063 $[M+H]^+$; Found 379.13980. Anal. Calcd for $C_{20}H_{18}N_4O_4$: C, 63.48; H, 4.79; N, 14.81; Found: C, 63.53; H, 4.91; N, 14.76.

***N*,*N*'-Bis(3-fuorophenyl)-1,4-benzenedimethanamine (41g)**. The title compound was prepared according to general procedure A as a white solid in 62% yield: mp 89-90 ^oC; R_f = 0.35 (Hexane/ethyl acetate, 4/1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 4H), 7.10 (q, *J* = 8.4 Hz, 2H), 6.44-6.39 (m, 4H), 6.32 (dt, *J* = 11.6, 2.4 Hz, 2H), 4.32 (s, 4H), 4.20 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.30 (d, *J* = 241.3 Hz), 149.98 (d, *J* = 11.3 Hz), 138.24, 130.51 (d, *J* = 10.6 Hz), 131.01, 108.94 (d, *J* = 2.3 Hz), 104.22 (d, *J* = 21.2 Hz), 99.74 (d, *J* = 25.0 Hz), 48.06; HRMS calcd for $C_{20}H_{19}N_2F_2$, 325.15163 $[M+H]^+$; Found 325,15076. Anal. Calcd for $C_{20}H_{18}N_2F_2$: C, 74.06; H, 5.59; N, 8.64; Found: C, 73.96; H, 5.60; N, 8.56.

***N*,*N*'-Bis(3-nitrophenyl)-1,4-benzenedimethanamine (41h)**. The title compound was prepared according to general procedure A as a yellow solid in 55% yield: mp 210-211 ^oC; R_f = 0.52 (Hexane/ethyl acetate, 1/1). ^1H NMR (400 MHz, DMSO-d_6) δ 7.34-7.26 (m, 10H), 7.00-6.95 (m, 4H), 4.32 (d, *J* = 6.0 Hz, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 149.65, 148.76, 137.78, 129.95, 127.36, 118.45, 109.95, 105.57, 45.91. HRMS calcd for $C_{20}H_{19}N_4O_4$, 379.14063 $[M+H]^+$; Found 379.13964. Anal. calcd for $C_{20}H_{18}N_4O_4$: C, 63.48; H, 4.79; N, 14.81; Found: C, 63.46; H, 4.83; N, 14.77.

***N*,*N*'-Bis(3-methoxyphenyl)-1,4-benzenedimethanamine (41i)**. Starting with terephthaldicarboxaldehyde (268 mg, 2.0 mmol) and *m*-anisidine (517.3 mg,

4.2 mmol) by treating with sodium triacetoxyborohydride (1271.6 mg, 5.0 mmol), general procedure A afford **41i** (597.1 mg, 94%) as a white solid: mp 80-82 ^{o}C; R_f = 0.48 (Hexane/ethyl acetate, 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 4H), 7.09 (d, *J* = 8.0 Hz, 2H), 6.32-6.26 (m, 4H), 6.20 (d, *J* = 2.4 Hz, 2H), 4.32 (s, 4H), 4.12 (bs, 2H), 3.76 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.99, 149.66, 138.55, 130.19, 127.99, 106.19, 102.84, 99.07, 55.25, 48.19. HRMS calcd for $C_{22}H_{25}N_2O_2$, 349.19160 $[M+H]^+$; Found 349.19073. Anal. Calcd for $C_{22}H_{24}N_2O_2$: C, 75.83; H, 6.94; N, 8.04; Found: C, 75.79; H, 6.93; N, 8.02.

***N*,*N*'-Bis(2-fuorophenyl)-1,4-benzenedimethanamine (41k).** The title compound was prepared according to general procedure A as a white solid in 44% yield: mp 97-99 ^{o}C; R_f = 0.58 (Hexane/ethyl acetate, 4/1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 (s, 4H), 7.02-6.97 (m, 4H), 6.71-6.64 (m, 4H), 4.45 (bs, 2H), 4.38 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.75 (d, *J* = 236.7 Hz), 138.26, 136.59 (d, *J* = 11.4 Hz), 127.96, 124.79 (d, *J* = 3.1 Hz), 117.16 (d, *J* = 6.8 Hz), 114.62 (d, *J* = 18.2 Hz), 112.58, 47.79; HRMS calcd for $C_{20}H_{19}N_2F_2$, 325.15163 $[M+H]^+$; Found 325.15075. Anal. Calcd for $C_{20}H_{18}N_2F_2$: C, 74.06; H, 5.59; N, 8.64; Found: C, 74.06; H, 5.62; N, 8.54.

***N*,*N*'-Bis(2-methoxyphenyl)-1,4-benzenedimethanamine (41l).** The title compound was prepared according to general procedure C as a white solid in 59% yield: mp 109-111 ^{o}C; R_f = 0.66 (Hexane/ethyl acetate, 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (s, 4H), 6.87-6.79 (m, 4H), 6.70 (td, *J* = 8.0, 1.2 Hz, 2H), 6.62 (dd, *J* = 8.0, 1.6 Hz, 2H), 4.70 (bs, 2H), 4.35 (s, 4H), 3.86 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.97, 138.66, 138.31, 127.97, 121.45, 116.83, 110.24, 109.56,

55.58, 47.95. HRMS calcd for $C_{22}H_{25}N_2O_2$, 349.19160 $[M+H]^+$; Found 349.19059. Anal. Calcd for $C_{22}H_{24}N_2O_2$: C, 75.83; H, 6.94; N, 8.04; Found: C, 75.77; H, 6.96; N, 7.97.

***N,N'*-(1,4-phenylenebis(methylene))bis(1-(pyridin-3-yl)methanamine) dihydrochloride (42).** A mixture of 1,4-diacetylbenzene (536 mg, 4.0 mmol), and 4-(aminomethyl)pyridine (908.4 mg, 8.4 mmol) in dry in 1,2-dichloethane (20 mL) was treated with sodium triacetoxyborohydride (2543.3 mg, 12 mmol) at room temperature. After being stirred for 12 h, the reaction mixture was quenched by adding aqueous NaOH (10%), extracted with ethyl acetate (3 x 20 mL). The combined organics were washed by brine and dried over anhydrous $MgSO_4$, concentrated under reduced pressure to give residue as a brown oil. The oil residue was dissolved in sat. methanolic hydrochloride. The addition of diethyl ether precipitate white solid, which was collected and recrystallized in methanol and diethyl ether to give **42** (0.793 g, 51%) as a white solid: mp 318-320 ^oC; ^1H NMR (600 MHz, D_2O) δ 8.62-8.59 (m, 3H), 7.99 (dt, *J* = 7.8, 1.8, 1.8 Hz, 2H), 7.57-7.54 (m, 6H), 4.39 (s, 4H), 4.37(s, 4H); ^{13}C NMR (100 MHz, D_2O) δ 149.85, 149.82, 139.26, 132.13, 130.81, 127.48, 124.83, 50.48, 48.15; Anal. Calcd for $C_{20}H_{24}Cl_2N_4 \cdot 0.3CH_3OH$: C, 60.81; H, 6.33; N, 13.97; Found: C, 60.45; H, 6.17; N, 13.89.

