Development and Application of
New Spiroketalization and Allylic Transposition

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THESIS
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Ac    Acetyl
acac  Acetylacetonyl
AIBN  2,2’-Azobis(isobutyronitrile)
Ar    Aryl
atm   Atmosphere
9-BBN 9-Borabicyclo[3.3.1]nonane
bda   Benzylidene acetone
BINAP 2,2’-Bis(diphenylphosphino)-1,1’-binaphthyl
BINOL 1,1’-bi-2,2’-Naphthol
bipy  2,2’-Bipyridyl
Bn    Benzyl
Boc   t-Butyloxycarbonyl
BOP-Cl Bis(2-oxo-3-oxazolidinyl)phosphinic chloride
bp    Boiling point
BQ    1,4-Benzoquinone
BSA   N,O-Bis(trimethylsilyl)acetamide
n-Bu  Butyl (normal)
t-Bu  tert-Butyl
Bz    Benzoyl
CAN   Cerium(IV) ammonium nitrate
CBS   Corey-Bakshi-Shibata reagent
Cbz   Carbobenzyloxy
CDI   Carbonyl diimidazole
CM    Cross metathesis
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<tr>
<td>cod</td>
<td>Cyclooctadiene</td>
</tr>
<tr>
<td>COSY</td>
<td>Correlation spectroscopy</td>
</tr>
<tr>
<td>Cp</td>
<td>Cyclopentadienyl</td>
</tr>
<tr>
<td>Cp*</td>
<td>Pentamethycyclopentadienyl</td>
</tr>
<tr>
<td>CSA</td>
<td>Camphorsulfonic acid</td>
</tr>
<tr>
<td>Cy</td>
<td>Cyclohexyl</td>
</tr>
<tr>
<td>δ</td>
<td>Chemical shift in parts per million downfield from tetramethylsilane</td>
</tr>
<tr>
<td>DABCO</td>
<td>1,4-Diazabicyclo[2.2.2]octane</td>
</tr>
<tr>
<td>DAST</td>
<td>(Diethylamino)sulfur trifluoride</td>
</tr>
<tr>
<td>dba</td>
<td>Dibenzylideneacetone</td>
</tr>
<tr>
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<td>1,5-Diazabicyclo[4.3.0]non-5-ene</td>
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<tr>
<td>DBU</td>
<td>1,8-Diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCC</td>
<td>Dicyclohexyl carbodiimide</td>
</tr>
<tr>
<td>DCE</td>
<td>Dichloroethane</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-Dichloro-5,6-dicyano-1,4-benzoquinone</td>
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<tr>
<td>de</td>
<td>Diastereomeric excess</td>
</tr>
<tr>
<td>DEAD</td>
<td>Diethyl azodicarboxylate</td>
</tr>
<tr>
<td>DET</td>
<td>Diethyl tartrate</td>
</tr>
<tr>
<td>DHP</td>
<td>3,4-Dihydro-2H-pyran</td>
</tr>
<tr>
<td>DIAD</td>
<td>Diisopropyl azodicarboxylate</td>
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<td>DIBAL-H</td>
<td>Diisobutylaluminum hydride</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-Dimethylaminopyridine</td>
</tr>
<tr>
<td>DMDO</td>
<td>Dimethyl dioxirane</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>DME</td>
<td>1,2-Dimethoxyethane</td>
</tr>
<tr>
<td>DMF</td>
<td>Dimethylformamide</td>
</tr>
<tr>
<td>DMP</td>
<td>Dess-Martin periodinane</td>
</tr>
<tr>
<td>DMPU</td>
<td>(N,N')-Dimethylpropylene urea</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide</td>
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<tr>
<td>dppe</td>
<td>1,2-Bis(diphenylphosphino)ethane</td>
</tr>
<tr>
<td>dppf</td>
<td>1,1'-\textit{Bis}(diphenylphosphino)ferrocene</td>
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<tr>
<td>(dr)</td>
<td>Diastereomeric ratio</td>
</tr>
<tr>
<td>(E)</td>
<td>Entgegen (opposite, trans)</td>
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<tr>
<td>EDC</td>
<td>1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride</td>
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<tr>
<td>(ee)</td>
<td>Enantiomeric Excess</td>
</tr>
<tr>
<td>EE</td>
<td>Ethoxyethyl</td>
</tr>
<tr>
<td>EI</td>
<td>Electron impact</td>
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<td>ESI</td>
<td>Electrospray ionization</td>
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<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>EVE</td>
<td>Ethyl vinyl ether</td>
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<tr>
<td>Grubbs I</td>
<td>Grubbs metathesis catalyst, first generation</td>
</tr>
<tr>
<td>Grubbs II</td>
<td>Grubbs metathesis catalyst, second generation</td>
</tr>
<tr>
<td>HMDS</td>
<td>Hexamethyldisilazane</td>
</tr>
<tr>
<td>HMPA</td>
<td>Hexamethylphosphoramide</td>
</tr>
<tr>
<td>IBX</td>
<td>\textit{ortho}-Iodoxybenzoic acid</td>
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<tr>
<td>Ipc</td>
<td>Isopinocamphenyl</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared spectroscopy</td>
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<tr>
<td>(J)</td>
<td>Coupling constant</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>KHMDS</td>
<td>Potassium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>LDA</td>
<td>Lithium diisopropylamide</td>
</tr>
<tr>
<td>LDBB</td>
<td>Lithium 4,4'-t-butylbiphenylide</td>
</tr>
<tr>
<td>LHMD</td>
<td>Lithium hexamethyldisilazide</td>
</tr>
<tr>
<td>mCPBA</td>
<td><em>meta</em>-Chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
</tr>
<tr>
<td>Mes</td>
<td>Mesityl</td>
</tr>
<tr>
<td>MOM</td>
<td>Methoxymethyl</td>
</tr>
<tr>
<td>Ms</td>
<td>Methanesulfonyl</td>
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<td>MTPA</td>
<td><em>α</em>-Methoxy-<em>α</em>-trifluoromethylphenylacetic acid (Mosher acid)</td>
</tr>
<tr>
<td>NaHMDS</td>
<td>Sodium hexamethyldisilazide</td>
</tr>
<tr>
<td>NBS</td>
<td><em>N</em>-Bromosuccinimide</td>
</tr>
<tr>
<td>NCS</td>
<td><em>N</em>-Chlorosuccinimide</td>
</tr>
<tr>
<td>NIS</td>
<td><em>N</em>-Iodosuccinimide</td>
</tr>
<tr>
<td>NMO</td>
<td><em>N</em>-Methylmorpholine-<em>N</em>-oxide</td>
</tr>
<tr>
<td>NMP</td>
<td><em>N</em>-methyl-2-pyrrolidinone</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>nOe</td>
<td>Nuclear Overhauser Effect</td>
</tr>
<tr>
<td>NOESY</td>
<td>Nuclear Overhauser Effect Spectroscopy</td>
</tr>
<tr>
<td>Ns</td>
<td>2-Nitrobenzenesulfonyl</td>
</tr>
<tr>
<td>PCC</td>
<td>Pyridinium chlorochromate</td>
</tr>
<tr>
<td>PDC</td>
<td>Pyridinium dichromate</td>
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LIST OF ABBREVIATIONS (continued)

Ph   Phenyl
PhH  Benzene
Phth Phthaloyl
PIFA Phenyliodonium bis(trifluoroacetate)
Piv  Pivaloyl
PMB  p-Methoxybenzyl
PMP  4-Methoxyphenyl
PPTS Pyridinium p-toluenesulfonate
PS   Polymer supported
Py   Pyridine
Red-Al Sodium bis(2-methoxyethoxy) aluminum hydride
RCM  Ring-closing metathesis
r.t.  Room temperature
SEM  2-Trimethylsilylethoxymethoxy
TASF Tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF Tetra-n-butylammonium fluoride
TBDPS t-Butyldiphenylsilyl
TBS  t-Butyldimethylsilyl
TBHP t-Butylhydroperoxide
TEMPO 2,2,6,6-Tetramethyl-1-piperidinyloxy free radical
TES  Triethylsilyl
Tf   Trifluoromethanesulfonate
TFA  Trifluoroacetic acid
THF  Tetrahydrofuran
<table>
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<tr>
<td>THP</td>
<td>Tetrahydropyranyl</td>
</tr>
<tr>
<td>TIPS</td>
<td>Triisopropylsilyl</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
</tr>
<tr>
<td>TMEDA</td>
<td>N,N,N',N'-Tetramethylethylenediamine</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethylsilyl</td>
</tr>
<tr>
<td>TPAP</td>
<td>Tetra-n-propylammonium perruthenate</td>
</tr>
<tr>
<td>Ts</td>
<td><em>para</em>-Toluenesulfonyl</td>
</tr>
<tr>
<td>Z</td>
<td>Zusammen (together, <em>cis</em>)</td>
</tr>
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SUMMARY

The research projects described in this thesis deal with the development of synthetic approaches for bis-spiroketalts, rhenium-catalyzed regio- and stereoselective allylic [1,3]-transposition, and the application of allylic transpositions of silyl ethers to the syntheses of complex natural products.

In particular, a synthetic strategy to control regioselectivity in the [1,3]-transposition of cyclic silyl ethers was developed relying on the relief of ring strain. In this transformation, eight-membered ring siloxadienes undergo a ring contraction to form functionalized six-membered siloxenes bearing Z-trisubstituted alkene moiety. A gold-catalyzed intramolecular allylation of silylalkynes, ruthenium-catalyzed ring-closing metathesis and a rhenium-catalyzed allylic transposition were employed consecutively. The ring-contractive transposition was successfully employed for the preparation of a key vinyl silane intermediate toward the asymmetric total synthesis of (−)-amphidinolide V. Moreover, a carefully designed synthetic route illustrates the effectiveness of silicon-tethered ring-closing enyne and diene metathesis as well as the direct proline-mediated cross-aldol condensation of aldehydes in complex molecule synthesis.

Additionally, a 13-steps asymmetric total synthesis of (−)-dactylolide was accomplished. This synthetic maneuver highlights several methodologies designed for the construction of the delicate functionalities presented in the target molecule. A tandem sequence of ruthenium-catalyzed Alder-ene reaction followed by a palladium-catalyzed π-allyl intramolecular etherification was implemented for the stereoselective construction of 2,6-disubstituted tetrahydropyran subunit. Regio- and stereoselective [1,3]-transposition of silyl ethers bearing tethered boronate moiety was employed for the synthesis of a key (Z)-trisubstituted vinylboronate building block. Furthermore, a challenging 18-membered lactone formation at the terminal stage of the synthesis was accomplished via ring-closing metathesis to construct the C16–C17 trisubstituted double bond.
Finally, an efficient one-step protocol for the synthesis of 5-5-5, 5-5-6, and 6-5-6 bis-spiroketal structures of polyketide natural products was developed relying on thermodynamically-controlled \( \pi \)-Lewis acid-catalyzed hydroalkoxylolation–hydration of 4,6-diyn-1,n-diols and 5,7-diyn-1,n-diols. The equilibrium behavior of \( cis \) and \( trans \)-bis-spiroketals and the factors that dictate their ratio were also explored.
PART I
ASYMMETRIC TOTAL SYNTHESIS OF (–)-DACTYLOLIDE

1.1. Introduction and Background*

(+)-Dactylolide (1-01) was isolated from marine sponge of the genus Dactylospongia by Riccio and co-workers off the coast of the Vanuatu islands in 2001 (Figure 1.1). It displayed 63% inhibition of lymphatic leukemia in mice (L1210) and 40% inhibition of ovarian carcinoma (SK-OV-3) at 3.2 µg/mL. Structurally, dactylolide is a highly unsaturated 18-membered macrolactone containing a 2,6-cis-disubstituted tetrahydropyran and an aldehyde functionality. The complete stereochemical assignment of the relative and absolute stereochemistry of dactylolide was realized by Smith via total syntheses of both (+)-dactylolide and as well as (+)-zampanolide (Figure 1.1).

Fugure 1.1 Naturally Occurring (+)-Dactylolide and (–)-Zampanolide

(–)-Zampanolide (1-02) was isolated by Higa and Tanaka as a minor constituent of the completely different marine sponge Fasciospongia rimosa collected off Cape Zampa on the island of Okinawa, Japan in 1996. (–)-Zampanolide exhibited more potent cytotoxicity than (+)-dactylolide against the P388, A549, HT29, and MEL28 tumor cell lines on the order of 1–5 ng/mL, blocking G to M transition in the cell cycle through the stabilization of microtubules, similar to the characteristic actions of taxol, laumalide, and pelorusides.

The similarity between dactylolide and zampanolide in their structures and the metabolite make-up of the host sponges imply a common biosynthetic precursor, possibly the result of two genetically related symbiotic microorganisms. However, the total synthesis of (+)-dactylolide revealed the absolute stereochemistry of the two natural products is opposite. Therefore, dactylolide is not a degradation product of, or biosynthetic precursor for zampanolide.

1.2. Review of Previous Total Syntheses

Because of structural complexity and promising biological activities, dactylolide and zampanolide have attracted considerable synthetic interest. To date, ten and four total syntheses of dactylolide and zampanolide respectively have been reported since their first synthesis in 2002 and 2001. In 2003, Hoye reported a one-step conversion of (–)-dactylolide into (–)-zampanolide, demonstrating that the synthesis of dactylolide constitutes a formal synthesis of zampanolide. These syntheses are reviewed here focusing on the major structural challenges including the formation of the cis-2,6-disubstituted-4-methylene tetrahydropyran, the E- and Z-trisubstituted double bonds, and the 18-membered ring lactone.

1.2.1. Smith Synthesis of (+)-Dactylolide

Smith’s strategy involved a Horner-Wadsworth-Emmons olefination to form the macrocycle at the C2–C3 double bond and a Petasis-Ferrier rearrangement to generate the pyran subunit (Scheme 1.2.1). The synthesis started with Brown asymmetric allylation of aldehyde followed by protection of the resulting alcohol as the TES ether. Ozonolysis afforded aldehyde, which was subsequently oxidized to the carboxylic acid. Bis-silylation with HMDS followed by condensation with aldehyde promoted by TMSOTf led to dioxanone (10:1 dr). Methylenation of and the Petasis-Ferrier rearrangement afforded pyranone. The installation of the exo-methylene via Wittig olefination, silyl ether deprotection, and Mitsunobu reaction with thiotetrazole provided sulfone after oxidation. Sulfone was coupled with aldehyde under the Julia-Kocienski protocol to install the C8–C9 double bond. The cuprate derived from vinyl bromide was then merged with epoxide, giving alcohol. For the macrocyclization, phosphonate was prepared by initial esterification between
1-14 and 1-15 followed by selective primary TBS-ether deprotection and oxidation. Macrocyclization via Horner-Wadsworth-Emmons olefination, deprotection of TBS and DMB groups followed by oxidation of the C20 hydroxyl group afforded (+)-dactylolide ([α]_{D}^{RT} = +128.9°, c = 0.45, C_{6}H_{5}).

**Scheme 1.2.1 Smith Synthesis of (+)-Dactylolide**

(+)-Dactylolide could also be accessed by degradation of (+)-zampanolide. Authors has shown that heating (+)-zampanolide in benzene at 85 °C for 1.5 h lead to clean formation of (+)-dactylolide, giving further confirmation of their relative and absolute stereochemistry.

**1.2.2. Hoye Synthesis of (–)-Dactylolide and (–)-Zampanolide**

Hoye and Hu reached zampanolide by direct addition of the N-acyl hemiaminal side chain to dactylolide via an aza-aldol reaction. Other key steps include the formation of the ester by titanium-
mediated opening of a 2,3-epoxy alcohol with a carboxylic acid and a ring-closing metathesis to generate the macrocycle.

**Scheme 1.2.2.** Hoye Synthesis of (−)-Dactylolide

The synthesis commenced with formation of the cis-2,6-disubstituted-4-methylene tetrahydropyran 1-20 via coupling of aldehyde 1-18 with allylsilane 1-19 (Scheme 1.2.2). A three-step manipulation of the primary pivalate in 1-20 to the corresponding terminal alkene provided 1-21, which was subjected to silyl deprotection and the Sharpless asymmetric epoxidation to install important C19 stereochemistry, delivering epoxide 1-22. Treatment of 1-22 and carboxylic acid 1-23 with Ti(O^tBu)_4 at 75 °C delivered ester 1-24 in 67% yield. The regiochemistry of the epoxide opening is the consequence of titanium chelate formation on the epoxyalcohol, leading to nucleophilic attack at the carbon proximal to the alcohol. Macrocyclization via ring-closing metathesis to form the C8-C9 bond gave allylic alcohol 1-25, which was selectively oxidized with oxoammonium salt 1-26. The final oxidative cleavage of the 1,2-diol afforded (−)-dactylolide ([α]_D^RT = −128°, c = 0.39, MeOH). (−)-Dactylolide was further converted to
(−)-zampanolide as a 1:1 mixture of C20 epimers by aza-aldol addition of 1-27, derived from \((Z,E)\)-sorbamide and DIBAL-H.

### 1.2.3. Jennings Synthesis of (−)-Dactylolide

In 2005, Jennings reported a synthesis of (−)-dactylolide relying on ring-closing metathesis as the key macrocyclization step. Similar to the Hoye’s synthesis, 1,3-dienoic acid 1-23 was esterified with the pyran-containing subunit at the later stage prior to the macrocycle formation (Scheme 1.2.3). The preparation of 1-23 commenced with aldehyde 1-28 via Horner-Wadsworth-Emmons olefination, deprotection of the silyl ether, and oxidation of primary alcohol, leading to the \((E,Z)\)-conjugated ester 1-29. Addition of vinylmagnesium bromide to 1-29, TBS-protection, and saponification afforded racemic acid 1-23.

**Scheme 1.2.3. Jennings Synthesis of (−)-Dactylolide**
For the preparation of pyran moiety via a tandem nucleophilic addition-diastereoselective reduction of an *in situ* generated oxonium ion, the C16-C17 trisubstituted alkene in 1-33 was installed via a two-step protocol involving an initial conjugate addition of benzenethiol to ynoate 1-31 followed by an addition-elimination reaction with methylmagnesium bromide. Conversion of the ester to an aldehyde followed by Brown allylation afforded 1-33. Acylation of alcohol 1-33 with acryloyl chloride and subsequent ring-closing metathesis gave lactone 1-34, epoxidation of which with basic hydroperoxide followed by regioselective C–O bond cleavage using PhSeH\(^{11}\) afforded 1-35. The conversion of 1-35 to 2,6-cis-disubstituted tetrahydropyran was achieved in 76% yield via the addition of allylmagnesium bromide to the lactone and subsequent reduction of corresponding lactol with Et\(_3\)SiH and TFA. The required 2,6-cis-stereochemistry was set by the axial attack of an incoming hydride onto a half-chair conformation of an oxonium intermediate. Installation of the *exo*-methylene functionality was accomplished by manipulation of 1-36 to ketone 1-37 and its Wittig methylation. Esterification of 1-38 with 1-23 under Yamaguchi conditions, ring-closing metathesis, and final oxidation of both the primary and allylic alcohols afforded (−)-dactylolide ([*α*]\(^{RT}\)\(_D\) = −136°, c = 1.2, MeOH).

**1.2.4. Floreancig Synthesis of (+)-Dactylolide**

The Floreancig synthesis published in 2005\(^8\)c relies on the asymmetric vinylogous Mukaiyama aldol reactions\(^12\) by which two advanced fragments for the *cis*-2,6-disubstituted-4-methylene tetrahydropyran were prepared. The macrocycle was formed via Horner-Wadsworth-Emmons olefination at the C2–C3 position as shown in Smith’s synthesis.

The synthesis commenced with an asymmetric vinylogous Mukaiyama aldol reaction between 1-40 and 1-41, which was catalyzed by Cu-Pybox complex 1-42\(^13\) (Scheme 1.2.4). This reaction established the *E*-trisubstituted double bond as well as the C19 stereocenter with 95% ee. Silyl protection and reduction of the ester afforded aldehyde 1-44. The C4–C5 double bond was set by hydroalumination of 2-butynol 1-45 followed by trapping of aluminum intermediate with tributylstannyl chloride to form vinyl stannane 1-46. After protection as the TBDPS ether, 1-46 was coupled with bromide 1-47, which was then
hydrolyzed upon work-up, giving aldehyde 1-48. A second Mukaiyama aldol reaction between 1-48 and 1-49 catalyzed by Denmark’s bisphosphoramide ligand\(^{14}\) (not shown) set the stereochemistry of the newly formed allylic hydroxyl group in 1-50.

**Scheme 1.2.4. Floreancig Synthesis of (+)-Dactylolide**

With ester 1-50 in hand, the two coupling partners were joined. Acid-catalyzed condensation of 1-50 with 1-44 provided acetal 1-51, which was treated with excess TMSCH\(_2\)MgCl and CeCl\(_3\) and worked up under acidic conditions. This multi-step transformation includes addition of two equivalents of the nucleophile to the ester, inducing a Peterson olefination\(^{15}\) to generate an allyl silane. Upon acidic workup, the acetal ionized, forming an oxonium ion, which was trapped by the allyl silane to generate desired pyran 1-52 in 75% yield. With the pyran formed, an allylic [1,3]-transposition of the C7–C9 allylic alcohol was required. Toward this end, alcohol 1-52 was converted to a selenide by displacement with
PhSeCN and Bu$_3$P. Upon oxidation, the resultant selenoxide underwent a [2,3]-sigmatropic rearrangement, delivering the transposed alcohol,$^{16,17}$ which was subjected to protecting group manipulations to give 1-53. Selective oxidation at the primary alcohol and esterification with 1-15 provided macrocycle 1-54 via Horner-Wadsworth-Emmons olefination upon treatment with NaHMDS. Deprotection of the C7 and C19 hydroxyl groups and bis-oxidation provided (+)-dactylolide. ([α]$^\text{RT}_{D}$ = +163°, c = 0.29, MeOH) in 49% yield over two steps.

1.2.5 Keck Synthesis of (+)-Dactylolide

The synthesis by Keck and Sanchez$^{8d}$ shares strategic similarity with that of Smith, Hoye, and Floreancig. This includes a macrocyclization via Horner-Wadsworth-Emmons olefination to establish the C2–C3 bond and the pyran formation via intramolecular attack of an allylic silane to an incipient oxonium species. One of the unique features of this synthesis involves the catalytic asymmetric allylation using allyl silanes and stannanes developed in the same group.$^{18}$

The synthesis started with the asymmetric allylation of aldehyde 1-40 with functionalized allylic stannane 1-55 (Scheme 1.2.5). The reaction was catalyzed by a BINOL-titanium tetraisopropoxide (BITIP),$^{19}$ which provided 1-56 in 93% ee. The trisubstituted alkene 1-57 was accessed by isomerization of the β,γ-unsaturated ester to a more stable α,β-unsaturated isomer. This reaction gave best results for the desired E-isomer when the counter-cation was sodium. A second BITIP-catalyzed allylation between aldehyde 1-59 and allylic stannane 1-60 afforded allylic silane 1-61 in 91% yield and 95% ee. The pyran annulation reaction occurred between 1-60 and 1-58, giving the pyran subunit 1-62 in 85% yield. The right arm of pyran 1-62 was homologated by conversion to aldehyde 1-63 followed by Horner-Wadsworth-Emmons olefination with ketophosphonate 1-64 to install the C8–C9 alkene. The trisubstituted alkene of 1-64 was derived from conjugate addition of methylocuprate to an ynoate similar to that described Smith’s synthesis. With 1-65 in hand, the final elaboration to dactylolide closely followed those of Floreancig and Smith.
Scheme 1.2.5. Keck Synthesis of (+)-Dactylolide

After minor protecting group manipulations, 1-65 was coupled with 1-15 using polymer bound DCC to simplify isolation. Horner-Wadsworth-Emmons macrocyclization of 1-67 gave 1-68 the deprotection and oxidation of which led to (+)-dactylolide ([α]_{D}^{RT} = +134°, c = 0.065, MeOH).

1.2.6. McLeod Synthesis of (−)-Dactylolide

McLeod and coworkers have reported a synthesis of (−)-dactylolide in 2006. This approach implements a macrocyclic RCM to form the C8–C9 double bond employing C1–C8 subunit 1-23, which is a common feature in the syntheses of Hoye and Jennings. However, the synthesis of the exo-methylene tetrahydropyran subunit via an asymmetric hetero Diels–Alder reaction is unique in this approach. An
Ireland-Claisen rearrangement was implemented for the installation of the trisubstituted C16–C17 double bond.

The synthesis began with an asymmetric hetero-Diels–Alder reaction between 1-69 and 1-70 with Jacobsen’s chiral chromium(III) catalyst 1-71, affording 1-72 in 82% yield and 99% ee (Scheme 1.2.6). Deprotection of the PMB-ether and oxidation to the aldehyde followed by Wittig reaction of both the aldehyde and ketone afforded 1-73. Deprotection of the silyl ether, oxidation, and alkylation with isopropenyl lithium in the presence of magnesium bromide delivered 1-74 (86:14 dr). Esterification of 1-74 to 1-75 followed by an Ireland-Claisen rearrangement and reduction gave 1-76, which simultaneously set both the C16–C17 double bond geometry and the C19 stereochemistry.

**Scheme 1.2.6.** McLeod Synthesis of (−)-Dactyloleide
Protecting group manipulations of 1-76 provided secondary alcohol 1-77 necessary for the esterification with subunit 1-23, which was synthesized from acrylate 1-78. A three-step sequence involving an RCM, partial reduction of the lactone moiety, and Horner-Wadsworth-Emmons olefination delivered (2E,4Z)-diene ester 1-80. Conversion of 1-80 to allylic alcohol 1-81 followed by TBS-protection and saponification afforded acid 1-23.

The union of 1-77 and 1-23 was achieved to afford 1-39 via a Mitsunobu reaction with the inversion at the C19 stereocenter. Desilylation of 1-39 followed by an RCM to form the macrocycle and the final TBS-deprotection and oxidation completed the synthesis of (–)-dactylolide ([α]$_{D}^{RT}$ = −169°, c = 0.42, MeOH).

1.2.7. Uenishi and Tanaka Synthesis of (–)-Dactylolide

The strategy of Uenishi and Tanaka$^{8}$ for (–)-dactylolide involved a Trost-Kita method$^{20}$ to close the macrocycle and a Sakurai reaction similar to the syntheses of Hoye and Keck to assemble the tetrahydrofuran subunit. Other key steps include a stereoselective intramolecular $O$-Michael reaction for the 2,6-cis-tetrahydrofuran moiety and a stepwise metal-catalyzed cross-coupling of 1,1-dibromodiene to install Z-trisubstituted alkene$^{21}$ in the C1–C8 subunit.

The synthesis started with ring opening of PMB-protected (R)-glycidol with lithium reagent 1-82 followed by pivalate formation to afford 1-83 (Scheme 1.2.7). Removal of the silyl ether and oxidation gave aldehyde 1-84, which was coupled with allylic silane 1-85 under Sakurai conditions, providing diastereomers 1-86R and 1-86S. Stereochemistry at the C15 of 1-86R was inverted by Mitsunobu reaction followed by methanolysis. Conversion of 1-86S to the cyclization precursor 1-88 was realized via ethoxyethyl protection of secondary alcohol, cleavage of silyl ether and oxidation to form 1-87 followed by Wittig reaction, and hydrolysis of ethoxyethyl ether. The $O$-Michael reaction of 1-88 gave separable cis/trans tetrahydrofurans (1.8:1 dr). Reduction of the ester with DIBAL-H afforded aldehyde 1-89.
The C1–C8 subunit was synthesized from aldehyde 1-90. Dibromomethylation and stereoselective Sonogashira coupling gave dienyne 1-91, which upon Kumada coupling with methylmagnesium bromide afforded 1-92 with an inversion of olefin geometry. The stereochemical outcome can be explained by the isomerization of a (Z)-alkenyl Ni-intermediate\(^{21}\) to the corresponding (E)-alkenyl Ni-complex via a reversible 1,3-metal migration whereby the unfavorable steric repulsions are attenuated. Subsequent transmetallation and reductive elimination from this intermediate should provide the observed product. Dienyne 1-92 was elaborated to β-ketophosphonate 1-95 in four steps via the intermediacy of methyl ester 1-93.

**Scheme 1.2.7.** Uenishi and Tanaka Synthesis of (−)-Dactylolide
The Horner-Wadsworth-Emmons reaction between 1-89 and 1-95 installed C8–C9 double bond and Trost-Kita macrocyclization of 1-96 afforded cyclic product 1-97 in modest yield. Final deprotection of PMB-ether and oxidation delivered (−)-dactylolide. ([α]D = −167.8°, c = 0.45, MeOH).

1.2.8. Altmann and Gertsch Synthesis of (−)-Dactylolide

Published in 2010 Altmann and Gertsch synthesis of (−)-dactylolide relied on Horner-Wadsworth-Emmons olefination to install C8–C9 double bond as a macrocyclization step. The synthesis of the tetrahydropyran subunit was unique in that it employed a highly stereoselective Prins-type reaction involving a segment coupling originally developed by Rychnovsky.

Scheme 1.2.8. Altmann and Gertsch Synthesis of (−)-Dactylolide

The synthesis commenced with the copper-catalyzed opening of epoxide 1-98 with vinylmagnesium bromide, generating homoallylic alcohol 1-99 (Scheme 1.2.8). Alcohol 1-99 was then elaborated to the acetal 1-100 via esterification with 2-butynoic acid, reduction with DIBAL-H, and trapping of the
aluminate intermediate with Ac₂O. Treatment of 1-100 with TMSI resulted in stereoselective Prins-type cyclization to generate cis-2,6-disubstituted 4-iodotetrahydropyran core.²² The exo-methylene functionality was installed by converting iodide 1-101 to secondary alcohol 1-102, followed by oxidation and Wittig methelenation. Internal triple bond in 1-103 was then converted to (E)-vinyl iodide 1-104 by stannyl cupration with Bu₃Sn(Bu)CuCNLi₂ followed by Sn–I exchange with NIS. The necessary three-carbon unit was introduced by opening of epoxide 1-105 with the vinyl lithium reagent derived from iodide 1-104. Yamaguchi esterification with phosphonate 1-107, desilylation, and oxidation afforded macrocyclization precursor 1-108. Intramolecular Horner-Wadsworth-Emmons reaction of 1-108 in the presence of activated Ba(OH)₂, deprotection of PMB-ether, and oxidation of the C20 primary alcohol delivered (–)-dactylolide ([α]D = −258.3°, c = 0.11, MeOH).

1.2.9. Ghosh Synthesis of (–)-Dactylolide and (–)-Zampanolide

Ghosh has reported synthesis of (–)-dactylolide and (–)-zampanolide in 2011.⁸ This route involves the synthesis of dactylolide on which the N-acyl hemiaminal side chain was directly introduced via a stereoselective organocatalytic reaction. 18-Membered macrocycle was installed by forming the C8–C9 alkene by an RCM reaction like in the syntheses of Hoye and Jennings. The C1–C8 building block, similar to 1-23 in Hoye’s synthesis, was prepared via the sequence of Reformatsky and Wittig reactions. For the synthesis of the pyran subunit, DDQ-mediated generation of an oxonium intermediate and its trapping with a tethered allyl silane moiety was employed.

The synthesis was initiated by Pd-catalyzed etherification of secondary alcohol 107 with tert-butylcinnamyl carbonate 1-110 to generate cinnamyl ether 1-111 (Scheme 1.2.9). Conversion of the ester moiety of 1-111 to allyl silane 1-112 was achieved in 81% yield via a one-step protocol developed by Bunnelle.²³ Treatment of allyl silane 1-112 with DDQ and PPTS provided cis-2,6-disubstituted tetrahydropyran 1-113 in good yield. At this point, the cross metathesis to install the trisubstituted alkene at the C16–C17 was not successful probably due to the low reactivity of styrene moiety, which thus was converted to the corresponding terminal alkene 1-114 via dihydroxylation, diol cleavage, and Wittig
olefination. Cross metathesis of 1-114 and 1-115 provided a separable 1.7:1 mixture of (Z)-alkene 1-116 and (E)-alkene 1-117 in 46% overall yield after desilylation. (Z)-Alkene 1-116 was converted to 1-117 by photochemical isomerization.

**Scheme 1.2.9.** Ghosh Synthesis of (−)-Dactylolide and (−)-Zampanolide

Selective oxidation of primary alcohol in 1-117 followed by methylenation afforded 1-118, which was coupled with acid 1-119 under Yamaguchi conditions. RCM of 1-120, PMB-deprotection and oxidation delivered (−)-dactylolide in 52% yield ([(α)_{D}^{RT} = −148°, c = 0.09, MeOH). (−)-Dactylolide was converted to (−)-zampanolide by Bronsted acid-catalyzed addition of 1-121 to the C20 formyl group. Chemoselectivity and stereoselectivity of this reaction using chiral phosphoric acid (S)-TRIP was significantly higher (51% of (−)-zampanolide and 18% of its epimer) than that of Uenishi and Tanaka.8f

None of bis-amide formation was observed in this reaction.
1.2.10. Hong and Kim Synthesis of (+)-Dactylolide

The most recent synthesis of (+)-dactylolide was achieved by Hong and Kim in 2012. The synthetic route realized in their approach is significantly different from those previously reported in syntheses of dactylolide and zampanolide. The synthesis relies on unprecedented NHC-catalyzed oxidative macrolactonization of ω-hydroxyaldehyde to form 18-membered macrolactone. For the installation of 2,6-cis-disubstituted tetrahydropyran subunit authors utilized 1,6-oxa-conjugate addition reaction of 1,3-dienal intermediate. Another notable element of Hong and Kim strategy is previously unutilized disconnection at the C6–C7 single bond which allowed employment of cyanohydrin alkylation to introduce the C1–C6 building block in the molecule.

The preparation of 2,6-cis-tetrahydropyran moiety commenced with the coupling of dithiane 1-122 with allylic chloride 1-123 in the presence of n-BuLi and n-Bu₂Mg to afford 1-124 after cleavage of THP-ether and Parich-Doering oxidation (Scheme 1.2.10). Nucleophilic addition of vinylzinc reagent derived from iodide 1-125 in the presence of lithiated (1S,2R)-N-methylephedrine was used to set the C15 stereochemistry (7.7:1 dr) of allylic alcohol 1-126. TBS-cleavage and MnO₂ oxidation afforded 1,3-dienal precursor for the key 1,6-oxa conjugate addition reaction. Organocatalytic oxa-Michael reaction of 1-127 proceeded with high diastereoselectivity when catalyzed by piperidine (10:1 dr) which was further improved by utilization of Jørgensen’s prolinol-based catalyst. Under these conditions the tetrahydropyran core of natural product was constructed in > 20:1 dr. The α,β-unsaturated aldehyde of 1-128 was then converted to TBS-protected cyanohydrin which was subjected to α-alkylation with allylic chloride 1-130 to afford the substrate for the subsequent oxidative macrolactonization after concomitant one-pot deprotection and oxidation. NHC-catalyzed oxidative macrolactonization of hydroxyaldehyde 1-131 was efficient only with employment of diphenylquinone 1-132 as stoichiometric oxidant which afforded 18-membered macrocycle in 65% yield.
Scheme 1.2.10. Hong and Kim Synthesis of (+)-Dactylolide

After hydrolysis of 1,3-dithiane group of 1-133 Wittig methylenation of resultant ketone introduced exocyclic double bond on the tetrahydropyran core of the intermediate 1-134. Final desilylation of TBDPS-ether which was accompanied by liberation of the C7 ketone and oxidation of resultant alcohol delivered (+)-dactylolide ([α]_{D}^{20} +208.4°, c = 0.152, MeOH).

1.3. Retrosynthetic Analysis

Although there have been a multitude of syntheses reported for dactylolide and zampanolide, most of them share quite similar key bond disconnections and overall synthetic strategies. We envisioned a new strategy involving completely different bond disconnections from the reported approaches. In order to
achieve this, our group has developed several new synthetic methodologies that rely on transition metal-catalyzed manipulations of unsaturated functional units. The ability of these catalysts to engage relatively unactivated alkenes and alkynes as substrates is a key to minimize the number of synthetic steps, especially for synthetic targets of multiple unsaturation, such as dactylolide. Our strategy for the macrocyclization relies on a late stage ring-closing metathesis\textsuperscript{24} to form the C16–C17 double bond from \textbf{1-135} or its corresponding relay metathesis\textsuperscript{25} substrate \textbf{1-136} (Scheme 1.3). This novel bond disconnection is adventurous considering the number of alkenes in the molecule and a predisposed difficulty in forming trisubstituted double bonds via metathesis let alone the desired $E$-stereochemistry. The C3–C4 bond was planned to be constructed via Suzuki cross-coupling between iodoacrylate \textbf{1-137} or \textbf{1-138} and cyclic boronic acid half ester \textbf{1-139}. Alkenyl boron species \textbf{1-139} would be accessed by using a ruthenium-catalyzed Alder-ene reaction (RCAER)\textsuperscript{26} between terminal alkene \textbf{1-140} and borylated alkyne \textbf{1-141} to form the C5–C6 bond followed by a regioselective\textsuperscript{27} rhenium(VII)-catalyzed\textsuperscript{28} allylic [1,3]-transposition.\textsuperscript{29} The pyran subunit in \textbf{1-140} would be installed using a tandem ruthenium-catalyzed Alder-ene reaction and subsequent palladium-catalyzed ring closure\textsuperscript{30} from readily accessible building blocks \textbf{1-142} and \textbf{1-143}.

\begin{equation*}
\textbf{1-135} (R = H) \quad \textbf{1-136} (R = \text{CH}_2\text{OAlllyl}) \quad \textbf{1-137} (R = H) \quad \textbf{1-138} (R = \text{CH}_2\text{OAlllyl}) \quad \textbf{1-139}
\end{equation*}

\begin{equation*}
\textbf{1-140} \quad \textbf{1-141} \quad \textbf{1-142} \quad \textbf{1-143}
\end{equation*}

\textbf{Scheme 1.3. Retrosynthetic Approach toward (−)-Dactylolide}
1.4. Synthesis of (–)-Dactylolide

1.4.1. Preparation of the Pyran Subunit

The synthesis of (–)-dactylolide commenced with preparation of the pyran subunit **1-147** (Scheme 1.4.1.1). Homopropargylic alcohol **1-142**, the substrate for the Alder-ene reaction was synthesized from commercially available (4S)-(+)–4-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxolane **1-144** via epoxide **1-145** according to the known procedure.\(^{31}\) The Alder-ene reaction\(^ {26b,32}\) between **1-142** and homoallylic carbonate **1-143** followed by a cycloetherification under the palladium-catalyzed conditions\(^ {33}\) led to the formation of pyran **1-147**. In general, this transformation was best achieved in DMF employing the procedure developed by Trost,\(^ {34}\) but in case of the conversion of **1-146** to **1-147** the stereoselectivity was only modest (cis:trans = 4:1) under the standard conditions (0 °C to r.t.) with (S,S)-DPPBA. Gratifyingly, running the reaction in acetone followed by its evaporation and addition of a premixed solution of Pd-catalyst and ligand in CH\(_2\)Cl\(_2\) at –25 °C improved the selectivity for cis-**1-147** up to a 11:1 ratio and 72% isolated yield.

**Scheme 1.4.1.1.** Synthesis of the Pyran Subunit of Dactylolide

Stereochemical outcome of the cyclization can be predicted/explained relying on working model proposed by Trost for the reactions with DPPBA ligands\(^ {35}\) (Scheme 1.4.1.2). In this Pd-catalyzed allylic alkylation mechanism, there are two possible stereochemistry-determining steps: ionization of the leaving group and addition of a nucleophile. If the rate of equilibration of diastereomeric π-allyl-Pd complexes is
slower than the rate of nucleophilic addition, the ionization step is stereochemistry-determining. On the other hand, if the rate of equilibration is faster than the nucleophilic addition, the stereochemical outcome will be determined at this stage. The nature of the nucleophile is of profound importance for high selectivity in these reactions. “Soft” nucleophiles react faster with π-allyl-Pd complexes, which makes the ionization step stereochemistry-determining. With “hard” nucleophiles, the rate of trapping becomes comparable to or slower than \( \eta'^1 \)- and \( \eta'^3 \)-allyl interconversion. Alcohols are relatively poor nucleophiles for Pd-catalyzed allylic alkylations due to their “hard” nature. Therefore, the rate of addition is lower than that of π-allyl interconversion, and thus nucleophilic addition becomes stereochemistry-determining. Under this model, allylic carbonate 1-146 in the presence of (S,S)-DPPBA-complexed palladium catalyst would undergo an ionization dictated by chiral environment of the ligand to form π-allyl-Pd complex A. While the intermediate A is in equilibrium with an isomeric complex B, an addition of the oxygen nucleophile onto a matched face of B would lead to (S)-stereochemistry of the newly created stereogenic center in 1-147.

**Scheme 1.4.1.2. Stereocontrol of Cyclization**

### 1.4.2. Preparation of the (Z)-Trisubstituted Vinylboronate

The pyran subunit 1-147 was elaborated into triene 1-140 in four steps (Scheme 1.4.2.1). Removal of the pivalate group from 1-147 with DIBAL-H and oxidation of the resultant alcohol with \( \alpha \)-iodobenzoic
acid (IBX) afforded aldehyde 1-147. Leighton asymmetric allylation\textsuperscript{36} and subsequent TBS-protection of the homoallylic alcohol gave 1-140 in 83% yield (8:1 dr). At this point all necessary functionality were introduced for the sequence of Alder-ene reaction with borylated alkynes\textsuperscript{26a} and an allylic transposition\textsuperscript{27c} for the stereoselective construction of C4–C9 fragment of dactylolide.

Scheme 1.4.2.1. Synthesis of Cyclic Boronic Acid Half Ester

Ruthenium-catalyzed Alder-ene reaction of 1-140 and borylated alkyne 1-141\textsuperscript{37} occurred selectively with least hindered double bond at the C7 position and afforded vinyl boronate 1-149 exclusively with the expected Z-selectivity of the C4–C5 trisubstituted alkene (Z:E = 5:1). Conversion of 1-140 was low; however, acceptable yields were obtained by recycling the alkene counterpart. Exclusive formation of the branched product in the Alder-ene reaction is assumed to be the result of a strong directing effect of a boronate to form ruthenacyclopentene intermediate 1-153 (Scheme 1.4.2.2). The tendency for internal alkynes with bulky substituents favoring this pathway is well established for silicon\textsuperscript{38} and carbon-containing\textsuperscript{39} alkynes. In order to explain the unusual cis-stereochemistry, two possible mechanisms were formulated by the extension of the general mechanisms of the Alder-ene reaction proposed by Trost et al.\textsuperscript{32a,c,e,40} The formation of cis-1-152 would be the consequence of an isomerization of 1-154 to 1-155 after β-hydride elimination from ruthenacyclopentene 1-151 (pathway A). An alternate mechanism involves an allylic C–H activation to form a π-allyl ruthenium hydride complex 1-156 and trans-
hydridoruthenation\textsuperscript{41} sequence, where the isomerization of 1-157 to 1-158 would be slower than its and reductive elimination (pathway B). The allylic transposition of 1-149 proceeded at room temperature in the presence of 5 mol \% of Re$_2$O$_7$ to generate the cyclic boronic acid half ester 1-139 in 65\% yield with completed chirality transfer of transposed alcohol.

Scheme 1.4.2.2. Possible Mechanisms for the Formation of cis-Vinyl Boronates

A plausible mechanism that accounts for the formation of the cyclic boronic acid is shown in Scheme 1.4.2.3. Upon activation of the Si–O bond of substrate 1-159 with rhenium oxide via 1-160, the resultant intermediate 1-161 undergoes an allylic transposition into 1-162 via either a [3,3]-sigmatropic rearrangement or an ion pair of the corresponding allylic carbocation. A ligand exchange via the expected Lewis acid-base interaction on 1-163 leads to a penultimate intermediate 1-164, which upon another ligand exchange with a substrate will release product 1-165, regenerating intermediate 1-161. The initially formed boronate 1-165 readily hydrolyzes during the purification on silica gel, providing the final product 1-166.
Scheme 1.4.2.3. Plausible Mechanisms for the Allylic Transposition

1.4.3. Macrocyclic Ring-Closing Metathesis and Completion of Dactylolide Synthesis

*(E)-Vinyl iodide coupling partner 1-137* for the Suzuki reaction was prepared from TBS-protected *(S)-glycidol* (Scheme 1.4.3.1).