***N,N'*-(1,4-phenylenebis(methylene))bis(1-(pyridin-2-yl)methanamine) tetrahydrochloride (43).** The title compound was prepared from 1,4-diacetylbenzene (536 mg, 4.0 mmol), and 4-(aminomethyl)pyridine (908.2 mg, 8.4 mmol) by treating with $NaBH(OAc)_3$ (2.543 g, 12.0 mmol) in accordance with

procedure described above for **42** as a white solid (1.3364 g, 72%): mp 236-238 ^{o}C; ^{1}H NMR (400 MHz, D_2O) δ 8.76 (d, *J* = 4.8 Hz, 2H), 8.35 (dt, *J* = 6.8, 6.8, 1.2 Hz, 2H), 7.92-7.84 (m, 4H), 7.60 (s, 4H), 4.62 (s, 4H), 4.47(s, 4H); ^{13}C NMR (100 MHz, D_2O) δ 146.12, 145.53, 144.95, 131.84, 131.07, 127.47, 127.26, 51.18, 47.92; Anal. Calcd for $C_{20}H_{26}Cl_4N_4 \cdot 0.5CH_3OH \cdot 0.5H2O$: C, 50.32; H, 5.97; N, 11.45; Found: C, 50.53; H, 6.08; N, 11.42.

***N,N'*-(1,4-phenylenebis(methylene))bis(1-(pyridin-4-yl)methanamine) tetrahydrochloride (44).** The title compound was prepared from 1,4-diacetylbenzene (536 mg, 4.0 mmol), and 4-(aminomethyl)pyridine (908.2 mg, 8.4 mmol) by treating with $NaBH(OAc)_3$ (2543.3 mg, 12.0 mmol) in accordance with procedure described above for **42** as a white solid (1.8186 g, 98%): mp 244-246 ^{o}C (dec.); ^{1}H NMR (400 MHz, D_2O) δ 8.88-8.86 (m, 4H), 8.13 (d, *J*=7.2 Hz, 4H), 7.63 (s, 4H), 4.66 (s, 4H), 4.48(s, 4H); ^{13}C NMR (100 MHz, D_2O) δ 151.21, 142.45, 131.84, 131.18, 127.47, 51.35, 49.03; Anal. Calcd for $C_{20}H_{26}Cl_4N_4 \cdot 0.7H2O$: C, 50.37; H, 5.79; N, 11.75; Found: C, 50.57; H, 5.77; N, 11.55.

***N,N'*-(1,4-phenylenebis(methylene))diquinolin-8-amine (45). General procedure B:** A mixture of terephthaldicarboxaldehyde (134 mg, 1.0 mmol) and 8-amino-quinolin (302.8 mg, 2.1 mmol) in 1,2-dichloroethane (20 mL) was stirred for 5 min, following the addition of HOAc (0.12 mL, 2.0 mmol). After being stirred overnight, the reaction was quenched by aqueous NaOH (10%), and diluted with ethyl acetate (30 mL). After separation, the organics were washed with brine, and the aqueous phase was further extracted with ethyl acetate (2 x 10 mL). The

combined organics were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resultant residue was purified by flash column chromatography (Hexane/ethyl acetate, 2/1 with 0.5% NH_4OH) to afford **45** (302.4 mg, 77%) as a yellow solid: mp 163-166^oC; R_f**=** 0.67 (Hexane/ethyl acetate, 2/1); ^1H NMR (600 MHz, $CDCl_3$) δ 8.73 (dd, *J*=3.6, 1.2 Hz, 2H); 8.08(dd, *J*=7.8, 1.2 Hz, 2H), 7.43(s, 4H); 7.37(m, 4H); 7.07(d, *J*=7.8 Hz, 2H,); 6.67(d, *J*=7.8 Hz, 2H); 6.6(t, *J*=5.4 Hz, 2H); 4.57(d, *J*=5.4 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.14, 144.77, 138.43, 138.36, 136.23, 128.84, 127.98, 127.94, 121.63, 114.36, 105.32, 47.67. HRMS calcd for $C_{26}H_{23}N_4$ 391.19227 $[M+H]^+$, found 391.19121; Anal. Calcd for $C_{26}H_{22}N_4 \cdot 0.3CH_3CO_2CH_2CH_3$: C, 78.36; H, 5.90; N, 14.44. Found: C, 77.97, 5.61, 13.84

***N,N'*-(1,4-phenylenebis(methylene))diisoquinolin-1-amine (46).** Starting from terephthaldicarboxaldehyde (335 mg, 2.5 mmol) and 8-amino-quinoline (760.2 mg, 5.25 mmol), general procedure B afforded **46** (526.1 mg, 54%) as a pale yellow solid: mp. 152-155 ^oC; R_f= 0.25 (Hexanes/ethyl acetate, 1/1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 6.0 Hz, 2H); 7.78 (d, *J* = 8.0 Hz, 2H); 7.70 (d, *J* = 8.0 Hz, 2H); 7.60 (td, *J* = 7.6, 7.6, 1.6 Hz, 2H); 7.45 (td, *J* = 7.6, 1.6, 1.6 Hz, 2H); 7.424 (s, 4H); 6.98 (d, *J* = 5.2 Hz, 2H); 5.57 (bs, 2H); 4.81 (d, *J* = 5.2 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.96, 141.33, 138.71, 137.26, 130.03, 128.59, 127.42, 126.22, 121.69, 118.28, 111.49, 45.90. HRMS Calcd for $C_{26}H_{23}N_4$ 391.19227 $[M+H]^+$, found 391.19127. Anal. Calcd for $C_{26}H_{22}N_4 \cdot 0.3CH_3CO_2Et$: C, 78.36; H, 5.90; N, 13.44. Found: C, 77.97; H, 5.65; N, 13.32.

***N*,*N*'-Di-2-pyridinyl-1,4-benzenedimethanamine 47.** Starting from 1,4-benzenedialdehyde (2.68 g, 20.0 mmol) and 2-aminopyridine (3.95 g, 42.0 mmol), the crude obtained from general procedure B was purified by recrystallization in ethyl acetate to give product **47** (3.25 g, 56%) as white crystalline: mp192-194 ^{o}C; R_f = 0.37 (Ethyl acetate); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (dd, J = 5.2, 0.8 Hz, 2H), 7.34 (ddd, J = 8.4, 6.8, 2.0 Hz, 2H), 7.25 (s, 4H), 6.96 (t, J = 6.0 Hz, 2H), 6.47-4.43 (m, 4H), 4.42 (d, J = 6.0 Hz, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.66, 147.53, 138.84, 136.60, 127.11, 111.67, 108.11, 43.92; HRMS Calcd for $C_{18}H_{19}N_4$ 291.16097 $[M+H]^+$, found 291.15997; Anal. Calcd for $C_{18}H_{18}N_4$: C, 74.46, H, 6.25, N, 19.30; Found: C, 74.25, H, 6.18, N, 18.98. The analytical data are in agreement with those reported in the literature.[41, 42]

***N*,*N*'-Di-3-pyridinyl-1,4-benzenedimethanamine (48).** Starting with 1,4-diacetylbenzene (670 mg, 5.0 mmol), and 3-aminopyridine (988.3 mg, 10.5 mmol) by treatment with sodium triacetoxyborohydride (3179.1 mg, 15.0 mmol), the crude residue obtained according to general procedure B was purified by recrystallization from hot methanol to afford **48** (631.6 mg, 44%) as a white solid: mp 255-256 ^{o}C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.96 (d, J = 3.0 Hz, 2H), 7.26 (dd, J = 4.8, 0.8 Hz, 2H) 7.32 (s, 4H), 7.02 (dd, J = 4.2, 4.2 Hz, 2H), 6.86 (ddd, J =7.8, 1.2, 1.2 Hz, 2H), 6.46 (t, J = 6.0 Hz, 2H), 4.25(d, J = 6.0 Hz, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 145.30, 138.79, 137.57, 136.17, 128.00, 124.21, 118.39, 46.42. HRMS Calcd for $C_{18}H_{19}N_4$ 291.16097 $[M+H]^+$, found 291.15989. Anal. Calcd for $C_{18}H_{18}N_4$: C, 74.46; H, 6.25; N, 19.30. Found: C, 74.42; H, 6.29; N, 19.09.