Scheme 1.4.3.1. Suzuki Coupling and Ring Closure Attempt
The epoxide opening with 2-propenylmagnesium bromide to form 1-167 and its subsequent Mitsunobu reaction\textsuperscript{42} in the presence of 2-iodoacrylic acid 1-168\textsuperscript{43} provided ester 1-137. The coupling between 1-137 and 1-139 preceded smoothly using conditions developed by Roush,\textsuperscript{44} providing 1-135 in 79\% yield. At this stage a ring-closing metathesis was attempted by treating a dilute solution of 1-135 with Grubbs second-generation catalyst, however, the desired ring closure product was not observed. Instead, an alternative mode of ring closure involving the C2–C3 double bond led to 1-169.

To steer the ring-closing metathesis toward the formation of desired 18-membered macro lactone, we oxidized the C7 alcohol of 1-135 with Dess-Martin periodinane in 89\% yield (Scheme 1.4.3.2).

\begin{center}
\includegraphics[width=\textwidth]{Scheme_1.4.3.2.pdf}
\end{center}

**Scheme 1.4.3.2.** Completion of the Synthesis

This conversion is based on the notion that the local conformation of the resultant ketone 1-170 around C7 would resemble that of dactylolide more closely than alcohol 1-135 does such that the desired ring closure would become more accessible. Gratifyingly, treatment of 1-170 with Grubbs second-generation catalyst in the presence of benzoquinone\textsuperscript{45} produced desired macrocycle 1-171 in 45\% yield.
To improve the efficiency of cyclization, we have explored other catalysts such as Grubbs-Hoveyda second-generation catalyst and sterically less encumbered catalyst as well as the first-generation Grubbs catalyst, but none of them provided 1-**171** in an increased yield. We expected that ring closure would be facilitated by generating propagating alkylidene species on the more sterically hindered trisubstituted double bond. To test this hypothesis, an RCM substrate 1-**172** that contains a relay metathesis tether was prepared. However, 1-**172** did not cyclize directly into 1-**171**, it rather deactivated itself to 1-**170** by cleaving off the relay tether. This futile metathesis is the result of a faster methylene transfer with intermediate 1-**173** compared to its macrocyclic ring closure. Based on the RCM behaviors of 1-**135**, 1-**170**, and 1-**172**, we concluded that the local conformation of the linear substrates plays a more important role than the steric hindrance on or near the reacting alkene moieties.

Completion of (–)-dactylolide was accomplished by removal of the TBS group from 1-**170** followed by oxidation of the resultant alcohol with Dess–Martin periodinane. The spectroscopic data of the synthetic material are identical to those reported in the literature for dactylolide ([α]RTD = −140.0°, c = 0.03, MeOH).

1.4.4. Summary

In conclusion, a concise total synthesis of (–)-dactylolide was achieved via a longest linear sequence of 13 steps with 7.5% overall yield. This synthetic maneuver highlights several new synthetic methodologies designed for the construction of the delicate functionalities presented in the target molecule. A ruthenium-catalyzed Alder-ene reaction of homoallylic carbonates and homopropargylic alcohols followed by a palladium-catalyzed π-allyl etherification was used for stereoselective construction of 2,6-disubstituted-4-methylene-tetrahydropyrans. A tandem sequence of ruthenium-catalyzed Alder-ene reaction of alkynyl boronates and a rhenium-catalyzed allylic transposition was implemented to install the C4–C5 Z-trisubstituted and C8–C9 disubstituted double bonds with a good regio- and stereochemical control. The novel late stage ring-closing metathesis was employed to simultaneously construct the macrocycle and the trisubstituted double bond at C16–C17. The
effectiveness and versatility of transition metal-catalyzed reactions for the synthesis of complex and
delicate carbon frameworks has been demonstrated in the current synthesis of dactylolide.

1.5. Experimental Details

1.5.1. Materials and Methods

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried
solvents. Tetrahydrofuran (THF) and diethyl ether (Et₂O) were dried by distillation from sodium and
benzophenone. Methylene chloride (CH₂Cl₂), 1,2-dichloroethane (DCE), toluene (PhMe), triethylamine
(Et₃N), acetonitrile (CH₃CN), dimethylformamide (DMF), and dimethylsulfoxide (DMSO), were dried by
distillation from calcium hydride. All reactions were monitored by thin-layer chromatography using E.
Merk silica gel 60 Å F-254 pre-coated plates (0.25 mm) and were visualized by UV, p-anisaldehyde, or
KMnO₄ staining. Flash column chromatography was performed using silica gel 60 Å (32–63 mesh)
purchased from Sorbent Technologies.¹H NMR and ¹³C NMR spectra were recorded on a Bruker Avance
DRX-500 or Bruker AV-500 spectrometers. ¹H and ¹³C chemical shifts are referenced to internal solvent
resonances (CHCl₃ ¹H, δ = 7.26; CDCl₃ ¹³C, δ = 77.0) and reported relative to SiMe₄; multiplicities are
indicated by s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet), m (multiplet) and br (broad
signal). Coupling constants, J, are reported in Hertz. Electrospray ionization (ESI) mass spectra were
recorded on a Micromass LCT equipped with a time-of-flight analyzer at the Mass Spectrometry
Laboratory in the University of Illinois at Urbana-Champaign. IR spectra were recorded using ATI
Mattson, Genesis series FTIR. Optical rotations were measured on a JASCO DIP-370 digital polarimeter
using a 100 mm path-length cell at 589 nm.
1.5.2. Experimental Procedures

Alcohol 1-142 was obtained by the modified method of Pattenden\textsuperscript{31} in 5 steps from (4S)-(+)4-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxolane. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 4.37–4.29 (m, 1H), 4.17 (dt, \(J = 11.1, J = 5.5\) Hz, 1H), 3.89–3.81 (m, 1H), 2.55 (d, \(J = 4.8\) Hz, 1H), 2.49–2.36 (m, 2H), 2.07 (t, \(J = 2.6\) Hz, 1H), 1.98–1.89 (m, 1H), 1.86–1.77 (m, 1H), 1.20 (s, 9H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) 178.8, 80.4, 71.0, 66.9, 61.2, 38.7, 35.2, 27.3, 27.1; HRMS (ESI) calcd for C\textsubscript{11}H\textsubscript{18}O\textsubscript{3}Na [M+Na]\textsuperscript{+}: 221.1154, found 221.1147. \([\alpha]\)\textsubscript{D}\textsuperscript{25} = -10.7° (c = 0.05, CH\textsubscript{2}Cl\textsubscript{2}).

Two-step / one-pot pyran synthesis: To a flame dried round-bottom flask was added alkene 1-143 (3.5 g, 17.6 mmol) and alkyne 1-142 (5.0 g, 34.7 mmol) in 20 mL of acetone. The solution was degassed by bubbling N\textsubscript{2} through the solution for 10 min. RuCp(CH\textsubscript{3}CN)PF\textsubscript{6} (530 mg, 1.2 mmol) was then added in three portions over 30 min and the reaction was stirred at room temperature for 2 h. The solvent was then removed under a stream of N\textsubscript{2}. The residue was taken up in 20 mL of CH\textsubscript{2}Cl\textsubscript{2} and cooled to -20 °C. In a separate round-bottom flask was added Pd\textsubscript{2}(dba)\textsubscript{3}·CHCl\textsubscript{3} (36 mg, 0.35 mmol) and (S,S)-Trost ligand (730 mg, 1 mmol) in 5 mL of CH\textsubscript{2}Cl\textsubscript{2}. This solution was stirred for 20 min allowing the initially purple solution to turn bright orange. This catalyst solution was added via canula to the solution described above and allowed to warm to room temperature over 1 h. After this time the solvent was removed in vacuum and the residue was purified by silica gel chromatography (20:1 hexanes:ether) to give 3.1 g (70%) of the desired cis-pyran. For 1-146: \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 5.80 (dt, \(J = 15.3, J = 6.8\) Hz, 1H), 5.63 (dt,
\[ J = 15.3 \text{ Hz}, J = 6.2 \text{ Hz}, 1\text{H}) , 4.92 \text{ (s, 1H)}, 4.90 \text{ (s, 1H)}, 4.59 \text{ (d, } J = 6.2 \text{ Hz, 2H)}, 4.32 \text{ (m, 1H)}, 4.20 \text{ (q, } J = 6.9 \text{ Hz, 2H)}, 4.18 \text{ (m, 1H)}, 3.81 \text{ (m, 1H)}, 2.80 \text{ (d, } J = 6.8 \text{ Hz, 2H)}, 2.20 \text{ (m, 3H)}, 1.77 \text{ (m, 2H)}, 1.31 \text{ (t, } J = 6.9 \text{ Hz, 3H}), 1.21 \text{ (s, 9H)}; ^{13}\text{C NMR (75 MHz, CDCl}_3 \text{) } \delta 179.0, 155.2, 144.3, 133.8, 125.9, 114.2, 68.1, 66.3, 64.2, 61.7, 44.4, 39.1, 39.0, 36.3, 27.4, 14.5; \text{ IR (film): } 3513, 2973, 1733, 1481, 1398 \text{ cm}^{-1}; \text{ HRMS (ESI) calcd for C}_{18}\text{H}_{30}\text{O}_{6}\text{Na [M+Na}\]^{+} \text{: } 365.1904, \text{ found } 365.1943. [\alpha]_D^{25} = -12.1^\circ \text{ (c = 0.01, CH}_2\text{Cl}_2). \text{ For S1: } ^{1}\text{H NMR (500 MHz, CDCl}_3 \text{) } \delta 5.81 \text{ (ddd, } J = 17.2 \text{ Hz, } J = 10.6 \text{ Hz, } J = 5.7 \text{ Hz, 1H}), 5.18 \text{ (dt, } J = 17.2 \text{ Hz, } J = 1.5 \text{ Hz, 1H}), 5.12 \text{ (d, } J = 10.6 \text{ Hz, 1H}), 4.69 \text{ (s, 2H)}, 3.76 \text{ (m, 1H)}, 3.72 \text{ (t, } J = 5.3 \text{ Hz, 2H}), 3.50 \text{ (m, 1H)}, 3.10 \text{ (t, } J = 5 \text{ Hz 1H}), 2.21 \text{ (d, } J = 13.2 \text{ Hz, 1H)}, 2.15 \text{ (d, } J = 13.2 \text{ Hz, 1H)}, 2.02 \text{ (m, 1H)}, 1.87 \text{ (m, 2H)}, 1.19 \text{ (s, 9H)}; ^{13}\text{C NMR (125 MHz, CDCl}_3 \text{) } \delta 178.4, 143.8, 138.5, 115.0, 109.1, 78.7, 75.1, 61.3, 40.5, 40.4, 38.6, 35.1, 27.1; \text{ IR (film): } 3076, 2959, 1729, 1653, 1480, 1285, 1159 \text{ cm}^{-1}; \text{ HRMS (ESI) calcd for C}_{15}\text{H}_{24}\text{O}_{3}\text{Na [M+Na}\]^{+} \text{: } 275.1623, \text{ found } 275.1629. [\alpha]_D^{25} = -19.8^\circ \text{ (c = 0.01, CH}_2\text{Cl}_2). \]

A solution of pyran 1-147 (1.5 g, 5.9 mmol) in 20 mL of CHCl3 was cooled to -78 °C. DIBAL-H (1.75 g, 3 equiv) was added dropwise over 15 min and the reaction mixture was stirred for additional 30 min. After this time, the reaction was quenched with ethyl acetate and allowed to warm to room temperature. After cooling to 0 °C, 10 mL of a saturated solution of sodium potassium tartrate was added slowly. After stirring 1 h, 30 mL of ether was added and the layers separated. The ether layer was washed successively with 10 mL of H2O and 10 mL of brine and dried over MgSO4. The solvent was removed and the residue was purified by silica gel chromatography (5:1 hexanes:EtOAc) to yield 960 mg (96%) of a colorless oil. \text{ For S1: } ^{1}\text{H NMR (500 MHz, CDCl}_3 \text{) } \delta 5.81 \text{ (ddd, } J = 17.2 \text{ Hz, } J = 10.6 \text{ Hz, } J = 5.7 \text{ Hz, 1H}), 5.18 \text{ (dt, } J = 17.2 \text{ Hz, } J = 1.5 \text{ Hz, 1H}), 5.12 \text{ (d, } J = 10.6 \text{ Hz, 1H}), 4.69 \text{ (s, 2H)}, 3.76 \text{ (m, 1H)}, 3.72 \text{ (t, } J = 5.3 \text{ Hz, 2H}), 3.50 \text{ (m, 1H)}, 3.10 \text{ (t, } J = 5 \text{ Hz 1H}), 2.21 \text{ (d, } J = 13.2 \text{ Hz, 1H)}, 2.15 \text{ (d, } J = 13.2 \text{ Hz, 1H)}, 2.02 \text{ (m, 1H)}, 1.87 \text{ (m, 2H)}, 1.19 \text{ (s, 9H)}; ^{13}\text{C NMR (125 MHz, CDCl}_3 \text{) } \delta 178.4, 143.8, 138.5, 115.0, 109.1, 78.7, 75.1, 61.3, 40.5, 40.4, 38.6, 35.1, 27.1; \text{ IR (film): } 3076, 2959, 1729, 1653, 1480, 1285, 1159 \text{ cm}^{-1}; \text{ HRMS (ESI) calcd for C}_{15}\text{H}_{24}\text{O}_{3}\text{Na [M+Na}\]^{+} \text{: } 275.1623, \text{ found } 275.1629. [\alpha]_D^{25} = -19.8^\circ \text{ (c = 0.01, CH}_2\text{Cl}_2). \]
\[ \text{1.93} (t, J = 13 \text{ Hz}, 2\text{H}), \text{1.77} (m, 2\text{H}) \]; \text{^{13}C NMR} (125 \text{ MHz, CDCl}_3) \delta \text{143.5, 138.3, 115.1, 109.1, 78.9, 77.9, 60.6, 40.5, 40.3, 38.1}; \text{HRMS (ESI) calcd for C}_{10}\text{H}_{16}\text{O}_2\text{Na [M+Na]}^+: 191.1048, \text{found 191.1038.}

Dess-Martin periodinane (2.3 g, 8.2 mmol) was added portion-wise to a solution of alcohol \text{S1} (900 mg, 5.34 mmol) in \text{CH}_2\text{Cl}_2 at 0 °C. The reaction was warmed to room temperature over 1 h. The reaction was quenched with 5 mL of sat. NaHCO\textsubscript{3} and 5 mL of sat. Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3}. Ether was added and the layers were separated and the ether layer was dried over MgSO\textsubscript{4}. The residue was purified by silica gel chromatography (5:1 hexanes:EtOAc) to afford \text{840 mg (95%)} of a colorless oil. \textit{For 1-148: ^{1}H NMR} (500 MHz, CDCl\textsubscript{3}) \delta \text{9.78} (t, J = 2.0 Hz, 1H), 5.85 (ddd, J = 17.3 Hz, J = 10.7 Hz, J = 5.6 Hz, 1H), 5.24 (dt, J = 17.2 Hz, J = 1.5 Hz, 1H), 5.11 (dt, J = 10.5 Hz, 1.5 Hz, 1H), 4.77 (brs, 2H), 3.88 (m, 2H), 2.69 (ddd, J = 16.5 Hz, J = 7.5 Hz, J = 2.4 Hz, 1H), 2.54 (ddd, J = 16.5 Hz, J = 4.9 Hz, J = 1.8 Hz, 1H), 2.27 (m, 1H), 2.25 (m, 1H), 2.04 (q, J = 11.5 Hz, 2H); \text{^{13}C NMR} (125 MHz, CDCl\textsubscript{3}) \delta \text{20.9, 142.9, 138.1, 115.5, 109.7, 78.9, 73.4, 49.6, 40.2, 40.1}; \text{HRMS (ESI) calcd for C}_{10}\text{H}_{16}\text{O}_2\text{Na [M+H]}^+: 167.1072, \text{found 167.1072.}

To a cooled solution (-10 °C) of (S,S)-Leighton reagent\textsuperscript{36} in \text{CH}_2\text{Cl}_2 (50 mL) was added to a solution aldehyde \textit{1-148} (800 mg, 4.8 mmol) in \text{CH}_2\text{Cl}_2 (5 mL). The reaction mixture was stirred for 12 h at -10 °C. After this time, the reaction was quenched, while still cold, with 1 N HCl and the mixture was stirred at r.t. for 15 min. The organic layer was separated and the aqueous layer was extracted with Et\textsubscript{2}O. The combined organic extracts were washed with brine, dried over MgSO\textsubscript{4} and filtered. The filtrate was concentrated and the residue was purified on silica gel (6:1 hexanes:EtOAc) to afford \text{S2} as a colorless oil (850 mg, 85%). \textit{For S2: ^{1}H NMR} (500 MHz, CDCl\textsubscript{3}) \delta \text{5.84} (m, 2H), 5.23 (dt, J = 17.4 Hz, 1.5 Hz, 1H), 5.11 (m, 3H), 4.75 (m, 2H), 3.92 (q, J = 5.5 Hz, 1H), 3.84 (m, 1H), 3.78 (s, 1H), 3.61 (m, 1H), 2.28 (m,
2H), 2.20 (m, 2H), 2.06 (m, 2H), 1.68 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 143.3, 138.0, 134.9, 117.2, 115.4, 109.4, 79.5, 79.0, 71.1, 41.9, 40.8, 40.3; IR (neat): 3457, 2974, 2900, 1652, 1421, 1314; HRMS (ESI) calcd for C$_{13}$H$_{20}$O$_2$Na [M+Na]$^+$: 231.1361, found 231.1364. [α]$^D_{-25}$ = -29.8 ° (c = 1, CHCl$_3$).

To a solution of alcohol S2 (800 mg, 3.8 mmol) in DMF (10 mL) was added TBSCl (860 mg, 5.7 mmol) and imidazole (400 mg, 5.8 mmol). After stirring for 1 h, water (30 mL) was added and the mixture was extracted with Et$_2$O. The extracts were dried over MgSO$_4$, filtered and concentrated. The residue was purified on silica gel (20:1 hexanes:Et$_2$O) to afford 1-140 as a colorless oil (1.2 g, 98%). For 1-140: $^1$H NMR (500 MHz, CDCl$_3$) δ 5.88 (ddd, $J$ = 17.3 Hz, $J$ = 10.8 Hz, $J$ = 5.2 Hz, 1H), 5.82 (m, 1H), 5.26 (dt, $J$ = 17.4 Hz, $J$ = 1.5 Hz, 1H), 5.11 (dt, $J$ = 10.6 Hz, $J$ = 1.5 Hz, 1H), 5.05 (m, 1H), 5.03 (m, 1H), 4.74 (d, $J$ = 1.6 Hz, 2H), 3.91 (quint, $J$ = 5.9 Hz, 1H), 3.76 (m, 1H), 3.45 (m, 1H), 2.25 (m, 4H), 1.99 (m, 2H), 1.84 (dt, $J$ = 14 Hz, $J$ = 6.7 Hz, 1H), 1.59 (dt, $J$ = 14 Hz, $J$ = 5.9 Hz, 1H), 0.88 (s, 9H), 0.06 (s, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 144.6, 139.1, 135.3, 117.1, 114.8, 108.8, 78.9, 69.0, 43.5, 42.0, 40.9, 40.8, 26.1, 18.3, 14.8, -4.0, -4.3; HRMS (ESI) calcd for C$_{19}$H$_{34}$O$_2$SiNa [M+Na]$^+$: 345.2226, found 345.2235. [α]$^D_{-25}$ = +8.0° (c = 0.01, CH$_2$Cl$_2$).

In a flame-dried flask under N$_2$ atmosphere was combined alkene 1-140 (200 mg, 0.62 mmol) and alkyne$^{37}$ 1-141 (120 mg, 0.72 mmol) in 10 mL acetone. The solution was degassed by bubbling N$_2$ for 10 min. RuCp(CH$_3$CN)PF$_6$ (27 mg, 0.062 mmol) was added in three portions over 20 min and the reaction was stirred for additional 10 min. After this time the solvent was evaporated and the residue was purified by silica gel chromatography (25:1 hexanes:Et$_2$O) to yield 200 mg (66%) of the desired product as a 5:1 mixture of boronate isomers along with 30 mg of recovered alkene (78% brsm). $^1$H NMR (300 MHz,
CDCl₃) δ 5.88 (ddd, J = 17.3 Hz, J = 10.7 Hz, J = 4.7 Hz, 1H), 5.49 (m, 2H), 5.25 (d, J = 17.3 Hz, 1H), 5.14 (brs, 1H), 5.10 (dt, J = 10.7 Hz, J = 1.7 Hz, 1H), 4.72 (brs, 2H), 4.31 (m, 1H), 3.71 (m, 1H), 3.53 (m, 1H), 3.10 (d, J = 5.5 Hz, 2H), 2.24 (m, 2H), 1.95 (m, 4H), 1.81 (brs, 3H), 1.24 (s, 12H), 0.87 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 161.1, 144.6, 139.1, 134.4, 129.2, 114.7, 108.8, 82.8, 78.7, 75.6, 71.0, 44.9, 40.8, 39.3, 26.5, 25.0, 21.3, 18.4, -3.8, -4.5; HRMS (ESI) calcd for C₂₈H₄₉BO₄SiNa [M+Na]+: 511.3391; found 511.3374. [α]D₂⁵ = +1.8° (c = 0.01, CH₂Cl₂).

To a suspension of CuI (1.46 g, 7.69 mmol) in anhydrous THF (50 mL) was added vinyl magnesium bromide (46 mL, 0.5 M in THF, 23.1 mmol) at -50 °C. Solution of epoxide (1.45 g, 7.69 mmol) in 10 mL of THF was then added to the resultant yellow suspension and the reaction mixture was stirred for 2 h at -50 °C. The reaction was quenched with aq. NH₄Cl (100 mL) and extracted with CH₂Cl₂ (2 × 20 mL). Combined organic extracts were dried over MgSO₄ and concentrated. The residue was purified by flash column chromatography (30:1 hexanes:EtOAc) to afford alcohol 1-167 (1.54 g, 87%) as a colorless oil.

¹H NMR (500 MHz, CDCl₃) δ 4.84 (s, 1 H), 4.78 (s, 1 H), 3.85–3.78 (m, 1 H), 3.62 (dd, J = 9.9 Hz, J = 3.8 Hz, 1 H), 3.46 (dd, J = 9.9 Hz, J = 6.9 Hz 1 H), 2.37 (d, J = 3.5 Hz, 1 H), 2.17 (d, J = 6.7 Hz, 2H), 1.77 (s, 3H), 0.91 (s, 3H), 0.08 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 142.3, 112.9, 69.6, 66.8, 41.6, 25.9, 22.6, 18.3, -5.3, -5.4.

To a solution of alcohol 1-167 (460 mg, 2.0 mmol), acid 1-168 (415 mg, 2.1 mmol) and triphenylphosphine (550 mg, 2.10 mmol) in THF (10 mL) at 0 °C was added DIAD (424 mg, 2.10 mmol) dropwise over 1 h. After this time the solution was allowed to warm to room temperature and the reaction was stirred for an additional 1 h. Ether (20 mL) was then added and the solution washed with water (10 mL) and brine (10 mL). The organic layer was dried with MgSO₄, filtered and the solvent was removed in vacuo. The resulting residue was purified by silica gel chromatography (15:1 hexanes:EtOAc) to give 710...
mg (87%) of a pale yellow oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.85 (d, $J = 14.8$ Hz, 1H), 6.86 (d, $J = 14.8$ Hz, 1H), 5.15–5.08 (m, 1H), 4.79 (s, 1H), 4.73 (s, 1H), 3.66 (d, $J = 5.3$ Hz, 2H), 2.38–2.24 (m, 2H), 1.75 (s, 3H), 0.88 (s, 9H), 0.04 (s, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) 163.8, 141.3, 136.8, 113.7, 99.4, 73.6, 64.1, 39.1, 26.0, 22.7, 18.4, -5.1; HRMS (ESI) calcd for C$_{13}$H$_{27}$IO$_3$SiNa [M+Na]$^+$: 433.0672, found: 433.0685. $[\alpha]_D^{25} = -5.9^\circ$ (c = 0.01, CH$_2$Cl$_2$).

To a flame-dried flask was added boronate 1-149 (200 mg, 0.4 mmol) and Et$_2$O (5 mL). Re$_2$O$_7$ (4 mg, 0.008 mmol) in 1 mL Et$_2$O was added. After stirring for 20 min 4 mg of Re$_2$O$_7$ was added and the reaction mixture was diluted with 5 mL of CH$_2$Cl$_2$. After 20 min 12 mg of Re$_2$O$_7$ was added in three portions over 1 h. The reaction mixture was stirred for an additional 30 min. After this time the solvent was evaporated and the residue was purified by silica gel chromatography (5:1 hexanes:EtOAc) to yield 73 mg (65%) of the desired product 1-139. A sample flask was charged with 1-139 (73 mg, 0.27 mmol) and vinyl iodide 1-137 (160 mg, 0.39 mmol) was added as a solution in 5 mL of 3:1 THF:H$_2$O mixture. The solution was degassed with N$_2$ before Pd(PPh$_3$)$_4$ (15 mg, 0.013 mmol) was added. After stirring for 5 min, TIOEt (140 mg, 0.56 mmol) was added resulting in the precipitation of yellow salts. After 1 h the reaction was completed. The reaction was quenched with 1 mL of sat. NaHSO$_3$ and the solution was filtered through the celite. Ether was added and the water layer was removed. The ether layer was dried over MgSO$_4$. The solvent was then removed and the residue was purified by silica gel chromatography (3:1 hexanes:EtOAc) to afford 110 mg (79%) of a pale yellow oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.55 (dd, $J = 15.0$ Hz, $J = 11.6$ Hz, 1H), 6.10 (d, $J = 11.6$ Hz, 1H), 5.88 (ddd, $J = 17.1$ Hz, $J = 10.7$ Hz, $J = 5.5$ Hz, 1H), 5.79 (d, $J = 15.0$ Hz, 1H), 5.74 (dt, $J = 15.2$ Hz, $J = 6.6$ Hz, 1H), 5.57 (dd, $J = 15.2$ Hz, $J = 6.4$ Hz, 1H), 5.26 (d, $J =$
17.1 Hz, 1H), 5.13 (d, J = 10.7 Hz, 1H), 5.10 (m, 1H), 4.78 (brs, 1H), 4.74 (brs, 3H), 4.27 (m, 1H), 3.77 (m, 1H), 3.69–3.65 (m, 2H), 3.35 (ddt, J = 11.2 Hz, J = 6.3 Hz, J = 2.3 Hz, 1H), 2.63 (dd, J = 13.4 Hz, J = 8.2 Hz, 1H), 2.43–2.18 (m, 8H), 2.07–1.95 (m, 1H), 1.92 (s, 3H), 1.76 (s, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); 13C NMR (125 MHz, CDCl₃) 167.1, 145.7, 144.2, 141.8, 140.5, 138.8, 134.6, 128.1, 126.7, 120.1, 115.3, 113.4, 109.1, 79.0, 77.8, 72.6, 71.4, 64.2, 40.8, 40.6, 40.2, 39.2, 26.0, 25.2, 22.8, 18.4, -5.1; HRMS (ESI) calcd for C₃₁H₅₀O₅SiNa [M+Na]+: 553.3325, found: 553.3326. [α]D₂₅ = -17.9° (c = 0.01, CH₂Cl₂).

To a solution of alcohol 1-135 (100 mg, 0.19 mmol) in CH₂Cl₂ was added Dess-Martin periodinane (160 mg, 0.38 mmol). After 1 h the solvent was removed and ether containing a small amount of pyridine was added. The reaction was filtered through celite and the solvent was removed. The residue was purified by silica gel chromatography (3:1 hexanes:EtOAc) to give 88 mg (89%) of a colorless oil. For 1-170: 1H NMR (500 MHz, CDCl₃) δ 7.46 (dd, J = 15.0 Hz, J = 11.1 Hz, 1H), 6.94 (dt, J = 15.8 Hz, J = 7.0 Hz, 1H), 6.20 (d, J = 11.1 Hz, 1H), 6.19 (dt, J = 15.8 Hz, J = 1.4 Hz, 1H), 5.90 (ddd, J = 17.5 Hz, J = 10.5 Hz, J = 5.3 Hz, 1H), 5.85 (d, J = 15.0 Hz, 1H), 5.27 (dt, J = 17.5 Hz, J = 1.4 Hz, 1H), 5.14 (dt, J = 10.5 Hz, J = 1.4 Hz, 1H), 5.11 (m, 1H), 4.78 (brs, 3H), 4.74 (brs, 1H), 3.80 (m, 1H), 3.69–3.65 (m, 2H), 3.53 (s, 2H), 3.48 (m, 1H), 2.52 (dt, J = 14.9 Hz, J = 6.9 Hz, 1H), 2.43 (dt, J = 14.9 Hz, J = 5.7 Hz, 1H), 2.36 (dd, J = 14.0 Hz, J = 5.5 Hz, 1H), 2.29 (dd, J = 14.0 Hz, J = 8.0 Hz, 1H), 2.28 (d, J = 13.3 Hz, 1H), 2.21 (d, J = 13.3 Hz, 1H), 2.04 (t, J = 12.6 Hz, 1H), 1.97 (t, J = 12.6 Hz, 1H), 1.89 (s, 3H), 1.76 (s, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); 13C NMR (125 MHz, CDCl₃) 196.1, 167.0, 144.5, 143.6, 142.0, 141.7, 139.9, 138.5, 131.2, 127.1, 121.0, 115.5, 113.4, 109.6, 79.1, 76.8, 72.8, 64.2, 44.8, 40.5, 40.4, 39.3, 39.2, 26.0, 25.1, 22.8, 18.4, -5.3; HRMS (ESI) calcd for C₃₁H₅₀O₅SiNa [M+Na]+: 551.3169, found: 551.3144.
[\alpha]_D^{25} = -8.2° (c = 0.01, CH₂Cl₂). To a solution of 1-170 (16 mg, 0.03 mmol) in 25 mL CH₂Cl₂ was added Grubbs second generation catalyst (3 mg, 0.003 mmol). The reaction was stirred in a sealed Schlenk tube at 65 °C for 3 h. After this time the solvent was removed in vacuo and the residue was purified by silica gel chromatography (5:1 hexanes:EtOAc) to afford 7.5 mg (50%) of a colorless oil. For 1-171: \(^1\)H NMR (500 MHz, CDCl₃) δ 7.63 (dd, J = 15.0 Hz, J = 11.5 Hz, 1H), 6.84 (ddd, J = 16.2 Hz, J = 9.9 Hz, J = 4.3 Hz, 1H), 6.11 (d, J = 11.5 Hz, 1H), 5.93 (d, J = 15.0 Hz, 1H), 5.91 (d, J = 16.2 Hz, 1H), 5.23–5.16 (m, 2H), 4.72 (brs, 2H), 4.19 (d, J = 13.5 Hz, 1H), 3.97 (ddd, J = 10.7 Hz, J = 8.3 Hz, J = 2.8 Hz, 1H), 3.73–3.66 (m, 2H), 3.27 (t, J = 10.9 Hz, 1H), 2.97 (d, J = 13.5 Hz, 1H), 2.41–1.81 (m, 8H), 1.78 (s, 3H), 1.71 (s, 3H), 0.89 (s, 12H), 0.07 (s, 3H), 0.06 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl₃) 198.3, 166.9, 146.5, 143.9, 142.8, 139.3, 132.9, 131.6, 129.4, 125.6, 121.4, 109.2, 76.7, 76.1, 71.3, 65.2, 45.2, 42.4, 41.2, 40.9, 40.5, 26.0, 23.6, 18.4, 16.8, -5.04, -5.09; HRMS (ESI) calcd for C₂₉H₄₄O₅SiNa [M+Na]⁺: 523.2856 , found: 523.2854. [\alpha]_D^{25} = -87.7° (c = 0.0054, CH₂Cl₂).

To a solution of 1-171 (7 mg, 0.14 mmol) in 2 mL MeOH and 0.5 mL CH₂Cl₂ was added 2 drops of 1 M HCl. The reaction stirred at room temperature for 2 hours. After this time ether was added and the solution was washed with sat. NaHCO₃. The organic layer was then dried and the solvent removed in vacuum. The residue was purified by silica gel chromatography (2:1 hexanes:EtOAc) to give 5 mg (95%) of a colorless oil. For S3: \(^1\)H NMR (500 MHz, C₆D₆) δ 7.65 (dd, J = 15.0 Hz, J = 11.5 Hz, 1H), 6.84 (ddd, J = 16.2 Hz, J = 9.3 Hz, J = 4.2 Hz, 1H), 6.12 (d, J = 11.7 Hz, 1H), 5.95 (d, J = 15.0 Hz, 1H), 5.93 (d, J = 16.2 Hz, 1H), 5.29 (m, 1H), 5.18 (d, J = 8.0 Hz, 1H), 4.73 (brs, 2H), 4.17 (d, J = 13.7 Hz, 1H), 3.98 (ddd, J = 11.1 Hz, 8.1 Hz, J = 2.8 Hz, 1H), 3.74 (m, 2H), 3.28 (t, J = 10.5 Hz, 1H), 3.03 (d, J = 13.7 Hz, 1H), 2.40–1.90 (m, 8H), 1.80 (s, 3H), 1.73 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl₃) δ 198.2, 167.1,
To a solution of alcohol S3 (4 mg, 0.01 mmol) and pyridine (2 μL) in CH₂Cl₂ (1 mL) was added dropwise a solution of Dess-Martin periodinane (9 mg in 1mL of CH₂Cl₂) at 0 °C. The reaction mixture was warmed to r.t. and stirred for 1 h. The mixture was diluted with Et₂O and filtered through a pad of celite. The filtrate was concentrated and the residue was purified by silica gel chromatography (3:2 hexanes:EtOAc) to give 3.7 mg (95%) of a colorless solid. For (-)-1-01: \textbf{1H NMR} (500 MHz, CDCl₃) δ 9.67 (s, 1H), 7.63 (dd, J = 15.1 Hz, J = 11.6 Hz, 1H), 6.84 (ddd, J = 16.1 Hz, J = 8.6 Hz, J = 5.9 Hz, 1H), 6.15 (d, J = 11.5 Hz, 1H), 6.00 (d, J = 16.2 Hz, 1H), 5.96 (d, J = 15.0 Hz, 1H), 5.32 (dd, J = 11.5 Hz, J = 2.5 Hz, 1H), 5.24 (d, J = 8.0 Hz, 1H), 4.74 (s, 2H), 3.97 (m, 2H), 3.32 (dddd, J = 11.4 Hz, J = 9.1 Hz, J = 2.5 Hz, J = 2.5 Hz, 1H), 3.23 (d, J = 14.5 Hz, 1H), 2.55 (d, J = 14.0 Hz, 1H), 2.39–2.28 (m, 3H), 2.17 (ddd, J = 13.2 Hz, J = 1.6 Hz, J = 1.6 Hz, 1H), 2.11 (ddd, J = 13.0 Hz, J = 1.6 Hz, J = 1.6 Hz, 1H), 1.86 (s, 3H), 1.72 (s, 3H); \textbf{13C NMR} (125 MHz, CDCl₃) δ 199.0, 197.4, 166.3, 146.0, 144.0, 143.5, 140.4, 131.4, 130.9, 130.5, 125.6, 119.8, 109.3, 76.4, 75.7, 75.3, 44.9, 40.8, 40.5, 39.73, 39.69, 24.1, 16.0; \textbf{HRMS} (ESI) calcd for C₂₃H₂₉O₅ [M+H]⁺: 385.2015, found: 385.2006. [\alpha]_D^{25} = -140° (c = 0.03, MeOH).
1.6. References


PART II

ONE-STEP SYNTHESIS OF BIS-SPIROKETALS VIA GOLD-CATALYZED HYDROALKOXYLATION–HYDRATION SEQUENCE

2.1. Introduction and Structural Features of bis-Spiroketal

The tricyclic bis-spiroketal ring system\(^1\) (Figure 2.1.1) is an architecturally complex structural motif that consists of three rings joined through ketal spiro-centers in the way that ketal oxygens of each spiro-atom belong to two different rings. In other words, bis-spiroketal structure contains two spiroketal moieties, which share a common central ring. Although many combinations of ring sizes and junctions (e.g. A-F) are theoretically possible, only tricyclic spirokets of general types B, C, and E are found in number of biologically active natural products such as spirolides,\(^2\) pinnatoxins and pteriatoxins,\(^3\) spirastrellolides,\(^4\) and azaspiracids.\(^5\)

![Figure 2.1.1. Various bis-Spiroketal Ring Systems](image)

Two oxygen atoms adjacent to the central ring of bis-spiroketal structure can be located on the same side to give cis-\(O\)-spiroketal. Positioning of oxygen atoms on opposite sides of the common ring results in a trans-\(O\)-spiroketal (Scheme 2.1.1). The trioxadispiroketals can exist in several different isomeric forms due to the facile isomerization of two spirocenters under mild acidic conditions. Thermodynamic stability of these compounds depends on several factors, including combined endo- and exo-anomeric effect, steric effects, dipole-dipole interactions, and chelation effects such as hydrogen bonding. In cases of unsubstituted bis-spiroketals, the doubly anomerically stabilized isomer in transoidal form is preferred.
However, the substituents on the carbon chain and introduction of other controlling elements may significantly alter this preference. As a result, formation of bis-spiroketals under equilibrating conditions usually leads to a thermodynamic mixture of products. Prediction of the composition of resultant mixture can be complicated because multiple factors influence overall stability of the bis-spiroketal systems. For example, a cis-isomer of simple 6-6-6 bis-spiroketal \((cis-O-2-01)\) if existed in an all-chair form should be more stable than the corresponding trans-\(O-2-01\) due to the most favorable anomeric effect. Though, it has been demonstrated both experimentally and computationally that the transoidal isomer is lower in energy by 0.3–0.7 kcal/mol because of dipole-dipole repulsion (Scheme 2.1.1). The central ring of the bis-spiroketal adopts a twist-boat geometry to maximize anomeric stabilization and minimize 1,3-diaxial- and dipole-dipole interactions. Consequently, the most thermodynamically favorable trans-isomer benefits by four anomeric effects, whereas the corresponding cis-isomer loses some anomeric stabilization to relieve the destabilizing dipole-dipole interactions.

![Scheme 2.1.1. Equilibrium Behavior of 6-6-6-bis-Spiroketals](image)

**Scheme 2.1.1. Equilibrium Behavior of 6-6-6-bis-Spiroketals**

In general, most 6-6-5 bis-spiroketal ring systems are less stable than 6-5-6 spirocycles due to the destabilizing 1,3-diaxial repulsion. The difference in potential energy between model compounds \(2-03\) and \(2-04\) (Scheme 2.1.2) was calculated to be 1.8 kcal/mol (MM2) and 2.5 kcal/mol (AM1). Therefore, thermodynamically controlled spirocyclization would lead to the preferential formation of 6-5-6 bis-spiroketal over 6-6-5 ring system. However, formation of the latter can be facilitated in the presence of
other stabilizing interactions. Among the isomers of model 6-5-6 trioxadispiroketal **2-03** the *cis*-isomer with axially oriented C–O bonds (*cis*-O-ax,ax) is the most thermodynamically preferable due to a double anomeric effect and equatorially oriented methyl groups. The corresponding *trans*-isomer (*trans*-O-ax,eq) with two equatorial methyl groups is higher in energy by 2.2-2.5 kcal/mol, which is caused by the loss of one of the anomeric stabilization. Placing one methyl group in an axial position with two axial C–O bonds (*trans*-O-ax,ax) costs the energy value of 1.7-2.3 kcal/mol. However, having an axial methyl substituent with the loss of one anomeric interaction leads to an isomer (*cis*-O-ax,eq) that is higher in energy by 5-6 kcal/mol.

![Scheme 2.1.2. Relative Energies of Isomeric 6-5-6- and 6-6-5-bis-Spiroketals](image)

This trend, however, is less pronounced for the model compound **2-05** bearing an additional tertiary alcohol substituent on the 6-membered ring, which is the substitution pattern found in the BCD-ring system of pinnatoxins. The doubly anomeric *cis*-O-ax,ax isomer is the most stable form, and the *trans*-O-ax,eq spiroketal is slightly higher in energy by 1.1 kcal/mol (MM2), but it becomes most stable if a hydrogen bonding between the tertiary hydroxyl group and the oxygen of tetrahydropyran ring is
established. Thus, the extent of stabilization by hydrogen bonding overrides the loss of an anomic effect. This result is consistent with the experimental observations for trans-\(O\text{-}ax\),eq isomer of 2-05. The axially oriented secondary methyl group in trans-\(O\text{-}ax\),ax isomer is destabilizing only by 0.5 kcal/mol, whereas cis-\(O\text{-}ax\),eq isomer becomes significantly less stable because of the loss of a stabilizing anomic effect.

2.2. Synthetic Approaches toward bis-Spiroketal

Compared to the numerous syntheses of simpler bicyclic spiroketas,\(^9\) there are only a limited number of synthetic methods toward tricyclic bis-spiroketal, a less common ketal scaffold of polyketide-based natural products.\(^2\)-\(^5\) The most widely used approach for the synthesis of this structural fragment is an acid-catalyzed cyclization of 1,4- or 1,5-diketodiols, which yields the most thermodynamically stable bis-spiroketal as a major product.\(^10\) Therefore, the synthesis of nonanomeric bis-spiroketal present in several natural products is challenging, and often requires acid-catalyzed postequilibration at the late stage of the synthesis to allow additional interactions within the molecule.\(^9\) The typical synthesis involves installation of two carbonyl groups or their masked equivalents and two protected hydroxyl groups, which often requires multi-step manipulations for protection and deprotection of these functional groups. Several insightful approaches that do not involve the acid-catalyzed spiroketalization have been developed for the construction of a bis-spirocyclic core.\(^11\),\(^12\),\(^13\),\(^14\),\(^15\) Majority of these approaches give mixtures of tricyclic ketal, therefore, an acid-catalyzed equilibration to improve the product selectivity is still required. On the contrary, the formation of nonthermodynamic bis-spiroketal scaffolds presents a significant challenge, and only a few methods appeared recently for the synthesis of simple bicyclic spiroketal of this type.\(^16\)

2.2.1. Electrochemical Oxidation of Furans

In 1963 Ponomarev and Markushina have reported the first synthesis of tricyclic bis-spiroketal ring system by electrochemical oxidation of furan bearing tethered hydroxyl groups.\(^17\) Electrolytic alkoxylation using nickel cathode and carbon anode afforded bis-spiroketal trans-2-06 and alkylated
trans-2-07 with good efficiency, although the yield of tricyclic spiroketal trans-2-08 bearing a phenyl substituent was low (Scheme 2.2.1.1).

Scheme 2.2.1.1. Synthesis of bis-Spiroketals via Electrochemical Oxidation of Furans

2.2.2. Double Addition of Organocerium Reagents to Cyclic Anhydrides

Synthesis of 5,5,5-bis-spiroketals relying on sequential addition of organocerium nucleophiles to lactones was achieved by Cohen in 1990.\(^\text{18}\) Due to the high oxophilicity of cerium, organocerium reagents undergo preferential monoaddition to five-, six-, and seven-membered lactones without opening of the lactol cerium alkoxide intermediate. This property of cerium organometallics allowed for the preparation of bis-spiroketals by sequential addition of dichlorocerium reagent to succinic anhydride (Scheme 2.2.2.1). The organocerium reagent was prepared by reductive opening of 3,3-dimethyloxetane with LDBB followed by transmetallation with CeCl\(_3\).

Scheme 2.2.2.1. Synthesis of bis-Spiroketals via Double Addition of Organocerium Reagents

Addition of one equivalent of 2-09 to succinic anhydride followed by protonation yielded spirolactone 2-10, which was then treated with a second equivalent of 2-09 to afford diastereomeric mixture of trans-
and cis-2-11 in good yield. The ratio of spiroketals depends on the conditions used for acidic workup. Interestingly, monoaddition of cerium reagent 2-09 to maleic and phtalic anhydrides delivered the corresponding spirolactones in reduced yields of 40% and 25%, respectively.

2.2.3. Alkylation of Lactones with Sulfonyl Anions

The sequence of nucleophilic addition of an α-sulfonyl anion addition to δ-valerolactone followed by acid-catalyzed spiroketalization was employed in the synthesis of 6-6-6 bis-spiroketal by Brimble (Scheme 2.2.3.1).19 Thus, addition of lithiated sulfone 2-12 to δ-valerolactone at -78 °C afforded an equilibrium mixture of linear ketol and cyclic hemiketals. This mixture without isolation was then subjected to acid-catalyzed cyclization in the presence of CSA to give tricyclic spiroketal 2-13 as a mixture of diastereomers in a 1:1 ratio.

![Scheme 2.2.3.1. Lactone Alkylation in the Synthesis of 6-6-6-bis-Spiroketals](image)

2.2.4. Photochemical Cyclization of Tetrahydropyranyl Ketoketals

The radical-based approach for the synthesis of 5-6-5 bis-spiroketal ring systems was reported by Descoutes in 1891.20 Photochemical transformation of ketoacetal 2-14 via the formation of an oxygen-centered radical followed by 1,6-hydrogen translocation and a subsequent recombination of the resulting radical at the anomeric center afforded a kinetic mixture of spiroketals 2-15 (Scheme 2.2.4.1). Treatment of the product mixture with 4-hydroxybutan-2-one under acidic conditions delivers products of transacetalization anti- and syn-2-16 in a 2:1 ratio. Subjection of individual isomers of 2-16 to
photocyclization conditions gave four possible isomers of bis-spiroketal 2-17 from each substrate, which suggests that no spiroisomerization occurred under the reaction conditions. The authors have also shown that the acid-catalyzed isomerization of kinetically formed bis-spiroketals produces a thermodynamic mixture of diastereomers of 2-17.

Scheme 2.2.4.1. Synthesis of 5-6-5 bis-Spiroketals via Photolysis of Tetrahydropyranyl Ketoketals

2.2.5. Oxidative Radical Cyclizations with Hypervalent Iodine

Hypoiodite-based oxidative radical spiroketalisation has been widely utilized by Baker and Brimble in the synthesis of bis-spiroketal scaffolds. This protocol employs the Suárez modification of an oxidative radical cyclization with iodobenzene diacetate PhI(OAc)₂ as an oxidant. Synthesis of tricyclic
spirokets using this free radical functionalization can be commenced from preformed spirokets via a single oxidative cyclization or in sequential fashion from tetrahydropyranyl alcohols. The early applications of this method can be found in the syntheses of 6-6-5 spiroketal structures of salinomycin-narasin class of natural products. For instance, in a synthetic study of natural product 17-epi-20-deoxysalinomycin, the Brimble group utilized precursors 2-20 and 2-21, prepared from lactone 2-18 and alkyne 2-19, for radical spiroketalisation. Irradiation of individual spirokets 2-20 and 2-21 in the presence of iodobenzene diacetate and iodine produced 1.7:1 ratio of bis-spiroketals trans-2-22 and cis-2-22 (Scheme 2.2.5.1). The major trans-isomer has the most thermodynamically stable configuration in the 1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene ring system present in the salinomycin family of polyether antibiotics. Moreover, trans-2-22 possesses the same stereochemistry as 17-epi-20-deoxysalinomycin, which makes it a key intermediate in the synthesis.

Scheme 2.2.5.1. Synthesis of 17-epi- and 17-epi-21-epi-Salinomycin bis-Spirokets via an Oxidative Radical Cyclization

The stereochemical outcome of this reaction can be explained based on the mechanism of oxidative cyclization (Scheme 2.2.5.2). Photochemical homolytic cleavage of hypoiodite intermediates derived from the reaction of free alcohol moiety of the substrates 2-20 and 2-21 with Phl(OAc)_2 generates
corresponding alkoxy radicals 2-23 and 2-24. The subsequent 1,5-H-abstraction by the oxygen-centered radical forms common intermediate radical 2-25 which undergoes oxidation with iodine to carbocation 2-26. The subsequent nucleophilic attack by an hydroxyl group from a less hindered $\alpha$-face delivered major trans-2-22 isomer. Alternatively, ring formation from a more sterically crowded $\beta$-face leads to the cis-product.

Scheme 2.2.5.2. Mechanism of Photochemical Hypoiodite Oxidation

Interestingly, a different stereochemical outcome of radical cyclization was observed by the Brimble group in a synthetic study of bis-spirocyclic core of CP44,161 (Scheme 2.2.5.3). Thus, an oxidative cyclization of 1:1 diastereomeric mixtures of model hydroxyspiroketals 2-27a,b and 2-30a,b afforded a reversed ratio of the corresponding bis-spiroketals products cis-2-28/2-29a and cis-2-31/2-29b. In each case the cis-compound of 17-epi-21-epi-salinoketal configuration (cis-2-28 or cis-2-31) was obtained as the major diastereomer.
Scheme 2.2.5.3. Synthesis of 17-epi-21-epi-Salinomycin and CP44,161 bis-Spiroketal via an Oxidative Radical Cyclization

The corresponding trans-isomers with the 17-epi-salinomycin configuration (trans-2-28 or trans-2-31) were not observed as they underwent epimerization at the C17 ketal position to form salinomycin-configured cis-bis-spiroketal 2-29a and 2-29b, respectively as a consequence of unfavorable 1,3-diaxial repulsion caused by the methyl substituent. The minor bis-spiroketal 2-29b has the same stereochemistry at C24 as that of both salinomycin and CP44,161 natural products.

Suárez and co-workers found that the synthesis of tricyclic spiroketal could be achieved via an iterative oxidative radical cyclization from tetrahydropranyl alcohols. In 1996, they reported that
treatment of substrate mixture 2-32 derived from tri-O-acetyl-D-glucal with PhI(OAc)$_2$/I$_2$ system in CCl$_4$ gave spiroacetal 2-33 as a single product (Scheme 2.2.5.4). Subsequently, the removal of the silyl protecting group delivered an intermediate alcohol, which was subjected to the second intramolecular hydrogen abstraction/cyclization to give bis-spiroketals cis-2-34 and trans-2-34 in 58% and 20% yield respectively.

Scheme 2.2.5.4. Synthesis of 6-6-5 bis-Spiroketal via an Iterative Radical Cyclization

This approach was further elaborated by Brimble and co-workers in their campaign$^{25}$ toward an enantioselective synthesis of 5-5-6 bis-spiroketal present in spirolides B and D (Scheme 2.2.5.5). Thus, irradiation of 2-35, which was prepared as a 1:1 mixture of epimers, with a 60 W desk lamp in the presence of iodobenzene diacetate and iodine, delivered a 1:1 mixture of spiroketals 2-36. The resultant mixture was subjected to a second oxidative radical cyclization after cleavage of the tert-butylidiphenylsilyl ether to afford bis-spiroketal 2-37 in 81% yield as a 1:1:1:1 mixture of diastereomers. Treatment of this mixture with m-CPBA delivered β-epoxide 2-38 as a single diastereomer. In the presence of m-CPBA, diastereomeric bis-spiroketals underwent equilibration to the most thermodynamically stable isomer, which in turn underwent stereoselective epoxidation from the β-face due to the directing effect of the oxygen atom on tethahydrofuran ring. The regioselective reductive opening of epoxide moiety with DIBAL-H, oxidation of intermediate alcohol, and methylation of the
resultant ketone introduced a tertiary alcohol that present in the spirolides. The resultant \textit{trans}-spiroketal 2-39 is the most thermodynamically stable isomer and its structural integrity can be maintained by a hydrogen bonding network of the tertiary alcohol. Equilibration of this bis-spiroketal to the corresponding \textit{cis}-isomer found in spirolides is expected after incorporation of this functionality to the macrocyclic structure where other factors would stabilize this \textit{cisoidal} conformation.

![Scheme 2.2.5.5. Synthesis of Spirolides B and D bis-Spiroketal via an Oxidative Radical Cyclization](image)

\subsection*{2.2.6. Oxidative Rearrangement of 2-Acylfurans}

The oxidative rearrangement of 2-acylfurans was developed for the syntheses of 6-6-5 spirocyclic core of salinomycin-nasarin\textsuperscript{22} natural products. Preparation of the model tricyclic spiroketal by this method was reported in 1989 by Albizati.\textsuperscript{26} The sequential alkylation and acylation of furan afforded 2-furyl ketone 2-40, the oxidation of which with NBS in THF-H\textsubscript{2}O solution delivered an equilibrium mixture of 5-6 spiroketal 2-42 through the intermediacy of diketoalcohol 2-41 (Scheme 2.2.6.1). Treatment of this mixture with 5% HF in acetonitrile induced the cleavage of primary TBS silyl ether followed by subsequent spiroketalization-equilibration to afford a 1:1 thermodynamic mixture of trioxaspiroketal 2-43.
Scheme 2.2.6.1. Synthesis of a Model 6-6-5 bis-Spiroketal via an Oxidative Rearrangement of 2-Acylfuran

In a similar approach by Kocienski treatment of ketone 2-40 with bromine in methanol afforded 6-5 spiroketal intermediate 2-44, which rearranged to a 1:1 mixture of bis-spiroketals 2-43 upon treatment with 40% HF in acetonitrile (Scheme 2.2.6.1).

An elegant application of this method in natural product synthesis was demonstrated by Brown and Kocienski in their total synthesis of salinomycin. The oxidative rearrangement of 2-acylfuran 2-45 with NBS in THF-\(\text{H}_2\text{O}\) mixture followed by treatment with hydrogen fluoride afforded a 3:1 mixture of bis-spiroketal products favoring the isomer cis-2-46 with undesired 17-epi-21-epi-configuration (Scheme 2.2.6.2). The unwanted 17-epi-21-epi- stereochemistry was corrected at the later stage of the synthesis by acidic equilibration of cisoidal 2-47 to transoidal 2-48 bis-spiroketal bearing only incorrect stereochemistry at C17.
Scheme 2.2.6.2. Synthesis of Salinomycin by Brown and Kocienski

This synthetic intermediate was further elaborated to 17-episalinomycin, which was subjected to a second acid-catalyzed isomerization to deliver the natural product. The late stage equilibration of 17-epi-configuration to the less thermodynamically stable conformation of bis-spiroketal core adopted by natural salinomycin was possible due to its stabilization by the long distance hydrogen bonding between the ether oxygen in the five-membered ring and the C9 hydroxyl group.

2.2.7. Bromonium Ion-Induced Oxidative Cyclization of Furanyl Diols

The oxidative cyclization of two pendant hydroxyl groups on the furan core induced by bromonium ion to form 5-5-5 and 6-5-6 bis-spiroketal moieties was reported by Stockman in 2005. This approach similar to that of Albizati and Kocienski employs the bromination of properly tethered furanyl diols with NBS in THF-H₂O mixture at 0 °C to induce a tandem addition of two hydroxyl groups. This method allowed for the formation of 5-5-5 bis-spiroketal as an inseparable 1:1 mixture of cis- and trans-isomers in 46% yield (Scheme 2.2.7.1). Similarly, 6-5-6 product 2-50 was isolated as a 1:1 mixture of
diastereomers in 65% yield. The 6-5-6 trioxaspiroketalts are separable by column chromatography, however, they undergo equilibration in solution in a period of seven hours.

Scheme 2.2.7.1. Bromonium Ion-Induced Oxidative Cyclization

2.2.8. Singlet Oxygen-Mediated Oxidative Cyclization of Furan Derivatives

Different tactic for an oxidative spirocyclization of furanyl diols in the synthesis of model 5-5-5 and 6-5-6 bis-spiroketalts has been developed by Vassilikogiannakis. The oxidative [4+2]-cycloaddition between furan substrates of type 2-51 and singlet oxygen generated in the presence of methylene blue as a sensitizer gives endoperoxide 2-52, which undergoes an intramolecular nucleophilic attack by the pendant hydroxyl group to afford spiroketal hydroperoxide 2-53 (Scheme 2.2.8.1). In situ reduction of this hydroperoxide with dimethyl sulfide forms the corresponding hemiketal, which undergoes subsequent cyclization to deliver trioxaspiroketal under the influence of traces of acid.

Scheme 2.2.8.1. Synthesis of bis-Spiroketalts via a Singlet Oxygen-Mediated Oxidative Cyclization
Through this sequence, 5-5-5 bis-spiroketal \(2-49\) was obtained in 80% yield as 1:1 mixture of \(cis-/trans-\)isomers. Analogously, 6-5-6 product \(2-50\) was isolated in 77% as a 55:45 mixture of diastereoisomers. Tricyclic 6-5-6 compound \(2-54\) bearing a trisubstituted double bond for the subsequent functionalization to pinnatoxin and pteriatoxin spiroketal moiety was also prepared in 80% yield as a \(cis-/trans-\) mixture. The advantage of using singlet oxygen for an oxidative cylizations of furans as oppose to the electrophilic oxidation with NBS or \(\text{Br}_2\) (See sections 2.2.6 and 2.2.7) is its selectivity for the furan functionality, which eliminated functional group protection manipulations.

This tandem Diels-Alder cycloaddition – reductive spiroketalization method was further applied to the synthesis of the 6-6-5 tricyclic spiroketal of salinomycin-nasarin natural products.\(^{22}\) Visible light irradiation of a mixture containing cyclization precursor \(2-55\) (prepared in three steps from furan) and methylene blue as a sensitizer under oxygen bubbling followed by sequential addition of dimethyl sulfide and \(p\)-TsOH delivered separable a 2:1 mixture of 6-6-5 bis-spiroketals \(cis-2-61\) and \(trans-2-61\) in 53% yield (Scheme 2.2.8.2).\(^{29}\) In addition, the product of undesired fragmentation of spirolactone \(2-60\) was isolated in 22% yield.

Scheme 2.2.8.2. Synthesis of a Model 6-6-5 bis-Spiroketal via a Singlet Oxygen-Mediated Oxidative Cyclization
The authors explained the outcome of this reaction based on the mechanistic rationale shown in Scheme 2.2.14. In this mechanism, upon exposure of the substrate to singlet oxygen endoperoxide 2-56 was formed. Due to the increased electrophilicity of carbonyl group in 2-56, it underwent a facile nucleophilic addition of the tethered alcohol to form hemiketal 2-57. Subsequent fragmentation of the endoperoxide via the kinetically favorable pathway A resulted in the formation of hydroperoxide 2-58, which upon reduction with dimethyl sulfide afforded intermediate 2-59. Transketalization of 2-59 in the presence of p-TsOH yielded a mixture of bis-spiroketalts 2-61. The formation of undesired sporilactone 2-60 is a consequence of a competing γ-butyrolactone elimination followed by reduction (fragmentation pathway B).

The efficient one-step assembly of 5-5-5 bis-spirolactone moiety found in prunolides\(^3^0\) via double photooxygenation of a 1,2-difuryl alkene precursor was demonstrated by the same group in 2005 (Scheme 2.2.8.3).\(^3^1\)

\textbf{Scheme 2.2.8.3}. Synthesis of the 5-5-5 bis-Spiroketal Core of Prunolides
The cyclization precursor 2-62 was prepared from furan by a three-step sequence including silylation of 2-lithiofuryl anion, Weinreb ketone synthesis, and McMurry coupling as a 3:1 mixture of \( E/Z \)-isomers. After separation of double bond isomers, they were subjected to photooxygenation conditions under visible light irradiation in the presence of Rose Bengal sensitizor to afford a 2:1 mixture of \( trans/cis \)-bis-spiroketals 2-67. The major product \( trans \)-2-67 possesses the same stereochemistry as the spiroketal core found in natural prunolides. This cascade transformation starts with a double [4+2]-cycloaddition between two furan moieties of 2-62 and \( O_2 \). Silyl migration – fragmentation of the endoperoxides in 2-63 followed by double ketalization of diacid 2-64 affords the corresponding butenolide intermediate 2-65. Dehydration of 2-65 induced by participation of the methoxy-group followed by rotation around the C–C single bond and subsequent cyclization afforded spiroketal products.

2.2.9. Iodoetherification – Dehydroiodination of Alkenyl Diols

The synthesis of trioxadispiroketalts could be achieved from suitably tethered alkenyldiols via a sequence of iodoetherification – dehydroiodination developed by Mootoo and co-workers.\(^{15}\) The synthesis of spirocycles commences with cross-metathesis between two terminal alkenes employed for a quick installation of the necessary internal double bond of cyclization precursor. Thus, cross-metathesis between sugar derivative 2-68 and an excess amount of 5-hexen-1-ol afforded ketal-alkene substrate 2-69 as a mixture of \( E/Z \)-isomers after treatment with PPTS in methanol (Scheme 2.2.9.1). Iodoetherification of 2-69 with iodonium dicollidine perchlorate produced a mixture of cyclic ethers 2-70 via 6-exo-trig pathway, which was subsequently exposed to AgOTf in wet THF to afford a mixture of bis-spiroketal products 2-71 in 52% overall yield. Dehydroiodination leads to the formation of a highly reactive enol ether intermediate, which undergoes spiroketalization under mild acidic conditions via the generation of an oxycarbenium ion. Stereoselectivity of the spiroketalization step is not affected by the stereochemistry of the iodoether precursor 2-70, which is consistent with a mechanism involving the cyclic oxocarbenium ion. In this addition-elimination process the alkene moiety is regioselectively functionalized to a ketal and, therefore, overall process is equivalent to a metal-free regioselective alkyne hydroalkoxylation.
Cross Metathesis – Iodoetherification – Dehydroiodination Sequence

The iodoetherification – dehydroiodination sequence was initially developed for the synthesis of the ABCD-ring system of azasparacid-1. The spirocyclization substrate 2-74 was prepared by the Julia-Kocienski olefination of 2-72 and 2-73 with concomitant desilylation as a 5:1 mixture of $E/Z$-isomers (Scheme 2.2.9.2).

Treatment of 2-74 with iodonium dicollidine resulted in the formation of a mixture of unstable iodoethers 2-75. The crude mixture was then treated with AgOTf followed by addition of water and PPTS.
to obtain bis-spiroketal 2-77 as a sole product in 62% isolated yield through the intermediacy of oxocarbenium ion 2-76. Formation of the single product of the reaction is a result of the most thermodynamically favorable configuration of bis-spiroketal 2-76 found in azaspiracids due to a double anomic effect.

2.2.10. π-Lewis Acid-Catalyzed Hydroalkoxylation of Alkynes

π-Lewis acid-catalyzed hydration of alkynes is widely employed in the synthesis of simple spiroketals. It employs alkyne as a synthetic equivalent of ketone if high regioselectivity of addition can be achieved. A similar approach in the synthesis of bis-spiroketal 2-76 is less apparent. Nevertheless, the synthesis of azaspiracid trioxadispiroketal moiety based on this transformation was reported in 2007 by Forsyth (Scheme 2.2.10.1). The alkyne moiety at C10–C11 in cyclization precursor 2-80 was designed as an equivalent of ketone functionality at C10 to reduce the possibility of C7–C8 alkene isomerization into C8–C9 alkene, which might occur if ketone is present at this position. To prepare enyne 2-80, two precursors 2-78 and 2-79 were coupled under copper-catalyzed conditions and the acetate was reductively cleaved. The prepared enyne 2-80 was then converted into the desired bis-spiroketal 2-84 in 75% upon treatment with AuCl and PPTS.

Scheme 2.2.10.1. Synthesis of the ABCD-Ring System of Azaspiracid-1 by Forsyth
The authors suggest that the reaction sequence starts with either initial associative syn-addition of the C6-hydroxyl group to an activated alkyne to generate A-ring enol ether 2-81. Alternatively, anti-oxametalation would generate an isomeric enol vinyl gold specie followed by protiodeauration to liberate the catalyst. Protonation of the resultant enol ether at C11 would give oxocarbenium ion 2-82 upon which a nucleophilic addition of C13 methoxy oxygen closes the B ring. Subsequent transfer of the methyl group to a solvent molecule delivers the bis-spiroketal 2-84 as a sole product under acid-catalyzed equilibration conditions.

Another transition metal-promoted hydroalkoxylation of internal alkyne was recently demonstrated by Smith in the synthesis of 5-5-6 bis-spiroketal containing the C26–C40 fragment of Spirostrellolide B. Interestingly, regioselectivity of this hydroalkoxylation depends on the choice of catalyst as well as the environment around the triple bond. Thus, treatment of cyclization substrate 2-85 bearing a protected alcohol at C38 with Zeise’s dimer in ether triggered the expected 6-exo-dig cyclization to afford a mixture of hemiacetals 2-86 after an aqueous workup (Scheme 2.2.10.2). This mixture was subjected to a deprotection/cyclization sequence to furnish the 5-6-6 bis-spiroketal of spirastrellolide B in 38% overall yield as a 7:1 mixture of diastereomers. The double anomic structure of the major isomer of 2-87 was determined by the analysis of NMR data of desilylated compound 2-88. Notably, all attempts to achieve alkyne hydroalkoxylation/spiroketalization sequence employing AgCl in different solvents were unrewarding. Different outcome was observed in the cyclization of a fully deprotected compound. Treatment of 2-89 with DDQ afforded a mixture of hemiketals 2-90. Exposure of this mixture to a catalytic amount of AuCl and PPTS in MeOH resulted in the formation of the corresponding furan (not shown). On the other hand, the reaction in THF yielded a small amount of 5-5-7 bis-spiroketal 2-91 in addition to the furan product. This result suggests that the conversion of 2-90 to a 5-6-6 tricycle by the intramolecular attack of the C27 hydroxyl group on the AuCl-activated alkyne through a 6-exo-dig pathway is not favorable. Instead, a fast 5-exo-dig cyclization of hemiketal hydroxyl group leads to the functionalization of alkyne moiety at C32 and the formation of 5-5-7 product 2-91.
Scheme 2.2.10.2. Synthesis of the C26–C40 Fragment of Spirastrellolide B by Smith

2.2.11. Transposition of Allylic Alcohols

Bis-spiroketalization through a rhenium-catalyzed transposition of allylic alcohols was demonstrated by Floreancig in 2011. Exposure of diketodiol 2-93 obtained by an oxidative enolate coupling reaction from 2-92 to a catalytic amount of rhenium oxide in dichloromethane afforded an equilibrium mixture of trans-2-94 and cis-2-94 in a 1:1 ratio (Scheme 2.2.11.1). The reaction proceeds via double 1,3-transposition of alcohols followed by ketalization trapping. Due to a reversible nature of allylic transposition and sufficient acidity of rhenium oxide, the initially formed cyclization intermediates undergoes facile equilibration to form a thermodynamic mixture of products. The degree of stereocontrol in this process is related to the thermodynamic differences between diastereomeric products and to the propensity of the individual steps for equilibration. Although only a single example of bis-spiroketal
formation was reported, this method can find wide application for the synthesis of thermodynamically favorable spiroketals.

Scheme 2.2.11.1. Synthesis of 6-5-6 bis-Spiroketals via [1,3]-Transposition of Allylic Alcohols

2.2.12. Synthesis of bis-Spiroperoxyketals

Scheme 2.2.12.1. Synthesis of bis-Spiroperoxyketals via Ozonolysis

An interesting method relying on internal trapping of carbonyl oxides during ozonolysis was reported in 2006 for the synthesis of novel class of bis-spiroperoxyketals. Birch reduction of aromatic compound 2-95 gave 1,4-dihydro product 2-96, which was subjected to ozonolysis without purification followed by
treatment with a catalytic amount of \( p\)-TsOH to afford \textit{trans}-spiroperoxyketal 2-97 as a single diastereomer in 27\% yield for three steps (Scheme 2.2.12.1). Analogous reaction of substrate 2-98 gave a 1:1 diastereomeric mixture of spiroketals 2-99 and 2-100.

\textbf{2.2.13. Acid-Catalyzed Spiroketalization}

As it was mentioned earlier, most bis-spiroketal syntheses are based on acid-catalyzed spiroketalization of suitably functionalized diketodiols.\textsuperscript{9} Although several examples of forming three rings simultaneously have been reported,\textsuperscript{10} the majority of acid-catalyzed spiroketalizations require two independent cyclization steps separated by functionalization of the substrate or protection – deprotection reactions. Therefore, this approach requires elaborated liner precursors, which entails lengthy synthetic sequences. As the examples of this method, only the acid-catalyzed double cyclization of 1,4-diketone substrates in context of the synthesis of the BCD-ring system of pinnatoxins, and the double intramolecular hetero-Michael addition (DIHMA) in the synthesis of the ABCD-moiety of azaspiracid-1 will be discussed here.

The first synthesis of the BCD-dispiroketal moiety of \((\rightarrow)-pinnatoxin\ A\) was reported by Murai and co-workers in 1997.\textsuperscript{10b,37} Exposure of tetraketone 2-101 to aqueous hydrogen fluoride in acetonitrile afforded desired double anomeric bis-spiroketal 2-102 as a major product together with a small amount of other spiroketalization products (Scheme 2.2.13.1). The mixture was separated by column chromatography and minor diastereomers were converted to 2-102 by resubjection to the reaction conditions. The ketone at C15 was stereoselectively methylated to afford \textit{cis}-2-103. The equilibration behavior of bis-spiroketal products was then investigated. It was found that ketone tricyclic ketal 2-102 is stable under acidic conditions, however, methylated \textit{cis}-2-103 undergoes rapid isomerization in the presence of traces of acid to afford a thermodynamic mixture with less anomerically stabilized \textit{trans}-2-103. The equilibrium ratio of two spiroketals depends on the acid and the solvent used in the reaction. It has been suggested that a less thermodynamically favorable structure is stabilized by hydrogen bonding between an equatorial hydroxyl group at C15 and the tetrahydropyranyl oxygen of the D-ring. The increased stability of bis-spiroketal
2-102 bearing ketone functionality is attributed to an enhanced anomeric effect caused by the carbonyl group.

Scheme 2.2.13.1. Synthesis of the BCD-bis-Spiroketal of (−)-Pinnatoxin A by Murai

The reversed ratio of spiroketal products favoring a less thermodynamically stabilized isomer was observed by Hirama and co-workers. Treatment of 2-104 with p-TsOH in t-BuOH gave a mixture of undesired trans-2-105 and desired cis-2-105 in a 2.6:1 ratio (Scheme 2.2.13.2). When spiroketalization reaction was performed in toluene as a less polar aprotic solvent the double anomeric isomer cis-2-105 was formed as a major product in a 1.3:1 ratio.

Scheme 2.2.13.2. Synthesis of the BCD-bis-Spiroketal of Pinnatoxin A by Hirama
In later report\(^{38}\) the authors describe that the desired BCD-spiroketal of natural (+)-pinnatoxin can be obtained as a sole product of the reaction upon fine tuning of the reaction conditions. Thus, exposure of substrate 2-106 to camphorsulfonic acid in methanol at room temperature to remove the acetonide followed by replacement of methanol with toluene selectively generated bis-spiroketal 2-107 in 84\% yield. The authors hypothesize that the observed selectivity is due to the stabilization caused by a long range hydrogen bond.

In the first total synthesis of (−)-pinnatoxin A, Kishi employed an acid-catalyzed cyclization of diketone 2-108 to afford a mixture of cis- and trans-bis-spiroketals 2-109.\(^{10d}\) Composition of this mixture can be affected by the choice of acids and solvents or by the addition of metal ions (Scheme 2.2.13.3). In the presence of MgBr\(_2\), cis-2-109 completely epimerizes to the less thermodynamically favorable isomer. On the other hand, silylation of alcohol at C15 converted the equilibrium mixture to product 2-110 possessing a naturally configured spiroketal unit.

**Scheme 2.2.13.3.** Synthesis of the BCD-bis-Spiroketal of (−)-Pinnatoxin A by Kishi

A similar behavior was observed by the Zakarian group in their synthetic studies toward (+)-pinnatoxin A (Scheme 2.2.13.4).\(^{10g}\) When spiroketalization was performed in methanol, a 2.2:1 ratio of diastereomeric spiroketalts was obtained favoring desired cis-2-112. This ratio increases in less polar solvents. Equilibration in dichloromethane delivered cis/trans-2-112 in a 2.7:1 ratio, which becomes 4.8:1 in toluene, and the optimal selectivity (9.8:1) was achieved when cyclohexene was used as the solvent.
Scheme 2.2.13.4. Synthesis of the BCD-bis-Spiroketal of (+)-Pinnatoxin A by Zakarian

An elegant approach for the ABCD-trioxabisspiroketal core of azaspiracid-1 as well as the DEF-ring system of spirastrellolide A based on DIHMA spiroketalization process was developed by Forsyth. In this vein, an ynone functionality was incorporated in substrate 2-113 as a synthetic equivalent of the ketone at C10 and as a handle for subsequent incorporation of the C7–C8 double bond (Scheme 2.2.13.5). Selective cleavage of the C6 and C17 TES ethers upon treatment of 2-113 with p-TsOH in toluene initiates the C-ring closure through an attack of the liberated C17 oxygen on the C13 ketone.

Scheme 2.2.13.5. Synthesis of the ABCD-bis-Spiroketal of Azasparacid-1 by Forsyth

Subsequent B-ring formation via a 5-exo-dig conjugate addition of the exocyclic C13 oxygen of hemiketal intermediate on the C8–C10 ynone leads to the formation of enone 2-114. Final closure of the
A-ring by the second hetero-Michael addition of the C6 hydroxyl furnishes bis-spiroketal 2-115 in moderate yield after thermodynamic equilibration at room temperature for 1-2 days.

Acid-catalyzed conditions were not effective for the spiroketalization of ynone 2-116 in the synthesis of the DEF-fragment of spirastrellolide A due to a facile β-elimination of the C37 ether functionality (Scheme 2.2.13.6). To overcome this problem, a stepwise hetero-Michael addition was employed.

Scheme 2.2.13.6. Synthesis of the DEF-ring System of Spirastrellolide A by Forsyth

In order to suppress the undesired elimination, the TES-ethers in 2-116 were cleaved at low temperature. The obtained diol was then treated with potassium tert-butoxide, which induced the addition of C37 alkoxide onto C35 ketone followed by conjugate addition of the C35–38 hemiketal to the C29–C31 ynone to form spiroketal 2-117. Subsequent treatment of enone 2-117 with CSA in benzene allowed for a second hetero-Michael addition of the C17 hydroxyl group to afford trioxadispiroketal 2-118.
2.3. Synthesis of bis-Spiroketals from 4,6/5,7-Diyne-1,n-diols via Gold-Catalyzed Hydroalkoxylation – Hydration Sequence*

Examination of the available methods for bis-spiroketal synthesis indicates that the majority of the approaches requires multistep sequences and orchestrated use of protection – deprotection and oxidation manipulations to engage alcohol functionalities into selective cyclizations. Therefore, there is a need for the development of an efficient method for the synthesis of bis-spiroketals possibly without or with minimal number of protection and deprotection steps. With this aim in mind, we envisaged a strategy that involves a dimerization of 4-pentynol and 5-hexynol derivatives to form 4,6-diyne-1,n-diols and 5,7-diyne-1,n-diols followed by their one-step conversion into bis-spiroketal structures via tandem additions of tethered hydroxyl groups and a water molecule on the diynes catalyzed by π-acids 41 (Scheme 2.3.1).

Scheme 2.3.1. Synthetic Approach toward bis-Spiroketal Structures

The regioselectivity in the addition of nucleophiles to π-acid-complexed alkynes has been shown to depend on the electronic and steric factors on and around the reaction center as well as the nature of the incoming nucleophile. 42 The hydration of internal alkynes 43 catalyzed by transition metals is a convenient

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synthetic method to introduce a carbonyl group to carbon frameworks, although the low regioselectivity of this process is yet to be addressed.\textsuperscript{44}

In terms of developing a new synthetic method for bis-spiroketal moieties based on regioselective hydration of alkynes, we hypothesized that a diyne with tethered hydroxyl groups should be an ideal substrate because one of the alkyne moieties would behave as a regio-directing element due to its electron-withdrawing nature while the other alkyne moiety undergoes metal-catalyzed hydroalkoxylation (Scheme 2.3.1). If the hydroalkoxylation of the second alkyne moiety, via the cyclization of the newly formed 3° glycosidic hydroxyl in 5-endo-mode or that of the other hydroxyl in 6-exo-mode were still regioselective, the overall formal double hydration process of a diyne would constitute an effective method for the construction of a bis-spiroketals moiety. The preference between cis-/trans- isomers is expected to depend primarily on the anomeric effect and the A-values of R and R' groups.

Our hypothesis was first tested with 5,7-dodecadiyne-1,12-diol 2-119a. With a platinum-based catalyst system PtCl\textsubscript{2}/CO\textsuperscript{45} in toluene and water as an additive, the expected 6-5-6 bis-spiroketal trans-2-120a and cis-2-120a were isolated in 41\% yield in 2.2:1 ratio (Table 2.3.1, entry 1).\textsuperscript{46} With this encouraging initial result in hand, we further examined the general reactivity trend of 2-119a under different reaction conditions and other π-acid catalysts. The reaction of 2-119a with PtCl\textsubscript{2} in absence of CO required higher reaction temperature (110 °C), which provided only 20\% of 2-120a (entry 2). The combination of PtCl\textsubscript{2} and CuCl\textsubscript{2} did not improve the yield but the reaction proceeded at a lower temperature and catalyst loading (entry 3). However, under otherwise identical conditions, the Ph\textsubscript{3}PAuCl–AgOTf catalyst system gave only trace amount of 2-120a (entry 4). To improve yield and shorten the reaction time, microwave irradiation was employed.\textsuperscript{47} Initial reactions under these conditions showed promising results: cyclization of 2-119a with PtCl\textsubscript{2}–CuCl\textsubscript{2} at 80 °C afforded 2-120a in a 50\% yield compared to 20\% yield without microwave irradiation (entry 5). Replacement of platinum catalyst with Ph\textsubscript{3}PAuCl–AgOTf in a toluene-methanol system provided slightly improved efficiency (entry 6), which was further optimized by increasing catalyst loading up to 12 mol \% (entry 7).
Table 2.3.1. Optimization of Catalyst and Reaction Conditions

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<th>Catalyst system</th>
<th>Catalyst (mol %)</th>
<th>T (°C)/t (h)</th>
<th>Yield (%)$^b$</th>
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<td>9</td>
<td>D</td>
<td>Ph$_3$PAuCl–AgOTf$^d$</td>
<td>12</td>
<td>60/4.5</td>
<td>75</td>
</tr>
<tr>
<td>10</td>
<td>D</td>
<td>2-121</td>
<td>12</td>
<td>45/1.5</td>
<td>56</td>
</tr>
</tbody>
</table>


It was found that the same reaction in an alternative solvent system (CH$_2$Cl$_2$–methanol, 4:1) at a lower temperature (60 °C) afforded the highest yield (75%) of 2-120a (entry 9). In the presence of a different cationic gold complex (acetonitrile)[(2-biphenyl)di-tert-butylphosphine]gold(I) hexafluoroantimonate (2-121),$^{48}$ the reaction was completed within 1.5 h at 45 °C even without microwave irradiation, but the yield dropped to 56% (entry 10).

The generality of bis-spiroketal formation via gold-catalyzed reactions of diynediols was further examined with a variety of substrates under the optimized conditions (Table 2.3.2). Treatment of 2-119b with Ph$_3$PAuCl–AgOTf under conditions D (CH$_2$Cl$_2$–methanol, 4:1, 12 equivalents of water) with microwave irradiation gave 6-5-5 bis-spiroketalts trans-2-120b and cis-2-120b in a 2.1:1 ratio with 68%
yield (entry 2). On the other hand, under the same conditions, 2-119c afforded 28% of 5-8 bicyclic spiroketal 2-122 in addition to the expected 5-5-5 bis-spiroketals trans-2-120c and cis-2-120c (1.9:1) in 43% yield (entry 3). It is interesting to note that 5-5-6 and 6-5-6 bis-spiroketals are substructures in many compounds occurring in nature but any natural product with a 5-5-5 spiroketal moiety like in 2-120c has not been discovered. The lack of 2-120c in nature may imply that bis-spiroketal 2-120c is not stable enough as a structural element to be adopted by nature. Therefore, we surmised that 2-120c should tend to isomerize to a more stable structural isomer 2-122. Surprisingly, however, the isolated cis-2-120c and trans-2-120c readily interconvert to reach their equilibrium ratio (1.9:1) without any sign of their conversion to 2-122, and the isolated 2-122 remained intact for a long period of time in neat or in chloroform. The stereochemistry of these bis-spiroketal structures was tentatively assigned on the basis of their dipole-dipole interactions between two C–O bonds, where the trans-isomer is expected to be lower in energy than the corresponding cis-isomer.

To gain further insight into the stereochemical course of the reaction, combinations of 1° and 2° alcohols on the diynediol substrates were employed. Under the optimized conditions, diol 2-119d with 1° and 2° alcohols provided bis-spiroketals trans-2-120d and cis-2-120d in a 2.7:1 ratio with 67% yield (entry 4). Diol 2-119e with both 2° alcohols provided trans-2-120e and cis-2-120e (plus another isomer) in a 1.2:1 ratio with good yield (entry 5). In this case we expected to obtain four compounds (cis/trans-isomers of d,l- and meso-compound), however, only three products, tentatively assigned as trans-2-120e and cis-2-120e (plus an inseparable isomer), were isolated.49 Substrate 2-119f with an isopropyl group provided an inseparable mixture of bis-spiroketals trans-2-120f and cis-2-120f in a 2.0:1 ratio with 64% yield (entry 6). Similar reaction with 2-119g gave four isomers of 2-120g that contain a methyl substituent on the five-membered ring as an inseparable mixture only in 55% isolated yield primarily due to its volatility (entry 7). In contrast, 2-119h afforded trans-2-120h and cis-2-120h that contain a methyl group on the six-membered ring in a 2.3:1 ratio with good yield (entry 8).
Table 2.3.2. Tandem Cyclization of Diynediols Catalyzed by a Gold Complex

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dyne</th>
<th>T (°C)/t (h)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Products</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OH</td>
<td>60/4.5</td>
<td>trans-2-120a, cis-2-120a</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>OH</td>
<td>40/0.5</td>
<td>trans-2-120b, cis-2-120b</td>
<td>68</td>
</tr>
<tr>
<td>3</td>
<td>OH</td>
<td>35/0.5</td>
<td>trans-2-120c, cis-2-120c, 2-122</td>
<td>71</td>
</tr>
<tr>
<td>4</td>
<td>OH</td>
<td>45/3.5</td>
<td>trans-2-120d, cis-2-120d</td>
<td>67</td>
</tr>
<tr>
<td>5</td>
<td>OH</td>
<td>45/1.5</td>
<td>trans-2-120e, cis-2-120e, isomer</td>
<td>68</td>
</tr>
<tr>
<td>6</td>
<td>OH</td>
<td>45/1.0</td>
<td>trans-2-120f, cis-2-120f</td>
<td>64</td>
</tr>
<tr>
<td>7</td>
<td>OH</td>
<td>40/1.0</td>
<td>trans-2-120g, cis-2-120g, isomers</td>
<td>55</td>
</tr>
<tr>
<td>8</td>
<td>OH</td>
<td>45/0.5</td>
<td>trans-2-120h, cis-2-120h</td>
<td>61</td>
</tr>
</tbody>
</table>

[a] Reactions were run with 12 mol % of Ph₃PAuCl-AgOTf catalyst and 12 equiv of water in CH₂Cl₂-methanol (4:1) solvent mixture under microwave irradiation. [b] Isolated yields. [c] Ratios of formed products were determined by ¹H NMR.
These results indicate that the substituent in the equatorial orientation on the six-membered ring plays an important role to control the stability of the spiroketals. All isolated cis- and trans-bis-spiroketals in their pure form slowly isomerized to reach their equilibrium composition in about a month at room temperature in chloroform although a noticeable difference of their interconversion rates were observed. Furthermore, the cis/trans composition of bis-spiroketals was found to be dependent on the number and nature of the substituents. In case of disubstituted diyndiols diastereomeric d,l- and meso-isomers provided different product compositions.

To understand how the stereochemistry affects the formation and the behavior of bis-spiroketal isomers, C<sub>2</sub>-symmetric diyndiol 2-119i and meso-isomer 2-119j were prepared and their spiroketalization was examined (Scheme 2.3.2). Enantiomerically pure C<sub>2</sub>-symmetric substrate 2-119i gave bis-spiroketal trans-2-120i as a single product in 74% yield upon treatment with catalyst 2-121. Formation of only one isomer can be rationalized based on the most favorable anomeric effect and the two equatorially oriented methyl groups. As expected, the most stable isomer trans-2-120i remained unchanged even after more than one year.

On the other hand, meso-substrate 2-119j afforded a mixture of two bis-spiroketals cis-2-120j and trans-2-120j in a 2.3:1 ratio (60%). The isolated cis-2-120j and trans-2-120j in their pure forms slowly isomerized to their equilibrium composition within three weeks at room temperature in chloroform. The
**trans-2-120j** may assume an alternative conformation **trans-2-120j’**, where both methyl groups become equatorial at the cost of anomeric stabilization on one of the spiroketals. On the basis of two distinctive methyl and methine proton resonances in $^1$H NMR, we tentatively concluded that the minor isomer is **trans-2-120j** not **trans-2-120j’**.50

For a plausible reaction mechanism, we propose that the first ring closure occurs in a regioselective manner to generate pyranyl enol ether **2-123** (Scheme 2.3.3). The regioselectivity of the first addition of a nucleophile to the $\pi$-acid-activated diynes should be the consequence of the remote triple bond that behaves as an electron-withdrawing substituent while the proximal triple bond is reacting. With enol ether **2-123**, two different reactions can occur under the given conditions. Hydration of the enol ether moiety would form **2-124**, whereas the second 6-**exo**-dig addition would generate bis-enol ether **2-125**.

![Scheme 2.3.3. Plausible Mechanism for Gold-Catalyzed bis-Spiroketal Formation from Diynediols](image)

Mono-hydration of **2-125** would lead to **2-126**, which can be generated via another path from mono tetrahydropyran derivative **2-124**. Final ring closure of **2-126** catalyzed by either a metal catalyst or proton would form bis-spiroketal **2-120a**. Alternatively, a 5-**endo**-dig addition51 of the 3° hydroxyl group to the alkyne would form dihydrofuran derivative **2-127**, which then ring-close to render the formation of **2-120a**. Another scenario would involve dihydration of **2-125** to form **2-128** followed by its dehydrative ring closure. Interruption of the spiroketalization of **2-119i** after 1 h resulted in the formation of bis-enol...
ether similar to 2-125 and bis-spiroketal trans-2-120i in a 1:1 ratio. This mixture readily gives trans-2-120i as a single product at room temperature in chloroform even without any catalyst within 24 h. This result indicates that one of the possible reaction pathways involves the formation of bis-enol ether as an intermediate although other reaction pathways cannot be excluded.

2.4. Synthetic Attempts toward the BCD-Ring System of (+)-Pinnatoxin A

Encouraged by the generality of bis-spiroketal formation via hydroalkoxylation–hydration of diynediols, we envisioned a synthesis of the BCD-subunit of (+)-Pinnatoxin A by applying the newly developed strategy. Retrosynthetically, we planned to access bis-spiroketal 2-129 from an advanced intermediate diyne 2-130, which can be prepared via Cadiot–Chodkiewicz coupling52 of bromoalkyne 2-131 and alkylnol 2-132 (Scheme 2.4.1).

Scheme 2.4.1. Retrosynthetic Analysis of the BCD-Subunit of (+)-Pinnatoxin A

Homoallylic alcohol at C12 of 2-131 was planned to introduce via asymmetric allylation of aldehyde precursor 2-133. Tertiary stereocenter at C15 of aldehyde 2-133 would in turn be accessible from the rearrangement of epoxide 2-134 derived from geraniol. Coupling partner 2-132 was planned to be
synthesized through a regioselective opening of epoxide 2-135 with a hydride donor. The epoxide 2-135 can be traced back to conjugated ester 2-136, which could be generated from 5-hexyn-1-ol.

Synthesis of spiroketalization substrate 2-130 commenced with Sharpless asymmetric epoxidation\(^5\) of geraniol to afford epoxyaldehyde 2-134 in quantitative yield (Scheme 2.4.2). Chlorination of 2-134 and a double elimination with the chloroepoxide upon treating with \(n\)-BuLi afforded the C15 alcohol and the alkyne moieties of enyne 2-137. The tertiary alcohol was then protected as its TBS-ether. The trisubstituted double bond was then oxidatively cleaved with osmium tetroxide followed by treatment with sodium periodate to furnish aldehyde 2-133. The Leighton asymmetric allylation\(^5\) and subsequent bromination of the alkyne 2-138 gave 2-131 in 8:1 \(dr\).

Scheme 2.4.2. Synthesis of Building Blocks for Diyne Spirocyclization Precursor

Synthesis of the coupling partner 2-132 commenced with the conversion of 5-hexyn-1-ol to trimethylsilyl substituted alkyne 2-139 by a three-step sequence. Alcohol 2-139 was then oxidized and the resultant aldehyde was subjected to the Horner–Wadsworth–Emmons reaction with triethyl
phosphonoacetate to afford alkene 2-136 stereoselectively. Reduction of the ester moiety with DIBAL-H followed by the Sharpless asymmetric epoxidation delivered epoxyacohol 2-135. The regioselective opening of the epoxide at a proximal carbon was achieved by treatment of 2-135 with Red-Al, providing diol 2-141 after desilylation with TBAF. Selective protection of the primary alcohol as its TIPS-silyl ether afforded 2-132.