***N*,*N*'-Di-2-pyridinyl-1,3-benzenedimethanamine (49).** Starting with

1,3-diacetylbenzene (536 mg, 4.0 mmol), and 3-aminopyridine (790.6 mg, 8.4 mmol) by treatment with sodium triacetoxyborohydride (2.539 g, 12.0 mmol), general procedure B afforded **49** (904.9 mg, 78%) as a white solid. mp 125-126 ^{o}C; R_f= 0.66 (CH_2Cl_2/MeOH, 4/1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10 (d, *J*=4.8 Hz, 2H); 7.40 (tt, *J*=6.0 Hz, 1.8Hz, 2H); 7.37 (1H, s); 7.31 (2H, m); 7.28(1H, s); 6.60 (t, *J*=6.0 Hz, 2H); 6.36 (d, *J* = 8.4 Hz, 2H); 4.89 (t, *J* = 6.0 Hz, 2H); 4.50 (d, *J* = 6.0 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.77, 148.44, 139.91, 137.67, 129.16, 126.64, 126.52, 113.42, 107.08, 46.42; HRMS Calcd for $C_{18}H_{19}N_4$ 291.16097 $[M+H]^+$, found 291.15997. Anal. Calcd for $C_{18}H_{18}N_4$: C, 74.46; H, 6.25; N, 19.30. Found C, 74.36; H, 6.25; N, 19.09.

***N,N′*-(1,4-phenylenebis(methylene))bis(5-fluoropyridin-2-amine) (51)**. Starting with terephthaldicarboxaldehyde (268 mg, 2.0 mmol) and 5-fluoropyridin-2-amine (448 mg, 4.0 mmol) by treating with sodium triacetoxyborohydride (1.272 g, 6.0 mmol), general procedure B delivered product **51** (397 mg, 61%) as a white solid: mp 163-165 ^{o}C; R_f= 0.47 (Hexanes/ethyl acetate, 1/1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90 (d, *J* = 3.0 Hz, 2H), 7.33 (dt, *J* = 8.8, 8.8, 3.1 Hz, 2H), 7.24 (s, 4H), 7.01 (t, *J* = 5.9, 5.9 Hz, 2H), 6.51 (dd, *J* = 9.2, 3.6 Hz, 2H), 4.38 (d, *J* = 6.0 Hz, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.69, 152.47 (d, *J* = 236.7 Hz), 138.70, 133.42 (d, *J* = 23.6 Hz), 125.03 (d, *J* = 21.2 Hz), 108.78 (d, *J* = 4.1 Hz), 44.40; HRMS Calcd for $C_{18}H_{17}F_2N_4$ 327.14213 $[M+H]^+$, found 327.14117; Anal. Calcd for $C_{18}H_{16}F_2N_4$: C, 66.25; H, 4.94; N, 17.17. Found: C, 77.31; H, 4.96; N, 17.00.

***N,N′*-(1,4-phenylenebis(methylene))bis(6-fluoropyridin-2-amine) (52).**

Starting from terephthaldicarboxaldehyde (268 mg, 2.0 mmol) and 6-fluoro-2-aminopyridine (471 mg, 4.2 mmol) by treatment with sodium triacetoxyborohydride (1.272 g, 6.0 mmol), general procedure B furnished product **52** (418.3 mg, 64%) as a white solid: mp 182-185 ^{o}C; R_f= 0.68 (Hexane/ethyl acetate, 1/1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.48 (dd, J = 16.8, 7.9 Hz, 2H), 7.43 (t, J = 6.0, 6.0 Hz, 2H), 7.26 (s, 4H), 6.35 (dd, J = 8.1, 2.4 Hz, 2H), 6.08 (dd, J = 7.6, 2.2 Hz, 2H), 4.37 (d, J = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.79 (d, J = 232.2 Hz), 158.23 (d, J = 17.1 Hz), 141.43 (d, J = 8.5 Hz), 138.30, 127.26, 104.49, 93.56 (d, J = 36.9 Hz), 43.96; HRMS Calcd for $C_{18}H_{17}F_2N_4$ 327.14213 $[M+H]^+$, found 327.14156. Anal. Calcd for $C_{18}H_{16}F_2N_4$: C, 66.25; H, 4.94; N, 17.17. Found: C, 65.91; H,5.01; N, 16.82.

***N*,*N*'-Di-2-pyrimidinyl-1,4-benzenedimethanamine (53) and alcohol 55.** In a 500 mL one-necked round-bottomed flask equipped with a stirrer, terephthaldicarboxaldehyde (5.36 g, 40 mmol), 2-amino-pyrimidine (7.82 g, 82 mmol), acetic acid (4.7 mL, 80 mmol) were mixed in 1,2-dichloroethane (250 mL). After being stirred at room temperature until 2-amino-pyrimidine completely dissolved (approximately 10 minutes), 4Å molecular sieves (20 g) were added to the mixture. After being stirred for 10 min, the resulting mixture was treated with sodium triacetoxyborohydride (25.43 g, 120 mmol). After stirred for 24 hours at room under an argon atmosphere, the solvent was removed under reduced pressure. The resulting residue was washed by hot water and hot methanol consecutively. The hot water phase was extracted by ethyl acetate which combined with the methanol phase. The solvent was removed to get the crude **55**

which was purified by column chromatography (Ethyl acetate) to give alcohol **55** as a white solid (2.98g, 35%): mp 120-121 ^{o}C; R_f =0.46 (Ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$,) δ 8.30 (d, *J* = 4.8 Hz, 2H),7.35 (s, 4H), 6.57 (t, *J*=4.8 Hz, 1H), 5.42 (bs, 1H), 4.69 (d, *J*=5.6 Hz, 2H), 4.64 (d, *J*=5.6 Hz, 2H), 1.83 (t, *J*=5.6 Hz, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.27, 157.93, 140.71, 138.75, 126.74, 126.36, 110.14, 62.73, 43.65; HRMS Calcd for $C_{12}H_{14}N_3O$ 216.11369 $[M+H]^+$, found 216.11284.

The solid residue from washing by hot water and hot methanol dissolves in acetic acid and the insoluble molecular sieves were filtered off. The resulting acetic acid solution was concentrated to give white solid, which was neutralized by 10% aqueous NaOH and extracted by ethyl acetate, dried by MgSO4, then the solvent was removed to give pure **53** as white solid (2.92g, 25%): mp 211-213 ^{o}C; R_f =0.32 (Ethyl acetate); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (d, *J* = 4.7 Hz, 4H); 7.65 (t, *J* = 6.3, 6.3 Hz, 2H); 7.21 (s, 4H); 6.54 (t, *J* = 4.7, 4.7 Hz, 2H); 4.43 (d, *J* = 6.4 Hz, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.26, 157.95, 138.59, 126.86, 110.15, 43.62; HRMS calcd for $C_{16}H_{17}N_6$ 293.15147 $[M+H]^+$, found 293.15046; Anal. Calcd for $C_{16}H_{16}N_6$: C, 65.74; H, 5.52; N, 28.75. Found: C, 65.43; H, 5.47; N, 28.73.

A water soluble salt form of compound **53** was prepared by the following procedure. To a solution of methanesulfonic acid (10.0 mL) in methanol (10.0 mL), compound **53** (818.6 mg, 2.8 mmol) was added carefully at 0 ^{o}C. After stirred for 30 min at 0 ^{o}C, diethyl ether was added dropwise to give a white precipitate. The resulting mixture was put in the refrigerator (-7 ^{o}C) for 2-4 h, at which point the

white precipitate was collected and dried to give the product WZ811Ms (1.59g, 98%) as a pale white solid: mp 198-201 ^{o}C; 1H NMR (400 MHz, CDCl3) δ 8.53 (bs, 4H), 7.38 (s, 4H), 7.02 (t, J = 5.2 Hz, 2H), 4.72 (s, 4H), 2.77 (s, 7.5H); 13C NMR (100 MHz, CDCl3) δ 154.07, 136.01, 127.73, 110.24, 44.45, 38.51; Anal. Calcd for $C_{16}H_{16}N_6 \cdot 2.5CH_3SO_3H$: C, 41.72; H, 4.92; N, 15.78. Found: C, 41.33; H, 4.91; N, 15.57.

2,2'-(1,4-phenylenebis(methylene))bis(azanediyl)dipyrimidine 1-oxide (54). To a solution of **54** (29.2 mg, 0.1 mmol) in 3 mL acetone was added *m*-chloroperoxybenzoic acid (70%, 74 mg, 0.3 mmol) at room temperature. After stirring for 24 h at room temperature, the mixture was treated with water until precipitation was complete. The white precipitate was collected and washed by cold acetone to give the product **54** (25.6 mg, 77%):mp 242-245 ^{o}C (dec.); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (t, *J* = 6.8 Hz, 2H), 8.40 (dd, *J* = 6.4, 1.6 Hz, 2H), 7.86 (dd, *J* = 4.8, 1.6 Hz, 2H), 7.24 (s, 4H), 6.68-6.70 (m, 2H), 4.54 (d, *J* = 6.8 Hz, 4H); ^{13}C NMR (100 MHz,DMSO-d_6) δ 153.7, 144.16, 142.25, 137.80, 127.08, 108.91, 43.37; HRMS Calcd for $C_{16}H_{18}N_6O_2$ 326.14912 $[M+H]^+$, found 325.14095. Anal. Calcd for $C_{16}H_{17}N_6O_2$: C, 59.25; H, 4.97; N, 25.91. Found: C, 59.01; H,5.01; N, 25.30.

***N,N'*-(1,4-phenylenebis(methylene))bis(5-fluoropyrimidin-2-amine) (58).** A mixture of 2,4-dichloro-5-fluoropyrimidine (50.99 g, 300 mmol) and zinc granules (59 g, 900 mmol) in THF (250 mL) was heated to reflux with vigorous stirring. Glacial acid (17.4 mL, 300 mmol) was added dropwise over 1 h. The resultant mixture was refluxed for 5 h. After cooling down, the zinc residue was

filtered off, and the filtrate was concentrated under reduced pressure. The residue was dissolved in ethyl acetate, washed with $NaHCO_3$ and brine sequentially, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by distillation (90 ^oC/100 mbar) to afford 2-chloro-5-fluoropyrimidine **57** (31 g, 78%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 2H); ^{13}C NMR (100 MHz,$CDCl_3$) δ 157.29 (d, *J* = 264.9 Hz), 156.18 (d, *J* = 2.5 Hz), 147.66 (d, *J* = 22.0 Hz); F NMR (376 MHz, $CDCl_3$) δ -140.52. The analytical data are in agreement with those reported in the literature.[46]

A mixture of 2-chloro-5-fluoropyrimidine **57** (918 mg, 6.9 mmol), 1,4-phenylenedimethanamine (449 mg, 3.3 mmol) and cesium carbonate (2580 mg, 7.9 mmol) in DMF (25 mL) was stirred at 100 ^oC for overnight. After removing the solvent under reduced pressure, the yellow residue was washed with H2O and hot ethanol to give product **58** (650.5 mg, 60%) as pale yellow solid: 220-226 ^oC (dec.);R_f= 0.28 (Hexane/ethyl acetate, 1/1); ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 8.18 (s, 4H), 7.31(s, 4H), 5,38 (bs, 2H), 5.00 (s, 2H), 4.58 (d, *J* = 6.0 Hz, 4H); ^1H NMR (400 MHz, DMSO-d_6) δ 8.33 (s, 4H), 7.78 (t, *J* = 6.0 Hz, 2H), 7.21 (s, 4H), 4.41 (d, *J* = 6.0 Hz, 4H); ^{13}C NMR (100 MHz,DMSO-*d*6) δ 159.47, 151.60 (d, *J* = 242.8 Hz), 145.49, 138.44, 126.86, 44.24; HRMS Calcd for $C_{16}H_{15}F_2N_6$ 329.13263 $[M+H]^+$, found 329.13192; Anal. Calcd for $C_{16}H_{14}F_2N_6$: C, 58.53; H, 4.30; N, 25.60. Found: C, 58.22; H, 4.44; N, 25.47.

***N,N'*-(1,4-phenylenebis(methylene))bis(4,6-dichloro-1,3,5-triazin-2-amine) (60).** To a solution of cyanuric chloride (1.94 g, 10.5 mmol) in THF (70 mL) was added 1,4-phenylenedimethanamine (0.681 g, 5.0 mmol) at 0 ^oC in portionwise,

followed by an addition of $NaHCO_3$ (1.05 g, 12.5 mmol). After being stirred for overnight at 0 ^oC, the reaction mixture was warmed to room temperature and stirred for additional 2h. The solvent was removed under reduced pressure, and the white solid residue was sequentially washed with water and ethanol to afford pure WZ61 (2.04 g, 94%) as a white solid: mp>400 ^oC; ^1H NMR (400 MHz, DMSO-d_6) δ 9.61 (t, J = 6.1, 6.1 Hz, 2H), 7.27 (s, 4H), 4.50 (d, J = 6.2 Hz, 4H); ^{13}C NMR (150 MHz,DMSO-d_6) δ 169.51, 168.63, 165.46, 136.51, 127.45, 43.71. HRMS Calcd for $C_{14}H_{11}Cl_4N_8$ 430.98638 $[M+H]^+$, found 430.96623. Anal. Calcd for $C_{16}H_{17}N_6O_2$: C, 38.92; H, 2.33; N, 25.93. Found: C, 39.45; H, 2.87; N, 25.30.