Cadiot–Chodkiewicz coupling$^{53}$ of bromoalkyne 2-131 and alkynol 2-132 afforded diyne 2-130 in 80% yield (Scheme 2.4.3). With diyne 2-130 in hand, we next turned to its gold-catalyzed hydroalkoxylation – hydration. Exposure of this substrate to standard cyclization conditions employing 2-121 as a catalyst afforded two products. To our disappointment, reaction gave only partially cyclized compounds lacking the C15-silyl ether, structures of which we were unable to fully characterize.

![Scheme 2.4.3. Spiroketalization Attempt of Fully Functionalized Substrate](image)

To simplify structural assignment of cyclization products, a model substrate 2-142 bearing a C15-tertiary siloxy substituent was prepared and its spiroketalization was investigated under several gold-catalyzed conditions (Table 2.4.1). Treatment of this substrate with catalyst 2-121 in CH$_2$Cl$_2$-MeOH-H$_2$O solvent mixture at 45 °C delivered two products: hemiketal 2-143 resulted from a 6-exo-dig cyclization of C12 alcohol, and enol ether 2-144 formed by cyclization of the primary hydroxyl group at C23 on the C18–C19 triple bond (entry 1). Interestingly, hemiketal 2-143 underwent elimination of the siloxy moiety to give a C14–C15 trisubstituted double bond. In product 2-144, however, the C15 siloxy-group was preserved. Similar results were obtained with employment of Ph$_3$PAuSbF$_6$ as a catalyst (entry 2). In order
to facilitate a cascade cyclization, PPTS was added to the reaction mixture, however, no improvements were observed. Reaction in the presence of 2-121 and 5 mol % of PPTS delivered only monocyclized products 2-143 and 2-144 (entry 3). Spiroketalization catalyzed by IPrAuSbF₆ (2-145) and PPTS delivered hemiketal 2-143 along with recovered starting material (entry 4). AuCl and Au(III) catalyst 2-146 were also ineffective (entries 5, 6).

Table 2.4.1. Spiroketalization Trials of Model Substrate

<table>
<thead>
<tr>
<th>Entry</th>
<th>Gold Catalyst</th>
<th>PPTS (mol %)</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-121</td>
<td>–</td>
<td>2-143 + 2-144</td>
</tr>
<tr>
<td>2</td>
<td>Ph₃PAuSbF₆</td>
<td>–</td>
<td>2-143 + 2-142</td>
</tr>
<tr>
<td>3</td>
<td>2-121</td>
<td>5</td>
<td>2-143 + 2-144</td>
</tr>
<tr>
<td>4</td>
<td>2-145</td>
<td>5</td>
<td>2-143 + 2-142</td>
</tr>
<tr>
<td>5</td>
<td>2-146</td>
<td>5</td>
<td>2-143 + 2-142</td>
</tr>
<tr>
<td>6</td>
<td>AuCl</td>
<td>5</td>
<td>2-143 + 2-142</td>
</tr>
</tbody>
</table>

These results suggest that the enol ether intermediate formed upon 6-exo-dig cyclization of C12-alcohol undergoes the facile elimination of a silanol to form conjugated diene. This elimination is faster than protonation of enol ether to form oxocarbenium intermediate followed by its hydration to afford hemiketal bearing the preserved C15 stereocenter.
To slow down the undesired elimination, a substrate possessing an unprotected alcohol at C15 was prepared (Scheme 2.4.4). However, subjection of this compound to cyclization conditions delivered the same hemiketal 2-143 as a sole product although higher reaction temperature was required for the complete conversion of starting material.

Scheme 2.4.4. Spiroketalization of C15-Unprotected Substrate

At this point, it was clear that the tertiary oxy-functionality at C15 was problematic for cascade hydroalkoxylation – hydration under the employed Lewis acidic conditions. Therefore, we decided to prepare spiroketalization precursor bearing a secondary alcohol at this position. Thus, heating of a mixture of 1,1-dimethylallyl alcohol and ethyl vinyl ether in the presence of mercury acetate induced a Claisen rearrangement of the formed ether intermediate to give aldehyde 2-148 (Scheme 2.4.5).

Scheme 2.4.5. Spiroketalization of Substrate Bearing C15-Secondary Alcohol
Addition of lithium acetylide to 2-148 produced propargyl alcohol 2-149. Subsequent oxidative cleavage of the trisubstituted double bond of 2-149 followed by allylation furnished diol coupling partner 2-151. Cadiot–Chodkiewicz reaction\textsuperscript{52} of 2-151 and 2-152 afforded spiroketalization substrate 2-153. Subjection of this compound to the hydroalkoxylation – hydration conditions led only to fast decomposition of starting material.

Preliminary results of spiroketalization reactions of 2-130, 2-142, 2-147, and 2-153 indicate that substituent at the propargylic position of diynediol plays a critical role for the outcome of overall cyclization cascade. Therefore, more investigation is necessary to explore the substitution effect at propargylic positions. Based on the obtained data, preparation of carefully designed substrate that would allow for the cyclization reaction and subsequent functionalization at C15 is critical for successful synthesis of the BCD-subunit of pinnatoxin A.

2.5. Summary

In conclusion, we have developed an efficient one-step synthesis of 5-5-5, 5-5-6, and 6-5-6 bis-spiroketals from 4,6-diyne-1,n-diols and 5,7-diyne-1,n-diols catalyzed by \pi-\text{acids}. A mixture of \textit{cis}- and \textit{trans}-bis-spiroketals was generally obtained from each substrate and most isolated \textit{cis}- and \textit{trans}-bis-spiroketals undergo interconversion to reach their equilibrium composition except for compounds originally formed as single isomers due to the strong thermodynamic preference for their formation. Anomeric effect and the number and nature of equatorial substituents on the pyran rings are important factors that dictate the ratio of \textit{cis}- and \textit{trans}-bis-spiroketals. Application of the developed bis-spiroketalization method to the synthesis of the BCD-spiroketal of (+)-pinnatoxin A revealed that substitution at the propargylic position of diynediol significantly suppresses the cyclization. New strategy based on installation of the requisite tertiary alcohol moiety after spiroketalization is necessary for the synthesis of the BCD bis-spiroketal of natural product.
2.6. Experimental Details

2.6.1. Materials and Methods

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF) and diethyl ether (Et₂O) were dried by distillation from sodium and benzophenone. Methylene chloride (CH₂Cl₂), toluene (PhMe), triethylamine (Et₃N), acetonitrile (CH₃CN), dimethylformamide (DMF), and dimethylsulfoxide (DMSO), were dried by distillation from calcium hydride. All reactions were monitored by thin-layer chromatography using E. Merk silica gel 60 Å F-254 pre-coated plates (0.25 mm) and were visualized by UV, p-anisaldehyde, or KMnO₄ staining. Flash column chromatography was performed using silica gel 60 Å (32–63 mesh) purchased from Sorbent Technologies. Microwave assisted reactions were performed using single-mode CEM Discover microwave synthesis system. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker Avance DRX-500 or Bruker AV-500 spectrometers. ¹H and ¹³C chemical shifts are referenced to internal solvent resonances (CHCl₃ ¹H, δ = 7.26; CDCl₃ ¹³C, δ = 77.0) and reported relative to SiMe₄; multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet), m (multiplet) and br (broad signal). Coupling constants, J, are reported in Hertz. Electrospray ionization (ESI) mass spectra were recorded on a Micromass LCT equipped with a time-of-flight analyzer at the Mass Spectrometry Laboratory in the University of Illinois at Urbana-Champaign.
2.6.2. Experimental Procedures

4-Pentyne-1-ol (1.5 g, 17.8 mmol), TMEDA (5.3 mL, 35.7 mmol), copper chloride (0.88 g, 8.9 mmol) and acetone (65 mL) were introduced in a 250 mL round bottom flask. Oxygen was then bubbled through the solution, which was vigorously stirred for 3 hours. After that acetone was evaporated and water (10 mL) was added to the reaction mixture. Product was extracted with CH$_2$Cl$_2$ (3 × 15 mL), combined extracts were dried over MgSO$_4$ and solvent was removed under vacuum. The reaction mixture was purified by flash column chromatography (2:1 hexanes:EtOAc) to afford diyne 2-119c (1.42 g, 96%) as a colorless oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 3.72 (t, $J = 6.0$ Hz, 4H), 2.37 (t, $J = 7.0$ Hz, 4H), 1.94 (brs, 2H), 1.76 (qn, $J = 6.2$ Hz, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 76.9, 65.6, 61.3, 31.0, 15.7; HRMS (ESI) calcd for C$_{10}$H$_{14}$O$_2$Na [M+Na]$^+$: 189.0891, found 189.0882.

Bromoalkyne S1 was prepared in 96% overall yield according to the literature procedure.$^{56}$ Diyne S2 was obtained following the general procedure for diyne synthesis.$^{52}$ CuCl (238 mg, 2.4 mmol) was added to a 30% $n$-BuNH$_2$ (11 mL) aqueous solution at room temperature that resulted in the formation of a blue solution. A few crystals of hydroxylamine hydrochloride were added to discharge the blue color. The alkyne (525 mg, 5.35 mmol) was added to the solution at room temperature forming a yellow acetylide suspension that was immediately cooled in an ice-water mixture. The bromoalkyne (1.56 g, 5.35 mmol) was added at once and the ice bath was removed. More crystals of hydroxylamine hydrochloride were added throughout the reaction as necessary to prevent the solution from turning blue or green. After several additions of hydroxylamine hydrochloride (10 min), the reaction mixture had a rusty color. At this point the reaction was complete according to TLC. Products were extracted with CH$_2$Cl$_2$ (3 × 10 mL),
dried over MgSO₄, and concentrated under reduced pressure. Flash column chromatography (gradient elution from 10:1 to 5:1 hexanes:EtOAc) afforded diyne S2 (1.15 g, 70%) as a colorless oil. The spectral data matches that reported in literature.⁵⁷

To a solution of silyl ether S2 (308 mg, 1.0 mmol) in methanol (10 mL) was added p-toluenesulfonic acid monohydrate (19 mg, 0.1 mmol) and the reaction mixture was stirred at room temperature for 1 hour. Methanol was removed in vacuum and water (5 mL) was added. Reaction mixture was extracted with CH₂Cl₂ (3 × 10 mL), combined extracts were dried over MgSO₄ and concentrated under reduced pressure. Diol 2-119a was purified by flash column chromatography (2:1 hexanes:EtOAc) to give a colorless oil (168.8 mg, 87%). ¹H NMR (500 MHz, CDCl₃) δ 3.62 (t, J = 6.4 Hz, 4H), 2.28 (t, J = 6.8 Hz, 4H), 2.09 (brs, 2H), 1.61 (m, 8H); ¹³C NMR (125 MHz, CDCl₃) δ 77.2, 65.6, 62.3, 31.7, 24.6, 19.0; HRMS (ESI) calcd for C₁₂H₁₈O₂Na [M+Na]⁺: 217.1204, found 217.1209.

To a stirred solution of alcohol S2 (600 mg, 1.95 mmol) in CH₂Cl₂ (20 mL) at 0 °C were added NaHCO₃ (1.5 g), celite (3 g) and pyridinium chlorochromate (840 mg, 3.9 mmol). The resulting mixture was warmed to room temperature, stirred for 30 min and poured onto a short silica gel column. Aldehyde was eluted with hexane:Et₂O mixture (20:1) and solvent was removed under reduced pressure. Compound was directly subjected to the next step.

Crude aldehyde from the previous step was dissolved in THF (10 mL) and a 3.0 M solution of methylmagnesium bromide in Et₂O (0.65 mL, 1.95 mmol) was added at -78 °C. Reaction mixture was
slowly warmed to room temperature and quenched with sat. NH₄Cl solution (3 mL). Product was extracted with CH₂Cl₂ (3 × 10 mL), dried over MgSO₄ and concentrated under reduced pressure.

The residue was dissolved in methanol (5 mL) and p-toluenesulfonic acid monohydrate (37 mg, 0.2 mmol) was added. Reaction mixture was stirred at room temperature for 1 hour. The solvent was removed under vacuum and water (5 mL) was added. Extractive work-up with CH₂Cl₂ (3 × 10 mL) followed by flash column chromatography purification (2:1 hexanes:EtOAc) afforded 2-119d as a colorless oil (227.3 mg, 56% for 3 steps). ¹H NMR (500 MHz, CDCl₃) δ 3.76 (m, 1H), 3.60 (t, J = 6.2 Hz, 2H), 2.32 (brs, 2H), 2.25 (m, 4H), 1.66–1.44 (m, 8H), 1.16 (d, J = 6.2 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 77.2, 77.1, 65.50, 65.46, 61.9, 38.1, 31.6, 24.6, 24.5, 23.4, 19.0, 18.9; HRMS (ESI) calcd for C₁₃H₂₀O₂Na [M+Na]^+: 231.1361, found 231.1361.

The procedure for the preparation of 2-119f is similar to that of 2-119d. Alcohol S2 (360 mg, 1.17 mmol) underwent PCC oxidation followed by treatment with isopropenylmagnesium bromide and deprotection of TBS-ether to give diol 2-119f (176.7 mg, 64% for 3 steps) as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 3.67 (m, 2H), 3.36 (m, 1H) 2.30 (t, J = 6.6 Hz, 4H), 1.81–1.40 (m, 9H), 1.32 (brs, 2H), 0.94 (d, J = 6.9 Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 76.5, 65.8, 62.5, 33.8, 33.5, 32.0, 25.1, 24.8, 19.5, 19.2, 19.0, 17.3; HRMS (ESI) calcd for C₁₅H₂₄O₂Na [M+Na]^+: 259.1674, found 259.1678.

To a stirred solution of diol 2-119a (700 mg, 3.6 mmol) in CH₂Cl₂ (30 mL) at 0 °C were added NaHCO₃ (1.5 g), celite (3 g) and pyridinium chlorochromate (3.1 g, 14.4 mmol). The resulting mixture
was warmed to room temperature, stirred for 30 min and poured onto a short silica gel column. Aldehyde was eluted with hexanes:CH₂Cl₂ mixture (1:1), solvent was removed under vacuum and product was directly subjected to the next step.

Crude aldehyde from the previous step was dissolved in THF (20 mL) and a 3.0 M solution of methylmagnesium bromide in Et₂O (2.6 mL, 7.9 mmol) was added at -78 °C. Reaction mixture was slowly warmed to room temperature and quenched with sat. NH₄Cl solution (3 mL). Product was extracted with CH₂Cl₂ (3 × 10 mL), dried over MgSO₄ and concentrated under reduced pressure. Residue was purified by flash column chromatography (2:1 hexanes:EtOAc) to afford diol 2-119e (560 mg, 70%) as a colorless oil. ^1H NMR (500 MHz, CDCl₃) δ 3.82 (m, 2H), 2.30 (t, J = 6.2 Hz, 4H), 1.71–1.52 (m, 8H), 1.40 (brs, 2H), 1.21 (d, J = 6.2 Hz, 6H); ^13C NMR (125 MHz, CDCl₃) δ 77.3, 67.6, 65.6, 38.3, 24.6, 23.7, 19.2. HRMS (ESI) calcd for C₁₄H₂₃O₂ [M+H]^+: 223.1698, found 223.1704.

The procedure for the preparation of diyne 2-119b is similar to that of 2. 4-Pentyne-1-ol (430 mg, 5.1 mmol) and bromoalkyne S3 (0.9 g, 5.1 mmol) under Cadiot-Chodkiewicz coupling conditions afforded diyne 2-120b (781 mg, 85%) as a colorless oil. ^1H NMR (500 MHz, CDCl₃) δ 3.73 (t, J = 6.2 Hz, 2H), 3.66 (t, J = 6.2 Hz, 2H), 2.38 (t, J = 7.0 Hz, 2H), 2.30 (t, J = 6.8 Hz, 2H), 1.95 (brs, 2H), 1.77 (qn, J = 6.5 Hz, 2H), 1.72–1.54 (m, 4H); ^13C NMR (125 MHz, CDCl₃) δ 76.7, 65.6, 65.5, 62.2, 61.3, 31.7, 31.0, 24.6, 19.0, 15.8; HRMS (ESI) calcd for C₁₁H₁₆O₂Na [M+Na]^+: 203.1048, found 203.1051.

The procedure for the preparation of diyne S5 is similar to that of S2. Alkyne S4 (300 mg, 1.51 mmol) and bromoalkyne S3 (266 mg, 1.51 mmol) under Cadiot-Chodkiewicz coupling conditions afforded diyne S5 (781 mg, 85%) as a colorless oil. ^1H NMR (500 MHz, CDCl₃) δ 3.73 (t, J = 6.2 Hz, 2H), 3.66 (t, J = 6.2 Hz, 2H), 2.38 (t, J = 7.0 Hz, 2H), 2.30 (t, J = 6.8 Hz, 2H), 1.95 (brs, 2H), 1.77 (qn, J = 6.5 Hz, 2H), 1.72–1.54 (m, 4H); ^13C NMR (125 MHz, CDCl₃) δ 76.7, 65.6, 65.5, 62.2, 61.3, 31.7, 31.0, 24.6, 19.0, 15.8; HRMS (ESI) calcd for C₁₁H₁₆O₂Na [M+Na]^+: 203.1048, found 203.1051.
afforded diyne \textbf{S5} (369 mg, 83\%) as a colorless oil. \textbf{\(^1\)H NMR} (500 MHz, CDCl\(_3\)) \(\delta\) 3.65 (m, 4H), 2.30 (m, 4H), 1.74–1.53 (m, 7H), 0.87 (s, 9H), 0.04 (s, 6H); \textbf{\(^{13}\)C NMR} (125 MHz, CDCl\(_3\)) \(\delta\) 76.8, 65.6, 65.3, 62.2, 61.4, 31.7, 31.3, 25.9, 24.6, 19.0, 18.3, 15.6, -5.4; \textbf{HRMS} (ESI) calcd for C\(_{17}\)H\(_{30}\)O\(_2\)SiNa [M+Na]\(^+\): 317.1913, found 317.1910.

The procedure for the preparation of \textbf{2-119h} is similar to that of \textbf{2-119d}. Alcohol \textbf{S5} (640 mg, 2.17 mmol) underwent PCC oxidation followed by treatment with methylmagnesium bromide and deprotection of TBS-ether to give diol \textbf{2-119h} (257.5 mg, 61\% for 3 steps) as a colorless oil. \textbf{\(^1\)H NMR} (500 MHz, CDCl\(_3\)) \(\delta\) 3.80 (m, 1H), 3.73 (t, \(J = 6.2\) Hz, 2H), 2.38 (t, \(J = 7.0\) Hz, 2H), 2.28 (t, \(J = 6.1\) Hz, 2H), 1.72 (m, 2H), 1.77 (m, 6H), 1.19 (d, \(J = 6.2\) Hz, 3H); \textbf{\(^{13}\)C NMR} (125 MHz, CDCl\(_3\)) \(\delta\) 77.4, 76.7, 67.6, 65.7, 65.5, 61.4, 38.2, 31.0, 24.6, 23.6, 19.2, 15.7; \textbf{HRMS} (ESI) calcd for C\(_{12}\)H\(_{18}\)O\(_2\)Na [M+Na]\(^+\): 217.1204, found 217.1210.

The procedure for the preparation of \textbf{S6} is similar to that of \textbf{S2}. Starting from bromoalkyne \textbf{S1} (420 mg 1.44 mmol) and 4-pentyn-1-ol (121 mg, 1.44 mmol) under Cadiot-Chodkiewicz coupling conditions\(^{52}\) diyne \textbf{S6} was obtained as a colorless oil (344 mg, 81\%). \textbf{\(^1\)H NMR} (500 MHz, CDCl\(_3\)) \(\delta\) 3.74 (t, \(J = 6.2\) Hz, 2H), 3.61 (t, \(J = 5.9\) Hz, 2H), 2.38 (t, \(J = 7.0\) Hz, 2H), 2.27 (t, \(J = 6.6\) Hz, 2H), 1.77 (qn, \(J = 6.4\) Hz, 2H), 1.64–1.50 (m, 5H), 0.88 (s, 9H), 0.04 (s, 6H); \textbf{\(^{13}\)C NMR} (125 MHz, CDCl\(_3\)) \(\delta\) 77.6, 76.5, 65.8, 65.3, 62.5, 61.4, 31.8, 31.0, 25.9, 24.8, 19.0, 18.3, 15.8, -5.3; \textbf{HRMS} (ESI) calcd for C\(_{17}\)H\(_{36}\)O\(_2\)SiNa [M+Na]\(^+\): 317.1913, found 317.1900.
The procedure for the preparation of **2-119g** is similar to that of **2-119d**. Alcohol **S6** (300 mg, 1.0 mmol) underwent PCC oxidation followed by treatment with methylmagnesium bromide and deprotection of TBS-ether to afford diol **2-119g** (118.7 mg, 60% for 3 steps) as colorless oil. **\(^{1}\)H NMR** (500 MHz, CDCl\(_3\)) \(\delta\) 3.93 (m, 1H), 3.66 (t, \(J = 6.2\) Hz, 2H), 2.38 (m, 2H), 2.30 (t, \(J = 6.8\) Hz, 2H), 1.72–1.42 (m, 8H), 1.21 (d, \(J = 5.9\) Hz, 3H); **\(^{13}\)C NMR** (125 MHz, CDCl\(_3\)) \(\delta\) 76.9, 66.8, 65.6, 65.5, 62.3, 37.2, 31.7, 24.6, 23.4, 19.0, 15.8; **HRMS** (ESI) calcd for C\(_{12}\)H\(_{18}\)O\(_2\)Na [M+Na]\(^+\): 217.1204, found 217.1209.

A mixture of the (R)-(−)-5-hexen-2-ol (825 mg, 8.2 mmol) and imidazole (1.4 g, 20.6 mmol) in dry CH\(_2\)Cl\(_2\) (10 mL) was stirred with TBSCl (1.5 g, 9.9 mmol) under nitrogen atmosphere at room temperature for 1.5 h. The reaction was quenched with water (50 mL) and extracted with CH\(_2\)Cl\(_2\) (2 × 5 mL). The combined extracts were washed with brine (30 mL), dried (MgSO\(_4\)) and concentrated under reduced pressure. The residue was purified by column chromatography (20:1 hexanes:EtOAc) to furnish product **S7** (1.7 g, 98%) as a colorless liquid. Both **\(^{1}\)H** and **\(^{13}\)C** NMR spectra match the reported data.

To a 100 mL round-bottom flask was added solution of alkene **S7** (2.5 g, 11.8 mmol) in 10 mL of dry THF. Solution of 9-BBN in THF (47 mL, 0.5 M) was then added dropwise at 0 °C. The reaction mixture was warmed to room temperature and stirred for 0.5 h. After that the reaction mixture was cooled to 0 °C and aq. NaOH (15 mL, 3 M) was slowly added followed by slow addition of H\(_2\)O\(_2\) (5 mL, 35 w/w aq. soln.). After vigorous gas evolution, the reaction mixture was warmed to room temperature followed by reflux for 1 h. Reaction mixture was extracted with CH\(_2\)Cl\(_2\) (3 × 10 mL), combined extracts were dried over MgSO\(_4\) and solvent was removed under vacuum.
The crude alcohol from previous step was dissolved in 10 mL of dry CH₂Cl₂ and to the solution were added DMSO (8.5 mL) and Hüning’s base (8.4 mL). Reaction mixture was cooled to 0 °C and sulfur trioxide pyridine complex (4.8 g, 30.2 mmol) was added in three portions over 10 min. Reaction mixture was stirred at 0 °C for 20 min and quenched with water (20 mL). The organic layer was extracted twice with 10 mL portions of CH₂Cl₂. Combined organic extracts were dried (MgSO₄) and concentrated. Product was quickly purified by filtration of the reaction mixture through a short silica gel plug (20:1 hexanes: EtOAc).

A solution of triphenylphosphine (12.6 g, 48.0 mmol) and carbon tetrabromide (8.0 g, 24.1 mmol) in CH₂Cl₂ (50 mL) was stirred at 0 °C for 5 min followed by addition of the aldehyde solution in CH₂Cl₂ (10 mL). The reaction mixture was stirred at 0 °C for 10 min, diluted with hexanes (150 mL) and transferred to a silica gel column. Dibromoalkene S8 was purified by flash column chromatography (20:1 hexanes:EtOAc) to afford colorless liquid (2.9 g, 64% for 3 steps). Both ¹H and ¹³C NMR spectra match the reported data for its enantiomer.⁶⁰

![Chemical structure of S8 and S9](image)

To a solution of dibromoalkene S8 (1.0 g, 2.59 mmol) in THF (30 mL) was added a solution of n-BuLi (2.5 M in hexanes) (2.1 mL, 5.31 mmol) at -78 °C and reaction mixture was stirred for 30 min. The reaction mixture was allowed to warm to ambient temperature and quenched with saturated solution of aqueous NH₄Cl (10 mL). The layers were separated, and the aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic extracts were washed with brine (1 × 50 mL), dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by column chromatography (200:1 hexanes:EtOAc) to furnish alkyne S9 (499 mg, 85%) as a colorless liquid. Both ¹H and ¹³C NMR spectra match the reported data.⁶¹
Bromoalkyne S10 was obtained by the method of Mori\textsuperscript{62} as a pale yellow liquid (654 mg, 76%). \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 3.82 (m, 1H), 2.25 (m, 2H), 1.69–1.51 (m, 4H), 1.33 (brs, 1H), 1.21 (d, \(J = 6.2\) Hz, 3H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) 80.1, 67.7, 38.2, 38.0, 24.6, 23.7, 19.7.

The procedure for the preparation of diyne S11 is similar to that of S2. Alkyne S9 (728 mg, 3.22 mmol) and bromoalkyne S10 (614 mg, 3.22 mmol) under Cadiot-Chodkiewicz coupling conditions\textsuperscript{52} afforded diyne S11 (colorless oil, 767 mg, 71%) among with diol 2-119i (colorless oil, 71 mg, 10%). For diyne S11 \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 3.80 (m, 2H), 2.29 (m, 2H), 2.25 (m, 2H), 1.71–1.45 (m, 8H), 1.35 (brs, 1H), 1.20 (d, \(J = 6.2\) Hz, 3H), 1.12 (d, \(J = 6.0\) Hz, 3H), 0.88 (s, 9H), 0.04 (d, \(J = 2.2\) Hz, 6H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) 77.6, 68.0, 67.6, 65.7, 65.4, 38.7, 38.3, 25.9, 24.6, 23.8, 23.6, 19.3, 19.2, 18.1, -4.4, -4.7. HRMS (ESI) calced for C\textsubscript{20}H\textsubscript{36}O\textsubscript{2}SiNa [M+Na]\textsuperscript{+}: 359.2382, found 359.2380. For diol 2-119i \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 3.79 (m, 2H), 2.27 (t, \(J = 6.1\) Hz, 4H), 1.80–1.49 (m, 10H), 1.18 (d, \(J = 6.2\) Hz, 6H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) 77.3, 67.5, 65.6, 38.2, 24.6, 23.5, 19.2; HRMS (ESI) calced for C\textsubscript{14}H\textsubscript{23}O\textsubscript{2} [M+H]\textsuperscript{+}: 223.1698, found 223.1704.

To a solution of silyl ether S11 (135 mg, 0.4 mmol) in methanol (3 mL) was added \(p\)-toluenesulfonic acid monohydrate (3.8 mg, 0.02 mmol) and the reaction mixture was stirred at room temperature for 1 hour. Methanol was removed under vacuum and the product was purified by flash column chromatography (2:1 hexanes:EtOAc) to give 2-119i as a colorless oil (78.8 mg, 89%). \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 6.30 (d, \(J = 6.0\) Hz, 1H), 6.28 (d, \(J = 6.0\) Hz, 1H), 3.80 (dd, \(J = 16.0, 12.0\) Hz, 1H), 3.78 (dd, \(J = 16.0, 12.0\) Hz, 1H), 3.70 (s, 3H), 3.68 (s, 3H).
MHZ, CDCl$_3$) $\delta$ 3.79 (m, 2H), 2.27 (t, $J$ = 6.1 Hz, 4H), 1.80–1.49 (m, 10H), 1.18 (d, $J$ = 6.2 Hz, 6H); $^{13}$C NMR (125 MHZ, CDCl$_3$) $\delta$ 77.3, 67.5, 65.6, 38.2, 24.6, 23.5, 19.2; HRMS (ESI) calcd for C$_{14}$H$_{22}$O$_2$ [M+H]$^+$: 223.1698, found 223.1704.

To a solution of alcohol S11 (342 mg, 1.0 mmol), benzoic acid (174 mg, 1.4 mmol) and triphenylphosphine (426 mg, 1.6 mmol) in THF (10 mL) at 0 °C was added a solution of DIAD (315 µL, 1.6 mmol) in THF (5 mL) dropwise over 1 h. After this time the solution was allowed to warm to room temperature and the reaction was stirred at 60 °C for an additional 1 h. THF was removed in vacuum and the resulting residue was quickly purified by silica gel chromatography (40:1 hexanes:EtOAc) to give crude ester.

The crude ester was dissolved in methanol (3 mL) and $p$-toluenesulfonic acid monohydrate (3.7 mg, 0.02 mmol) was added. Reaction mixture was stirred at room temperature for 1 h. NaOH (31.4 mg, 0.79 mmol) and water (0.5 mL) were then added and reaction mixture was stirred at room temperature for 12 h. 1 M HCl was added until neutral pH and methanol was removed under vacuum. Product was extracted with CH$_2$Cl$_2$ (3 x 3 mL), dried over MgSO$_4$ and concentrated under reduced pressure. Flash column chromatography (2:1 hexanes:EtOAc) afforded diol 2-119j (81 mg, 36% for 3 steps) as a viscous colorless oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 3.80 (m, 2H), 2.27 (t, $J$ = 6.1 Hz, 4H), 1.86 (brs, 2H), 1.71–1.47 (m, 8H), 1.18 (d, $J$ = 6.2 Hz, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 77.3, 67.6, 65.6, 38.2, 24.6, 23.5, 19.2; HRMS (ESI) calcd for C$_{14}$H$_{22}$O$_2$Na [M+Na]$^+$: 245.1517, found 245.1516.
To a vial containing 5,7-dodecadiyne-1,12-diol 2-119a (28.4 mg, 0.146 mmol) was added a CH$_2$Cl$_2$–MeOH (4:1) solution (580 µL, 0.03 M) of Ph$_3$PAuOTf (12 mol %), which was prepared by mixing stoichiometric amounts of Ph$_3$PAuCl and AgOTf in CH$_2$Cl$_2$ followed by filtration through a plug of celite to remove precipitated AgCl and dilution with MeOH. Water (31.5 µL, 12 equiv) was then added and the vial was closed. Reaction mixture was stirred at 60 °C for 4.5 h under microwave irradiation. The solvent was removed under reduced pressure and residue was purified by flash column chromatography (7:1 hexanes:EtOAc) to give a mixture of two isomers 2-120a (pale yellow oil, 23.3 mg, 75%). Product isomers were separated by gravity column chromatography (gradient elution from 25:1 to 15:1 hexanes:EtOAc). For less polar isomer (pale yellow oil) $^1$H NMR (500 MHz, CDCl$_3$) δ 3.89 (dt, $J$ = 11.3 Hz, $J$ = 3.0 Hz, 2H), 3.60 (ddd, $J$ = 9.0 Hz, $J$ = 4.2 Hz, $J$ = 2.0 Hz, 2H), 1.99–1.83 (m, 6H), 1.76–1.46 (m, 10H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 106.5, 62.1, 36.2, 35.4, 25.3, 20.4; HRMS (ESI) calcd for C$_{12}$H$_{20}$O$_3$Na [M+Na]$^+$: 235.1310, found 235.1305. For more polar isomer (pale yellow oil) $^1$H NMR (500 MHz, CDCl$_3$) δ 3.98 (dt, $J$ = 11.5 Hz, $J$ = 3.0 Hz, 2H), 3.73 (m, 2H), 2.10 (m, 2H), 1.94–1.75 (m, 4H), 1.70–1.48 (m, 10H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 106.9, 62.9, 37.2, 35.4, 25.3, 20.2; HRMS (ESI) calcd for C$_{12}$H$_{20}$O$_3$Na [M+Na]$^+$: 235.1310, found 235.1301.

The procedure for cyclization of diol 2-119b is similar to that of 2-119a. Under microwave irradiation diol (32.1 mg, 0.178 mmol) with 12 mol % of Ph$_3$PAuOTf (conc. cat 2.4 mM in CH$_2$Cl$_2$–MeOH) at 40 °C for 30 min gave mixture of two compounds 2-120b (colorless oil, 22.3 mg, 68%). For less polar isomer
(colorless oil) $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.01 (m, 1H), 3.88 (m, 2H), 3.62 (m, 1H) 2.38–1.24 (m, 14H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 115.6, 106.1, 67.6, 62.2, 37.2, 36.9, 35.2, 33.9, 25.5, 24.6, 20.4; HRMS (ESI) calcd for C$_{11}$H$_{19}$O$_3$ [M+H]$^+$: 199.1334, found 199.1341. For more polar isomer (colorless oil) $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 3.94 (m, 3H), 3.70 (m, 1H), 2.32 (m, 1H), 2.21–1.40 (m, 13H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 115.7, 106.4, 67.7, 62.6, 37.8, 36.8, 35.1, 34.3, 25.4, 24.6, 20.4; HRMS (ESI) calcd for C$_{11}$H$_{19}$O$_3$ [M+H]$^+$: 199.1334, found 199.1338.

The procedure for cyclization of 4,6-decadynie-1,10-diol 2-119c is similar to that of 2-119a. Under microwave irradiation 4,6-decadyne-1,10-diol (31.3 mg, 0.188 mmol) with 12 mol % of Ph$_3$PAuOTf (conc. cat 2.4 mM in CH$_2$Cl$_2$–MeOH) at 35 °C for 35 min gave mixture of three compounds 2-120c and 2-122 (colorless oil, 21.6 mg, 71%). For less polar isomer (colorless oil) $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 3.96 (m, 2H), 3.81 (m, 2H), 2.29–1.83 (m, 12H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 115.1, 67.5, 36.5, 34.9, 24.6; HRMS (ESI) calcd for C$_{10}$H$_{16}$O$_3$Na [M+Na]$^+$: 207.0997, found 207.0996. For more polar isomer (colorless oil) $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 3.97 (m, 2H), 3.87 (m, 2H), 2.27 (m, 2H), 2.07–1.80 (m, 10H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 115.1, 67.7, 36.6, 35.4, 24.6; HRMS (ESI) calcd for C$_{10}$H$_{16}$O$_3$Na [M+Na]$^+$: 207.0997, found 207.1001. For 2-122 (colorless oil) $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 3.86 (d, $J$ = 6.6 Hz, $J = 3.7$ Hz, 2H), 3.64 (m, 2H), 2.85 (m, 2H), 2.50 (dd, $J = 8.2$ Hz, $J = 5.3$ Hz, 2H), 2.12–1.72 (m, 4H), 1.70–1.40 (m, 4H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 209.3, 96.5, 62.4, 61.8, 56.7, 42.6, 36.1, 25.7, 24.9, 19.0; HRMS (ESI) calcd for C$_{10}$H$_{16}$O$_3$Na [M+Na]$^+$: 207.0997, found 207.1003.
The procedure for cyclization of diol 2-119d is similar to that of 2-119a. Under microwave irradiation, diol 2-119d (18.9 mg, 0.091 mmol) with 12 mol % of Ph₃PµAuOTf (conc. cat 5.4 mM in CH₂Cl₂–MeOH) at 40 °C for 30 min gave mixture of two compounds 2-120d (colorless oil, 13.8 mg, 67%). For less polar isomer (colorless oil) ¹H NMR (300 MHz, CDCl₃) δ 3.90 (m, 2H), 3.60 (m, 1H), 2.07–1.77 (m, 5H), 1.77–1.42 (m, 10H), 1.34–1.02 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 107.1, 106.7, 66.9, 62.4, 36.9, 36.4, 36.0, 34.8, 33.0, 25.6, 22.3, 20.7; HRMS (ESI) calcd for C₁₃H₂₂O₃Na [M+Na]⁺: 249.1467, found 249.1463. For more polar isomer (colorless oil) ¹H NMR (300 MHz, CDCl₃) δ 4.06 (m, 1H), 3.90 (dt, J = 11.4 Hz, J = 3.3 Hz, 1H), 3.70 (m, 1H), 2.10 (m, 2H), 2.00–1.43 (m, 13H), 1.30–1.06 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 107.5, 106.9, 68.4, 62.8, 37.8, 37.4, 35.4, 35.3, 32.9, 25.5, 22.2, 20.5, 20.4; HRMS (ESI) calcd for C₁₃H₂₂O₃Na [M+Na]⁺: 249.1467, found 249.1478.

The procedure for cyclization of diol 2-119e is similar to that of 2-119a. Diol 2-119e (31.5 mg, 0.142 mmol) in the presence of 12 mol % of Ph₃PµAuOTf (conc. cat 2.0 mM in CH₂Cl₂–MeOH) under microwave irradiation at 45 °C for 1.5 h gave a mixture of two compounds 2-120e (colorless oil, 23.2 mg, 68%). For less polar isomer (colorless oil) ¹H NMR (300 MHz, CDCl₃) δ 3.93 (m, 2H), 2.05–1.83 (m, 6H), 1.69–1.53 (m, 8H), 1.23–1.05 (m, 8H); ¹³C NMR (75 MHz, CDCl₃) δ 106.8, 66.7, 36.7, 34.9, 32.7, 22.1, 20.5; HRMS (ESI) calcd for C₁₄H₂₅O₃ [M+H]⁺: 241.1804, found 241.1795. For more polar isomer (colorless oil) ¹H NMR (300 MHz, CDCl₃) δ 3.98 (m, 2H), 2.12 (m, 2H), 1.91–1.71 (m, 4H), 1.66–1.51
(m, 8H), 1.24–1.10 (m, 8H); \(^{13}\text{C NMR}\) (75 MHz, CDCl\(_3\)) \(\delta\) 107.2, 67.8, 37.5, 34.7, 32.7, 22.0, 20.4; \text{HRMS}\) (ESI) calcd for C\(_{13}\)H\(_{25}\)O\(_3\) [M+H]\(^+\): 241.1804, found 241.1815.

The procedure for cyclization of diol 2-119f is similar to that of 2-119a. Diol 2-119f (35.3 mg, 0.186 mmol) in the presence of 12 mol % of Ph\(_3\)PAuOTf (conc. cat 2.4 mM in CH\(_2\)Cl\(_2\)--MeOH) under microwave irradiation at 45 °C for 1 h gave an inseparable mixture (2:1) of two diastereomers 2-120f (colorless oil, 24.3 mg, 64%). \(^1\text{H NMR}\) (300 MHz, CDCl\(_3\)) \(\delta\) 3.92 (m, 1H), 3.59 (m, 2H), 3.45 (m, 1H), 2.17–1.42 (m, 23H), 1.30–1.04 (m, 2H), 1.00–0.79 (m, 9H); \(^{13}\text{C NMR}\) (75 MHz, CDCl\(_3\)) \(\delta\) 107.4, 106.9, 106.8, 106.6, 75.6, 63.1, 62.4, 37.8, 37.5, 36.9, 36.5, 35.9, 35.6, 35.3, 34.9, 33.4, 33.3, 28.13, 28.06, 25.60, 25.56, 20.75, 20.67, 20.53, 20.46, 19.0, 18.94, 18.90, 18.8; \text{HRMS}\) (ESI) calcd for C\(_{15}\)H\(_{26}\)O\(_3\)Na [M+Na]\(^+\): 277.1780, found 277.1789.

The procedure for cyclization of diol 2-119g is similar to that of 2-119a. Diol 2-119g (30.6 mg, 0.158 mmol) in the presence of 12 mol % of Ph\(_3\)PAuOTf (conc. cat 2.4 mM in CH\(_2\)Cl\(_2\)--MeOH) under microwave irradiation at 40 °C for 1 h gave an inseparable mixture of four diastereomers 2-120g (pale yellow oil, 18.4 mg, 55%). \(^1\text{H NMR}\) (500 MHz, CDCl\(_3\)) \(\delta\) 4.33–4.16 (m), 4.10 (m), 4.01–3.78 (m), 3.66 (m), 3.59 (m), 2.35–1.39 (m), 1.37–1.14 (m); \(^{13}\text{C NMR}\) (125 MHz, CDCl\(_3\)) \(\delta\) 115.7, 115.4, 105.8, 105.7, 76.1, 76.0, 74.7, 74.5, 62.3, 62.1, 38.5, 38.1, 37.8, 37.5, 37.1, 37.0, 36.9, 36.7, 35.2, 35.1, 34.84, 34.79, 34.4, 33.9, 32.7, 32.55, 32.47, 32.0, 31.7, 25.9, 25.5, 25.3, 25.2, 23.2, 22.8, 21.4, 20.2; \text{HRMS}\) (ESI) calcd for C\(_{12}\)H\(_{20}\)O\(_3\)Na [M+Na]\(^+\): 235.1310, found 235.1304.
The procedure for cyclization of diol 2-119h is similar to that of 2-119a. Diol 2-119h (36.2 mg, 0.186 mmol) in the presence of 12 mol % of Ph₃P=CEtOTf (conc. cat 2.4 mM in CH₂Cl₂–MeOH) under microwave irradiation at 45 °C for 30 min gave mixture of two compounds 2-120h (colorless oil, 24.1 mg, 61%). For less polar isomer (colorless oil) ¹H NMR (300 MHz, CDCl₃) δ 4.00 (m, 1H), 3.82 (m, 2H), 2.29 (m, 1H), 2.19–1.46 (m, 12H), 1.34–1.00 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 115.4, 106.2, 67.5, 66.7, 37.5, 37.0, 34.2, 33.7, 32.7, 24.5, 21.9, 20.3; HRMS (ESI) calcd for C₁₂H₂₀O₃Na [M+Na]⁺: 235.1310, found 235.1304. For more polar isomer (colorless oil) ¹H NMR (300 MHz, CDCl₃) δ 3.93 (m, 3H), 2.31 (m, 1H), 2.17–1.69 (m, 8H), 1.67–1.48 (m, 4H), 1.30–1.04 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 115.4, 106.4, 67.3, 67.1, 38.1, 36.5, 34.4, 34.0, 32.7, 24.3, 22.0, 20.2; HRMS (ESI) calcd for C₁₂H₂₁O₃ [M+H]⁺: 213.1491, found 213.1498.

To a solution of diol 2-119i (27.7 mg, 0.125 mmol) in CH₂Cl₂–MeOH mixture (3.0 mL, 4:1) were added catalyst 2-121 (11.5 mg, 12 mol %, 5 mM) and water (26.9 µL, 12 equiv). Reaction mixture was then stirred at 45 °C for 2 h and solvent was removed under reduced pressure. The residue was purified by gravity column chromatography (gradient elution from 35:1 to 20:1 hexanes:EtOAc) to afford single product trans-2-120i (22.2 mg, 74%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 3.93 (m, 2H), 2.05–1.95 (m, 2H), 1.94–1.81 (m, 4H), 1.69–1.53 (m, 8H), 1.17 (m, 2H), 1.09 (d, J = 6.2 Hz, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 106.8, 66.7, 36.7, 34.9, 32.7, 22.1, 20.5; HRMS (ESI) calcd for C₁₄H₂₅O₃ [M+H]⁺: 241.1804, found 241.1798.
The procedure for preparation of 2-119j is similar to that of 2-119i. Diol 2-119j (44.5 mg, 0.20 mmol) underwent cyclization in the presence of 12 mol % of gold catalyst 2-121 (conc. cat 5 mM in CH₂Cl₂–MeOH) at 45 °C for 2 h to give a mixture of two compounds 2-120j (colorless oil, 28.7 mg, 60%). For less polar isomer (colorless oil) ¹H NMR (500 MHz, CDCl₃) δ 3.98 (m, 2H), 2.12 (m, 2H), 1.92–1.80 (m, 2H), 1.80–1.71 (m, 2H), 1.66–1.51 (m, 8H), 1.24–1.10 (m, 8H); ¹³C NMR (125 MHz, CDCl₃) δ 107.2, 67.8, 37.5, 34.7, 32.7, 22.0, 20.4; HRMS (ESI) calcd for C₁₄H₂₅O₃ [M+H]⁺: 241.1804, found 241.1815. For more polar isomer (colorless oil) ¹H NMR (500 MHz, CDCl₃) δ 3.94 (m, 1H), 3.63 (m, 1H), 2.15 (m, 1H), 1.95–1.85 (m, 3H), 1.82–1.48 (m, 10H), 1.27–1.16 (m, 5H), 1.08 (d, J = 6.4 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 109.0, 106.2, 71.0, 66.6, 36.7, 36.6, 33.5, 32.7, 32.5, 30.7, 22.2, 22.0, 21.4, 20.3; HRMS (ESI) calcd for C₁₄H₂₅O₃ [M+H]⁺: 241.1804, found 241.1795.