Aldehyde 61. Oxidation of 55. Dess-Martin periodinane (5.24 g, 12.3 mmol) was added in solid to a solution of alcohol **55** (2.22 g, 10.3 mmol) in CH_2Cl_2 (50 mL) at 0 ^oC. After being stirred for 10 min, the reaction mixture was allowed to warm to room temperature and was stirred for another 1h. The reaction mixture was diluted with diethyl ether (100 mL) and quenched by saturated aqueous $NaHCO_3$. The organic phase was separated, and the aqueous phase was further extracted with diethyl ether (3 x 20 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified through flash column chromatography (Ethyl acetate) to furnish aldehyde **61** (2.07 g, 94%) as a white solid: mp 114-115 ^oC; R_f= 0.44 (Ethyl acetate); ^1H NMR (400 MHz, $CDCl_3$) δ 10.00 (s, 1H), 8.29 (d, J = 4.8 Hz, 2H), 7.85 (d, J = 8.2 Hz, 2H), 7.52 (d, J = 8.1 Hz, 2H), 6.60(t, J = 4.8, 4.8 Hz, 1H), 5.82 (bs, 1H), 4.75 (d, J = 6.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.13, 162.30, 158.35, 146.69, 135.69, 130.31, 127.86, 111.52, 45.25; HRMS Calcd for $C_{12}H_{12}N_3O$ 214.09804

$[M+H]^+$, found 214.09718.

***N*-(4-((phenylamino)methyl)benzyl)pyrimidin-2-amine (62a). General procedure C:** A mixture of aldehyde **61** (320 mg, 1.5 mmol) and aniline (147 mg, 1.6 mmol) in 1,2-dichloroethane (15 mL) was treated with sodium triacetoxyborohydride (477 mg, 2.25 mmol). After being stirred at room temperature for overnight, the reaction mixture was quenched by adding aqueous NaOH (1.0 N), extracted with ethylacetate (2 x 30 mL). The combined organic phases were washed by brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (Hexanes/ethyl acetate, 1/1) to afford product **62a** (410 mg, 94%) as a white solid: mp 131-132 ^oC; R_f= 0.36 (Ethyl acetate); ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 4.7 Hz, 2H), 7.34 (s, 4H), 7.21-7.15 (m, 2H), 6.72 (tt, *J* = 7.4, 7.4, 1.0, 1.0 Hz, 1H), 6.65-6.0 (m, 2H), 6.54 (t, *J* = 4.8, 4.8 Hz, 1H), 5.59 (s, 1H), 4.63 (d, *J* = 5.9 Hz, 2H), 4.32 (s, 2H), 4.04 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.48, 160.40, 158.33, 148.27, 138.66, 138.29, 129.47, 127.96, 117.77, 113.02, 111.12, 48.19, 45.31; HRMS Calcd for $C_{18}H_{19}N_4$ 291.16097, $[M+H]^+$ found 291.1033. Anal. Calcd for $C_{18}H_{18}N_4$: C, 74.46; H, 6.25; N, 19.30. Found: C, 74.12; H,6.28; N, 19.01.

***N*-(4-((2-fluorophenylamino)methyl)benzyl)pyrimidin-2-amine (62b).** Starting from aldehyde **61** (53.4 mg, 0.25 mmol) and 2-fluoroaniline (29.2 mg, 0.26 mmol), general procedure C gave **62b** (44.2 mg, 57%) as a white solid: mp 126-128 ^oC; R_f= 0.5 (Ethyl acetate); ^1H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 4.8 Hz, 2H), 7.35 (s, 4H), 7.01-6.94 (m, 2H), 6.69-6.61 (m, 2H), 6.57 (t, *J* = 4.8, 4.8 Hz,

1H), 5.52 (bs, 1H), 4.65 (d, *J* = 6.0 Hz, 2H), 4.36 (s, 2H), 4.32 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ162.47, 158.26, 151.68 (d, *J* = 237.5 Hz), 138.58 (d, *J* = 32.6 Hz), 136.75, 136.64, 128.02, 127.81, 124.76 (d, *J* = 3.0 Hz), 116.98 (d, *J* = 6.8 Hz), 114.55 (d, *J* = 18.2 Hz), 112.44 (d, *J* = 3.8 Hz), 110.98, 47.70, 45.29; HRMS Calcd for $C_{18}H_{18}FN_4$ 309.15155 $[M+H]^+$, found 309.15050. Anal. Calcd for $C_{18}H_{17}FN_4$: C, 70.11; H, 5.56; N, 18.17. Found: C, 74.12; H,6.28; N, 19.01.

***N*-(4-((pyridin-2-ylamino)methyl)benzyl)pyrimidin-2-amine (62c).** Starting from aldehyde **61** (426.6 mg, 2.0 mmol) and 2-aminopyridine (225.9 mg, 2.4 mmol) by treatment with sodium triacetoxyborohydride (635.8 mg, 3.0 mmol) and HOAc (0.13 mL, 2.2 mmol), general procedure C gave white solid, which was washed by methanol to afford **62c** (354.4 mg, 61%) as a white solid: mp 172-174 ^{o}C; R_f= 0.5 (Ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 4.8 Hz, 2H), 8.11 (d, *J* = 4.8 Hz, 1H), 7.43-7.39 (m, 1H), 7.34 (s, 4H), 6.62-6.58 (m, 1H), 6.57 (t, *J* = 4.8, 4.8 Hz, 1H), 6.37 (d, *J* = 8.4 Hz, 1H), 5.41 (bs, 1H), 4.88 (bs, 1H), 4.64 (d, *J* = 6.0 Hz, 2H), 4.50 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.48, 158.65, 158.33, 148.05, 138.36, 138.29, 137.90, 127.96, 127.86, 113.37, 111.14, 107.11, 46.24, 45.30; HRMS Calcd for $C_{17}H_{18}N_5$ 292.15622 $[M+H]^+$, found 292.15518. Anal. Calcd for $C_{17}H_{17}N_5$: C, 70.08; H, 5.88; N, 24.04. Found: C, 70.02; H, 5.82; N, 23.89.

***N*-(4-((5-fluoropyridin-2-ylamino)methyl)benzyl)pyrimidin-2-amine (62d).** Starting from aldehyde **61** (213.3 mg, 1.0 mmol) and 5-fluoro-2-aminopyridin (112.11 mg, 1.0 mmol) by treatment with sodium triacetoxyborohydride (318 mg, 1.5 mmol) and HOAc (0.06 mL, 1.0 mmol), general procedure C gave **62d** (277.8

mg, 90%) as a white solid: mp 167-169 °C; R_f= 0.4 (Ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 4.8 Hz, 2H), 7.96 (d, *J* = 2.8 Hz, 1H), 7.33 (s, 4H), 7.21-7.16 (m, 1H), 6.57 (t, *J* = 4.8, 4.8 Hz, 1H), 6.32 (dd, *J* = 9.2, 3.2 Hz, 1H), 5.49 (bs, 1H), 4.85 (bs, 1H), 4.63 (d, *J* = 6.0 Hz, 2H), 4.46 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ162.43, 158.35, 155.44, 153.72 (d, *J* = 161 Hz), 138.32 (d, *J* = 19.3 Hz), 134.80 (d, *J* = 16.5 Hz), 127.96, 127.88, 125.61 (d, *J* = 13.7 Hz), 111.19, 107.40 (d, *J* = 2.8 Hz), 46.73, 45.30; HRMS Calcd for $C_{17}H_{17}FN_5$ 310.14680 $[M+H]^+$, found 310.14588. Anal. Calcd for $C_{17}H_{16}FN_5$: C, 66.01; H, 5.21; N, 22.64. Found: C, 65.66; H, 5.21; N, 22.34.