Alcohol 2-137 was prepared in 65% overall yield according to the literature procedure for its enantiomer.⁶³ To a solution of alcohol 2-137 (931.6 g, 6.12 mmol) and Et₃N (2.56 mL, 18.36 mmol) in CH₂Cl₂ (25 mL) was added TBSOTf (1.55 mL, 6.73 mmol) at -78 °C and the reaction mixture was warmed to 0 °C and stirred for additional 3 h at this temperature. The reaction mixture was then quenched with water, extracted with hexanes (3 × 10 mL), and concentrated under reduced pressure to give crude silyl ether as a colorless oil which was used without further purification.

To the solution of crude silyl ether in an acetone–H₂O mixture (0.08 M, 75 mL, 5:1) were added osmium tetroxide (200 µL, 0.2 M in H₂O) and NMO (1.80 g, 15.3 mmol) at room temperature. The reaction mixture was stirred for 4 h (at this point the reaction was complete according to TLC), and NaIO₄
(2.62 g, 12.24 mmol) was added. The resultant mixture was stirred for 2 h and quenched with saturated aqueous Na₂SO₃ (10 mL). Formed in the reaction white precipitate was then filtered through a pad of celite. After removing acetone under reduced pressure the residue was extracted with Et₂O (3 × 10 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (30:1 hexanes:EtOAc) to give aldehyde 2-133 (1.17 g, 80%) as a colorless oil. For 2-137: ¹H NMR (500 MHz, CDCl₃) δ 5.20–5.13 (m, 1 H), 2.46 (s, 1H), 2.35–2.24 (m, 1 H), 2.23–2.11 (m, 2H), 1.76–1.67 (m, 5H), 1.65 (s, 3H), 1.50 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 132.6, 123.6, 87.5, 71.4, 68.3, 43.1, 29.8, 25.7, 23.6, 17.7; For 2-133: ¹H NMR (500 MHz, CDCl₃) δ 9.81 (s, 1H), 2.59–2.73 (m, 2H), 2.45 (s, 1H), 2.04–1.90 (m, 2H) 1.49 (s, 3H), 0.85 (s, 9H), 0.18 (s, 3H), 0.17 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 202.5, 87.1, 72.7, 68.3, 39.8, 37.5, 31.0, 25.6, 18.0, -2.9, -3.3.

To a cooled solution (-10 °C) of (R,R)-Leighton reagent⁵⁴ (3.0 g, 11.2 mmol) in toluene (50 mL) was added a solution aldehyde 2-133 (1.17 g, 4.87 mmol) in 5 mL of toluene. The reaction mixture was stirred for 6 h at -10 °C. After this time, the reaction was quenched, while still cold, with 1 N HCl and the mixture was stirred at room temperature for 15 min. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic extracts were washed with brine, dried over MgSO₄ and filtered. The filtrate was concentrated and the residue was purified on silica gel (gradient elution from 30:1 to 10:1 hexanes:EtOAc) to afford 2-138 as a colorless oil (1.15 g, 83%, 8:1 dr). The diastereomeric excess of product was determined by derivatization with (R)-Mosher acid ((R)-MTPA) ¹H NMR (500 MHz, CDCl₃) δ 5.91–5.78 (m, 1H), 5.19–5.10 (m, 2H), 3.72–3.64 (m, 1 H), 2.42 (s, 1H), 2.35–2.28 (m, 1H), 2.23–2.13 (m, 1H), 1.87–1.58 (m, 5H), 1.46 (s, 3H), 0.86 (s, 9H), 0.17 (s, 6H); ¹³C
NMR (125 MHz, CDCl$_3$) δ 134.8, 118.1, 80.1, 72.0, 70.7, 68.8, 41.9, 41.1, 31.6, 31.0, 25.7, 18.0, -2.9, -3.2.

$N$-Bromosuccinimide (69.3 mg, 0.389 mmol) and AgNO$_3$ (12.0 mg, 0.07 mmol) were added to a solution of 2-138 (100 mg, 0.354 mmol) in acetone (10 mL). Reaction flask was wrapped with aluminum foil and the reaction mixture was stirred at r.t. for 1 h. After this time the reaction mixture was diluted with water and extracted with Et$_2$O (3 × 10 mL). Ether extract was dried over MgSO$_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (gradient elution from 30:1 to 10:1 hexanes:EtOAc) to afford bromoalkyne 2-131 (123.5 mg, 97%) as a colorless oil. The minor diastereomer is denoted by (†).

1H NMR (500 MHz, CDCl$_3$) δ 5.90–5.77 (m, 1H), 5.20–5.10 (m, 2H), 3.71–3.62 (m, 1H), 2.36–2.27 (m, 1H), 2.22–2.12 (m, 1H), 1.87–1.55 (m, 5H), 1.44 (s, 3H), 0.86 (s, 9H), 0.15 (s, 6H); 13C NMR (125 MHz, CDCl$_3$) δ 134.7, 118.2, 84.1, 70.6, 70.0, 44.0, 42.0†, 41.9, 41.2†, 41.0, 31.8†, 31.6, 30.9†, 30.7, 25.7, 18.0, -3.0, -3.3.

**Oxidation:** To a stirred solution of alcohol 2-139$^{64}$ (1.0 g, 5.87 mmol) in CH$_2$Cl$_2$ (30 mL) were added pyridinium chlorochromate (3.16 g, 14.68 mmol) and 4 Å MS (3 g) at 0 ºC. The resulting mixture was warmed to room temperature, stirred for 30 min, and poured onto a short silica gel column. Aldehyde was eluted with hexanes:CH$_2$Cl$_2$ mixture (1:1), and solvent was removed under vacuum. Crude aldehyde was directly subjected to the next step.

**Olefination:** To a solution of triethyl phosphonoacetate (1.392 mL, 6.96 mmol) in 25 mL of THF was added NaHMDS (7.0 mL, 1 M in THF, 6.96 mmol) at 0 ºC and the reaction mixture was stirred for
30 min. The reaction mixture was cooled to -78 °C and solution of crude aldehyde from previous step in 10 mL of THF was slowly added. The reaction mixture was slowly warmed to 0 °C over 3 h and quenched with saturated NH₄Cl solution. Crude product was extracted with Et₂O (3 × 10 mL), combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (gradient elution from 50:1 to 30:1 hexanes:EtOAc) to afford ester 2-136 (812 mg, 58%) as a pale yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 6.94 (dt, J = 15.6 Hz, J = 7.0 Hz, 1H), 5.84 (dt, J = 15.6 Hz, J = 1.4 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 2.36–2.21 (m, 4H), 1.72–1.63 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H), 0.14 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 166.6, 148.0, 122.0, 106.3, 85.3, 60.2, 31.0, 26.8, 19.3, 14.3, 0.1.

To a solution of ester 2-136 (738 mg, 3.10 mmol) in 30 mL of THF was added DIBAL-H (6.5 mL, 1 M in hexanes, 6.50 mmol) at -78 °C. The reaction mixture was slowly warmed to 0 °C and stirred at this temperature for 30 min. After this time the reaction mixture was quenched with MeOH followed by saturated solution of sodium potassium tartrate (20 mL). The reaction mixture was stirred at r.t. until two clear layers formed, and extracted with EtOAc (3 × 10 mL). Combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (gradient elution from 10:1 to 5:1 hexanes:EtOAc) to afford alcohol 2-140 (503 mg, 89%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 5.73–5.63 (m, 2H), 4.05–4.14 (br, 2H), 2.23 (t, J = 7.1 Hz, 2H), 2.18–2.12 (m, 2H), 1.65–1.57 (m, 2H), 1.34–1.24 (br, 1H), 0.14 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 132.1, 129.8, 107.0, 84.8, 63.7, 31.1, 27.9, 19.2, 0.1.
To a suspension of activated molecular sieves (MS 4 Å) in CH₂Cl₂ (750 mg in 10 mL) were added (−)-D-DIPT (44.8 mg, 0.191 mmol, 7.5 mol %) and Ti(i-PrO)₄ (37.0 µL, 0.127 mmol, 5 mol %) at 0 °C, and the reaction mixture was cooled to -20 °C. Solution of t-BuOOH (740 µL, 5.5 M in decane, 1.6 equiv) was then added and the reaction mixture was stirred at -20 °C for 30 min. To the resultant suspension was added solution of alcohol 2-140 (500 mg, 2.55 mmol) in 5 mL of CH₂Cl₂ and the reaction flask was sealed. The reaction mixture was kept at -20 °C in freezer for 12 h without stirring. After this time the reaction mixture was filtered through a pad of celite, quenched with FeSO₄ solution (30 wt. %), and extracted with EtOAc (3 x 10 mL). Combined organic extracts were concentrated under reduced pressure and the residue was purified by flash column chromatography (gradient elution from 10:1 to 5:1 hexanes:EtOAc) to yield epoxyalcohol 2-135 (colorless oil, 460.3 mg, 85%) as inseparable mixture with (−)-D-DIPT. ¹H NMR (500 MHz, CDCl₃) δ 3.91 (ddd, J = 12.6 Hz, J = 5.5 Hz, J = 2.6 Hz, 1H), 3.63 (ddd, J = 12.4 Hz, J = 7.3 Hz, J = 4.3 Hz, 1H), 3.02–2.96 (m, 2H), 2.96–2.91 (m, 2H), 2.34–2.23 (m, 2H), 1.84–1.76 (m, 1H), 1.76–1.60 (m, 4H), 0.14 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 106.5, 85.2, 61.5, 58.3, 55.3, 30.5, 24.9, 19.5, 0.1.

To a solution of epoxyalcohol 2-135 (382 mg, 1.80 mmol) in 10 mL of THF was added Red-Al (1.32 mL, 65 wt. %, 3.3 M in PhMe, 4.14 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 4 h and quenched by addition of Na₂SO₄·10 H₂O. The resultant mixture was stirred for additional 10 min and MgSO₄ was added. Formed suspension was stirred for 30 min, filtered, and concentrated under reduced pressure to give colorless oil.
The crude diol from previous step was dissolved in THF (10 mL) and a solution of TBAF (3.60 mL, 1M in THF, 3.60 mmol) was added. The reaction mixture was stirred at room temperature for 30 min and quenched with a saturated NH₄Cl solution. Product was extracted with EtOAc (3 × 10 mL), combined organic extracts were dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by flash column chromatography (graduate elution from 2:1 to 1:2 hexanes:EtOAc) to afford diol 2-141 (217.6 mg, 85%) as a pale yellow oil. \(^1\)H NMR (500 MHz, CDCl₃) δ 3.96–3.78 (m, 3H), 2.75 (br, 1H), 2.60 (br, 1H), 2.30–2.17 (m, 2H), 1.96 (t, J = 2.7 Hz, 1H), 1.77–1.53 (m, 6H); \(^1\)C NMR (125 MHz, CDCl₃) δ 84.3, 71.7, 68.6, 61.8, 38.3, 36.7, 24.4, 18.3.

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\begin{align*}
\text{TIPSOTf, Et₃N} & \rightarrow \\
\text{DCM -78 °C} & \rightarrow
\end{align*}
\]

To a solution of diol 2-141 (70.6 g, 0.492 mmol) and Et₃N (206 μL, 1.48 mmol) in CH₂Cl₂ (5 mL) was slowly added TIPSOTf (132 μL, 0.492 mmol) at -78 °C and the reaction mixture was stirred at this temperature for 10 min (After this time TLC analysis indicated 100% conversion). The reaction mixture was quenched, while still cold, with saturated NH₄Cl solution and warmed to room temperature. The reaction mixture was extracted with EtOAc (3 × 10 mL), combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (graduate elution from 20:1 to 5:1 hexanes:EtOAc) to give diol 2-132 (122.1 mg, 83%) as a yellow oil and bis-silylated compound (46.3 mg, 20%, yellow oil). For 2-141: \(^1\)H NMR (500 MHz, CDCl₃) δ 4.05–3.97 (m, 1H), 3.96–3.84 (m, 2H), 3.70 (s, 1H), 2.30–2.16 (m, 2H), 1.94 (t, J = 2.6 Hz, 1H), 1.78–1.51 (m, 6H), 1.20–0.96 (m, 21H); \(^1\)C NMR (125 MHz, CDCl₃) δ 84.5, 72.0, 68.3, 63.6, 38.2, 36.4, 24.5, 18.4, 17.9, 11.7; For S12: \(^1\)H NMR (500 MHz, CDCl₃) δ 4.09–4.00 (m, 1H), 3.77 (t, J = 6.5 Hz, 2H), 2.25–2.14 (m, 2H), 1.93 (t, J = 2.6 Hz, 1H), 1.84–1.53 (m, 6H), 1.14–0.98 (m, 42H); \(^1\)C NMR (125 MHz, CDCl₃) δ 84.5, 72.0, 68.3, 63.6, 38.2, 36.4, 24.5, 18.4, 17.9, 11.7.
Diyne 2-130 was obtained following the general procedure for diyne synthesis: CuCl (6.1 mg, 0.061 mmol) was added to a 30% aqueous solution of n-BuNH₂ (7 mL) at room temperature that resulted in the formation of a blue solution. A few crystals of hydroxylamine hydrochloride were added to discharge the blue color. The alkyne 2-132 (100.7 mg, 0.337 mmol) was added to the solution at room temperature forming a yellow acetylide suspension that was immediately cooled in an ice-water mixture. Solution of bromoalkyne 2-131 (110.8 mg, 0.307 mmol) in 300 μL of CH₂Cl₂ was added at once and the ice bath was removed. More crystals of hydroxylamine hydrochloride were added throughout the reaction as necessary to prevent the solution from turning blue or green. After several additions of hydroxylamine hydrochloride (10 min), the reaction mixture had a rusty color. At this point the reaction was complete according to TLC. The reaction mixture was extracted with CH₂Cl₂ (3 × 10 mL), combined organic extracts were dried over MgSO₄, and concentrated under reduced pressure. Flash column chromatography (gradient elution from 25:1 to 10:1 hexanes:EtOAc) afforded diyne 2-130 (142.4 g, 80%) as a viscous colorless oil. The minor diastereomer is denoted by (†) ¹H NMR (500 MHz, CDCl₃) δ 5.88–5.78 (m, 1H), 5.17–5.11 (m, 2H), 4.04–3.98 (m, 1H), 3.96–3.84 (m, 2H), 3.73 (d, J = 1.8 Hz, 1H), 3.70–3.62 (m, 1H), 2.38–2.27 (m, 3H), 2.22–2.13 (m, 1H), 1.87–1.51 (m, 10H), 1.45 (s, 3H), 1.16–1.04 (m, 21H), 0.86 (s, 9H), 0.17 (s, 3H), 0.17 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 134.8, 118.1, 81.1, 79.6, 72.0, 70.7, 69.4, 64.7, 63.6, 42.0†, 41.9, 41.3†, 41.2, 38.2, 36.5, 31.9†, 31.7, 31.0†, 30.8, 25.7, 24.3, 19.4, 18.0, 17.9, 11.7, -3.0, -3.2.
Bromoalkyne 2-152 was prepared according to the literature procedure.\textsuperscript{65} Diyne 2-142 was obtained following the general procedure for diyne synthesis.\textsuperscript{52} CuCl (7.0 mg, 0.07 mmol) was added to a 30% aqueous solution of \( n \)-BuNH\(_2\) (5 mL) at room temperature that resulted in the formation of a blue solution. A few crystals of hydroxylamine hydrochloride were added to discharge the blue color. The alkyne 2-138 (100.0 mg, 0.354 mmol) was added to the solution at room temperature forming a yellow acetylide suspension that was immediately cooled in an ice-water mixture. Solution of bromoalkyne 2-152 (75.2 mg, 0.425 mmol) in 300 \( \mu \)L of CH\(_2\)Cl\(_2\) was added at once and the ice bath was removed. More crystals of hydroxylamine hydrochloride were added throughout the reaction as necessary to prevent the solution from turning blue or green. After several additions of hydroxylamine hydrochloride (10 min), the reaction mixture had a rusty color. At this point the reaction was complete according to TLC. The reaction mixture was extracted with CH\(_2\)Cl\(_2\) (3 × 10 mL), combined organic extracts were dried over MgSO\(_4\), and concentrated under reduced pressure. Flash column chromatography (gradient elution from 5:1 to 3:1 hexanes:EtOAc) afforded diyne 2-142 (116.4 g, 87%) as a viscous colorless oil. The minor diastereomer is denoted by (†) \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 5.88–5.78 (m, 1H), 5.17–5.11 (m, 2H), 4.04–3.98 (m, 1H), 3.96–3.84 (m, 2H), 3.73 (d, \( J = 1.8 \) Hz, 1H), 3.70–3.62 (m, 1H), 2.38–2.27 (m, 3H), 2.22–2.13 (m, 1H), 1.87–1.51 (m, 10H), 1.45 (s, 3H), 1.16–1.04 (m, 21H), 0.86 (s, 9H), 0.17 (s, 3H), 0.17 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 134.7, 118.2, 80.8, 79.7, 70.7, 69.3, 69.2, 64.9, 62.3, 42.0†, 41.9, 41.3†, 41.1, 31.9†, 31.72, 31.66, 31.0†, 30.8, 25.7, 24.5, 19.1, 18.0, -3.0, -3.2.
Aldehyde 2-148 was prepared according to the literature procedure\textsuperscript{66} as a mixture with inseparable side product and was used crude in this reaction. Acetylene gas was bubbled through a solution of BuLi (10.7 mL, 26.75 mmol) in THF (20 mL) at -78 °C for 10 min. Solution of aldehyde 2-148 (1.5 g) in THF (5 mL) was then added, and the reaction mixture was warmed to room temperature and stirred for additional 30 min. The reaction mixture was quenched with saturated NH\textsubscript{4}Cl solution and extracted with EtOAc (3 × 10 mL). Combined organic extracts were dried over MgSO\textsubscript{4} and concentrated under reduced pressure. The residue was purified by flash column chromatography (gradient elution from 30:1 to 10:1 hexanes:EtOAc) to afford alcohol 2-149 (891 mg) as a pale yellow oil. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 5.18–5.06 (m, 1H), 4.45–4.33 (m, 1H), 2.47 (d, \(J = 2.0\) Hz, 1H), 2.25–2.11 (m, 2H), 1.89–1.84 (m, 1H, OH), 1.82–1.72 (m, 2H), 1.69 (s, 3H), 1.63 (s, 3H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) 132.9, 123.1, 84.9, 72.9, 62.0, 37.6, 25.7, 23.7, 17.7.

To the solution alcohol 2-149 (150 mg, 1.09 mmol) in an acetone–H\textsubscript{2}O mixture (0.08 M, 13.5 mL, 5:1) were subsequently added osmium tetroxide (100 µL, 0.2 M in H\textsubscript{2}O) and NMO (317.9 mg, 2.71 mmol) at room temperature. The reaction mixture was stirred for 1 h (at this point the reaction was complete according to TLC), and NaIO\textsubscript{4} (580 mg, 2.71 mmol) was added. The resultant mixture was stirred for 1 h and quenched with saturated aqueous Na\textsubscript{2}SO\textsubscript{3} (10 mL). Formed in the reaction white precipitate was then filtered through a pad of celite. After removing acetone under reduced pressure, the residue was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried over MgSO\textsubscript{4}, filtered, and concentrated under reduced pressure. The residue (mixture of aldehyde and hemiacetal diastereomers) was used for the next step without purification.
The crude reaction mixture from previous step was dissolved in THF (25 mL) and solution of allylmagnesium bromide (2.70 mL, 1 M in Et₂O, 2.71 mmol) was slowly added at -78 °C. The reaction mixture was warmed to room temperature and quenched with saturated NH₄Cl solution. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated and the residue was purified flash column chromatography (2:1 hexanes:EtOAc) to afford diol 2-151 as a colorless oil (101.6 mg, 63%). The product was obtained as mixture of diastereomers (1.5:1 dr). ¹H NMR (500 MHz, CDCl₃) δ 5.91–5.73 (m, 1H*, 1H†), 5.22–5.08 (m, 2H*, 2H†), 4.55–4.37 (m, 1H*, 1H†), 3.81–3.64 (m, 1H*, 1H†), 3.31 (br, 1H*), 3.04 (br, 1H†), 2.53–2.41 (m, 1H*, 1H†), 2.39–2.11 (m, 1H*, 2H†), 1.98–1.82 (m, 2H*, 2H†), 1.82–1.66 (m, 1H*, 1H†), 1.66–1.54 (m, 1H*); ¹³C NMR (125 MHz, CDCl₃) δ 134.5, 134.4, 118.6, 118.5, 84.8, 84.7, 73.0, 72.9, 70.6, 70.3, 62.1, 61.8, 42.2, 41.9, 34.0, 33.9, 32.2, 31.9.

![Reaction Scheme](attachment:image)

The procedure for the preparation of diyne 2-153 is similar to that of 2-142. Alkyne 2-151 (83.4 mg, 0.54 mmol) and bromoalkyne 2-152 (124.5 mg, 0.70 mmol) under Cadiot-Chodkiewicz coupling conditions afforded diyne 2-153 (colorless oil, 121.6 mg 90%) as a mixture of diastereomers. ¹H NMR (500 MHz, CDCl₃) δ 5.89–5.73 (m, 1H*, 1H†), 5.23–5.10 (m, 2H*, 2H†), 4.56–4.42 (m, 1H*, 1H†), 3.78–3.58 (m, 3H*, 3H†), 3.51–2.96 (m, 1H*), 2.44–2.07 (m, 6H*, 6H†), 1.93–1.38 (m, 6H*, 7H†); ¹³C NMR (125 MHz, CDCl₃) δ 134.5, 134.4, 118.6, 118.5, 81.14, 81.05, 77.2, 76.5, 70.6, 70.2, 65.6, 64.81, 64.78, 62.6, 62.4, 62.3, 62.2, 42.1, 41.8, 34.1, 33.9, 32.2, 32.0, 31.7, 31.6, 24.6, 24.4, 19.1, 19.0.
2.6. References


(41) For selected reviews, see: (a) Dyker, G. Angew. Chem., Int. Ed. 2000, 39, 4237–4239.
(c) Gorin, D. J.; Toste, F. D. Nature 2007, 446, 395–403.
(i) Shapiro, N. D.; Toste, F. D. Synlett 2010, 675–691.


The stereochemistry is tentatively assigned on the basis of the equilibration behaviors of these isomers and their expected relative stability by dipole moment considerations of the two C–O bonds.


(49) See Scheme 3.1.2 for more details, where *d,l*- and *meso*-isomers of 2-119e were reacted separately to obtain more accurate data.

(50) Although the two distinctive resonances between 3.5 and 4.0 ppm are assumed to be an axial and equatorial disposition of two methine protons there could be other factors that render the difference between the two protons.


PART III
DIRECT TRANSITION METAL-CATALYZED [1,3]-TRANSPOSITION OF ALLYLIC ALCOHOLS AND THEIR SILYL ETHERS

3.1. Introduction and Background

The direct transposition of a functional group within a molecule of interest is a powerful atom\(^1\) and step-economical\(^2\) process of structural reorganization. It allows for the preparation of a less accessible isomer from a more readily available precursor in a single operation without prefunctionalization of the substrate. Isomerization of allylic alcohols and their silyl ethers through metal-catalyzed [1,3]-transposition of hydroxyl or siloxy-moieties represents an example of such process (Figure 3.1.1).

![Figure 3.1.1. Transition Metal-Catalyzed [1,3]-Transposition of Allylic Alcohols](image)

Although this transformation has been known for over four decades\(^3\) the utility of this valuable synthetic tool was recognized only recently as demonstrated by the increased number of its applications in complex molecule synthesis. The limited use of [1,3]-allylic transposition in preparative organic chemistry is most likely caused by difficulties to control regio- and stereoselectivity of the reaction due to a reversible nature of the process as well as the availability of catalysts that can operate at low temperatures. Since the initial discovery of vanadium-catalyzed allylic [1,3]-transposition by Chabardes in late 1960s\(^3\) several high oxidation state transition metal oxo-complexes of V, W, Mo, and Re were identified to be suitable catalysts for isomerization. However, most of them either require high reaction temperature to achieve optimal catalyst performance or display limited stability and functional group compatibility. Due to the high oxidation state of metal oxo-complexes, all available catalysts possess significant Lewis acidity, which is more evident with increased number of oxo-ligands. Because of this Lewis acidic nature, side reactions such as dehydration, isomerization, condensation, and racemization of
substrates compete with the desired [1,3]-transposition. In addition, several oxo-complexes of Mo(VI) slowly oxidize alcohols, which ultimately reduces catalyst lifetime. Further catalyst screening and mechanistic studies resulted in the development of triphenylsilyl perrhenate Ph₃SiOReo₃,⁴ the most efficient catalyst for the [1,3]-transposition of allylic alcohols and their silyl ethers. This catalyst possesses high catalytic activity at or below room temperature without competing oxidation of substrates, which significantly exceeds the reactivity of previously known catalysts.⁵ Identification of this superior catalyst has elicited the interest of synthetic community to further develop regio- and stereoselective variants of allylic transpositions. Through subsequent investigations,⁶ the scope of the reaction, structural features of substrates favoring the position of equilibrium, and the degree of chirality transfer have been expanded for various synthetic applications. In these approaches, [1,3]-rearrangement lacking strong thermodynamic driving force has coupled with kinetically or thermodynamically favorable downstream events to achieve high regio- and stereocontrol of the transposition. Examples of the first tactic include the preferential trapping of one of the regioisomeric alcohols during the course of reaction employing N,O-bis(trimethylsilyl)acetamide⁶ and trapping of the equilibrating siloxy-moiety with a tethered boronate functionality.⁷ The second strategy is based on the initial trapping of a hydroxyl group with an electrophile followed by thermodynamically controlled postequilibration.⁸

3.2. Mechanism of Transition Metal-Catalyzed [1,3]-Transposition Allylic Alcohols

The mechanism of transition metal-catalyzed [1,3]-transposition of allylic alcohols was originally proposed by Chabardes for oxovanadium complexes.⁹ The reaction starts with the exchange of one of the alkoxy ligands of a vanadate catalyst with substrate alcohol 3-01 to generate vanadate ester 3-02 (Scheme 3.2.1). The subsequent isomerization of an allylic alkoxide via [3,3]-sigmatropic rearrangement forms intermediate ester 3-04, which upon ligand exchange with substrate 3-01 releases product 3-05 and returns vanadate ester 3-02 into the catalytic cycle. All steps of the mechanism are reversible and the rearrangement generates a thermodynamic mixture of isomeric alcohols. Composition of this mixture depends on the relative stabilities of isomeric products.
This mechanism was later proved both by experiments and DFT-calculations, and the details of charge distribution in the transition state and its effects on selectivity of the reaction were revealed. Kinetic studies for Ph₃SiOReO₃-catalyzed [1,3]-transposition performed by Osborn showed that this reaction is first order on both the catalyst and substrate alcohol. Isomerization of hexenol to (E)-hex-2-en-1-ol with this catalyst has $\Delta H^\neq = 13.3 \pm 0.3 \text{ kcal/mol}$ and $\Delta S^\neq = -14.8 \pm 1.0 \text{ e.u.}$, and for the reverse reaction $\Delta H^\neq = 12.4 \pm 0.6 \text{ kcal/mol}$ and $\Delta S^\neq = -18.3 \pm 2.2 \text{ e.u.}$ were found (Scheme 3.2.2). The large negative activation entropy in this reaction suggests that it proceeds via a [3,3]-sigmatropic pathway with highly ordered polarized transition state. In chair-like transition state, a partially positive allyl group migrates intramolecularly across a partially negatively charged perrhenate moiety. However, for the formation of (Z)-, the enthalpy of activation is $\Delta H^\neq = 20.9 \pm 0.4 \text{ kcal/mol}$ and the activation entropy equals $\Delta S^\neq = 3.1 \pm 1.5 \text{ e.u.}$ For its reverse reaction, these parameters were determined to be $\Delta H^\neq = 24.9 \pm 0.7 \text{ kcal/mol}$ and $\Delta S^\neq = 19.3 \pm 2.2 \text{ e.u.}$ The positive entropies of activation indicate that the rearrangement to (Z)- takes place via an ionization–recombination pathway with the formation of a solvent-separated positively charged allylic cation and a negatively charged perrhenate moiety in the transition state. Moreover, the formation of Z-isomer has low rate of 0.07 turnovers per minute compared with that for (E)-hexenol (9.00 turnovers per min). A similar rate of 0.16 turnovers per minute.
min was found for the conversion of (Z)-3-07 to other isomers. The authors explained that the observed selectivity for (E)-3-07 is the consequence of the minimized diaxial interactions between the oxo-ligand and a propyl substituent in a chair-like transition structure. Based on the proposed mechanism, the greater activity of Ph₃SiOReO₃ compared to other oxo-metal catalysts is attributed to the effective stabilization of a partially negatively charged perrenate moiety by the increased number of spectator oxo-ligands on the metal center.

Scheme 3.2.2. Mechanism of Allylic [1,3]-Transposition Proposed by Osborn

Based on thorough investigations of the scope and limitations of [1,3]-transposition of allylic alcohols Grubbs suggested a more detailed mechanistic rationale. Similar to the Osborn’s mechanism, he proposed that the isomerization occurs through an asynchronous [3,3]-sigmatropic rearrangement with polarized chair-like transition structure 3-12 (Scheme 3.2.3). In the transition state, the C–O bond cleavage precedes the other C–O bond formation, which results in a partial positive charge character on the allyl fragment and a partial negative charge character on the perrhenate moiety. Due to the strong polarization of the C–O bond in 3-12, the formation of ion pair intermediate 3-14 competes with a sigmatropic manifold of the rearrangement. The existence of 3-14 mainly accounts for the formation of
undesired side products via elimination (3-15) and condensation (3-16), as well as the racemization of enantiomerically enriched substrates. The selective formation of $E$-isomers from both ($E$)- and ($Z$)-allylic alcohols explained by the greater number of diaxial interactions in the transition state leading to the ($Z$)-configured alcohol in accordance with the Osborn’s rationale. Because of the high polarization in transition state 3-12, the electronic effect of substituents have a strong influence on the reaction rate and partitioning of rhenate ester intermediates between two manifolds of the reaction. Accordingly, functional groups capable of stabilizing a positive charge character on the allylic moiety, such as electron-donating groups, or more substituted alkenes would increase the rate of isomerization. However, they would also decrease regio- and stereoselectivity due to the facile formation of a free allylic cation. Transposition of alcohols bearing electron-withdrawing substituents or less substituted double bond would have more concerted nature, thus would have increased selectivity for the reaction.

![Scheme 3.2.3](image.png)

**Scheme 3.2.3.** Mechanism of Allylic [1,3]-Transposition Proposed by Grubbs

This proposal nicely explains the observed rearrangement tendency of allylic alcohols. For the reactions of electron-rich substrates, low reaction temperatures of –50–78 °C are required in order to
suppress the formation of ion pairs, which leads to the decomposition of allylic alcohols. However, reactions of electron-poor alcohols can be performed at room temperature but might not proceed at lower temperatures at all. Similarly, the degree of chirality transfer is affected by electronic nature of the substrate; it increases with electron-withdrawing capacity of substituents. Since a competing ionization–recombination pathway is responsible for racemization of allylic alcohols, electron-deficient substrates should be less prone to the isomerization through an ionic pathway.

3.3. Overview of Transition Metal–Catalyzed [1,3]-Transposition of Allylic Alcohols and Their Silyl Ethers

3.3.1. Vanadium-Catalyzed Processes

The early examples of [1,3]-transposition of allylic\(^3,9,11\) and propargylic\(^12\) alcohols were developed by using trialkyl orthovanadates VO(OR)\(_3\) as the catalysts, which were either prepared separately or formed \textit{in situ} from ammonium metavanadate and the corresponding alcohols. The isomerization of propargylic alcohols leads to the formation of allenyl vanadate esters such as 3-19, which upon subsequent alcoholsysis furnishes \(\alpha,\beta\)-unsaturated aldehydes 3-20 (Scheme 3.3.1.1). These reactions require 0.05–2 wt. % catalyst loading, and occur at high temperatures of 140–200 °C. The isomerization can be performed neat or in a hydrocarbon solvent. According to the reaction procedures, the transpositions of propargylic alcohols were not run to the completion and maximum conversion of 37% for dehydrolinalool 3-17 was obtained.

Analogous rearrangements of allylic alcohols are readily reversible and give thermodynamic mixtures of isomeric products. Accordingly, heating of linalool 3-21 in the presence of ammonium metavanadate at 150 °C for 6 h resulted in the formation of a mixture of primary alcohols 3-24 (geraniol and nerol) in 30% conversion. Reactions catalyzed by VO(OR)\(_3\) were generally effective for rearrangements of tertiary allylic alcohols to form primary alcohols and were applied commercially in the fragrance industry. The conversion of a tertiary alcohol to the corresponding borate ester or alternatively running the reaction in the presence of borate esters allowed for the improvement of isomerization efficiency.\(^13\) Thus, when
linalyl dibutyl borate 3-25 was heated with triethanolamine orthovanadate 3-26 at 160 °C for 2 h a mixture of geraniol and nerol was obtained in 83% yield after subsequent hydrolysis of the reaction mixture.

Scheme 3.3.1.1. Vanadium-Catalyzed Rearrangement of Propargylic and Allylic Alcohols

Activation of vanadium acetylacetonate with TMSOTMS generates a catalyst system that exhibits high activity at room temperature.\(^\text{14}\) It selectively isomerizes primary allylic alcohols to tertiary isomers, however, side reactions such as dehydration and isomerization were also observed. Thus, the isomerization of geraniol ((E)-3-24) in the presence of in situ generated catalyst gives a thermodynamic mixture of products containing linalool (3-21), nerol ((Z)-3-16), and α-terpineol (3-28) in a 68:8:2 ratio together with 10% of unreacted starting material (Scheme 3.3.1.2).

Scheme 3.3.1.2. VO(acac)\(_2\)/TMSOTMS-Catalyzed Isomerization of Geraniol
It was observed that isomerizations of secondary allylic alcohols are less selective, whereas those of primary alcohols give low conversions (Scheme 3.3.1.3). Thus, the treatment of secondary alcohol 3-29 with VO(acac)$_2$/TMSOTMS in dichloromethane afforded rearranged product 3-30 in 76% yield together with recovered starting material (20%). The isomerization of primary alcohol 3-31 afforded product 3-32 in 35% GC yield. The chirality transfer of [1,3]-transposition with VO(acac)$_2$/TMSOTMS was also investigated. The allylic transposition of cyclic alcohol 3-33 prepared in 40% $ee$ afforded rearranged product 3-34 and recovered starting material in 35% and 40% yield, respectively. Analysis of this reaction mixture indicated that the transposition occurred with partial racemization since the product was obtained in 29% $ee$. This result is consistent with the proposed mechanism for rearrangement though a highly ordered cyclic transition state. The partial loss of chiral information can be rationalized based on a competing ionic manifold of the reaction.

Scheme 3.3.1.3. VO(acac)$_2$/TMSOTMS-Catalyzed Rearrangements

The treatment of allenic alcohols such as 3-35 with VO(acac)$_2$–TMSOTMS catalyst mixture gives corresponding enones (3-36) in high yield. Although an active catalytic species VO(acac)$_2$–TMSOTMS system were not identified, it was suggested by authors that intermediates bearing a [V]–OOTMS structural element are present in the reaction mixture.
Several methodologies have been developed based on the [1,3]-transposition of allylic, propargylic, and allenic alcohols. Interception of vanadate enolate intermediates generated from the rearrangement of propargylic\textsuperscript{15} or allenic\textsuperscript{16} alcohols with aldehydes or imines allows for the synthesis of aldol or Mannich reaction products in unconventional way. Thus, heating of propargylic alcohol 3-37 with aldehyde 3-38 in the presence of tris(triphenylsilyl)vanadate (VO(OSiPh\textsubscript{3})\textsubscript{3}) in DCE at 80 °C afforded two aldol products 3-39 and 3-40 as Z-isomers (Scheme 3.3.1.4). Similar reactions in the presence of Ph\textsubscript{3}SiOReO\textsubscript{3} or bis(triphenylsilyl)molybdate (MoO\textsubscript{2}(OSiPh\textsubscript{3})\textsubscript{2}) were unsuccessful.\textsuperscript{15} The ratio of aldol products as well as E/Z-selectivity depends on the reaction time as prolonged heating resulted in an increased amount of rearranged product 3-40 and diminished E/Z-ratios.

Scheme 3.3.1.4. Tandem Rearrangement of Propargylic Alcohols and Their Trapping

Mechanistically, this cascade transformation starts with the formation of allenyl vanadate 3-43 by [1,3]-transposition of propargylic alcohol 3-41 through vanadate ester 3-42. Allenyl vanadate possesses
sufficient nucleophilicity to undergo addition to aldehyde 3-44 with the formation of vanadate ester 3-45. Vanadate ester 3-45 exists in equilibrium with isomeric 3-46 via allylic [1,3]-transposition. The ligand exchange of these intermediates with substrate alcohol 3-41 delivers addition products 3-47 and 3-48.

Allenic alcohols undergo [1,3]-transposition in the presence of VO(OiPr)$_3$ at room temperature. Thus, the trapping of vanadium enolate generated from alcohol 3-49 with benzaldehyde 3-50 afforded a syn-aldol product 3-51 in an 80:20 diastereomeric ratio (Scheme 3.3.1.5). Changing the catalyst to MoO$_2$(acac)$_2$ resulted in a mixture of aldol product 3-50 and Meyer-Schuster product enone in an 80:20 ratio (not shown). The more electron-rich oxovanadium complex VO(OiPr)$_2$ was unreactive, and VO(OSiMe)$_3$ gave an aldol product in 21% yield despite of extended reaction time.$^{16a}$

Scheme 3.3.1.5. Tandem Rearrangement of Allenic Alcohols and Their Trapping
Treatment of 3-49 with aldimine 3-52 in the presence of VO(OSiPh₃)₃ furnished Mannich adduct 3-53 in a 9:1 dr favoring an anti-diastereomer. Formation of a syn-adduct in the reaction with aldehydes and an anti-product in the reaction with imines can be rationalized by respective chair-like transition states 3-59 and 3-60.

The [3,3]-sigmatropic rearrangement of allenyl alcohol 3-54 via its vanadyl ester 3-55 preferentially generate (Z)-vanadium enolate 3-56. Subsequent nucleophilic addition to aldehyde 3-57 via chair-like transition state 3-59 leads to intermediate 3-61, which upon alcoholysis delivers syn-aldol product 3-63. Reaction of 3-56 with aldimine 3-58, however, occurs through transition state 3-60, which gives anti-Mannich adduct 3-64 after subsequent alcoholysis of generated vanadate ester 3-62.

The combination of vanadium-catalyzed [1,3]-transposition and lipase-catalyzed kinetic resolution was employed for the dynamic kinetic resolution (DKR) of allylic alcohols. A vanadium oxo-complex plays a role of a racemization catalyst, which elicits reversible allylic isomerization. Since the [1,3]-transposition of allylic alcohols proceeds mainly through a [3,3]-sigmatropic pathway, the racemization of mismatched enantiomer is only possible via a minor cationic manifold of the reaction (see section 3.2). The extent of a cationic manifold depends on the temperature and solvent used in the reaction. Due to the reversibility of transposition, prolonged reaction times lead to a greater amount of racemized material. In order to obtain high enantiomeric excess of the product under this continuous racemization conditions careful optimization of solvent, temperature and reaction time is necessary. Due to high enatio- and chemoselective abilities of lipases, only one regioisomer of a matched configuration undergoes esterification. Thus all regioisomers of allylic alcohols such as 3-65 and 3-66 (Scheme 3.3.1.6) are competent substrates and give the same optically active allylic ester 3-67 in a single step. After screening of commercially available lipases and solvents, the optimal conditions were found that involve Candida Antarctica lipase B (CAL-B), VO(OSiPh₃)₃ and vinyl acetate as an acyl donor in acetone at room temperature. Under the standard reaction conditions, both racemic secondary allylic alcohol 3-68
bearing two identical substituents on the double bond and tertiary allylic alcohol 3-69 afforded acetate 3-70 in 99% ee after 3–4 days with similar efficiency.

Scheme 3.3.1.6. Dynamic Kinetic Resolution of Allylic Alcohols

Due to slow racemization step, this method is not effective for DKR of unsymmetrically substituted substrates. To facilitate racemization raising the temperature to 35–50 °C in acetone or changing the solvent to more coordinating acetonitrile and performing the reaction at 35 °C is necessary. Under mild heating benzylic alcohol 3-71 obtained as a mixture of $E/Z$-isomers (23:77 $E/Z$) underwent efficient DKR to produce single isomer 3-72 in 99% enantiomeric excess (Scheme 3.3.1.7). The reaction of racemic tertiary alcohol 3-73 in the presence an increased amount of catalyst in acetonitrile afforded product 3-74 in both high yield and enantiomeric excess but only with 3:1 $E/Z$-selectivity. The same reaction, catalyzed by mesoporous silica immobilized catalyst V-MPS delivered enantiomerically enriched ester 3-74 as a 7:1 $E/Z$-mixture. Reaction with an immobilized catalyst requires only 1 mol % of vanadium loading and was completed in 24 hours.

The observed high catalytic activity of V-MPS is attributed to the facile racemization of substrate alcohols in the presence of this catalyst and the increased compatibility of immobilized on mesoporous (3 Å) silica oxovanadium complex with lipases. The increased compatibility arises from the minimized
interactions between the metal catalyst and the protein because of the uniform pore size of the carrier while maintaining the free access of the substrate to the metal center.

**Scheme 3.3.1.7.** Dynamic Kinetic Resolution under Different Conditions

The authors have also studied the catalytic activity of polymer-bounded oxovanadium complex 3-75,\(^{20}\) which was as effective as VO(OSiPh\(_3\))\(_3\). The V-MPS–CAL-B catalytic system displayed the broadest substrate scope and the DKR usually completes in 24 h for all allylic alcohols tested. High catalytic performance of V-MPS catalyst was sustained up to the sixth run, which indicates minimal leaching of the metal from the solid carrier.

**3.3.2. Tungsten-Catalyzed Processes**

Only a single example of the [1,3]-transposition of tertiary allylic alcohols has been reported with high oxidation state oxotungsten complexes.\(^{21}\) In this reaction, linalool 3-21 was heated in the presence of oxotungsten catalyst 3-76 at 200 °C for 3 h, which provided an equilibrium mixture of geraniol and nerol in 40% conversion (Scheme 3.3.2.1). Although conversions of other tested terpene-derived tertiary allylic alcohols catalyzed by oxotungsten complexes were similar to that of oxovanadium complexes reported by Chabardes\(^{3,9}\) the catalyst loadings in W-catalyzed isomerizations were significantly lower (W:V = 1:7). Another advantage of tungsten-catalyzed transposition is the facile separation of the catalyst by
distillation. The limitation of VO(OR)_3-catalyzed isomerization is that the trace amount of catalyst co-
distills with the mixture of alcohols, which results in their postisomerization. However, this problem can
be easily avoided by employing triethanolamine orthovanadate complex 3-26.

\[ \text{3-21} \xrightarrow{200 \degree C, 3 \text{ h}} \text{3-76 (0.01 mol %)} \]

(E)-3-24 (25%) + (Z)-3-24 (15%)

Scheme 3.3.2.1. WO(OSiEt)_3;Py-Catalyzed Isomerization of Linalool

3.3.3. Molybdenum-Catalyzed Processes

In the seminal work on molybdenum-catalyzed [1,3]-transposition of allylic alcohols, Osborn and co-
workers studied the catalytic behavior of bis-oxo MoO_2(OCR_2CH=CR\textsuperscript{1}_2)L_2, oxo-imido
Mo(O)(NR\textsuperscript{2})(OCR_2CH=CR\textsuperscript{1}_2)L_2, and bis-imido Mo(O)(NR\textsuperscript{2})_2(OCR_2CH=CR\textsuperscript{1}_2)L_2 complexes.\textsuperscript{22} Bis-oxo complex 3-77 was synthesized and its isomerization was monitored by \textsuperscript{1}H NMR in CD\textsubscript{3}CN (Scheme 3.3.3.1). It has been observed that 3-77 undergoes equilibration in solution with the formation of two new
oxomolybdenum species bearing rearranged allyloxo moieties. At equilibrium, the ratio of an initial
alkoxide OCMe\textsubscript{2}CH=CH\textsubscript{2} and a rearranged alkoxide OCH\textsubscript{2}CH=CMe\textsubscript{2} was found to be 1:3. Kinetic studies of the rearrangement revealed that the reaction proceeds intramolecularly via a mononuclear complex.

\[ \text{X} = \text{O}, \text{3-77} \]

\[ \text{X} = \text{NPn}, \text{3-78} \]

\[ \text{3-79} \]

\[ \text{3-80} \]

Scheme 3.3.3.1. Isomerization of Molybdenum bis-Oxo and Oxo-Imido Complexes

Isomerization of the corresponding imido complex 3-78 occurs at a much slower rate, which indicates
a significant charge polarization in transition state 3-79. In 3-79 a partial positive charge character is
developing on the migrating allyl moiety and a partial negative character is placed on the metal center. Therefore, electron-donating spectator imido ligand destabilizes the transition state thus increasing the activation barrier of the reaction.

Comparison of the reactivity of bis-oxo, oxo-imido, and bis-imido complexes indicates that transfer of allyl moiety to M=O is favored over that to Mo=NR, which is consistent with the greater stabilization of partial negative charge on the Mo(VI) center by the oxo over the imido ligand. The migration to Mo=O in oxo-imido complexes is significantly slower than that in bis-oxo congener, and migration to M=NR moiety is only observed in bis-imido complexes. Additionally, it was found that the oxidation of allyloxo ligands competes with allylic transposition, as evidenced by the formation of aldehydes after prolonged reaction times or increased reaction temperatures.\textsuperscript{22b} Reduction of Mo(VI) center deactivates the catalyst toward [1,3]-transposition, which has significant effect on the efficiency of the rearrangement of slow reacting substrates. The authors have also indicated that the [1,3]-transposition of allylic alcohols can be carried out at room temperature with MoO\textsubscript{2}(O′Bu)\textsubscript{2} as a catalyst precursor.

Recently, the isomerization of allylic alcohols at room temperature by molybdenum(VI) complex 3-82 bearing peroxo ligand has been demonstrated.\textsuperscript{23} Complex 3-82 was prepared from bis-oxo complex 3-81 by treating with hydrogen peroxide. In the presence of catalyst 3-82, several primary allylic alcohols such as geraniol ((E)-3-24) and 3-83 were selectively isomerized to the corresponding tertiary alcohols 3-21 and 3-84. In all cases the equilibrium of the reaction was established in the order of several days (Scheme 3.3.3.2). Although bis-oxo complex 3-81 catalyzes isomerization of geraniol, the rate of this reaction is much slower than that of 3-82. Peroxo complex 3-82 is also effective for the selective rearrangement of tertiary 3-85 and secondary 3-87 benzylic alcohols to the corresponding primary 3-86 and 3-88. In this case the driving force for the rearrangement is the resulting conjugation with a phenyl substituent. Labeling studies indicates that the mechanism of isomerization by complex 3-82 is similar to that of 3-77, proposed by Osborn. However, the initial dissociation of phosphine oxide ligand MePh\textsubscript{2}P=O
is required prior to the coordination of an allylic alcohol. A substantial decrease in rate of the isomerization of geraniol was observed when MePh$_2$P=O was added to the reaction mixture.

![Scheme 3.3.3.2](image)

**Scheme 3.3.3.2.** Isomerization of Allylic Alcohols in the Presence of Molybdenum Oxo-Peroxo Complex

Ill-defined catalyst system MoO$_2$(acac)$_2$/TMSOETMS similar to VO(acac)$_2$/TMSOETMS was reported for the selective isomerization of various primary allylic alcohols to the corresponding tertiary ones (see section 3.3.1).$^{14b}$ The Mo-catalyzed system, however, is less efficient and gives reduced yields of rearranged alcohols due to competing undesired side reactions. On the other hand, the rearrangements of allenic alcohols were more facile under Mo-catalysis (Scheme 3.3.3.3). Although the isomerization of 3-89 with MoO$_2$(acac)$_2$ could be carried out with or without peroxide addition, slightly better yield of 3-90 was observed in the former case.

![Scheme 3.3.3.3](image)

**Scheme 3.3.3.3.** MoO$_2$(acac)$_2$-Catalyzed Isomerization of Allenic Alcohol

An interesting example of Mo-catalyzed multidirectional [1,3]-transposition of allyl allenyl alcohol 3-91 was also investigated. It was found that the regioselectivity of rearrangement depends on the reaction
Temperature. Treatment of 3-91 with 5 mol % of MoO₂(acac)₂ in dichloromethane for 10 min at room temperature provided enone 3-92 in 90% yield (Table 3.3.3.1, entry 1). The same reaction performed at -78 °C afforded tertiary alcohol 3-93 without any sign of formation of enone 3-92 (entry 2). The addition of TMSOOTMS did not alter the selectivity of the reaction (entries 3, 4). Allylic alcohol 3-91 exists in equilibrium with tertiary alcohol 3-93 and dienyl alcohol 3-94 in the presence of Mo-catalyst (Scheme 3.3.3.4). Thus, at lower reaction temperature kinetically favored tertiary alcohol 3-93 is produced, however, at room temperature thermodynamically more stable enone 3-92 is formed from the tautomerization of 3-94. The reaction in the presence of VO(acac)₂ was less efficient and a maximum ratio of 11:1 between alcohol 3-93 and enone 3-92 was obtained when 15 mol % of TMSOOTMS was added (entry 5).

Table 3.3.3.1. Temperature Dependence of the [1,3]-Transposition of Allyl Allenyl Alcohol

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>TMSOOTMS (mol %)</th>
<th>T (°C)</th>
<th>Yield (%)</th>
<th>3-93</th>
<th>3-92</th>
<th>3-91</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MoO₂(acac)₂</td>
<td>–</td>
<td>25</td>
<td>&lt;2</td>
<td>90</td>
<td>&lt;2</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>MoO₂(acac)₂</td>
<td>–</td>
<td>–78</td>
<td>94</td>
<td>&lt;2</td>
<td>&lt;2</td>
<td>&lt;2</td>
</tr>
<tr>
<td>3</td>
<td>MoO₂(acac)₂</td>
<td>5</td>
<td>25</td>
<td>&lt;2</td>
<td>94</td>
<td>&lt;2</td>
<td>&lt;2</td>
</tr>
<tr>
<td>4</td>
<td>MoO₂(acac)₂</td>
<td>15</td>
<td>25</td>
<td>13</td>
<td>82</td>
<td>&lt;2</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>VO(acac)₂</td>
<td>15</td>
<td>25</td>
<td>7</td>
<td>80</td>
<td>&lt;2</td>
<td></td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 5 mol % catalyst loading, CH₂Cl₂, 10 min. [b] Isolated yield.

Scheme 3.3.3.4. Equilibrium in the Isomerization of Allyl Allenyl Alcohol
3.3.4. Rhenium-Catalyzed Processes

Several high oxidation state oxorhenium catalysts and catalytic systems have been reported for the [1,3]-transposition of allylic alcohols and their silyl ethers. These include Bu$_4$NReO$_4$/pTsOH·H$_2$O combination, methylrhenium trioxide (MeReO$_3$, MTO), Ph$_3$SiOReO$_3$, rhenium(VII) oxide (Re$_2$O$_7$), and Re$_2$O$_7$ supported on silica gel. Among them Ph$_3$SiOReO$_3$ is found a wide range of applications due to its solubility and high catalytic activity. In general, all oxorhenium complexes are significantly more active in the allylic transposition than oxo-complexes of vanadium (V), tungsten(VI), or molybdenum(V) due to the increased number of oxo-ligands around rhenium(VII) center that stabilize partial negative charge developing on the metal center during the rearrangement. Moreover, despite of the oxidation state of the metal, Re(VII) catalysts do not affect the oxidation of substrate alcohols, which ultimately increases catalyst longevity and allows for low catalyst loading.

Activation of tetrabutylannomium perrhenate (Bu$_4$NReO$_4$) with para-toluenesulfonic acid gives a catalyst system that is capable of isomerizing allylic alcohols at room temperature.$^{24}$ Thus, treatment of primary allylic alcohol 3-95 with 10 mol % of Bu$_4$NReO$_4$ and 5 mol % of pTSA for 24 h gives an equilibrium mixture of primary and secondary alcohols in 88% combined yield and a 63:37 ratio (Scheme 3.3.4.1). Under these acidic reaction conditions, however, alcohols undergo excessive dehydration. When secondary allylic alcohol 3-97 was subjected to the Bu$_4$NReO$_4$/pTsOH·H$_2$O a mixture of isomeric allylic alcohols 3-98 was obtained in 40% yield in 5 min, and after 18 h time period only a mixture of regioisomeric dienes 3-99 and 3-100 was isolated with all possible configurations of double bonds. For tertiary allylic alcohols dehydration occurred immediately to afford mixtures of conjugated dienes (not shown). Stereoselectivity of the reaction was investigated in the rearrangement of syn-substituted substrate 3-101. Treatment of this compound gave transposed alcohol 3-102 as a 2.5:1 mixture of syn/anti-diastereomers as well as recovered starting material in a 2:1 diastereomeric ratio. Prolonged reaction time delivered a mixture of two conjugated dienes 3-103 and 3-104 in 75% combined yield. The significant loss of diastereomeric excess of 3-101 indicates that the rearrangement occurs mainly through
an ionization pathway with the formation of a free allylic cation intermediate. Due to its harsh reaction conditions and the formation of all possible regio-, and stereoisomers of the rearranged alcohol this method does not offer any synthetic utility.

Scheme 3.3.4.1. Isomerizations of Allylic Alcohols in the Presence of Bu₄NReO₄/pTsOH System

Methylrhenium trioxide²⁵ is an air stable and efficient catalyst for a variety of transformations,²⁶ which include olefin epoxidation, Baeyer-Villiger oxidation, olefin metathesis, aromatic oxidation, and Diels-Alder cycloaddition. The earliest application of this complex for [1,3]-transposition of allylic alcohols can be found in patent literature.²⁷ MTO has been applied industrially for equilibration between secondary and primary alcohols. The amount of catalyst required for transposition is between 1:100 and 1:1000 ratios to substrate and reaction temperatures are ranging from 20 to 150 °C. If secondary alcohol is the desired product of isomerization it can be continuously distilled off from the reaction mixture in the same rate as it is formed. Thus, primary alcohol can be quantitatively converted to the secondary. For the preparation of primary alcohol, the isomerization process has to be stopped when equilibrium established and the reaction mixture has to be fractionally distilled. Using this method, the isomerization of 3-105 in the presence of MTO in 1:150 catalyst loading at 60 °C afforded primary alcohol 3-106 in 36% conversion (Scheme 3.3.4.2).
Scheme 3.3.4.2. MeReO₃-Catalyzed Equilibration between 1° and 2° Allylic Alcohols

Later studies²⁸ indicate the thermodynamic preference of aliphatic tertiary allylic alcohols over secondary and primary at equilibrium in the presence MeReO₃ catalyst. Accordingly, the isomerization of geraniol catalyzed by 5 mol % of MTO at room temperature gave linalool in 86% NMR yield after 2.5 days. Similarly, isomerization of 3-107 afforded secondary alcohol 3-108 in 61% NMR yield (Scheme 3.3.4.3). For alcohols bearing an aromatic substituent capable of being conjugated after the rearrangement, the equilibrium greatly favors a conjugated isomer. Thus, the rearrangement of tertiary alcohol 3-109 and secondary alcohol 3-87 delivered conjugated secondary 3-110 and primary 3-88 alcohols, respectively. The rate of allylic rearrangement induced by MeReO₃ is comparable to that catalyzed by molybdenum oxo-peroxo complex 3-74 (see section 3.3.3).

Scheme 3.3.4.3. [1,3]-Transposition of Allylic Alcohols Catalyzed by MeReO₃

Side reactions of MTO-catalyzed [1,3]-transposition are dehydration and condensation, especially for tertiary allylic alcohols, which become more evident with increased reaction times. Addition of water greatly inhibits rearrangement probably due to competition between water and alcohol for the metal binding site, leading to the formation of inactive hydrated form of catalysts. The mechanism for the isomerization of allylic alcohols using MeReO₃ is consistent with that proposed by Chabardes, Osborn,
and Grubbs, which was further bolstered by the rearrangement of $^{18}$O-labeled alcohol: the percentage of $^{18}$O atoms on the alcohol decreased and that on the Re complex increased.

In 1997 Osborn and co-workers disclosed that the isomerization of hex-1-en-3-ol (3-111a) to a thermodynamic mixture of regioisomers with 2 mol % of trimethylsilyl perrhenate (Me$_3$SiOReO$_3$) in acetonitrile at 25 °C was completed in less than 10 minutes (Scheme 3.3.4.4). The catalytic activity of a new class of catalysts was 100 higher than that of MoO$_2$(O’Bu)$_2$. The analogous complex Ph$_3$SiOReO$_3$ displayed even higher reactivity and gave an equilibrium mixture of hexenols in about 5 minutes at 0 °C. Greater catalytic activity of Ph$_3$SiOReO$_3$ compared to Me$_3$SiOReO$_3$ is a result of the condensation of trimethylsilanol to form hexamethyldisiloxane and water. Concomitant reaction of water with a catalyst gives perrhenic acid causing a loss of catalytic activity over time. This report set the starting point for the emergence of the most efficient catalysts in the field of [1,3]-transposition of allylic alcohols and their silyl ethers.

**Scheme 3.3.4.4.** Discovery of R$_3$SiOReO$_3$-Catalyzed [1,3]-Transposition of Alcohols and Silyl Ethers

Based on the investigation of Wilkinson on the synthesis of perrhenate esters (ROReO$_3$) by the reaction between silyl ethers ROSiMe$_3$ and Me$_3$SiOReO$_3$, Osborn expanded the scope of the [1,3]-transposition of allylic alcohols to their silyl ether derivatives. In this work isomerization of TMS-silyl ether 3-112b in the presence of 1 mol % of Me$_3$SiOReO$_3$ reached equilibrium in less than 60 minutes at room temperature in dichloromethane. When Ph$_3$SiOReO$_3$ was employed as a catalyst, a small induction period was observed. The position of equilibrium between two isomeric silyl ethers depends on the silyl ether structure.
group of the substrate. In case of unprotected alcohol 3-112a an equilibrium mixture in a 40:60 ratio was obtained favoring secondary alcohol. Trimethylsilyl derivarive 3-112b afforded a product mixture with an increased content of primary ether by 15% (55:45 ratio was recorded). Increasing the steric bulk of the silyl ether resulted in even a greater proportion. The rearrangement of TES- (3-112c) and TBS- (3-112d) derivatives afforded primary and secondary hexenyl ethers in 62:38 and 57:43 ratios, respectively. These catalytic processes, however, were relatively slow such that they required several hours to reach an equilibrium state. In a more coordinating solvent such as acetonitrile or THF, the rate of reaction was reduced significantly. The authors mentioned that Re₂O₇ also catalyzed [1,3]-transposition, however, the rate of isomerization was not measured due to limited solubility of the catalyst in dichloromethane.

After this major breakthrough in catalyst development, several methodologies for regioselective [1,3]-transposition of allylic alcohols and their silyl ethers have been developed and successfully utilized in natural product synthesis. Although some strategies to obtain high product selectivity based on introduction of substituents for increased conjugation²⁸,²⁹ and trapping of transposed alcohols with borate esters¹³ were reported earlier this reaction was not systematically investigated until 2005. In 2005 Grubbs undertook seminal studies⁶ to define the scope and limitations of Ph₃SiOReO₃-catalyzed transposition and investigated the chirality transfer with enantiomerically enriched substrate alcohols. Grubbs has demonstrated that a variety of secondary benzylic and heteroaromatic allylic alcohols selectively rearranged to their conjugated isomers in the presence of Ph₃SiOReO₃ in ethereal solvents at low temperatures (–78–50 °C) in short periods of time. Similar reactions at room temperature resulted in extensive dehydration and condensation side reactions. Analogously, the use of other solvents such as CH₂Cl₂, CH₃CN, or toluene gave a significant amount of by-products. The reactivity of allylic alcohols strongly depends on their electronic properties (Scheme 3.3.4.5). Thus, rearrangement of 3-113 at -50 °C afforded conjugated product in 98% yield and high E-selectivity. Substrate 3-115 containing an electron-poor allyl moiety underwent [1,3]-isomerization efficiently only at room temperature. On the other hand, substrate 3-117 possessing an electron-rich allylic functionality readily isomerized at -78 °C, and
exhibited extensive side product formation at higher reaction temperatures. These observations are consistent with the development of a partially cationic allylic moiety in the transition state. The side products formation resulting from competing reaction pathway involving an allylic cation becomes less favorable at low reaction temperatures.

**Scheme 3.3.4.5.** Ph$_3$SiOReO$_3$-Catalyzed [1,3]-Transposition of Allylic Alcohols Driven by Conjugation

Another tactic to obtain high product selectivity in the rearrangement of tertiary allylic alcohols is based on the combination of preferential silylation of the primary allylic alcohol over tertiary isomer with N,O-bis(trimethylsilyl)acetamide (BSA) and relatively slow rate of isomerization of the corresponding silyl ethers compared to their parent alcohols. Therefore, during the course of reaction the primary silyl ether is removed from equilibrium.

**Scheme 3.3.4.6.** BSA-Assisted [1,3]-Transposition of Allylic Alcohols Catalyzed by Ph$_3$SiOReO$_3$
Rearrangement of 3-119 (Scheme 3.3.4.6) in the presence of 1 equivalent of BSA and a catalytic amount of N-trimethylsilylacetamide (TMSA) as a promoter at 0 °C afforded primary alcohol 3-120 in 84% yield and 4.6:1 E/Z-selectivity after hydrolysis. Interestingly, the same reaction in the absence of silylating agent delivered a primary alcohol in only 30% yield, which indicates that 3-120 is thermodynamically disfavored regioisomer.

The chirality transfer in [1,3]-transposition was examined with two enantiomerically enriched substrates (S,E)-3-113 and (S,Z)-3-113 (Scheme 3.3.4.7). Isomerization of (S,E)-3-113 under optimal reaction conditions afforded product (S,E)-3-114 with a small loss of enantiopurity. Similarly, the rearrangement of (S,Z)-3-113 obtained in more than 98% ee furnished conjugated isomer (R,E)-3-114 in 72% enantiomeric excess.

Scheme 3.3.4.7. [1,3]-Transposition of Enantiomerically Enriched Allylic Alcohols Catalyzed by Ph3SiReO3

The absolute configuration of products (S,E)-3-114 and (R,E)-3-114 is controlled by the double bond geometry of starting materials. The [1,3]-transposition of (S,E)-3-113 occurs via chairlike transition state.
in which the E-alkene geometry results in equatorial position of the alkyl substituent leading to (S)-stereochemistry of the product. For the isomerization of (S,Z)-3-113 rearrangement proceeds through transition state 3-122 which gives (R)-configured product because of an axially oriented alkyl substituent.

The influence of the electronic nature of an aromatic substituent in stereochemical information transfer was also investigated. Accordingly, the rearrangement of substrate 3-123 bearing an electron-donating methoxy substituent at -78 °C delivered racemic product 3-124. In contrast, the isomerization of electron-deficient substrate 3-125 at -50 °C afforded enantioenriched alcohol 3-126. The [1,3]-transpositions of 3-113, 3-123, and 3-125 indicate that the loss of enantiopurity occurs via a cationic manifold. Therefore, electron-withdrawing substituents on the substrate increase the activation barrier of free allyl cation formation.

In the isomerization of enantioenriched cyanohydrin 3-127, high chirality transfer was observed at room temperature as alcohol 3-128 was obtained in excellent yield and enantiopurity (Scheme 3.3.4.8). High chirality transfer in this case is due to the low reactivity of cyanohydrins as a result of a strong electron-withdrawing nature of the cyano group. Only cyanohydrins bearing trisubstituted double bond participate in [1,3]-transposition reactions. Cyanohydrins possessing a terminal double bond or a disubstituted double bond are completely inert toward Ph₃SiOReO₃.

**Scheme 3.3.4.8.** [1,3]-Transposition of Allylic Cyanohydrins Catalyzed by Ph₃SiOReO₃

Introduction of a tethered boronate functionality in the structure of allylic silyl ethers allowed for the employment of Lewis acid-base interactions between the boronate and the rearranged siloxy moieties to shift the equilibrium of [1,3]-transposition in the desired direction. Substrates for [1,3]-transposition were prepared by Alder-ene reaction between alkynyl boronates and homoallylic alcohol silyl ethers,
which introduced Z-trisubstituted double bond with good stereoselectivity (Scheme 3.3.4.9). The allylic transposition of 3-131 proceeded at room temperature in the presence of 2.5 mol % Re₂O₇ to generate cyclic boronic acid half ester 3-132 in 72% yield with complete chirality transfer. TBS-protecting group of homoallylic alcohol was found to be most suitable for both the Alder-ene reaction and the allylic transposition step.

Scheme 3.3.4.9. Synthesis of Cyclic Boronic Acids via Re₂O₇-Catalyzed [1,3]-Transposition

The formation of the cyclic boronic acids as an allylic transposition product was explained based on the following mechanism. Upon activation of the Si–O bond of substrate 3-133 with rhenium oxide via 3-134, the resultant intermediate 3-135 undergoes an allylic transposition to 3-136 via an asynchronous [3,3]-sigmatropic rearrangement. A ligand exchange via the expected Lewis acid-base interaction on
3-137 leads to a penultimate intermediate 3-138, which upon another ligand exchange with a substrate releases product 3-139, regenerating intermediate 3-135. The initially formed boronate 3-139 readily hydrolyzes during the purification on silica gel, providing the final product 3-140.

More recently ketalization-based trapping strategy of transposed hydroxyl group to obtain high product and stereoselectivity was developed for the synthesis of most thermodynamically stable 1,3-diol benzylidene acetals.8a Accordingly, treatment of diol 3-141 with benzaldehyde dimethyl acetal and catalytic amount of Re₂O₇ in dichloromethane at room temperature afforded 3-142 in 98:2 diastereomeric ratio after 20 h (Scheme 3.3.4.10). This tandem [1,3]-transposition/ketalization occurred via the rapid formation of diastereomeric mixture of rearranged diol acetals followed by slow equilibration to a thermodynamically favorable 1,3-syn-product. Several other Re-based catalysts were tested for the reaction but they have demonstrated slower equilibration rate. Between these catalysts MeReO₃ was the least reactive one, giving a mixture of acetals in a 63:37 ratio after the same reaction time.

Scheme 3.3.4.10. Regiocontrol in Re₂O₇-Catalyzed [1,3]-Transposition/Ketalization Trapping

On the other hand, Ph₃SiOReO₃ delivered 3-142 in 96:4 dr although higher catalyst loading was required. Although different solvents (Et₂O, THF, toluene) can be employed for the rearrangement, dichloromethane is superior in terms of reaction rate. High regio- and stereoselectivity can be obtained
employing other diol masking groups such as acetonide or \( p \)-methoxybenzaldehyde acetal. Intramolecular benzylidene transfer was also observed in the rearrangement of 3-143. The [1,3]-transposition of alcohol 3-145 in the presence of \( p \)-methoxybenzaldehyde dimethyl acetal afforded 3-146 in an 85:15 diastereomeric ratio with concomitant silyl ether cleavage. In this case, the stereochemical information of the methyl substituent is translated to the transposed hydroxyl functionality of the product.

In 2011 an intramolecular version of ketalization trapping protocol was utilized for the stereoselective synthesis of heterocycles and spiroketal structures via dynamic thermodynamic stereocontrol.\(^8\) The degree of stereoselectivity in this approach is related to thermodynamic differences of the diastereomeric products due to the reversibility of each individual step. Thus, treatment of ketal 3-147 with \( \text{Re}_2\text{O}_7 \) delivered 3-148 as a sole product within 10 minutes (Scheme 3.3.4.11). The ring formation in 3-148 is reversible leading to thermodynamic equilibration to afford the most stable 2,6-\( \text{syn} \)-disubstituted tetrahydropyran.

![Scheme 3.3.4.11. Re\( _2\text{O}_7 \)-Catalyzed [1,3]-Transposition/Trapping in Heterocycle Synthesis](image)

Similarly, spirocyclization of 3-149 bearing stereochemically defined alcohol moiety gave a single stereoisomer of anomeric spiroketal 3-150. Thus, the stereochemistry of a remote hydroxyl group controls two newly created stereogenic centers. An oxa-Michael reaction as a trapping strategy for transposing
allylic alcohol functionality allowed for the synthesis of syn-disubstituted tetrahydropyran 3-152 with high diastereoselectivity.

Subsequently, allylic transposition/alcohol trapping strategy was expanded on epoxides as trapping agents.\textsuperscript{8c} In this approach rhenium oxide acts as a transposition catalyst as well as a Lewis acid to activate the epoxide moiety and to promote the product equilibration. Thus, the treatment of substrate 3-153 with Re\textsubscript{2}O\textsubscript{7} in dichloromethane at room temperature provided bis(tetrahydropyran) 3-154 within 12 h as a mixture of diastereomers (Scheme 3.3.4.12). The cascade transformation, however, required 3.5 days at room temperature to reach a complete equilibration to form a single stereoisomeric product.

\begin{center}
\includegraphics[width=\textwidth]{Scheme_3.3.4.12.png}
\end{center}

\textbf{Scheme 3.3.4.12. Cascade Reactions Employing [1,3]-Transposition/Trapping with Epoxides}

Additionally, a ketone moiety can be introduced in the substrate structure between epoxide and the allylic alcohol thus allowing alternative strategy for chirality transfer. In this approach the ketone moiety behaves as a nucleophile to open the epoxide activated by Lewis acidic catalyst with the formation of chiral oxocarbenium ion 3-157 that in turn acts as an electrophilic trap for the transposing alcohol via intermediate 3-158. Employing this strategy spiroketal 3-156 was prepared as a single stereoisomer from epoxyketone 3-155 in 93\% yield. Under equilibrating conditions thermodynamically less stable
spiroketals underwent reverse reaction to form 3-158 in which the incorrect stereochemistry of an alcohol moiety was edited through reversible allylic transposition.

Similar efficiency of these cascade transformations was obtained employing a silica gel-supported Re$_2$O$_7$ catalyst (10% w/w). For the preparation of immobilized catalyst, a slurry of Re$_2$O$_7$ and silica gel in Et$_2$O was stirred for several hours and then dried under vacuum. The obtained free-flowing catalyst is easily weighed even in humid environments wherein the corresponding nonimmobilized Re$_2$O$_7$ would readily liquefy. Because of superior dispersion of a supported Re$_2$O$_7$ catalyst, reactions do not have induction periods that are often observed in the case of free Re$_2$O$_7$. These favorable properties make immobilized catalyst a suitable alternative to Ph$_3$SiOReO$_3$.

3.3.5. Application of the Transition Metal-Catalyzed [1,3]-Transposition of Allylic Alcohols in Natural Product Synthesis and Medicinal Chemistry

All three Re-based catalysts (MeReO$_3$, Ph$_3$SiOReO$_3$, and Re$_2$O$_7$) were successfully employed for the selective [1,3]-transposition of allylic alcohols as a key step in the syntheses of several natural products. The first application of Ph$_3$SiOReO$_3$ catalyst is described in the enantioselective total synthesis of (−)-galanthamine, an alkaloid possessing selective acetylcholinesterase inhibitory activity. This molecule has been approved by FDA for the treatment of mild to moderate vascular dementia and Alzheimer's disease. According to the synthetic studies, the direct allylic oxidation of advanced intermediate 3-159 to (−)-galanthamine was not successful (Scheme 2.2.5.1). Therefore, in order to introduce alcohol at the C3 position, the following sequence was designed. Reaction of the tosylammonium salt of tertiary amine 3-159 with dimethyldioxirane afforded epoxide 3-161 after concomitant treatment with DBU. Regioselective opening of epoxide 3-161 with sodium phenylselenide delivered hydroxy selenide 3-162 in 98% yield. Chemoselective oxidation of selenide 3-162 by treatment with sodium periodate gave a 1:1 mixture of diastereomeric selenoxides 3-163. Heating of the resultant mixture at 80 °C in CHCl$_3$ induced an elimination reaction to furnish [1,3]-transposition precursor 3-164. Subsequent treatment of 3-164 with p-toluenesulfonic acid to protonate basic nitrogen, which otherwise deactivate Re-catalyst, followed by
exposure of ammonium salt to stoichiometric amounts of \( \text{Ph}_3\text{SiReO}_3 \) afforded a 3:1 mixture of alcohols \( 3-160 \) and \( 3-164 \). After separation of regioisomers by column chromatography, \((-\)-galanthamine was obtained in 50% yield. The stereochemistry of cyclic allylic alcohol was maintained during the [1,3]-transposition, which indicates that the reaction occurs via a [3,3]-sigmatropic rearrangement.

**Scheme 3.3.5.1. \( \text{Ph}_3\text{SiReO}_3 \)-Catalyzed Transposition in the Synthesis of \((-\)-Galanthamine**

High product selectivity was observed in the [1,3]-transposition of allylic alcohol \( 3-165 \), an early intermediate in the studies directed toward synthesis of amphidinolide B1 (Scheme 3.3.5.2).\(^3\)^ When \( 3-165 \) was treated with 1 mol % of \( \text{Ph}_3\text{SiReO}_3 \) in ether at -60 °C, complete isomerization to regioisomeric allylic alcohol \( 3-166 \) was observed within 5 min.

**Scheme 3.3.5.2. \( \text{Ph}_3\text{SiReO}_3 \)-Catalyzed Transposition in the Synthesis of \((-\)-Amphidinolide B1**
The origin of high regioselectivity of this allylic [1,3]-transposition is unclear and chirality transfer during rearrangement was not discussed.

In the synthetic effort toward diterpenoid cladiell-11-ene-3,6,7-triol an MeReO₃-catalyzed rearrangement of β-hydroxyketone to a conjugated enone was employed at the advanced stage (Scheme 3.3.5.3). Accordingly, treatment of 3-168 with 10 mol % of MeReO₃ in benzene at room temperature for 48 h afforded enone 3-169 in 99% yield with the retention of alcohol stereochemistry. Due to a strong electron-withdrawing effect of the carbonyl group next to the tertiary alcohol, which makes 3-168 electron-poor substrate for rearrangement, efficient chirality transfer was observed at room temperature. The reactivity of 3-168 is modulated by an electron-donating methyl substituent to compensate electron-withdrawing effect of the ketone, which allowed for the use of less reactive MeReO₃ as a catalyst.

Scheme 3.3.5.3. MeReO₃-Catalyzed Transposition in the Synthesis of Cladiell-11-ene-3,6,7-triol

Sequential allylic [1,3]-transposition/macrocyclization strategy has been developed as a key step in the formal synthesis of leucascandrolide A. Exposure of secondary allylic alcohol 3-171 to catalytic amount of Re₂O₇ in ether at room temperature for 2.5 h afforded macrocyclic hemiacetal 2-172 in 69% yield (Scheme 3.3.5.4). Although 3-171 and its transposed isomer are both secondary allylic alcohols the [1,3]-transposition occurred regioselectively under equilibrating conditions due to hydrogen bonding in
the transposed alcohol with a tetrahydropyranyl ether and the facile formation of unexpectedly stable leucascandrolide macrolactol hemiketal. Interestingly, subjection of C19 epimer of 3-171 to the reaction conditions provided the same macrolactol 3-172 in 49% yield. This result suggests that an epimerization takes place during the transposition. The authors rationalized the observed dynamic kinetic resolution based on feasible minor pathway of rearrangement through a boat-like transition state. Oxidation of 3-172 to 3-173 with PCC completed the formal synthesis of leucascandrolide macrolactone.

Scheme 3.3.5.4. Re$_2$O$_7$-Catalyzed Macrocyclization in the Synthesis of Leucascandrolide A

BSA-assisted regioselective [1,3]-transposition of tertiary allylic alcohols originally developed by Grubbs$^6$ was employed for the preparation of building block 3-175 in the early stage of the total synthesis of 6'-hydroxyarenarol (Scheme 3.3.5.5).$^{36}$ Introduction of an allyl silane moiety of this synthetic intermediate by Wittig olefination of ketone 3-174 was unsuccessful. Therefore, five-step protocol was implemented. Addition of vinyl magnesium bromide to form tertiary alcohol 3-176 followed by regioselective allylic transposition of a hydroxyl group in the presence of Ph$_3$SiOReO$_3$ and BSA and subsequent hydrolysis of a silyl ether afforded primary alcohol 3-177 bearing a trisubstituted double bond in a 4:1 E/Z-ratio. Chlorination and nucleophilic displacement of the resulting chloride in 3-178 by TMSLi furnished required allylic silane 3-175 with the concomitant cleavage of benzyl ether.
Scheme 3.3.5.5. BSA-Assisted [1,3]-Transposition in the Synthesis of 6'-Hydroxyarenarol

The same strategy of regioselectivity control of [1,3]-transposition gave a quick access to the advanced carboxylic acid subunit for the synthesis of a cytotoxic marine natural product (−)-apratoxin A. The synthesis of this natural product commenced with the preparation of allylic transposition precursor 3-180 (Scheme 3.3.5.6). Protection of ketol 3-179 obtained from a proline-catalyzed aldol reaction with PMB group followed by addition of vinylmagnesium bromide delivered 3-180.

Scheme 3.3.5.6. BSA-Assisted [1,3]-Transposition in the Synthesis of (−)-Apratoxin A

Subsequent rhenium-catalyzed isomerization in the presence of BSA with 3 mol % catalyst loading at 0 °C followed by the one-pot removal of the TMS group of primary silyl ether intermediates afforded a
separable mixture of allylic alcohols \((E)-3\text{-}181\) and \((Z)-3\text{-}181\) in a 1:1 ratio. After separation, the \(E\)-stereoisomer was elaborated to an advanced intermediate acid 3-182.

The synthetic utility of Ru-catalyzed Alder-ene reaction (RCAER)\(^{31}\) and regioselective Re\(_2\)O\(_7\)-catalyzed [1,3]-transposition of silyl ethers has been demonstrated in the total synthesis of \((-\)\(-\)dactylolide (Scheme 3.3.5.7).\(^{7b}\) RCAER of advanced intermediate 3-183 prepared as 8:1 mixture of diastereomers and borylated alkyne 3-129 occurred selectively at the C7 position of the least hindered double bond to afford vinyl boronate 3-184 with the expected Z-selectivity of C4–C5 trisubstituted alkene (5:1 \(Z:E\)). Although the conversion of 3-183 was low an acceptable overall yield was obtained by recycling the alkene counterpart. The allylic transposition of 3-184 to introduce a hydroxyl group at the C7 position proceeded at room temperature in the presence of 5 mol \% \(\text{Re}_2\text{O}_7\) and generated the cyclic boronic acid half ester 3-185 in 65% yield with complete chirality transfer of transposed alcohol. The boronate functionality of the product was subsequently coupled with iodoacrylate 3-186 under the Suzuki cross-coupling conditions to afford an advanced intermediate 3-187 in 79% yield (see chapter 1 for details).

![Scheme 3.3.5.7. Re\(_2\)O\(_7\)-Catalyzed [1,3]-Transposition in the Synthesis of \((-\)\(-\)Dactylolide](attachment:image.png)

Another application of MTO-catalyzed allylic transposition reported recently in a scalable synthesis of polyene 3-192 (Scheme 2.2.5.8).\(^{38}\) Compound 3-192 is described as a reagent capable of forming
useful composites with peptides and related heteropolymers. The synthesis started with the desimmetrization of isophthaldehyde via controlled olefination employing \((R)-(\rightarrow)\)phenylglycine derived phosphonoacetyl oxazolidinone 3-188. Product aldehyde 3-189 was then treated with vinyl magnesium chloride to generate a mixture of diastereoisomeric benzylic alcohols 3-190. The allylic transposition of 3-190 catalyzed by 3 mol % of MeReO₃ at room temperature followed by in situ silylation with TBSCI afforded a single isomer of cinnamyl ether 3-191 in 79% yield. Regioselectivity of the transposition is attributed to the formation of fully conjugated isomeric product.

![Scheme 3.3.5.8. MeReO₃-Catalyzed [1,3]-Transposition of Benzylic Alcohol](image)

In a recent total synthesis of laulimalide, a retrosynthetic strategy relied on stereoselective installation of anti-epoxyalcohol functionality via the Payne rearrangement of the isomer 3-194 (Scheme 3.3.5.9). However, the epoxide translocation was not successful under a variety of conditions, thus, an alternative approach was developed. The Re-catalyzed [1,3]-transposition of allylic alcohol 3-193 generated rearranged product 3-195 in good yield with complete chirality transfer. Employment of one equivalent of Ph₃SiReO₃ for 5 min in Et₂O at -50 °C was found to be the optimum conditions for the isomerization, providing the thermodynamic mixture of isomeric secondary alcohols 3-195 and 3-193 in a 4:1 ratio.
favoring the rearranged product. Alcohols were easily separated by flash column chromatography on silica gel to afford 3-195 in 78% yield (97% BRSM). Subsequent inversion of stereochemistry of the product alcohol via a sequence of DMP oxidation and Corey–Bakshi–Shibata (CBS) reduction furnished 3-196 in 93% yield. The Sharpless asymmetric epoxidation followed by DDQ deprotection completed the synthesis of laulimalide.

![Scheme 3.3.5.9. Ph₃SiReO₃-Catalyzed Transposition in the Synthesis of Laulimalide](image)

### 3.3.6. Transition Metal-Catalyzed Rearrangement of Cyclopropanemethanols

Transition metal-catalyzed isomerization of cyclopropanemethanols into homoallylic alcohols is an example of [3,3]-sigmatropic rearrangement involving oxometal cyclopropanemethanolate, which is accompanied by the cleavage C–C bond of cyclopropane ring. This process is chemically related to the [1,3]-transposition of allylic alcohols since cyclopropane can be considered as an equivalent of a double bond. Several high oxidation state transition metal complexes of V, Mo, and Re have been employed for this transformation. However, outcome of the reaction depends on the structural features of cyclopropanemethanols as well as the nature of catalyst employed. If the initial formation of homoallylic
alcohols follows by consecutive transition metal-catalyzed hydroalkoxylation tetrahydrofuran derivatives are obtained as major products (Scheme 3.3.6.1). Rearrangements of diarylsubstituted cyclopropanemethanol 3-197 in the presence of VOSO₄·nH₂O as a catalyst and a radical scavenger 2,6-di-tert-butyl-p-cresol (butylhydroxytoluene: BHT) at 80 °C afforded homoallylic alcohol 3-198 in 91% yield. Addition of BHT is essential for the high product yield due to polymerization of 3-198 under the reaction conditions. The use of more Lewis acidic MoO₂(acac)₂ as a catalyst afforded a mixture of 3-198 and disubstituted tetrahydrofuran 3-199 in a 17:82 ratio, respectively. The rearrangement in the presence of MeReO₃, however, delivered 3-199 as a sole product.

![Scheme 3.3.6.1. Transition Metal-Catalyzed Rearrangement of Cyclopropanemethanols](image)

Cyclopropanemethanols having an electron-donating substituent on a phenyl ring readily generate homoallylic alcohols in the presence of vanadium catalyst in high yield, while the reaction of electron-deficient cyclopropanemethanols afforded products in lower yields after longer reaction time (not shown). A similar trend was observed in the rearrangement of cyclopropanemethanols to tetrahydrofurans.
catalyzed by either Mo- or Re-complex. These results are also consistent with the tendency of electron-rich and electron-deficient allylic alcohols toward [1,3]-transpositions. Rearrangements of secondary alcohol 3-200 in the presence of V, Mo, or Re catalyst afforded homoallylic alcohol 3-201 as an exclusive product in low to moderate yields. Reactions of aryl, alkyl-substituted substrate 3-203 gave similar results to those of diarylsubstituted 3-197, however, the efficiency of isomerization was lower. Cyclopropanemethanol 3-206 bearing two alkyl substituents was the least reactive substrate. Thus, homoallylic alcohol 3-207 was obtained in low yield when the isomerization was catalyzed by VO(acac)_2, and tetrahydrofuran 3-208 was isolated in 68% yield in the presence of MeReO_3 as a catalyst.

The mechanism of transition metal-catalyzed isomerization of cyclopropanemethanols is presented in Scheme 3.3.6.2. A metal oxo-complex reacts with substrate 3-209 to generate alkoxide 3-210, which enters the catalytic cycle. The [3,3]-sigmatropic rearrangement of 3-210 via transition state 3-211 leads to the formation of rearranged intermediate metal alkoxide 3-212. Subsequent alcoholysis with substrate 3-209 generates homoallylic alcohol 3-213 and returns alkoxide 3-210 in the catalytic cycle. The rearrangement in the presence of complexes of Mo or Re with higher Lewis acidity furnishes tetrahydrofuran product 3-214 via intramolecular hydroalkoxylation of the initially formed homoallylic alcohol 3-213.

**Scheme 3.3.6.2. Mechanism of Metal-Catalyzed Isomerization of Cyclopropanemethanols**
3.3.7. Oxidative Transition Metal-Catalyzed [1,3]-Transposition of Allylic Alcohols

Compared to high oxidation state oxo-complexes of Mo and W, oxochromium(VI) compounds are powerful oxidizing agents, therefore, they cannot be employed for the [1,3]-transposition of primary and secondary allylic alcohols. Nevertheless, they can perform the oxidative [1,3]-transposition\textsuperscript{41} of tertiary allylic alcohols to $\alpha,\beta$-unsaturated carbonyl compounds, which has found wide application in organic synthesis. The most frequently utilized oxochromium(VI) reagents for the oxidative transposition are pyridinium chlorochromate (PCC),\textsuperscript{42} pyridinium dichromate (PDC),\textsuperscript{43} and the Collins reagent.\textsuperscript{44} However, the earliest examples of oxidative [1,3]-transposition were reported in the synthesis of jasmone employing Jones reagent (CrO$_3$/H$_2$SO$_4$).\textsuperscript{45} Due to a strong oxidizing nature and acidity of these reagents several side reactions were observed during the transpositions, which include overoxidation (epoxidation or C–C bond cleavage), dehydration, protecting group cleavage, unwanted oxidation of heteroatoms in the substrate, as well as the deactivation of oxochromium(VI) reagents through complexation with substrate. Despite these limitations and recent appearance of new milder catalyst systems for this transformation, oxochromium(VI) reagents are still most commonly utilized in synthetic sequences due to low cost and operational simplicity.

The mechanism\textsuperscript{41b} of oxidative transposition closely resembles that proposed for [1,3]-transposition of allylic alcohols. The reaction follows two pathways, which depends on structural features of the substrate and acidity of the oxochromium(VI) reagent employed (Scheme 3.3.7.1).

\textbf{Scheme 3.3.7.1.} Two manifolds of Oxidative [1,3]-Transposition of Tertiary Allylic alcohols
Initially formed chromate ester 3-216 may undergo ionization to form free allylic cation intermediate 3-217 (pathway A) when more acidic reagents such as the Jones reagent or PCC is used. Otherwise 3-217 can be directly generated by solvolysis of the tertiary alcohol substrate 3-215. Recombination of a carbocationic intermediate with a chromate anion generates isomeric chromate ester 3-219, which then undergoes elimination to afford enone 3-220. In case of less acidic reagents, such as PDC or Collins reagent, a [3,3]-sigmatropic rearrangement pathway operates (pathway B) to give common intermediate chromate ester 3-219.

Several detailed reviews have been written on the oxidative [1,3]-transposition and for the purpose of this section only one example of this transformation is shown below. In the synthetic approach toward saudin, tricyclic enone 3-222 was prepared in 92% yield employing the PCC/alumina-mediated transposition of alcohol 3-221 (Scheme 3.3.7.2). Despite the acidic nature of oxidizing reagent, the integrity of acetal was preserved during this transformation.