***N*-(4-((6-fluoropyridin-2-ylamino)methyl)benzyl)pyrimidin-2-amine (62e).** Starting from aldehyde **61** (426.6 mg, 2.0 mmol) and 6-fluoro-2-aminopyridine (246.6 mg, 2.4 mmol) by treatment with sodium triacetoxyborohydride (635.6 mg, 3.0 mmol) and HOAc (0.12 mL, 2.2 mmol), general procedure C gave **62e** (455.3 mg, 73%) as a white solid: mp 170-171 °C; R_f= 73 (Ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 4.4 Hz, 2H), 7.66 (t, *J* = 6.2 Hz, 1H), 7.51-7.40 (m, 2H), 7.24 (s, 4H), 6.55 (t, *J* = 4.8 Hz, 1H), 6.34 (dd, *J* = 8.0, 2.4 Hz, 1H), 6.08 (dd, *J* = 8.0, 2.8 Hz, 1H), 4.45 (d, *J* = 6.4 Hz, 2H), 4.35 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.77 (d, *J* = 230.6 Hz), 162.26, 158.22 (d, *J* = 17.5 Hz), 157.96, 141.42 (d, *J* = 8.6 Hz), 138.88, 137.99, 127.14, 126.99, 110.17, 104.46, 93.52 (d, *J* = 36.4 Hz), 43.96, 43.62; HRMS Calcd for $C_{17}H_{18}FN_5$ 310.14680 $[M+H]^+$, found 310.14954; Anal. Calcd for $C_{17}H_{16}FN_5$: C, 66.01; H, 5.21; N, 22.64. Found: C, 65.88; H, 5.24; N, 22.38.

***N*-(4-((5-chloropyridin-2-ylamino)methyl)benzyl)pyrimidin-2-amine (62f).**

Starting from aldehyde **61** (213.3 mg, 1.0 mmol) and 5-chloro-2-aminopyridine (141.5 mg, 1.1 mmol) by treatment with sodium triacetoxyborohydride (318 mg, 1.5 mmol) and HOAc (0.06mL, 1.1 mmol), general procedure C gave **62f** (195.5 mg, 60%) as a white solid: mp 163-165 ^{o}C; R_f= 0.60 (Ethyl acetate); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (d, J = 4.8 Hz, 2H), 7.93 (d, J = 2.8 Hz, 1H), 7.66 (t, J = 6.4 Hz, 1H), 7.41 (dd, J = 8.8, 2.4 Hz, 1H), 7.25 (d, J = 6.0 Hz, 1H), 7.23 (s, 4H), 6.55 (t, J = 4.8, 4.8 Hz, 1H), 6.51 (d, J = 8.8 Hz, 1H), 4.44 (d, J = 6.4 Hz, 2H), 4.39 (d, J = 6.4 Hz, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.27, 158.00, 157.26, 145.46, 138.81, 138.29, 136.48, 127.12, 126.97, 117.43, 110.18, 109.61, 44.08, 43.63; HRMS Calcd for $C_{17}H_{17}ClN_5$ 326.11725 $[M+H]^+$, found 326.11638. Anal. Calcd for $C_{17}H_{16}ClN_5$: C, 62.67; H, 4.95; N, 21.50. Found: C, 62.53; H, 5.12; N, 21.27.

***N*-(4-((6-chloropyridin-2-ylamino)methyl)benzyl)pyrimidin-2-amine (62g).** Starting from aldehyde **61** (213.3 mg, 1.0 mmol) and 6-chloro-2-aminopyridine (141.5 mg, 1.1mmol) by treatment with sodium triacetoxyborohydride (318 mg, 1.5 mmol) and HOAc (0.064 mL, 1.1 mmol), general procedure C gave **62g** (195.5 mg, 60%) as a white solid: mp 148-151 ^{o}C; R_f= 0.25 (hexanes/ethyl acetate, 1/1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (d, J = 4.8 Hz, 2H), 7.67 (t, J = 6.0 Hz, 1H), 7.43 (t, J = 6.0 Hz, 1H), 7.37 (t, J = 7.6 Hz, 1H), 7.25 (s, 4H), 6.55 (t, J = 4.8 Hz, 1H), 6.49 (d, J = 7.2 Hz, 1H), 6.42 (d, J = 8.0 Hz, 1H), 4.46 (d, J = 6.4 Hz, 2H), 4.37 (d, J = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.26, 158.89, 157.97, 148.39, 139.59, 138.93, 137.89, 127.24, 126.99, 110.20, 110.17, 106.42, 43.99, 43.62; HRMS Calcd for $C_{17}H_{17}ClN_5$ 326.11725 $[M+H]^+$, found 326.11640; Anal. Calcd for $C_{17}H_{16}ClN_5$: C, 62.67; H, 4.95; N, 21.50. Found: C, 62.64; H, 4.97; N,

21.51.

***N*-(4-((pyridin-2-ylmethylamino)methyl)benzyl)pyrimidin-2-amine (62h).** Starting from aldehyde **61** (213.3 mg, 1.0 mmol) and 2-methanaminepyridine (113.5 mg, 1.05 mmol) by treatment with sodium triacetoxyborohydride (317.9 mg, 1.5 mmol) and HOAc (0.06 mL, 1.0 mmol), general procedure K gave **62h** (247.4 mg, 81%) as a yellow solid: R_f= 0.39 (CH_2Cl_2/MeOH, 6/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 4.2 Hz, 1H), 8.19 (s, 2H), 7.62 (dt, *J* = 7.7, 7.7, 1.8 Hz, 1H), 7.33-7.28 (m, 5H), 7.16-7.13 (m, 1H), 6.50 (t, *J* = 4.8, 4.8 Hz, 1H), 6.00 (t, *J* = 4.8, 4.8 Hz, 1H), 4.61 (d, *J* = 5.8 Hz, 2H), 3.91 (s, 2H), 3.82 (s, 2H), 2.27 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.44, 159.85, 158.20, 149.46, 139.33, 137.92, 136.85, 128.66, 127.77, 122.51, 122.10, 110.86, 54.61, 53.32, 45.34; HRMS Calcd for $C_{18}H_{20}N_5$ 306.17187 $[M+H]^+$, found 306.17078.