Scheme 3.3.7.2. Oxidative [1,3]-Transposition in the Synthetic Studies toward Saudin

3.3.8. Transition Metal-Catalyzed Allylic [1,3]-Transposition with Other Functional Groups

Transition metal-catalyzed interconversion of functional groups around allylic moiety is also reported, however, this area of allylic [1,3]-transposition is still in its infancy. Several early transition metal complexes of Ti, Zr, and Nb have been employed for the transformation of allylic alcohols, halides, and ethers to allylic amines, allylic halides to allylic silyl ethers, as well as allylic alcohols to allylic chlorides. Most of the reported approaches require a stoichiometric amount of transition metal complex, which essentially limits the applicability of this powerful method. Regio- and stereoselective formation of protected allylic amines from silyl- or (trimethylsilyl)methyl ethers has been demonstrated in the presence
of zirconocene imido complex 3-224 (Scheme 3.3.8.1). Development of this transformation is based on preceding study of reaction between titanocene sulfido complex \(\text{Cp}^*\text{Ti}=\text{S}\) with allylic chlorides \((\text{ClCR}_2\text{CH}=\text{CR}_2)\), which gives \(\text{Cp}^*\text{Ti}(\text{Cl})(\text{SCR}_2\text{CH}=\text{CR}_2)\) complexes bearing a rearranged allylic moiety.\(^{48}\)

### Scheme 3.3.8.1. Zr-Catalyzed [1,3]-Transposition of Allylic Ethers to Allylic Amines

Reactions of 3-224 with several secondary TMS-silyl ethers 3-223a-d provided transposed Cbz-protected primary amines 3-225a-d in high yields upon treatment of the reaction mixture with CbzCl and \(\text{K}_2\text{CO}_3\). The size of the alkyl substituent has a significant effect on the reactivity of 3-224 as well as diastereoselectivity of the transposition. Thus, with increased steric bulk of the substrates elevated reaction temperatures are necessary. Moreover, reaction of tert-butyl substituted silyl ether 3-223d did not give any product. Reactions of ethyl- and isopropyl-substituted compounds 3-223b,c afforded the corresponding amines with \(E\)-stereochemistry of the double bond predominantly. It has also been shown that a primary \((Z)\)-configured \((\text{trimethylsilyl})\)methyl ethers undergo efficient transposition with 3-224 to afford Cbz-protected allylic secondary amines. For example in the reaction between 3-226 and 3-224 amine 3-227 was obtained in 92% yield after 12 h at 70 °C. However, transposition of \(E\)-configured substrates was significantly less efficient. [1,3]-Transposition of ethers to amines proceeds with complete
chirality transfer, which has been demonstrated by treatment of enantiomerically enriched 3-228 with a stoichiometric amount of 3-224. Product of this reaction amine 3-230 was obtained with the preservation of stereochemical information. Kinetic studies indicate that reaction exhibits a pseudo-first-order behavior with no observable intermediates. Based on this experimental evidence, authors proposed that the reaction occurs via an asynchronous [3,3]-sigmatropic rearrangement with transition state 3-229. This mechanism provides a rationale for lower reactivity of (E)-configured allylic ethers due to the unfavorable interactions between nitrogen-TBS group and R²-substituent in the transition state. The asynchronous [3,3]-sigmatropic nature of the mechanism was also supported by DFT-calculation.

Transposition of silyl ethers to amines was subsequently extended to allylic chlorides and bromides and, most notably, to allylic fluorides as substrates (Scheme 3.3.8.2). Due to increased electrophilicity, these allylic halides undergo transposition with 3-224 at room temperature. Moreover, the reaction does not depend on the geometry of the double bond. Thus, the [1,3]-transposition of allylic chloride 3-231 bearing Z-stereochemistry of the double bond was as efficient as that of (E)-alkene 3-222. A similar transposition of allylic fluoride 3-235 afforded Cbz-protected amine 3-236 in 88% yield. It has been noted by authors that allylic fluorides were also more reactive than the corresponding chlorides and bromides due the high affinity of zirconium(IV) to the fluoride anion.

Scheme 3.3.8.2. Zr-Catalyzed [1,3]-Transposition of Allylic Halides to Allylic Amines
Transformation of allylic alcohols to differently substituted allylic amines was achieved with stoichiometric titanium imido complex formed in situ by the reaction of Ti(NMe$_2$)$_4$ with free amine (Scheme 3.3.8.3). Treatment of 1,1-dimethylallyl alcohol 3-84 with benzylamine in the presence of 1 equivalent of Ti(NMe$_2$)$_4$ in toluene at 160 °C afforded rearranged primary amine 3-237 in 74% yield. For the ansymmetrically and monosubstituted allylic alcohols 3-85 and 3-239 respectively such interconversion afforded products 3-238 and 3-240 with low E/Z-stereoselectivity. Interestingly, 2-methylallyl alcohol and Me$_2$C=CHCH$_2$OH were inert under the reaction conditions (not shown) whereas 2-phenylallyl alcohol 3-230 delivered the corresponding product although in low yield (Scheme 3.3.8.4).

**Scheme 3.3.8.3.** Ti-Catalyzed [1,3]-Transposition of Alcohols to Allylic Amines

Based on the inhibitory effect of the methyl group in the second position, the [2+2]-cycloaddition/retro-[2+2]-cycliaddition mechanism of reaction was proposed. Accordingly, the reaction sequence commenced with the alcoholysis of Ti(NMe$_2$)$_4$ with substrate 2-241 followed by the reaction of alkoxide intermediate 2-243 with free amine to generate titanium imido species 3-244. The rearrangement of this intermediate through a [3,3]-sigmatropic pathway via chair-like transition state 3-245 would lead to titanium oxo-complex 2-246 the hydrolysis of which gives the final product 3-242. Alternatively, [2+2]-cycloaddition would give bicyclic structure 2-247, which upon retro-[2+2] cycloaddition would generate common intermediate 2-246. Relying on literature precedents for the inhibition of [2+2]-cycloadditions by olefin substitution, authors favor a cycloaddition pathway. Moreover, [2+2]-
Cycloaddition mechanism was found to be more energetically favorable over [3,3]-sigmatropic process in recent computational studies, however, no clear conclusion can be made at this point.\textsuperscript{50}

\begin{center}
\includegraphics[width=\textwidth]{scheme.png}
\end{center}

**Scheme 3.3.8.4.** Mechanisms of Ti-Catalyzed [1,3]-Transposition of Alcohols to Allylic Amines

Employment of zirconium oxo-complex 3-249 similar to zirconium imido compound 3-224 allowed for a stoichiometric conversion of \(E\)-substituted allylic chlorides to TBS-silyl ethers with perfect regio- and stereocontrol (Scheme 3.3.8.5).\textsuperscript{51} Thus, heating of allylic chloride 2-248 with oxozirconium reagent 2-249 at 75 °C followed by exposure of the reaction mixture to TBSOTf afforded silyl ether 2-250 bearing an exocyclic double bond in 92% yield.

\begin{center}
\includegraphics[width=\textwidth]{scheme2.png}
\end{center}

**Scheme 3.3.8.5.** Zr-Catalyzed [1,3]-Transposition of Allylic Halides to Allylic Silyl Ethers
Similar reaction of chiral substrate 3-251 at 45 °C delivered allylic alcohol 3-253 with complete chirality transfer upon quenching with $p$-trifluoromethyl phenol. Similar reactions of (Z)-configured allylic chlorides, however, were less regioselective and gave products of direct chloride displacement in addition to the desired products of transposition. As it has been observed for similar Cp$_2$(THF)Zr=NTBS complex 3-224 the [1,3]-transposition of allylic chlorides with 2-249 exhibited pseudo-first order kinetics with a rate-limiting C–O bond forming step. These results indicate that the reaction occurred via a [3,3]-sigmatropic rearrangement through transition state 3-252. By analogy, (Z)-allylic chlorides showed diminished regioselectivity due the unfavorable steric interactions between an axial Cp* ligand and an axially oriented alkyl group of the (Z)-allylic chloride in the transition state similar to 3-252.

The direct conversion of allylic alcohols to allylic halides via a formal S$_N$2' process has been developed by using early transition metal halogenides of high oxidation states.\textsuperscript{52} The reaction requires generation of allylic alkoxide either directly from allylic alcohol 3-255 or by the reaction between carbonyl compound 3-254 and appropriate vinylmagnesium halide (Scheme 3.3.8.6). The generated alkoxide 3-256 then undergoes transmetallation with more oxophilic metal chloride capable of weakening the C–O bond.

![Scheme 3.3.8.6. Mechanisms of [1,3]-Transposition of Allylic Alkoxides to Allylic Halides](attachment:Scheme_3.3.8.6.png)

The concerted [3,3]-sigmatropic pathway gives
transposed allylic chloride 3-259 in high regio- and stereoselectivity. On the other hand, the ionization path leads to a mixture of allylic halide regioisomers when no strong thermodynamic preference for the formation of single isomer exists, and this accounts for the formation of side reaction products.

The direct one-pot formation of allylic chlorides from aromatic allylic alcohols or aromatic aldehydes has been reported by using TiCl4 as transmetallation reagent.\textsuperscript{52a} The TiCl4-mediated C–O bond activation of magnesium alkoxides derived from the deprotonation of allylic alcohols afforded (E)-allylic chlorides with high stereoselectivity (Scheme 3.3.8.7). The transposition proceeds at room temperature and requires a substoichiometric amount of of TiCl4. When run at 80 °C, the reaction time could be diminished. In general, different substitution pattern around allylic moiety is well tolerated.

![Scheme 3.3.8.7. Ti-Mediated [1,3]-Transposition of Allylic Alkoxides](image)

For example, tertiary allylic alcohol 3-260 was converted to allyl chloride 3-261 in 78% yield, however, the reaction of alcohol 3-262 bearing disubstituted terminal alkene afforded only eliminated diene product 3-263. Aliphatic allylic alcohols proved to be significantly less reactive under the reaction conditions. Thus, employment of alcohol 3-264 in TiCl4-mediated transposition delivered chloride 3-265 in moderate yield after refluxing the reaction mixture for 1.5 days. To validate reaction mechanism scalemic alcohol 3-266 was prepared in 75% enantiomeric excess. [1,3]-Transposition of this substrate
afforded racemic product 3-267 as single E-stereoisomer. This result indicate that the reaction follows heterolytic C–O bond cleavage to give a free allylic cation similar to 3-258 (Scheme 3.3.8.6) followed by subsequent capture of the most stable isomer of the carbocationic intermediate to produce (E)-allylic chloride.

A similar approach based on the transposition of allylic alkoxides for the synthesis allylic chlorides was also developed employing NbCl₅, or NbBr₅ salts.⁵²b,c One-pot formation of allylic sulfides from aromatic (3-268) and aliphatic (3-270) aldehydes and ketones was demonstrated by the sequential reaction of carbonyl compounds with vinylmagnesium bromide followed by [1,3]-transposition with stoichiometric Nb(V)-halide and nucleophilic displacement of the resultant product with a sulfide (Scheme 3.3.8.8). This sequence provides regio- and stereoisomerically pure allylic sulfides with good overall efficiency, which indicates that the reaction proceeds via a concerted metalo-halo-[3,3] rearrangement. Allylic transposition with Nb(V) halides occurs at room temperature and NbBr₅ was found to be superior for the reaction of aliphatic substrates such as 3-270. The metalo-halo-[3,3] rearrangement was also extended to terminal propargylic alcohols. Deprotonation of 3-272 with KH followed by treatment with NbBr₅ delivered allenic bromide 3-273 in 65% yield.

**Scheme 3.3.8.8.** [1,3]-Transposition of Allylic Alkoxides with Nb(V)-Salts

For Nb(V)-catalyzed transpositions, the extent of concerted, ionic, or direct displacement mechanisms depends on the structure of substrate allylic alcohols. Thus, treatment of nerol with KH followed by
addition of NbCl₅ provided products resulting from complete ionization of the substrate. The reaction afforded mixture of all four possible allylic chlorides 3-274–3-277 in which cyclic product 3-277 was obtained as a major component (Scheme 3.3.8.9).

![Reaction diagram]

**Scheme 3.3.8.9.** NbCl₅-Mediated [1,3]-Transposition of Nerol

### 3.4. Ring Strain-Driven Allylic [1,3]-Transposition of 8-Membered Siloxadienes

With our continued interest in regioselective allylic transposition, we have searched for different reaction strategies to obtain high product selectivity. In this regard, we became intrigued by the possibility of using ring strain as a regioselectivity-controlling element. We envisioned that the allylic transposition of medium-sized ring systems involving ring contraction would be regioselective due to two main factors. First, the endocyclic double bonds in most medium rings are cis-, which would have a significant driving force to become a trans-double bond after the ring contraction. Second, due to their transannular interactions, the medium-sized rings are generally more strained than their smaller counterparts. Among medium-sized rings, the ring contraction of eight-membered rings to the corresponding six-membered rings would be most favorable because this transformation would render greater relief of ring strain compared to the process involving other rings. As a platform for the development of an allylic transposition strategy, we became interested in a 1,5-dien-4-ol motif containing a Z-trisubstituted double bond since it is a common structural motif found in many biologically active natural products including dactylolide/zampanolide,⁵³ bryostatin 1,⁵⁴ rubifolide,⁵⁵ and various amphidinolides⁵⁶ (Scheme 3.4.1). An economic access to allylic transposition precursors, eight-membered siloxacycles 3-280, has been

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previously developed in our laboratory. It relies on the allyl transfer–alcoholysis\textsuperscript{57} of silylalkynes \textbf{3-278} followed by ring-closing metathesis\textsuperscript{58} of corresponding silyl ethers \textbf{3-279}. The ring strain-driven allylic transposition of \textbf{3-280} would then afford 6-membered (Z)-trisubstituted vinylsilanes \textbf{3-281} containing a 1,5-dien-4-ol moiety.

\[ \text{Scheme 3.4.1. Synthesis and Ring Contraction of Eight-Membered Siloxacycles} \]

This strategy was first tested with benzyloxymethyl-substituted silylalkyne (\(R^1 = \text{CH}_2\text{OBn}\)) and allyl alcohol (Table 3.4.1). An intramolecular allyl transfer reaction driven by alcoholysis afforded silyl ether \textbf{3-279a} in high yield with Z-stereochemistry (entry 1). The silyl ether \textbf{3-279a} was treated with Grubbs second-generation catalyst (G-II) for 4 h at 25 °C in \text{CH}_2\text{Cl}_2, affording eight-membered siloxacycle \textbf{3-280a} in 96% yield. The proposed ring contraction was demonstrated by treatment of \textbf{3-280a} with a catalytic amount of \text{Re}_2\text{O}_7 (5 \text{ mol }\%, \text{ether, 25 °C, 3 h}), providing siloxene \textbf{3-281a} in 49% yield. Although the yield was marginal, this clearly illustrated the feasibility of the proposed reaction sequence. The low yield of the ring-contraction is most likely due to the formation of a thermodynamically less favorable terminal alkene from the internal one in the starting material.

Encouraged by this observation, eight-membered siloxadienes \textbf{3-280b} and \textbf{3-280c} were synthesized via the same sequence by one-pot reaction without isolating intermediates \textbf{3-279} (entries 2 and 3).
Table 3.4.1. Synthesis of Functionalized (Z)-Trisubstituted Vinylsilanes

<table>
<thead>
<tr>
<th>Entry</th>
<th>1-st step</th>
<th>Yielda (%)</th>
<th>2-nd step</th>
<th>Yieldb (%)</th>
<th>3-rd step</th>
<th>Yieldb (%)</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>3-279a, R = H</td>
<td>74</td>
<td>3-280a</td>
<td>96</td>
<td>3-281a</td>
<td>49</td>
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<tr>
<td>2</td>
<td>3-279b, R = iPr</td>
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<td>58c</td>
<td>3-281b</td>
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<td>51c</td>
<td>3-281c</td>
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<td>8</td>
<td>3-279h, R = Me</td>
<td>73</td>
<td>3-280h</td>
<td>60 (62:38)d</td>
<td>3-281h</td>
<td>76</td>
</tr>
<tr>
<td>9</td>
<td>3-279i, R = C6H11</td>
<td>78</td>
<td>3-280i</td>
<td>61 (63:37)d</td>
<td>3-281i</td>
<td>75</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
<td>3-269j</td>
<td>63 (67:33)d</td>
<td>3-281j</td>
<td>61</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td></td>
<td>3-280k</td>
<td>57 (71:29)d</td>
<td>3-281k</td>
<td>74</td>
</tr>
</tbody>
</table>

[a] 5 mol % of catalyst was used. [b] Isolated yield. [c] Isolated yield overall 2 steps. [d] NMR ratio of eight- and five-membered siloxacycles. [e] Combined yield of 3-281g and aromatized product.
Gratifyingly, treatment of 3-280b and 3-280c with Re₂O₇ (5 mol %, ether, 25 °C, 10 min) provided six-membered siloxenes 3-281b and 3-281c in good yields with trans-stereochemistry of the newly generated double bond. Under these reaction conditions the TBS-group of the primary alcohol was cleaved (entry 3), however, diphenylsilyl group migration from the secondary alcohol moiety to the primary one was not observed. Compounds 3-281d and 3-281e were obtained similarly from metoxymethyl-substituted silylalkyne (R¹ = CH₂OMe) and secondary allylic alcohols (entries 4 and 5).

The generality of the sequence was further investigated with a variety of substrates including allylic alcohols bearing aromatic substituents, tertiary allylic alcohols and propargylic alcohols. Influence of the substituent on the silylalkyne moiety was also examined. Allyl transfer-alcoholysis with propargylic alcohols afforded vinylsilanes 3-279f and 3-279g, which were subsequently ring-closed to give compounds 3-280f and 3-280g (entries 6 and 7). Although the ring-closing enyne metathesis of silyl ethers 3-279f and 3-279g required longer reaction times and an ethylene environment, eight-membered siloxacycles containing a 1,4-diene moiety were formed without difficulty albeit the yield of 3-280g is marginal. The rhenium oxide-catalyzed allylic transposition of 3-280f afforded siloxene 3-281f with high efficiency. However, the allylic transposition of 3-280g provided a mixture of 3-281g and aromatized by-product, which should be the result of methanol elimination. Not surprisingly, tertiary allylic and secondary benzylic alcohols were not compatible with the allyl transfer conditions as opposed to non-allylic tertiary and secondary allylic alcohols.⁵⁷ Probably, this is due to the formation of relatively stable allylic and benzylic cations from the starting alcohols or the products thereof.

Changing the nature of the substituent on the silylalkyne significantly affected the efficiency of both the gold-catalyzed allyl transfer reaction and RCM (entries 8–11). As opposed to the substrates with alkoxyalkyl substituents, those with simple methyl group showed slower allyl transfer and diminished yields of RCM under standard reaction conditions. However, with increased catalyst loading up to 5 mol % and changing the solvent to toluene, (Z)-vinylsilanes 3-279h–k were obtained in good yields and stereoselectivity. RCM of these silyl ethers required high reaction temperature (85 °C, toluene), and
provided mixtures of desired eight-membered cyclic siloxadiene together with a varying amount of five-membered siloxene. Nevertheless, the ring contraction of siloxadienes 3-280h–k under standard conditions afforded siloxenes 3-281h–k in good yields.

The chirality transfer during allylic transposition was next examined with substrates 3-280l and 3-280m obtained from (S)-1-octen-3-ol (ee > 95%) and (S)-3-pentyne-2-ol (ee > 99%) respectively (Scheme 3.4.2). The chiral HPLC analysis of the desilylated alcohol derived from siloxene 3-281l and Mosher’s ester analysis of the desilylated alcohol from 3-281m showed that the stereochemical integrity of the allylic alcohol was lost to some extent. When the reaction was carried out at room temperature, 3-281l and 3-281m were obtained in 79% and 76% ee respectively. The degree of racemization for Re₂O₇-catalyzed allylic transposition depends on the reaction time, and thus prolonged reaction time resulted in low ee values.

**Scheme 3.4.2.** Chirality Transfer in [1,3]-Transposition of Cyclic Silyl Ethers

Based on the allylic transposition of compounds 3-280l and 3-280m, it is reasonable to consider that there are two distinctive mechanisms for the allylic transposition catalyzed by rhenium oxide (Scheme 3.4.3). Upon activation of the Si–O bond of substrate with rhenium oxide a σ-bond metathesis takes place, which then followed by an allylic transposition via a [3,3]-sigmatropic rearrangement or ion-pair formation. The product of the concerted [3,3]-sigmatropic rearrangement pathway should be enantiomerically enriched with high ee value. On the other hand, due to the highly Lewis acidic nature of Re₂O₇, the allylic transposition may occur partially via an allylic cation intermediate, generating a product
with low or no ee value. The extent of these two manifolds of allylic transposition also depends on the steric and electronic nature of substituents $R^1$ and $R^2$. An electron-withdrawing $R^1$ should favor a concerted process, while an electron-donating substituent should facilitate the formation of ion pairs via an allylic cation intermediate.

![Scheme 3.4.3. Mechanism of Silyl-Directed Allylic Transposition/Ring Contraction](image)

3.5. Summary

In conclusion, we have developed a novel allylic transposition reaction that relies on the relief of ring strain. Through this process, eight-membered ring siloxadienes undergo a ring contraction to the corresponding six-membered siloxenes bearing an endocyclic double bond and an alkenyl substituent. The orchestrated use of three metal-catalyzed reactions, an intramolecular allyl transfer of silyl alkynes to set the Z-stereochemistry of vinylsilyl moiety, RCM to form the eight-membered ring, and a silyl-directed allylic transposition/ring contraction, constitutes an efficient entry to functionalized (Z)-trisubstituted vinylsilanes.

Despite the recent advances in the development of regioselective [1,3]-transposition of allylic alcohols and their silyl ethers, more investigations are required to overcome current limitations of allylic transposition method. Search for less acidic catalyst that would not cause undesired dehydration or isomerization yet possess the same level of reactivity, and the development of different reaction strategies.
to obtain high product selectivity are the main objectives to be explored. Another open field for investigations is the development of selective interconversion of hydroxyl groups to other functionalities such as amino, halogen, etc. In addition, asymmetric version of [1,3]-transposition is yet to be discovered.

3.6. Experimental Details

3.6.1. Materials and Methods

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF) and diethyl ether (Et₂O) were dried by distillation from sodium and benzophenone. Methylene chloride (CH₂Cl₂), toluene (PhMe), triethylamine (Et₃N), acetonitrile (CH₃CN), dimethylformamide (DMF), and dimethylsulfoxide (DMSO), were dried by distillation from calcium hydride. All reactions were monitored by thin-layer chromatography using E. Merk silica gel 60 Å F-254 pre-coated plates (0.25 mm) and were visualized by UV, p-anisaldehyde, or KMnO₄ staining. Flash column chromatography was performed using silica gel 60 Å (32–63 mesh) purchased from Sorbent Technologies. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker Avance DRX-500 or Bruker AV-500 spectrometers. ¹H and ¹³C chemical shifts are referenced to internal solvent resonances (CHCl₃ ¹H, δ = 7.26; CDCl₃ ¹³C, δ = 77.0) and reported relative to SiMe₄; multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet), m (multiplet) and br (broad signal). Coupling constants, J, are reported in Hertz. Electrospray ionization (ESI) mass spectra were recorded on a Micromass LCT equipped with a time-of-flight analyzer at the Mass Spectrometry Laboratory in the University of Illinois at Urbana-Champaign.
Alkynyl allyl silanes were obtained according to the literature procedure.\(^{57}\)

Colorless oil (82% yield); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.64–7.52 (m, 4H), 7.49–7.34 (m, 6H), 5.91–5.80 (m, 1H), 5.02–4.87 (m, 2H), 3.58 (s, 3H), 2.20 (d, \(J = 7.9\) Hz, 2H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 134.8, 134.2, 133.9, 130.0, 127.9, 115.1, 51.6, 21.5; HRMS (ESI) calcd for C\(_{16}\)H\(_{18}\)OSiNa [M+Na]\(^+\): 277.1025, found 277.1014.

Colorless oil (85% yield); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.75–7.62 (m, 4H), 7.50–7.29 (m, 11H), 5.95–5.83 (m, 1H), 5.07–4.90 (m, 2H), 4.69 (s, 2H), 4.32 (s, 2H), 2.22 (dd, \(J = 7.9\) Hz, \(J = 1.1\) Hz, 2H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 137.4, 134.9, 133.4, 132.9, 130.0, 128.5, 128.3, 128.0, 115.4, 105.9, 86.7, 71.5, 57.9, 22.0; HRMS (ESI) calcd for C\(_{25}\)H\(_{24}\)OSiNa [M+Na]\(^+\): 391.1494, found 391.1498.

Colorless oil (88% yield); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.67–7.63 (m, 4H), 7.44–7.34 (m, 6H), 5.93–5.80 (m, 1H), 5.00–4.89 (m, 2H), 4.23 (s, 2H), 3.44 (s, 3H), 2.17 (d, \(J = 7.6\) Hz, 2H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 134.9, 133.3, 132.9, 129.9, 128.0, 115.4, 105.7, 86.5, 60.5, 57.7, 22.0; HRMS (ESI) calcd for C\(_{19}\)H\(_{20}\)SiNa [M+Na]\(^+\): 315.1181, found 315.1168.

Colorless oil (94% yield); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.66–7.63 (m, 4H), 7.42–7.33 (m, 6H), 5.92–5.81 (m, 1H), 4.98–4.87 (m, 2H), 2.14 (dd, \(J = 8.0\) Hz, \(J = 1.1\) Hz, 2H), 2.01 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 134.9, 134.2, 133.3, 129.7, 127.9, 115.0, 107.5, 78.7, 22.3, 5.2; HRMS (ESI) calcd for C\(_{18}\)H\(_{18}\)SiNa [M+Na]\(^+\): 285.1075, found 285.1063.
Allylic alcohol $S_5$ was prepared in 68% overall yield according to the literature procedure.$^{62}$ Both $^1$H and $^{13}$C NMR spectra are matched with reported.$^{63}$

To a solution of methyl propargyl ether (71 µL, 0.84 mmol) in 5 mL of THF at -78 °C was added $^n$BuLi (2.5 M solution in hexanes, 320 µL, 0.81 mmol) under nitrogen. The resultant solution was stirred at -78 °C for 10 min and at 0 °C for 30 min. It was again cooled to -78 °C and trans-4-decenal (100 mg, 0.65 mmol) was added. The reaction mixture was warmed to room temperature, stirred for 30 min and quenched with saturated NH$_4$Cl solution. The reaction mixture was extracted with CH$_2$Cl$_2$ (3 × 5 mL), combined extracts were dried over MgSO$_4$ and solvent was removed under vacuum. The residue was purified by flash column chromatography (gradient elution from 10:1 to 5:1 hexanes:EtOAc) to afford alcohol $S_6$ (113.4 mg, 78%) as a colorless oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.51–5.34 (m, 2H), 4.46–4.39 (m, 1H), 4.13 (d, $J=1.5$ Hz, 2H), 3.38 (s, 3H), 2.20–2.12 (m, 2H), 2.01–1.88 (m, 3H), 1.83–1.71 (m, 2H), 1.38–1.20 (m, 6H), 0.88 (t, $J=7.0$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 131.8, 128.7, 87.5, 80.7, 62.0, 59.9, 57.6, 37.5, 32.5, 31.4, 29.2, 28.2, 22.5, 14.0; HRMS (ESI) calcd for C$_{14}$H$_{24}$O$_2$Na [M+Na]$^+$: 247.1674, found 247.1671.

Allylic alcohol $S_7$ was prepared in 68% overall yield according to the literature procedure.$^{64}$ Both $^1$H and $^{13}$C NMR spectra match the reported data.
To the solution of ethyl oleate (1.45 g, 4.67 mmol) in an acetone–H₂O mixture (0.08 M, 58 mL, 5:1) were added osmium tetroxide (100 µL, 0.2 M in H₂O) and NMO (1.37 g, 11.67 mmol) at room temperature. The reaction mixture was stirred for 6 h (at this point the reaction was complete according to TLC), and NaIO₄ (2.50 g, 11.67 mmol) was added. The resultant mixture was stirred for 2 h and quenched with saturated aqueous Na₂S₂O₃ (2 mL). A white precipitate formed in the reaction was filtered through a pad of celite. After removing acetone under reduced pressure, the residue was extracted with Et₂O (3 × 10 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated under vacuum. The residue was quickly purified by flash chromatography (from 40:1 to 15:1 hexanes:EtOAc) to give aldehyde S8 (840 mg, 87%) as a colorless oil and nonanal (540 mg, 81%) as a colorless volatile liquid.

The crude aldehyde S8 was dissolved in THF (10 mL) and a solution of vinylmagnesium bromide (1M in THF, 6.30 mL, 6.29 mmol) was added at -78 °C. Reaction mixture was slowly warmed to room temperature and quenched with a saturated NH₄Cl solution. Product was extracted with CH₂Cl₂ (3 × 10 mL), dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (from 30:1 to 10:1 hexanes:EtOAc) to afford allylic alcohol S9 (699.0 mg, 73%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 5.90–5.80 (m, 1H), 5.20 (dd, J = 17.5 Hz, J = 1.4 Hz, 1H), 5.08 (dd, J = 10.5 Hz, J = 1.3 Hz, 1H), 4.18–4.01 (m, 3H), 2.27 (dt, J = 7.7 Hz, J = 1.1 Hz, 2H), 1.67–1.16 (m, 16H); ¹³C NMR (125 MHz, CDCl₃) δ 173.9, 141.3, 114.5, 73.2, 60.2, 37.0, 34.4, 29.3, 29.2, 29.0, 25.2, 24.9, 14.3; HRMS (ESI) calcd for C₁₃H₂₄O₃Na [M+Na]⁺: 251.1623, found 251.1621.
Propargylic alcohol rac-S10 was prepared in 68% overall yield according to the literature procedure. Both $^1$H and $^{13}$C NMR spectra match the reported data. Kinetic resolution of racemate: To a solution of rac-S10 (683 mg, 5.4 mmol) in vinyl acetate (20 mL) was added Novozym 435 (100 mg). After stirring at 30°C for 34 h, the reaction mixture was worked up by filtration through the pad of celite. Evaporation and purification by flash chromatography (gradient elution from 30:1 to 10:1 hexanes:EtOAc) afforded (S)-S10 (305.5 mg, 47%) and (R)-S11 (426.7 mg, 49%). (S)-S10: >99% ee (determined by integration of protons on chiral centers after resolution with Eu(hfc)$_3$).

**Representative Procedure for Gold-Catalyzed Intramolecular Allylation of Alkynyl Allyl Silanes with Alkoxyethyl Substituents:**

To a mixture of silylalkyne S2 (100 mg, 0.27 mmol) and allyl alcohol (18.5 µL, 0.27 mmol) was added a pre-generated solution of Ph$_3$PAuSbF$_6$ in dichloroethane (1 mol %, 2.7 mL, 1 mM), which was prepared by mixing stoichiometric amounts of Ph$_3$PAuCl and AgSbF$_6$ in dichloroethane followed by filtration through a plug of celite to remove precipitated AgCl. The resulting solution was stirred at room temperature for 10 min. The solvent was removed under reduced pressure, and the crude product was purified by gravity column chromatography (gradient elution from 300:1 to 200:1 hexanes:EtOAc) to give vinyl silane 3-279a as a colorless oil (85.9 mg, 74%). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.72–7.64 (m, 4H), 7.47–7.28 (m, 11H), 6.11 (d, $J$ = 1.3 Hz, 1H), 5.94 (m, 1H), 5.54 (m, 1H), 5.33 (m, 1H), 5.11 (m, 1H), 4.94–4.84 (m, 2H), 4.56 (d, $J$ = 0.9 Hz, 2H), 4.27 (dt, $J$ = 3.0 Hz, $J$ = 1.5 Hz, 2H), 4.07 (s, 2H), 2.97 (d, $J$ = 6.8 Hz, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 157.9, 138.3, 136.8, 135.5, 135.3, 134.9, 129.9,
169

128.4, 127.9, 127.7, 127.6, 118.8, 116.7, 114.6, 73.9, 72.4, 64.5, 38.3; HRMS (ESI) calcd for C$_{28}$H$_{30}$O$_2$SiNa [M+Na]$^+$: 449.1913, found 449.1913.

Colorless oil (70% yield); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.67–7.70 (m, 4H), 7.33–7.42 (m, 6H), 6.05 (s, 1H), 5.52 (m, 1H), 4.91–4.78 (m, 2H), 4.57 (m, 1H), 3.94 (d, $J = 1.4$ Hz, 2H), 3.38 (s, 3H), 2.91 (d, $J = 6.9$ Hz, 2H), 1.70 (d, $J = 2.0$ Hz, 3H), 1.39 (d, $J = 6.4$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 157.6, 135.9, 135.6, 135.3, 139.9, 127.9, 119.2, 116.7, 81.7, 80.4, 76.4, 60.2, 58.4, 38.5, 25.7, 3.6; HRMS (ESI) calcd for C$_{23}$H$_{25}$O$_2$Si [M-CH$_3$]$^+$: 361.1624, found 361.1619.

Colorless oil (62% yield); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.75–7.66 (m, 4H), 7.45–7.28 (m, 11H), 6.13 (s, 1H), 5.54 (ddt, $J = 17.0$ Hz, $J = 10.2$ Hz, $J = 6.9$ Hz, 1H), 4.92–4.82 (m, 2H), 4.62 (m, 1H), 4.55 (s, 2H), 4.07 (s, 2H), 2.96 (dd, $J = 6.0$ Hz, $J = 5.0$ Hz, 2H), 2.07 (dt, $J = 6.9$ Hz, $J = 1.8$ Hz, 2H), 1.45–1.27 (m, 7H), 0.88 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 157.4, 138.4, 135.84, 135.77, 135.5, 135.1, 129.8, 128.4, 127.7, 127.6, 119.6, 116.5, 84.8, 82.3, 74.0, 72.3, 60.1, 38.3, 30.6, 25.6, 21.9, 18.4, 13.6; HRMS (ESI) calcd for C$_{33}$H$_{39}$O$_2$Si [M+H]$^+$: 495.2719, found 495.2728.

Representative Procedure for Gold-Catalyzed Intramolecular Allylation of Methyl Substituted Alkynyl Allyl Silanes:

To a mixture of 1-octen-3-ol (50 mg, 0.39 mmol) and silylalkyne S4 (174.0 mg, 0.66 mmol, 1.7 equiv) was added a pre-generated solution of Ph$_3$PAuSbF$_6$ in toluene (5 mol %, 9.7 mL, 2 mM), which was prepared by mixing stoichiometric amounts of Ph$_3$PAuCl and AgSbF$_6$ in CH$_2$Cl$_2$ (0.5 mL) followed by filtration through a plug of celite to remove precipitated AgCl and dilution with toluene. The resulting solution was stirred at room temperature for 4 h. The solvent was removed under reduced pressure,
the crude product was purified by gravity column chromatography (gradient elution from 400:1 to 200:1 hexanes:EtOAc) to give vinyl silane 3-279i as a colorless oil (118.8 mg, 78%). 1H NMR (500 MHz, CDCl₃) δ 7.69–7.61 (m, 4H), 7.44–7.32 (m, 6H), 5.81 (ddd, J = 17.0 Hz, J = 10.5 Hz, J = 6.6 Hz, 1H), 5.72 (s, 1H), 5.49 (ddt, J = 17.0 Hz, J = 10.1 Hz, J = 6.9 Hz, 1H), 5.09–4.95 (m, 2H), 4.91–4.77 (m, 2H), 4.25–4.20 (m, 1H), 2.84 (d, J = 7.0 Hz, 2H), 1.92 (s, 3H), 1.61–1.41 (m, 2H), 1.31–1.11 (m, 6H), 0.84 (t, J = 7.2 Hz, 3H); 13C NMR (125 MHz, CDCl₃) δ 158.6, 141.1, 136.6, 135.7, 135.1, 129.5, 127.6, 120.4, 116.3, 114.2, 74.7, 42.8, 37.7, 31.8, 26.4, 24.5, 22.6, 14.0; HRMS (ESI) calcd for C₂₆H₃₅OSi [M+H]+: 391.2457, found 391.2455.

Colorless oil (73% yield); 1H NMR (500 MHz, CDCl₃) δ 7.72–7.63 (m, 4H), 7.44–7.33 (m, 6H), 5.89 (m, 1H), 5.73 (d, J = 1.3 Hz, 1H), 5.51 (m, 1H), 5.14 (m, 1H), 4.98 (m, 1H), 4.93–4.78 (m, 2H), 4.44 (m, 1H), 2.87 (d, J = 6.9 Hz, 2H), 1.94 (m, 3H), 1.23 (m, 3H); 13C NMR (125 MHz, CDCl₃) δ 158.9, 142.3, 136.5, 135.7, 135.0, 129.6, 127.7, 120.2, 116.4, 113.0, 70.4, 42.8, 26.5, 24.0; HRMS (ESI) calcd for C₂₂H₂₆OSiNa [M+Na]+: 357.1651, found 357.1649.

Colorless oil (67% yield); 1H NMR (500 MHz, CDCl₃) δ 7.69–7.60 (m, 4H), 7.43–7.31 (m, 6H), 5.79 (dddd, J = 16.9 Hz, J = 10.3 Hz, J = 6.4 Hz, J = 0.9 Hz, 1H), 5.71 (s, 1H), 5.48 (m, 1H), 5.09–4.94 (m, 2H), 4.91–4.75 (m, 2H), 4.25–4.18 (m, 1H), 4.13 (q, J = 7.2 Hz, 2H), 2.83 (d, J = 7.0 Hz, 2H), 2.27 (t, J = 7.6 Hz, 2H), 1.92 (s, 3H), 1.65–1.38 (m, 4H), 1.34–1.13 (m, 11H); 13C NMR (125 MHz, CDCl₃) δ 173.9, 158.6, 141.0, 136.6, 135.7, 135.1, 129.6,
Representative Procedure for Ring-Closing Metathesis of Vinyl Silanes with Alkoxymethyl Substituents 3-279a-e, 3-279l:

Vinyl silane 3-279a (86.6 mg, 0.20 mmol) was dissolved in freshly distilled CH₂Cl₂ (0.002 M) and Grubbs 2nd generation catalyst (H₂Imes)(PCy₃)Cl₂Ru=CHPh (8.6 mg, 0.010 mmol, 5 mol %) was added under nitrogen. The reaction mixture was stirred at room temperature for 4 h and concentrated under reduced pressure. The residue was purified by gravity column chromatography (gradient elution from 200:1 to 150:1 hexanes:EtOAc) to afford eight-membered siloxacycle 3-280 as a colorless oil (77.4 mg, 96%).

1H NMR (500 MHz, CDCl₃) δ 7.69–7.61 (m, 4H), 7.45–7.29 (m, 11H), 6.14 (d, J = 1.1 Hz, 1H), 5.86 (dt, J = 10.1 Hz, J = 8.6 Hz, 1H), 5.55 (dt, J = 10.1 Hz, J = 4.3 Hz, 1H), 4.59 (s, 2H), 4.52 (d, J = 3.7 Hz, 2H), 4.12 (s, 2H), 3.20 (d, J = 8.6 Hz, 2H); 13C NMR (125 MHz, CDCl₃) δ 159.4, 138.2, 135.5, 134.7, 130.6, 130.3, 129.9, 128.5, 127.9, 127.8, 127.7, 120.1, 75.8, 72.3, 62.5, 30.8; HRMS (ESI) calcd for C₂₆H₂₇O₂Si [M+H]⁺: 399.1780, found 399.1783.

Colorless oil (58% yield, 2 steps); 1H NMR (300 MHz, CDCl₃) δ 7.67–7.56 (m, 4H), 7.40–7.28 (m, 11H), 6.06 (t, J = 1.4 Hz, 1H), 5.83 (ddt, J = 10.1 Hz, J = 8.7 Hz, J = 1.4 Hz, 1H), 5.45 (dd, J = 11.0 Hz, J = 5.2 Hz, 1H), 4.56 (s, 2H), 4.21 (t, J = 5.5 Hz, 1H), 4.09 (d, J = 1.4 Hz, 2H), 3.52 (dd, J = 13.3 Hz, J = 8.5 Hz, 1H), 2.76 (dd, J = 13.0 Hz, J = 9.0 Hz, 1H), 1.82 (m, 1H), 1.02 (d, J = 6.8 Hz, 3H), 0.90 (d, J = 6.9 Hz, 3H); 13C NMR (75 MHz, CDCl₃) δ 159.2, 138.5, 137.1, 135.8, 135.4, 134.7, 133.5, 131.2, 130.0, 129.7, 128.6, 127.99, 127.97, 127.90, 127.87, 121.2, 76.8, 76.3, 72.4, 34.9, 31.2, 19.1, 18.2; HRMS (ESI) calcd for C₂₉H₃₂O₂SiNa [M+Na]⁺: 463.2069, found 463.2063.
Colorless oil (51% yield, 2 steps); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.65–7.57 (m, 4H), 7.41–7.28 (m, 11H), 6.06 (s, 1H), 5.78 (q, $J = 10.5$ Hz, 1H), 5.44 (dd, $J = 10.9$ Hz, $J = 5.0$ Hz, 1H), 4.56 (s, 2H), 4.53–4.46 (m, 1H), 4.01 (s, 2H), 3.59 (t, $J = 6.1$ Hz, 2H), 3.43 (dd, $J = 12.7$ Hz, $J = 8.2$ Hz, 1H), 2.84 (dd, $J = 13.0$ Hz, $J = 9.1$ Hz, 1H), 1.74–1.38 (m, 6H), 0.89 (s, 9H), 0.04 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 159.1, 138.5, 136.9, 135.9, 135.2, 134.9, 134.8, 131.0, 130.0, 129.7, 128.6, 128.03, 127.97, 127.90, 127.86, 121.3, 76.2, 72.4, 71.6, 63.4, 38.0, 32.9, 31.0, 26.2, 22.3, 18.6, -5.0; HRMS (ESI) calcd for C$_{36}$H$_{46}$O$_3$Si$_3$Na [M+Na]$^+$: 607.3040, found 607.3022.

Colorless oil (69% yield, 2 steps); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.70–7.57 (m, 4H), 7.46–7.31 (m, 6H), 6.02 (s, 1H), 5.78 (dddd, $J = 10.7$ Hz, $J = 9.2$ Hz, $J = 7.8$ Hz, $J = 1.4$ Hz, 1H), 5.49 (dd, $J = 10.8$ Hz, $J = 5.1$ Hz, 1H), 4.74 (m, 1H), 4.01 (d, $J = 1.4$ Hz, 2H), 3.41 (s, 3H), 3.35 (dd, $J = 13.1$ Hz, $J = 7.9$ Hz, 1H), 2.92 (dd, $J = 13.1$ Hz, $J = 9.5$ Hz, 1H), 1.38 (d, $J = 6.5$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 159.0, 136.8, 136.06, 136.03 135.1, 134.8, 130.5, 130.0, 129.8, 128.1, 127.9, 120.8, 78.5, 67.6, 58.4, 30.9, 24.5; HRMS (ESI) calcd for C$_{21}$H$_{24}$O$_3$SiNa [M+Na]$^+$: 359.1443, found 359.1460.

Colorless oil (62% yield, 2 steps); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.73–7.58 (m, 4H), 7.46–7.32 (m, 6H), 6.04 (t, $J = 1.5$ Hz, 1H), 5.81 (dddd, $J = 10.6$ Hz, $J = 9.4$ Hz, $J = 81.8$ Hz, $J = 1.4$ Hz, 1H), 5.48 (dd, $J = 10.9$ Hz, $J = 5.1$ Hz, 1H), 4.53 (m, 1H), 4.02 (d, $J = 1.5$ Hz, 2H), 3.48–3.36 (m, 4H), 2.85 (dd, $J = 13.0$ Hz, $J = 9.2$ Hz, 1H), 1.80–1.18 (m, 8H), 0.90 (t, $J = 6.9$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 159.0, 137.0, 136.0, 135.2, 135.1, 134.8, 130.8, 129.9, 129.7, 128.0, 127.9, 120.8, 78.6, 71.5, 58.4, 38.2, 31.9, 31.0, 25.6, 22.9, 14.3; HRMS (ESI) calcd for C$_{25}$H$_{32}$O$_3$SiNa [M+Na]$^+$: 415.2069, found 415.2087.

Colorless oil (69% yield, 2 steps); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.66–7.58 (m, 4H), 7.41–7.25 (m, 11H), 6.07 (t, $J = 1.4$ Hz, 1H), 5.77 (dddd, $J = 17.3$ Hz, $J = 9.4$ Hz, $J = 8.2$ Hz, $J = 1.4$ Hz, 1H), 5.45 (dd, $J = 10.7$ Hz, $J = 5.2$ Hz, 1H), 4.56 (s, 2H), 4.52–4.46 (m, 1H), 4.09 (d, $J = 1.4$ Hz, 2H), 3.42 (dd, $J = 13.2$ Hz, $J = 8.2$ Hz, 1H), 2.85 (dd, $J = 13.2$ Hz, $J = 9.2$ Hz, 1H),
1.76–1.18 (m, 8H), 0.87 (t, J = 7.0 Hz, 3H); \(^{13}\text{C NMR}\) (75 MHz, CDCl\(_3\)) \(\delta\) 159.1, 138.5, 136.9, 135.9, 135.2, 135.1, 134.8, 130.9, 130.0, 129.7, 128.6, 128.0, 127.95, 127.8, 121.2, 76.2, 72.4, 71.5, 38.2, 31.9, 31.0, 25.6, 22.8, 14.2; \text{HRMS}\) (ESI) calcd for C\(_{31}\)H\(_{36}\)O\(_2\)SiNa [M+Na]\(^+\): 491.2382, found 491.2398.