Preparation of compound 64b. To a solution of 1,3-benzenediamine (5.2 g, 48 mmol) and triethylamine (11.2 mL, 80 mmol) in THF (50 mL) was added a solution of *tert*-butoxycarbonyl anhydride (9.2 mL, 40 mmol) in THF (10 mL) via syringe pump at 0 ^{o}C over 5 h. The resultant mixture was warmed to room temperature and stirred overnight. The reaction mixture was quenched with saturated $NaHCO_3$ and diluted with ethyl acetate (30 mL). After separation, the aqueous phase was further extracted with ethyl acetate (2 x 20 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (Hexanes/ethyl acetate, 1/1) to afford **64b** (7.02 g, 75%) as a pale white solid: R_f= 0.45 (Hexanes/ethyl acetate, 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (t, *J* = 8.0,

8.0 Hz, 1H), 6.99 (s, 1H), 6.54 (ddd, *J* = 8.0, 2.1, 0.8 Hz, 1H), 6.37 (ddd, *J* = 8.0, 2.2, 0.9 Hz, 1H), 3.68 (s, 1H), 1.52 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.88, 147.45, 139.55, 129.87, 110.01, 108.74, 105.23, 80.55, 28.51; The analytical data are in agreement with those reported in the literature.[59]

Preparation of compound 64a. 1,2-Benzenediamine (5.2 g, 48 mmol) was converted to amine **64a** (8.55 g, 91%) according to the procedure described above for **64b** as a pale white solid: R_f= 0.4 (Hexanes/ethyl acetate, 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 7.7 Hz, 1H), 7.00 (dt, *J* = 7.7, 7.6, 1.5 Hz, 1H), 6.78 (ddd, *J* = 17.4, 7.8, 1.3 Hz, 2H), 6.38 (bs, 1H), 3.73 (bs, 2H), 1.52 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.04, 140.11, 126.24, 124.87, 119.66, 117.68, 80.61, 28.47; The analytical data are in agreement with those reported in the literature.[60]

Preparation of compound 64c. 1,4-Benzenediamine (5.2 g, 48 mmol) was converted to amine **64c** (7.55 g, 81%) according to the procedure described above for **64b** as a pale white solid: R_f= 0.46 (Hexanes/ethyl acetate, 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, *J* = 7.3 Hz, 2H), 6.64 (d, *J* = 8.7 Hz, 2H), 6.27 (bs, 1H), 3.54 (bs, 2H), 1.51 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.54, 142.54, 129.87, 121.08, 115.77, 80.17, 28.55; The analytical data are in agreement with those reported in the literature.[60]

Preparation of compound 65b. A mixture of **64b** (0.937 g, 4.0 mmol), 1,4-dibromobutane (1.3 g, 6.0 mmol) and triethylamine (3.36 mL, 24 mmol) in toluene (30 mL) was refluxed for 24 h. After cooling down, the mixture was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced

pressure. The residue was purified by flash column chromatography (Hexanes/ethyl acetate, 4/1) to afford **65b** (0.903 g, 86%) as a pale white solid: R_f= 0.56 (Hexanes/ethyl acetate, 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (t, *J* = 8.1, 8.1 Hz, 1H), 6.73 (s, 1H), 6.56 (d, *J* = 7.8 Hz, 1H), 6.44 (s, 1H), 6.27 (dd, *J* = 8.2, 1.9 Hz, 1H), 3.30-3.17 (m, 4H), 2.00-1.97 (m, 4H), 1.53 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.94, 148.81, 139.47, 129.64, 106.89, 105.89, 101.86, 80.30, 47.84, 28.58, 25.62; HRMS Calcd for $C_{15}H_{23}N_2O_2$ 263.17595 $[M+H]^+$, found 263.17511.

Preparation of compound 65a. Aniline derivative **64a** (0.937 g, 4.0 mmol) was converted to pyrrolidine **65a** (0.918 g, 88%) according to the procedure described above for **65b** as a pale white solid: R_f= 0.83 (Hexanes/ethyl acetate, 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.35 (s, 1H), 7.09 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.04 (dt, *J* = 7.7, 7.7, 1.5 Hz, 1H), 6.97 (dt, *J* = 7.7, 7.7, 1.6 Hz, 1H), 3.03-2.98 (m, 4H), 1.96-1.92 (m, 4H), 1.53 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.40, 140.11, 133.55, 124.07, 122.97, 119.47, 119.22, 80.26, 52.47, 28.61, 24.62; HRMS Calcd for $C_{15}H_{23}N_2O_2$ 263.17595 $[M+H]^+$, found 263.17507.

Preparation of compound 65c. Aniline derivative **64c** (0.937 g, 4.0 mmol) was converted to pyrrolidine **65c** (0.979 g, 93%) according to the procedure described above for **65b** as a pale white solid: R_f= 0.5 (Hexanes/ethyl acetate, 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 6.6 Hz, 2H), 6.51 (d, *J* = 8.9 Hz, 2H), 6.27 (s, 1H), 3.27-3.23 (t, *J* = m, 4H), 2.11-1.87 (m, 24H), 1.52 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.71, 145.14, 127.04, 121.48, 112.02, 79.92, 48.06, 28.61, 25.59; HRMS Calcd for $C_{15}H_{23}N_2O_2$ 263.17595 $[M+H]^+$, found 263.17560.

Preparation of compound 62i. Starting from aldehyde **61** (426.6 mg, 2.0 mmol) and aniline **64a** (468.5 mg, 2.0 mmol) by treatment with sodium triacetoxyborohydride (634.9 mg, 3.0 mmol) and HOAc (0.12 mL, 2.0 mmol), general procedure C gave **62i** (768.5 mg, 95%) as a light yellow solid: mp 140-143 °C; R_f= 0.53 (Ethyl acetate/hexanes, 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 4.8 Hz, 2H), 7.37-7.30 (m, 5H), 7.06 (dd, *J* =7.6 1.6 Hz, 1H), 6.95 (td, *J* =7.6, 1.6 Hz, 1H), 6.70 (d, *J* = 7.6 Hz, 1H), 6.56 (t, *J* = 4.8 Hz, 1H), 6.13 (bs, 1H), 5.58 (bs, 1H), 4.65 (d, *J* = 6.0 Hz, 2H), 4.31 (d, *J* = 4.8 Hz, 2H), 4.21 (bs, 1H), 1.50 (s, 9H); ^{13}C NMR (100 MHz,$CDCl_3$.) δ 162.26, 158.14, 154.37, 142.17, 138.25, 138.20, 127.90, 126.67, 125.43, 124.31, 118.21, 112.71, 110.79, 80.61, 48.11, 45.21, 28.45; HRMS Calcd for $C_{23}H_{28}N_5O_2$ 406.22430 $[M+H]^+$, found 406.22538; Anal. Calcd for $C_{23}H_{27}N_5O_2$: C, 68.13; H, 6.71; N, 17.27. Found: C, 67.87; H, 6.66; N, 17.09.

Preparation of compound 62j. Starting from aldehyde **61** (426.6 mg, 2.0 mmol) and aniline **64b** (468.5 mg, 2.0 mmol) by treatment with sodium triacetoxyborohydride (636.2 mg, 3.0 mmol) and HOAc (0.12 mL, 2.0 mmol), general procedure C gave **62j** (769.4 mg, 95%) as a white solid: mp 149-150 °C; R_f= 0.53 (Ethyl acetate/hexanes, 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 4.8 Hz, 2H), 7.33 (s, 4H), 7.06 (t, *J* = 8.0 Hz, 1H), 6.86 (s, 1H), 6.57 (t, *J* = 4.8 Hz, 2H), 6.40 (s, 1H), 6.30 (dd, *J* = 8.0, 1.6 Hz, 1H), 5.51 (bs, 1H), 4.64 (d, *J* = 6.0 Hz, 2H), 4.31 (d, *J* = 4.8 Hz, 2H), 4.04 (bs, 1H), 1.51 (s, 9H); ^{13}C NMR (100 MHz,$CDCl_3$) δ 162.46, 58.28, 152.89, 149.06, 139.59, 138.52, 138.26, 129.86, 127.93, 111.04, 107.93, 107.74, 103.09, 80.45, 48.10, 45.30, 28.54; HRMS Calcd

for $C_{23}H_{28}N_5O_2$ 406.22430 $[M+H]^+$, found 406.2239; Anal. Calcd for $C_{23}H_{27}N_5O_2$: C, 68.13; H, 6.71; N, 17.27. Found: C, 67.93; H, 6.69; N, 17.21.

Preparation of compound 62k. Starting from aldehyde **61** (426.6 mg, 2.0 mmol) and aniline **64c** (468.5 mg, 2.0 mmol) by treatment with sodium triacetoxyborohydride (635.5 mg, 3.0 mmol) and HOAc (0.12 mL, 2.0 mmol), general procedure C gave **62k** (794.5 mg, 98%) as a white solid: mp 155-157 ^oC; R_f= 0.47 (Ethyl acetate/hexanes, 4/1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, J = 4.8 Hz, 2H), 7.33 (s, 4H), 7.14 (d, J = 7.2 Hz, 2H), 6.59-6.56 (m, 3H), 6.24 (bs, 1H), 5.49 (bs, 1H), 4.64 (d, J = 6.0 Hz, 2H), 4.29 (s, 2H), 1.65 (bs, 1H), 1.50 (s, 9H); ^{13}C NMR (100 MHz,$CDCl_3$) δ 162.43, 158.26, 153.59, 144.66, 138.64, 138.23, 128.98, 127.90, 121.32, 113.43, 110.99, 80.10, 48.51, 45.27, 28.57; HRMS Calcd for $C_{23}H_{28}N_5O_2$ 406.22430 $[M+H]^+$, found 406.22350; Anal. Calcd for $C_{23}H_{27}N_5O_2$: C, 68.13; H, 6.71; N, 17.27. Found: C, 67.74; H, 6.76; N, 17.13.

Preparation of compound 62m. A solution of **65b** (262.4 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) was treated with HCl solution in dioxane (5 mL, 4M in dioxane). After being stirred for 6 h at room temperature, the solvent was removed under reduced pressure to afforded yellow solid (270 mg).

The yellow solid prepared above was dissolved in 1,2-dichloroethane (20 mL), to which was added aldehyde **61** (192 mg, 0.9 mmol) and HOAc(0.06 mL, 1.0 mmol). The resulting light brown solution was treated with sodium triacetoxyborohydride (318 mg, 1.5 mmol). The reaction mixture was stirred overnight, and quenched by aqueous NaOH (1.0 N) followed by extraction with

ethyl acetate (2 x 30 mL). The combined organic phases were washed by brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (Ethyl acetate/hexanes, 2/1) to afford product **62m** (189 mg, 58%, 2 steps) as a pale white solid: mp 136-138 ^oC (dec.); R_f= 0.57 (Ethyl acetate/hexanes, 4/1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (bs, 2H), 7.38-7.33 (m, 4H), 7.06 (t, *J* =8.0 Hz, 1H), 6.50 (t, *J* = 4.8, 4.8 Hz, 1H), 6.28 (t, *J* = 5.6, 5.6 Hz, 1H), 6.03 (dd, *J* = 6.0, 2.0 Hz, 2H), 5.88 (t, *J* = 2.0, 2.0 Hz, 1H), 4.64 (d, *J* = 5.6, 5.6 Hz, 2H), 4.34 (s, 2H), 4.01 (bs, 1H), 3.30-3.24 (m, 4H), 2.01-1.95 (m, 4H); ^{13}C NMR (100 MHz,$CDCl_3$) δ 162.41, 158.14, 149.36, 149.15, 139.10, 138.04, 129.97, 127.90, 110.77, 102.24, 101.17, 96.34, 48.23, 47.65, 45.29, 25.54; HRMS Calcd for $C_{22}H_{26}N_5$ 360.21882 $[M+H]^+$, found 360.21805; Anal. Calcd for $C_{22}H_{25}N_5$: C, 73.51; H, 7.01; N, 19.48. Found: C, 73.47; H, 7.00; N, 19.32.

Preparation of compound 62l. Pyrrolidine **65a** (288.9 mg, 1.1 mmol) was converted to **62l** (305.5 mg, 85%, 2 steps) according to the procedure described above for **62m** as a pale white solid: mp 124-126 ^oC; R_f= 0.48 (Hexanes/ethyl acetate, 4/1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J*= 4.8 Hz, 2H), 7.33-7.39 (m, 4H), 7.05 (dd, *J* =7.6, 1.6 Hz, 1H), 6.95 (td, *J* =7.6, 1.6 Hz, 1H), 6.70 (td, *J* =7.6, 1.6 Hz, 1H), 6.59 (dd, *J* =7.6, 1.6 Hz, 1H), 6.55 (t, *J* = 4.8 Hz, 1H), 5.68 (bs, 1H), 4.91 (bs, 1H), 4.65 (d, *J* = 6.0 Hz, 2H), 4.36 (d, *J* = 5.2 Hz, 2H), 3.04-3.07 (m, 4H), 1.88-1.95 (m, 4H); ^{13}C NMR (100 MHz,$CDCl_3$) δ 162.48, 158.22, 143.51, 139.23, 137.97, 137.42, 127.93, 127.69, 124.22, 118.56, 117.10, 110.86, 110.47, 51.42, 48.22, 45.34, 24.23; HRMS Calcd for $C_{22}H_{26}N_5$ 360.21882 $[M+H]^+$, found

360.21805; Anal. Calcd for $C_{22}H_{25}N_5$: C, 73.51; H, 7.01; N, 19.48. Found: C, 73.52; H, 7.04; N, 19.33.

Preparation of compound 62n. Pyrrolidine **65c** (262.4 mg, 1.0 mmol) was converted to **62n** (297.4 mg, 92%, 2 steps) according to the procedure described above for **62m** as a pale white solid: mp 149-153 ^{o}C; R_f= 0.51 (Ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 4.8 Hz, 2H), 7.31-7.37 (m, 4H), 6.65 (bs, 2H), 6.57 (t, *J* = 4.8 Hz, 1H), 6.55 (bs, 2H), 5.41 (bs, 1H), 4.63 (d, *J* = 5.6 Hz, 2H), 4.27 (bs, 2H), 3.63 (bs, 1H), 3.20 (bs, 4H), 1.95-1.99 (m, 4H); ^{13}C NMR (100 MHz,$CDCl_3$) δ 162.48, 158.26, 142.07, 139.21, 138.00, 128.04, 127.87, 115.19, 113.31, 110.97, 49.63, 48.51, 25.44 HRMS Calcd for $C_{22}H_{26}N_5$ 360.21882 $[M+H]^+$, found 360.21829; C, 73.51; H, 7.01; N, 19.48.

2.5. References

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