**Representative Procedure for Ring-Closing Enyne Metathesis of Vinyl Silanes 3-279f, 3-279g, 3-279m:**

Vinyl silane 3-279m (100 mg, 0.20 mmol) was dissolved in freshly distilled CH\(_2\)Cl\(_2\) (0.002 M) and Grubbs 2nd generation catalyst (H\(_2\)Imes)(PCy\(_3\))Cl\(_2\)Ru=CHPh (8.6 mg, 0.010 mmol, 5 mol %) was added under nitrogen. Ethylene gas was then bubbled through the solution for 10 min and ethylene atmosphere was changed to nitrogen. The reaction mixture was refluxed at 55 °C for 12 h and concentrated under reduced pressure. The residue was quickly purified by flash column chromatography (50:1 hexanes:EtOAc) and the reaction mixture was resubjected to the reaction conditions with 5 mol % of Grubbs catalyst and refluxed for an additional 12 h. After this time the solvent was removed under vacuum and the residue was purified by gravity column chromatography (greduent elution from 250:1 to 150:1 hexanes:EtOAc) to give eight-membered siloxacycle 3-280m as colorless oil (84.1 mg, 84%).

\(^{1}\text{H NMR}\) (500 MHz, CDCl\(_3\)) \(\delta\) 7.69 (dd, J = 7.4 Hz, J = 1.9 Hz, 2H), 7.54 (dd, J = 7.9 Hz, J = 1.3 Hz, 2H), 7.46–7.28 (m, 11H), 6.06 (s, 1H), 5.74 (dd, J = 10.8 Hz, J = 7.5 Hz, 1H), 4.70 (q, J = 6.6 Hz, 1H), 4.65–4.54 (m, 3H), 4.42 (s, 1H), 4.21–4.06 (m, 3H), 2.52 (dd, J =12.5 Hz, J =7.5 Hz, 1H), 1.89–1.76 (m, 2H), 1.48 (d, J = 6.4 Hz, 3H), 1.25–1.10 (m, 4H), 0.86 (t, J = 7.0 Hz, 3H); \(^{13}\text{C NMR}\) (125 MHz, CDCl\(_3\)) \(\delta\) 159.1, 148.6, 145.7, 138.3, 136.7, 135.3, 134.5, 134.4, 129.9, 129.5, 128.5, 127.79, 127.76, 127.67, 126.8, 120.7, 110.5, 76.2, 72.2, 71.0, 34.6, 30.6, 30.2, 24.1, 22.5, 14.0; \text{HRMS}\) (ESI) calcd for C\(_{33}\)H\(_{39}\)O\(_2\)Si [M+H]\(^+\): 495.2719, found 495.2711.
Colorless oil (85% yield); $^1$H NMR (300 MHz, CDCl$_3$) δ 7.69–7.65 (m, 2H), 7.47–7.44 (m, 2H), 7.41–7.24 (m, 6H), 5.95 (s, 1H), 5.76 (dd, $J = 11.0$ Hz, $J = 7.4$ Hz, 1H), 4.70 (q, $J = 6.5$ Hz, 1H), 4.52 (s, 1H), 4.39 (s, 1H), 4.16 (t, $J = 11.9$ Hz, 1H), 4.00 (dq, $J = 14.0$, 1.5 Hz, 1H), 4.70 (q, $J = 6.5$ Hz, 1H), 4.52 (s, 1H), 4.39 (s, 1H), 4.16 (t, $J = 11.9$ Hz, 1H), 4.00 (dq, $J = 14.0$, 1.5 Hz, 1H), 4.70 (q, $J = 6.5$ Hz, 1H), 4.52 (s, 1H), 4.39 (s, 1H), 4.16 (t, $J = 11.9$ Hz, 1H), 4.00 (dq, $J = 14.0$, 1.5 Hz, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) 158.8, 145.9, 143.2, 136.7, 135.6, 134.6, 134.5, 130.0, 129.7, 127.9, 127.8, 127.5, 120.8, 111.3, 78.8, 70.5, 58.4, 30.3, 24.4, 21.9; HRMS (ESI) calcd for C$_{24}$H$_{28}$O$_2$SiNa [M+Na]$^+$: 399.1756, found 399.1742.

Colorless oil (47% yield, 2 steps); $^1$H NMR (300 MHz, CDCl$_3$) δ 7.64–7.58 (m, 2H), 7.51–7.45 (m, 2H), 7.39–7.20 (m, 11H), 6.03 (d, $J = 1.2$ Hz, 1H), 5.81–5.71 (m, 2H), 5.13 (t, $J = 3.1$ Hz, 1H), 4.58 (s, 2H), 4.14 (dd, $J = 2.7$ Hz, $J = 1.4$ Hz, 2H), 3.64 (m, 1H), 3.42 (ddd, $J = 14.5$, $J = 10.1$ Hz, $J = 1.5$ Hz, 1H), 3.33 (d, $J = 11.4$ Hz, 1H), 3.16 (s, 3H), 2.88 (dd, $J = 14.6$ Hz, $J = 7.1$ Hz, 1H), 2.52–2.35 (m, 1H), 2.16–2.01 (m, 2H), 1.66–1.52 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 158.4, 138.4, 137.2, 136.9, 136.8, 134.85, 134.80, 132.1, 130.5, 129.7, 129.4, 128.64, 128.02, 127.97, 127.88, 127.5, 125.3, 122.4, 76.5, 73.9, 72.5, 65.9, 57.9, 31.3, 29.7, 21.0; HRMS (ESI) calcd for C$_{32}$H$_{34}$O$_3$SiNa [M+Na]$^+$: 517.2175, found 517.2172.

**Representative Procedure for Ring-Closing Metathesis of Methyl Substituted Vinyl Silanes 3-279h-k:**

Vinyl silane 3-279h (150 mg, 0.45 mmol) was dissolved in freshly distilled toluene (0.002 M) and Grubbs 2$^{nd}$ generation catalyst (H$_2$Imes)(PCy$_3$)Cl$_2$Ru=CHPh (19.0 mg, 0.0224 mmol, 5 mol %) was added under nitrogen. The reaction mixture was refluxed at 85 °C for 24 h and concentrated under reduced pressure. The residue was quickly purified by flash column chromatography (50:1 hexanes:EtOAc) and the reaction mixture was resubjected to the reaction conditions with 5 mol % of Grubbs catalyst and
refluxed for an additional 24 h. After this time the solvent was removed under vacuum and the product was purified by gravity column chromatography (graduate elution from 400:1 to 300:1 hexanes:EtOAc) to give eight-membered siloxacycle 3-280h as colorless oil (81.8 mg, 60%).\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 7.64 (t, \(J = 5.9\) Hz, 4H), 7.45–7.31 (m, 6H), 5.84 (ddd, \(J = 10.8\) Hz, \(J = 9.4\) Hz, \(J = 7.6\) Hz, 1H), 5.75 (s, 1H), 5.48 (dd, \(J = 10.8\) Hz, \(J = 4.9\) Hz, 1H), 4.77 (m, 1H), 3.30 (dd, \(J = 12.9\) Hz, \(J = 7.6\) Hz, 1H), 2.94 (dd, \(J = 12.7\) Hz, \(J = 9.4\) Hz, 1H), 2.07 (s, 3H), 1.38 (d, \(J = 6.6\) Hz, 3H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) 160.3, 137.0, 136.3, 135.7, 134.8, 134.5, 130.1, 129.7, 129.4, 127.9, 127.7, 120.4, 67.2, 35.4, 29.3, 24.3; HRMS (ESI) calcd for C\textsubscript{20}H\textsubscript{23}OSi [M+H]\textsuperscript{+}: 307.1518, found 307.1510.

Colorless oil (61% yield); \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 7.74–7.60 (m, 4H), 7.46–7.32 (m, 6H), 5.88 (ddd, \(J = 10.8\) Hz, \(J = 9.5\) Hz, \(J = 8.1\) Hz, 1H), 5.77 (m, 1H), 5.48 (dd, \(J = 10.8\) Hz, \(J = 5.1\) Hz, 1H), 4.56 (m, 1H), 3.38 (dd, \(J = 12.8\) Hz, \(J = 8.1\) Hz, 1H), 2.91 (dd, \(J = 12.5\) Hz, \(J = 9.5\) Hz, 1H), 2.09 (s, 3H), 1.78–1.68 (m, 1H), 1.63–1.46 (m, 2H), 1.43–1.22 (m, 5H), 0.91 (dt, \(J = 7.1\) Hz, \(J = 1.1\) Hz, 3H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) 160.4, 137.3, 136.3, 135.0, 134.9, 134.5, 130.5, 129.6, 129.4, 127.8, 127.7, 120.5, 71.0, 38.0, 35.5, 31.8, 29.5, 25.4, 22.7, 14.1; HRMS (ESI) calcd for C\textsubscript{24}H\textsubscript{31}OSi [M+H]\textsuperscript{+}: 363.2144, found 363.2140.

Colorless oil (63% yield); \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 7.69 (dd, \(J = 7.6\) Hz, \(J = 1.6\) Hz, 2H), 7.61 (dd, \(J = 7.8\) Hz, \(J = 1.4\) Hz, 2H), 7.42–7.32 (m, 6H), 7.26 (t, \(J = 7.6\) Hz, 2H), 7.18 (t, \(J = 6.9\) Hz, 3H), 5.88 (ddd, \(J = 10.9\) Hz, \(J = 9.2\) Hz, \(J = 8.1\) Hz, 1H), 5.73 (d, \(J = 1.3\) Hz, 1H), 5.45 (dd, \(J = 10.9\) Hz, \(J = 5.0\) Hz, 1H), 4.54 (m, 1H), 3.43 (dd, \(J = 12.8\) Hz, \(J = 8.1\) Hz, 1H), 2.94–2.81 (m, 2H), 2.70 (dd, \(J = 13.9\) Hz, \(J = 10.1\) Hz, \(J = 6.3\) Hz, 1H), 2.07 (d, \(J = 0.9\) Hz, 3H), 2.04–1.97 (m, 1H), 1.91–1.80 (m, 1H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) 160.4, 142.3, 137.1, 136.1, 135.0, 134.5, 134.3, 131.0, 129.7, 129.5, 128.5, 128.3, 127.8, 127.7, 125.7, 120.4, 70.7, 39.7, 35.4, 32.0, 29.5; HRMS (ESI) calcd for C\textsubscript{27}H\textsubscript{29}OSi [M+H]\textsuperscript{+}: 397.1988, found 397.1989.
Colorless oil (57% yield); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.66–7.58 (m, 4H), 7.41–7.31 (m, 6H), 5.84 (ddd, \(J = 10.8\) Hz, \(J = 9.5\) Hz, \(J = 8.0\) Hz, 1H), 5.72 (d, \(J = 1.2\) Hz, 1H), 5.43 (dd, \(J = 10.8\) Hz, \(J = 5.1\) Hz, 1H), 4.51 (dd, \(J = 11.9\) Hz, \(J = 5.5\) Hz, 1H), 4.13 (q, \(J = 7.1\) Hz, 2H), 3.34 (dd, \(J = 12.8\) Hz, \(J = 8.0\) Hz, 1H), 2.86 (dd, \(J = 12.8\) Hz, \(J = 9.5\) Hz, 1H), 2.06 (s, 3H), 1.37–1.22 (m, 10H); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 173.9, 160.4, 137.2, 136.3, 135.0, 134.8, 134.5, 130.5, 129.6, 129.4, 127.8, 127.6, 120.4, 71.0, 60.1, 37.9, 35.4, 34.4, 29.4, 29.3, 29.2, 29.1, 25.6, 25.0, 14.3; HRMS (ESI) calcd for C\(_{29}\)H\(_{38}\)O\(_3\)Si [M+H]\(^+\): 463.2668, found 463.2667.

Representative Procedure for Ring-Contraction of Cyclic Siloxadines:

Eight-membered cyclic siloxadiene 3-280h (59.9 mg, 0.195 mmol) was dissolved in dry ether (0.3 M) and rhenium(VII) oxide (4.7 mg, 0.0098 mmol, 5 mol %) was added under nitrogen. The reaction mixture was stirred at room temperature for 10 min and solvent was evaporated under reduced pressure. The residue was immediately transferred onto silica gel and the product was purified by gravity column chromatography (from 400:1 to 300:1 hexanes:EtOAc) to yield six-membered siloxene 3-281h as colorless oil (45.6 mg, 76%). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.72–7.60 (m, 4H), 7.48–7.33 (m, 6H), 5.85–5.74 (m, 2H), 5.71–5.64 (m, 1H), 4.58 (m, 1H), 2.44 (dd, \(J = 17.4\) Hz, \(J = 10.5\) Hz, 1H), 2.18 (dd, \(J = 17.4\) Hz, \(J = 2.4\) Hz, 1H), 2.00 (s, 3H), 1.74 (d, \(J = 6.4\) Hz, 3H); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 158.4, 135.9, 135.2, 134.9, 134.7, 133.4, 130.0, 129.9, 127.9, 127.8, 126.3, 116.9, 72.7, 41.4, 28.8, 17.7; HRMS (ESI) calcd for C\(_{20}\)H\(_{19}\)OSi [M+H]\(^+\): 307.1518, found 307.1521.

Colorless oil (49% yield); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.70–7.61 (m, 4H), 7.49–7.29 (m, 11H), 6.20 (s, 1H), 6.01 (ddd, \(J = 17.0\) Hz, \(J = 10.4\) Hz, \(J = 5.1\) Hz, 1H), 5.40 (dd, \(J = 17.1\) Hz, \(J = 1.0\) Hz, 1H), 5.16 (dd, \(J = 10.4\) Hz, \(J = 0.8\) Hz, 1H), 4.64 (m,
1H), 4.58 (s, 2H), 4.07 (m, 2H), 2.43–2.29 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 157.3, 140.0, 138.1, 135.4, 134.9, 134.72, 134.68, 130.2, 130.1, 128.5, 128.0, 127.9, 127.8, 127.7, 117.6, 114.5, 75.5, 72.6, 72.5, 36.6; HRMS (ESI) calcd for C$_{26}$H$_{27}$O$_2$Si [M+H]$^+$: 399.1780, found 399.1781.

Colorless oil (83% yield); $^1$H NMR (300 MHz, CDCl$_3$) δ 7.66–7.58 (m, 4H), 7.44–7.28 (m, 11H), 6.15 (dd, $J = 3.7$, $J = 1.5$, 1H), 5.67 (ddd, $J = 15.5$ Hz, $J = 6.1$ Hz, $J = 0.8$ Hz, 1H), 5.58 (ddd, $J = 15.5$ Hz, $J = 6.0$ Hz, $J = 1.1$ Hz, 1H), 4.63–4.55 (m, 3H), 4.03 (m, 2H), 2.45–2.18 (m, 3H), 0.97 (d, $J = 6.6$ Hz, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 157.6, 138.6, 138.3, 135.7, 135.11, 135.08, 134.9, 130.3, 130.2, 129.2, 128.6, 128.1, 128.00, 127.97, 127.9, 117.7, 75.8, 73.1, 72.6, 37.4, 30.8, 22.44, 22.40; HRMS (ESI) calcd for C$_{29}$H$_{32}$O$_3$SiNa [M+Na]$^+$: 463.2069, found 463.2088.

Colorless oil (65% yield); $^1$H NMR (300 MHz, CDCl$_3$) δ 7.69–7.55 (m, 4H), 7.48–7.24 (m, 11H), 6.15 (dd, $J = 3.3$ Hz, $J = 1.5$ Hz, 1H), 5.80–5.56 (m, 2H), 4.63–4.51 (m, 3H), 4.03 (s, 2H), 3.63 (t, $J = 6.4$ Hz, 2H), 2.42–2.22 (m, 2H), 2.06 (dd, $J = 13.8$ Hz, $J = 6.8$ Hz, 2H), 1.61–1.41 (m, 5H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 157.6, 138.3, 135.6, 135.1, 135.0, 134.9, 132.5, 131.3, 130.3, 130.2, 128.6, 128.1, 128.00, 127.95, 127.9, 117.7, 75.7, 72.9, 72.6, 63.1, 37.3, 32.5, 32.1, 25.4; HRMS (ESI) calcd for C$_{36}$H$_{35}$O$_3$SiNa [M+Na]$^+$: 493.2175, found 493.2182.

Colorless oil (82% yield); $^1$H NMR (300 MHz, CDCl$_3$) δ 7.75–7.58 (m, 4H), 7.48–7.33 (m, 6H), 6.10 (dd, $J = 3.3$ Hz, $J = 1.5$ Hz, 1H), 5.87–5.61 (m, 2H), 4.60 (m, 1H), 3.96 (m, 2H), 3.41 (s, 3H), 2.39 (ddd, $J = 17.3$ Hz, $J = 10.1$ Hz, $J = 2.3$ Hz, 1H), 2.27 (dd, $J = 17.3$ Hz, $J = 2.9$ Hz, 1H), 1.73 (dd, $J = 6.2$ Hz, $J = 1.1$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 157.6, 135.6, 135.1, 135.0, 134.9, 133.4, 130.3, 130.2, 128.1, 128.0, 126.6, 117.4, 78.1, 72.9, 58.5, 37.1, 17.9; HRMS (ESI) calcd for C$_{27}$H$_{26}$O$_3$SiNa [M+Na]$^+$: 359.1443, found 359.1443.
Colorless oil (87% yield); $^1$H NMR (300 MHz, CDCl$_3$) δ 7.73–7.57 (m, 4H), 7.47–7.31 (m, 6H), 6.09 (dd, $J = 3.3$ Hz, $J = 1.5$ Hz, 1H), 5.74 (ddt, $J = 15.4$ Hz, $J = 6.4$ Hz, $J = 0.6$ Hz, 1H), 5.61 (ddt, $J = 15.3$ Hz, $J = 6.0$ Hz, $J = 1.1$ Hz, 1H), 4.58 (m, 1H), 3.93 (m, 2H), 3.37 (s, 3H), 2.35 (dd, $J = 17.3$ Hz, $J = 9.9$ Hz, $J = 2.3$ Hz, 1H), 2.22 (dd, $J = 17.3$ Hz, $J = 3.0$ Hz, 1H), 2.02 (dd, $J = 13.9$ Hz, $J = 6.7$ Hz, 2H), 1.42–1.21 (m, 6H), 0.88 (t, $J = 6.8$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 157.5, 135.7, 135.1, 135.0, 134.9, 132.0, 131.9, 130.3, 130.2, 128.1, 128.0, 117.5, 78.1, 73.0, 58.5, 37.2, 32.4, 31.7, 29.0, 22.7, 14.3; HRMS (ESI) calcd for C$_{25}$H$_{33}$O$_2$SiNa [M+Na]$^+$: 415.2069, found 415.2087.

Colorless oil (85% yield); $^1$H NMR (300 MHz, CDCl$_3$) δ 7.65–7.59 (m, 4H), 7.43–7.34 (m, 6H), 6.08 (dd, $J = 3.3$ Hz, $J = 1.5$ Hz, 1H), 5.75 (dq, $J = 6.8$ Hz, $J = 1.2$ Hz, 1H), 5.08 (dq, $J = 2.9$ Hz, $J = 1.4$ Hz, 1H), 4.71 (dd, $J = 2.4$ Hz, $J = 0.9$ Hz, 1H), 4.60 (m, 1H), 3.91 (m, 2H), 3.37 (s, 3H), 2.39–2.19 (m, 2H), 1.85 (m, 3H), 1.66 (dd, $J = 6.9$ Hz, $J = 1.0$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 158.0, 145.1, 142.7, 135.8, 135.2, 134.9, 134.8, 130.2, 130.1, 128.1, 128.0, 120.4, 117.1, 115.4, 78.0, 74.5, 58.4, 36.0, 23.7, 14.3; HRMS (ESI) calcd for C$_{24}$H$_{26}$O$_2$SiNa [M+Na]$^+$: 399.1756, found 399.1761.

Colorless oil (53% yield, combined with aromatized product); $^1$H NMR (300 MHz, CDCl$_3$) δ 7.72–7.61 (m, 4H), 7.48–7.29 (m, 11H), 6.17 (dd, $J = 3.3$ Hz, $J = 1.5$ Hz, 1H), 6.10 (t, $J = 3.8$ Hz, 1H), 5.86 (t, $J = 3.9$ Hz, 1H), 4.84 (m, 1H), 4.58 (d, $J = 1.0$ Hz, 2H), 4.06 (m, 2H), 3.91 (dd, $J = 11.3$ Hz, $J = 0.7$ Hz, 1H), 3.82 (d, $J = 11.3$ Hz, 1H), 3.05 (s, 3H), 2.56–2.35 (m, 2H), 2.21–2.03 (m, 4H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 158.3, 138.7, 138.4, 135.7, 135.2, 135.1, 133.3, 130.3, 130.2, 128.6, 128.1, 127.98, 127.95, 127.9, 127.5, 123.4, 117.2, 75.7, 73.7, 72.6, 70.9, 57.6, 36.8, 22.4; HRMS (ESI) calcd for C$_{32}$H$_{34}$O$_3$SiNa [M+Na]$^+$: 517.2175, found 517.2176.

Colorless oil (75% yield); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.67–7.58 (m, 4H), 7.46–7.32 (m, 6H), 5.79 (s, 1H), 5.72 (dt, $J = 15.3$ Hz, $J = 6.6$ Hz, 1H), 5.61 (dd, $J = 15.4$ Hz, 1H), 5.48 (m, 1H), 4.42 (m, 1H), 3.96 (s, 3H), 2.35 (dd, $J = 17.3$ Hz, $J = 9.9$ Hz, 2H), 1.41 (dd, $J = 13.9$ Hz, $J = 6.7$ Hz, 2H), 1.34–1.14 (m, 8H), 0.88 (t, $J = 6.8$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 157.5, 135.7, 135.1, 135.0, 134.9, 132.0, 131.9, 130.3, 130.2, 128.1, 128.0, 117.5, 78.1, 73.0, 58.5, 37.2, 32.4, 31.7, 29.0, 22.7, 14.3; HRMS (ESI) calcd for C$_{25}$H$_{33}$O$_2$SiNa [M+Na]$^+$: 415.2069, found 415.2087.
Hz, J = 6.2 Hz, 1H), 4.56 (m, 1H), 2.41 (ddd, J = 17.4 Hz, J = 10.3 Hz, J = 1.0 Hz, 1H), 2.16 (dd, J = 17.5 Hz, J = 2.7 Hz, 1H), 2.03 (dd, J = 14.5 Hz, J = 7.0 Hz, 2H), 1.97 (s, 3H), 1.40–1.23 (m, 6H), 0.90 (t, J = 7.0 Hz, 3H); \(^{13}\text{C} \text{NMR} \) (125 MHz, CDCl\(_3\)) δ 158.4, 135.9, 135.3, 134.9, 134.7, 132.0, 131.6, 130.0, 129.9, 127.9, 127.8, 116.9, 72.8, 41.5, 32.2, 31.5, 28.8, 22.6, 14.1; \(^{1}\text{H} \text{NMR} \) (ESI) calcd for C\(_{24}\)H\(_{31}\)OSi [M+H]\(^+\): 363.2144, found 363.2138.

Colorless oil (61% yield); \(^{1}\text{H} \text{NMR} \) (500 MHz, CDCl\(_3\)) δ 7.69–7.63 (m, 2H), 7.62–7.58 (m, 2H), 7.49–7.33 (m, 6H), 7.29 (t, J = 7.6 Hz, 2H), 7.20 (t, J = 7.5 Hz, 3H), 5.84–5.75 (m, 2H), 5.66 (ddd, J = 15.3 Hz, J = 6.1 Hz, J = 1.2 Hz, 1H), 4.56 (m, 1H), 2.71 (m, 2H), 2.43–2.33 (m, 3H), 2.15 (dd, J = 17.6 Hz, J = 2.6 Hz, 1H), 1.98 (s, 3H); \(^{13}\text{C} \text{NMR} \) (125 MHz, CDCl\(_3\)) δ 158.3, 142.0, 135.9, 135.2, 134.9, 134.7, 132.7, 130.4, 130.0, 129.9, 128.5, 128.3, 127.9, 127.8, 125.8, 116.9, 72.6, 41.4, 35.6, 34.1, 28.8; \(^{1}\text{H} \text{NMR} \) (ESI) calcd for C\(_{27}\)H\(_{29}\)OSi [M+H]\(^+\): 397.1988, found 397.1991.

Colorless oil (74% yield); \(^{1}\text{H} \text{NMR} \) (500 MHz, CDCl\(_3\)) δ 7.64 (m, 2H), 7.59 (d, J = 6.6 Hz, 2H), 7.45–7.32 (m, 6H), 5.79 (s, 1H), 5.75–5.68 (m, 1H), 5.60 (ddd, J = 15.4 Hz, J = 6.1 Hz, 1H), 4.55 (m, 1H), 4.13 (q, J = 7.2 Hz, 2H), 2.40 (dd, J = 17.3 Hz, J = 10.4 Hz, 1H), 2.29 (t, J = 7.5 Hz, 2H), 2.16 (dd, J = 17.4 Hz, J = 2.6 Hz, 1H), 2.02 (d, J = 14.2 Hz, J = 6.9 Hz, 2H), 1.97 (s, 3H), 1.61 (dd, J = 13.8 Hz, J = 6.6 Hz, 2H), 1.40–1.23 (m, 11H); \(^{13}\text{C} \text{NMR} \) (125 MHz, CDCl\(_3\)) δ 173.9, 158.3, 135.9, 135.3, 134.8, 134.7, 132.0, 131.4, 130.0, 129.9, 127.7, 116.9, 72.6, 41.5, 34.4, 32.2, 29.11, 29.04, 29.02, 28.8, 25.0, 14.3; \(^{1}\text{H} \text{NMR} \) (ESI) calcd for C\(_{29}\)H\(_{39}\)O\(_3\)Si [M+H]\(^+\): 463.2668, found 463.2671.

Colorless oil (71% yield, 79% ee); \(^{1}\text{H} \text{NMR} \) (300 MHz, CDCl\(_3\)) δ 7.66–7.58 (m, 4H), 7.43–7.28 (m, 11H), 6.15 (dd, J = 3.3 Hz, J = 1.5 Hz, 1H), 5.66 (dt, J = 15.4 Hz, J = 6.5 Hz, 1H), 5.60 (ddt, J = 15.1 Hz, J = 5.8 Hz, J = 1.1 Hz, 1H), 4.60–4.52 (m, 3H), 4.03 (m, 2H), 2.35 (ddd, J = 17.5 Hz, J = 9.7 Hz, J = 3.0 Hz, 1H), 2.24 (dd, J = 17.5 Hz, J = 3.0 Hz, 1H), 2.01 (dd, J = 14.3 Hz, J = 6.9 Hz, 2H), 1.21–1.42 (m, 6H), 0.88 (t, J = 6.9 Hz, 3H);
$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 157.6, 138.4, 135.7, 135.09, 135.07, 134.9, 131.98, 131.97, 130.3, 130.2, 128.6, 128.1, 128.00, 127.97, 127.90, 117.7, 75.7, 73.0, 72.6, 37.3, 32.4, 31.7, 29.0, 22.7, 14.3; HRMS (ESI) calcd for C$_{31}$H$_{36}$O$_2$SiNa [M+Na]$^+$: 491.2382, found 491.2377.

Colorless oil (66% yield, 76% ee); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.71–7.62 (m, 4H), 7.50–7.29 (m, 11H), 6.19 (s, 1H), 5.88 (m, 1H), 5.09 (s, 1H), 4.76 (d, $J$ = 1.8 Hz, 1H), 4.65–4.53 (m, 3H), 4.05 (m, 2H), 2.39–2.28 (m, 2H), 2.15 (dd, $J$ = 14.0 Hz, $J$ = 6.9 Hz, 2H), 1.70 (d, $J$ = 6.8 Hz, 3H), 1.45–1.25 (m, 4H), 0.89 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 158.0, 146.7, 144.5, 138.2, 135.7, 135.0, 134.8, 134.6, 130.06, 129.98, 128.4, 127.9, 127.81, 127.77, 127.70, 120.9, 117.0, 114.0, 75.4, 73.8, 72.4, 36.3, 36.1, 29.9, 22.6, 14.3, 14.0; HRMS (ESI) calcd for C$_{33}$H$_{39}$O$_2$Si [M+H]$^+$: 495.2719, found 495.2710.

Desilylation of 3-281m and Mosher’s Ester Preparation:

Six-memebered cyclic siloxene 3-281m (17.2 mg, 0.035 mmol) was dissolved in dry THF (1 mL) and solution of TBAF in THF (105 µL, 1 M, 3 equiv) was added under nitrogen. The reaction mixture was heated to 60 ºC and stirred for 30 min. After that reaction mixture was cooled to room temperature and solvent was evaporated under reduced pressure. The residue was quickly purified by flash column chromatography (10:1 hexanes:EtOAc) to afford desilylated product as colorless oil (1.8 mg, 16%).

In a round bottom flask (R)-MTPA (10 mg) was dissolved in dry DCM (0.5 mL) and excess of oxalyl chloride (50 µL) was added under nitrogen followed by addition of dry DMF (5 µL). The reaction mixture was stirred for 1 h at room temperature and concentrated under reduced pressure to remove excess of oxalyl chloride. To the flask containing desilylated alcohol from previous step were added 4-dimethylaminopyridine (2 mg) and dry triethylamine (50 µL) and resulted solution was added via
syringe to the Mosher’s acid chloride which immediately generated a milky white slurry. The reaction mixture was stirred for 1 h at room temperature and concentrated under reduced pressure. The residue was quickly purified by flash column chromatography (30:1 hexanes:EtOAc) to afford Mosher’s ester as colorless oil (76% ee). The ee was determined by integration of resonances of methoxy-groups in $^1$H NMR spectra.

The procedure for the desilylation of 3-281l is similar to that of 3-281m. Alcohol was obtained in 28% yield and 79% ee. The ee was determined by chiral HPLC analysis using a chiralcel OD column. HPLC Conditions: Chiralcel OD, Hex:i-PrOH 98:2, 1 mL/min.
3.7. References


(59) It is unusual to observe this five membered ring product because RCM of vinylsilanes are known to be difficult with Grubbs catalyst. (a) Denmark, S. E.; Yang, S.-M. Org. Lett. 2001, 3, 1749–1752. (b) Denmark, S. E.; Yang, S.-M. Tetrahedron 2004, 60, 9695–9708.

(60) We surmise that the five-membered ring formation is most likely the consequence of direct RCM of the acyclic precursors because resubjection of the eight-membered siloxacycle to the reaction conditions did not provide any five-membered ring product.


PART IV

ASYMMETRIC TOTAL SYNTHESIS OF (–)-AMPHIDINOLIDE V

4.1. Amphidinolide V: Isolation and Structural Characterization and SAR Studies*

Amphidinolides belong to the structurally diverse family of secondary metabolites isolated from symbiotic dinoflagellates Amphidinium sp.1 (+)-Amphidinolide V was extracted from Amphidinium strain Y-5 along with 14 other members of this family. The marine plankton was separated from the inside of the cell of a flatworm Amphiscolops sp. collected off Chatan beach, Okinawa. This scarce (0.00005% of the wet weight) natural metabolite exhibited cytotoxicity against murine lymphoma L1210 (IC₅₀, 3.2 μg/mL) and human epidermoid carcinoma KB cells (IC₅₀, 7 μg/mL) in vitro. Amphidinolide V is a 14-membered macrolactone possessing a syn-epoxyalcohol subunit, three isolated and two vicinal exo-methylene groups, and an unsaturated side chain (Figure 4.1.1). The relative configurations of its four stereogenic centers (C8, C9, C10, and C13) were deduced from ¹H–¹H coupling constants and NOESY data.²

![Figure 4.1.1. (–)-Amphidinolide V and Its Synthetic Analogs](image)

The first total synthesis of (–)-amphidinolide V by Fürstner and coworkers in 2007,³ however, revealed a singular mismatch in C–H signal at C8 for the reported ¹H NMR data of natural product and

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that obtained for synthesized material. Therefore, other feasible congeners (4-02, 4-03, and 4-04) bearing trans-epoxide moiety but possessing different stereochemistry of individual stereogenic centers were prepared and their spectroscopic data were compared. Analysis of the obtained data indicated that synthesized analogues had significantly different signal pattern in both $^1$H and $^{13}$C NMR spectra compared to that reported for natural product. Therefore, the relative stereochemistry of amphidinolide V was concluded to be same as the proposed structure (−)-4-01 and the singular mismatch in the $^1$H NMR data was the consequence of a typographical error. The absolute configuration of natural amphidinolide V was later determined to be opposite to that of the initially synthesized compound by comparison of the synthetic materials by HPLC and CD spectroscopy with an authentic sample re-extracted from natural source." Additionally, the structure-activity relationship studies were performed using different cancer cell lines than originally employed for the validation of biological activity (Figure 4.1.2).

![Figure 4.1.2. SAR Studies of (+)-Amphidinolide V](image)

It has been found that the cytotoxicity of (+)-amphidinolide V against murine lymphoma P388 originates from a particular conformation of the macrocycle as congeners with altered stereochemistry of epoxyalcohol (4-02) as well as the C13 lactone moiety (4-03, 4-05) were inactive toward selected cancer
cell line. On the other hand, modifications of the side chain do not significantly alter cytotoxicity of the compound (analogs 4-06 and 4-07).

The mechanism of action of amphidinolide V as well as of many others members of aphidinolide family is not known although the biological mode of action of significantly more potent amphidinolides B and H has been investigated. These studies indicate that amphidinolide H behaves as an F-actin stabilizer via covalent binding, whereas amphidinolide B enhances the interaction of actin and myosin directly and increases the contractile response of myofilaments.

4.2. Total Synthesis of (−)-Amphidinolide V by Fürstner

To date, only one total synthesis of both (+)- and (−)-amphidinolide V has been reported, which was accomplished by the Fürstner group. The distinctive feature of their highly convergent approach is the construction of the 14-membered macrocycle by ring-closing alkyne metathesis (RCAM) with subsequent elaboration of the resulting cycloalkyne into a macrocyclic 1,3-diene by enyne cross-metathesis (enyne CM) with ethylene gas (Scheme 4.2.1).

Scheme 4.2.1. Synthetic Approach for (−)-Amphidinolide V by Fürstner

The disconnection at C7–C8 bond allowed for the synthesis of several congeners of this natural product class. Thus, the syn-configuration of epoxyalcohol moiety in 4-10 was introduced via the
stereoselective addition of organozinc reagent 4-13 onto epoxyaldehyde 4-11. Alternatively, anti-stereochemistry of epoxyalcohol in amphidinolide V analogs was installed by chelation-controlled reduction of corresponding epoxyketone.

The synthesis commenced with the preparation of epoxyaldehyde 4-22 for subsequent stereoselective reaction with vinylzinc reagent (Scheme 4.2.2). Accordingly, copper-catalyzed opening of TBS-protected (R)-glycidol with vinylmagnesium reagent 4-15 afforded vinylsilane 4-16.

Scheme 4.2.2. Fürstner Synthesis of (-)-Amphidinolide V
After the three-step exchange of a silyl group to the corresponding bromide, resultant bromide 4-17 was subjected to a Suzuki cross-coupling with trifluoroborate 4-18 in anhydrous THF with t-BuNH₂ as a base to furnish diene 4-18 in 84% yield. Subsequent coupling of alcohol 4-19 with 4-hexynoic acid 4-12 under EDC/HOAt conditions delivered ester 4-20. THP-deprotection followed by the Sharpless asymmetric epoxidation in the presence of (–)-D-DET introduced the epoxyalcohol moiety in 4-22. Subsequent DMP oxidation delivered epoxyaldehyde 4-23. At this stage, a chelation-controlled addition of vinyl organometallic reagent was employed to establish the desired syn-epoxyalcohol functionality of the natural product. Poor stereocontrol of epoxyaldehyde alkylations is well-known, however, authors surpassed this obstacle by introducing epoxyaldehyde 4-23 slowly into a salt-free solution of bis(vinyl)zinc reagent 4-13 in toluene in the presence of (+)-N-methylephedrine ((+)-NME). Under these conditions bis(TBS-silyl) ether 4-10 was obtained in 55% yield and up to 7:1 d.r. after concomitant silylation of the syn-epoxyalcohol intermediate. The formation of a strained 14-membered cycloalkyne 4-09 was achieved by RCAM of methyl-capped substrate 4-10 using a catalyst generated in situ from molybdenum complex 4-24 (20 mol %) and CH₂Cl₂ in toluene at 80 °C. The labile vinyl epoxide and allylic silyl ether moieties present in the molecule remained intact in the reaction. Consecutive enyne metathesis between 4-24 and ethylene (1.8 atm) using the Grubbs second-generation catalyst (10 mol %) delivered 1,3-diene 4-08 in 90% yield. Next, selective desilylation of primary TBS-ether in 4-08 followed by sequence of DMP oxidation and Julia-Kocienski olefination with sulfone 4-26 introduced the side chain of the molecule with ca. 10:1 E/Z stereoselectivity. Final unmasking of epoxyalcohol by treatment with TASF furnished (–)-amphidinolide V.

As mentioned in the previous section, several congeners of amphidinolide V have also been synthesized to validate the accuracy of structural assignment of the natural product (Scheme 4.2.3). Accordingly, analog 4-03 bearing an altered configuration of syn-epoxide was prepared via a similar sequence of steps from 4-20 changing only tartrate ligand for the Sharpless asymmetric epoxidation to (+)-L-DET. For the installation of anti-epoxyalcohol in 4-02 and 4-04 a chelation-controlled reduction of
corresponding ketones 4-28 and 4-30 was employed. Thus, oxidation of epoxyalcohol 4-27 followed by addition of vinylmagnesium reagent onto obtained epoxyaldehyde intermediate and subsequent oxidation of diastereomeric mixture of product alcohols delivered intermediate 4-28. Treatment of 4-28 with NaBH₄ in the presence of CaCl₂ afforded anti-epoxyalcohol 4-29 in 11:1 d.r. Similar tactics was employed for the preparation of anti-epoxyalcohol 4-31 from 4-23, which in turn was elaborated to an analog 4-04. The prepared macrolactones 4-02, 4-03, 4-04 represent a complete set of possible diastereomers for amphidinolide V. Based on the distinct difference of NMR data of synthesized congeners and that of the natural product, these compounds do not represent the actual target.

Scheme 4.2.3. Synthesis of (−)-Amphidinolide V Analogs
4.3. Allylic Transposition Approach for Amphidinolide V: Initial Retrosynthetic Analysis

One of the most distinctive structural features of amphidinolide V is the densely arrayed alkene moieties, two pairs of which are 1,3-dienes. Based on the connectivity patterns we envisioned that the requisite 1,3-diene subunits could be effectively installed by enyne metathesis. In addition, the structure of natural product possesses a functionalized 1,5-diene-4-ol subunit. Therefore, we planned to access this moiety via the ring-contractive allylic transposition of cyclic silyl ethers (see section 3). According to initially proposed retrosynthetic approach, the 14-membered macrocycle of (−)-4-01 could be forged by a suitable macrolactonization protocol (Scheme 4.3.1). Despite potential complications in stereoselective alkylation of epoxyaldehydes or syn-selective reductions of epoxyketones, this tactic was realized by Fürstner. Thus, we reasoned that the syn-epoxyalcohol moiety of precursor seco-acid 4-32 could be introduced by the stereoselective alkylation of epoxyaldehyde 4-34 with an organometallic reagent 4-33.

Scheme 4.3.1. First Generation Approach for Amphidinolide V
For the installation of requisite 1,3-diene functionality of 4-33 enyne cross-metathesis (CM) between the corresponding internal alkyne and ethylene gas was envisioned. The acceptor aldehyde 4-34 would be accessed via the functionalization of 6-membered siloxene 4-35, which in turn could arise from the ring-contraction of 8-membered silacyclodiene 4-36 via Re-catalyzed 1,3-transposition. Intermediate 4-36 would be derived from silane 4-38 and alcohol 4-39 via gold-catalyzed allyl transfer–alcoholysis followed by ring-closing metathesis (RCM) of siloxane 4-37. The trimethylsilyl-substituted 1,3-diene moiety of 4-39 could be constructed by enyne RCM of alkynylsilyl ether 4-41 and subsequent ring opening via methyllithium addition. Alkynyl silane 4-41 could be accessed from readily available starting materials 4-42 and 4-43 by previously developed base-catalyzed alkynyl silane alcoholysis.

4.4. Synthesis of (−)-Amphidinolide V

4.4.1. Initial Attempts of Gold-Catalyzed Allyl Transfer–Alcoholysis

One of the challenges in the designed synthetic route was the employment of alkynyl allylsilane bearing extended conjugation (4-38) in a three-step sequence leading to 6-membered siloxene 4-35 (Scheme 4.3.1). We reasoned that in the presence of an additional double bond some complications could arise in the allyl transfer–alcoholysis step due to a carbocationic nature of the transition state.

![Scheme 4.4.1.1. Synthesis of Allyl Alkynylsilane for Allyl Transfer–Alcoholysis](image-url)
Additionally, the RCM of silyl ether 4-37 could potentially give a mixture of products due to the possible involvement of the C9–C10 disubstituted double bond. Therefore, a synthetic strategy toward intermediate 4-35 was first explored on racemic substrates. First, the allyl and alkynyl moieties of silane 4-45 were introduced by sequential additions of allylmagnesium bromide and propargylmagnesium bromide to diphenyldimethoxysilane, providing a building block 4-45 (Scheme 4.4.1.1). The vinyl iodide counterpart acrylate (E)-4-46 was prepared according to known procedures from ethyl propiolate. The Sonogashira cross-coupling of 4-45 and (E)-4-46 delivered enyne 4-47 which upon reduction of the ester moiety and subsequent esterification furnished allyl transfer–alcoholysis substrate 4-38.

Preparation of the alcohol coupling partner for gold-catalyzed intramolecular allylation commenced with base-induced alcoholysis of alkynysilane 4-42 with homoallylic alcohol 4-48 as previously reported (Scheme 4.4.1.2). The obtained silyl ether 4-49 was then converted to cyclic siloxene 4-50 by enyne RCM with the Grubbs second-generation catalyst (GII). Subsequent ring-opening of silacycle 4-50 with methyllithium unmasked the hydroxyl group and the trimethylsilyl-substituted 1,3-diene subunit to deliver secondary alcohol 4-51. Additionally, desilylated alcohol 4-52 was prepared by treating 4-51 with TBAF under reflux.

![Scheme 4.4.1.2. Synthesis of Alcohol Coupling Partner for Allyl Transfer–Alcoholysis](image)

Scheme 4.4.1.2. Synthesis of Alcohol Coupling Partner for Allyl Transfer–Alcoholysis

With both the coupling partners in hand, we turned to their gold-catalyzed allyl transfer–alcoholysis (Scheme 4.4.1.3). Unfortunately, intramolecular allylation of 4-38 in the presence of either 4-51 or 4-52 and 1 mol % of Ph₃PAuSbF₆ was unsuccessful due to the decomposition of starting materials. To address this failure, the stability of substrates under the reaction conditions was investigated. Thus, exposure of
silyl enynes bearing differently protected allylic alcohol moiety (4-38, and 4-55a-d) and phenol as alcohol coupling partner to 1 mol % of Ph₃PAuSbF₆ did not deliver desired silyl ether 4-56. Only a complex mixture of products was formed in these test reactions. Moreover, fast decomposition of allylic alcohols 4-51 and 4-52 was observed in the presence of a gold catalyst due to the facile formation of conjugated tetraene. Intramolecular allyl transfer was only possible with substrate 4-47 bearing a conjugated ester functionality. However, in this case phenoxide 4-57 was obtained as a mixture of Z/E isomers of trisubstituted double bond (4:1 Z/E) in moderate yield. Low stereoselectivity of allyl transfer is attributed to post-isomerization of initially formed (Z)-4-56 under Lewis acidic conditions with prolonged reaction time. Efficiency of the allyl transfer–alcoholysis of 4-47 was not satisfactory in terms of mass balance in this synthetic route. Therefore, a revised plan was necessary.

Scheme 4.4.1.3. Allyl Transfer–Alcoholysis Attempts

4.4.2. Second-Generation Approach: Introduction of Dehydrogenative Coupling

The second-generation approach was envisioned in a way to avoid the incompatibility problem of both substrates 4-38 and 4-51 with the allyl transfer–alcoholysis conditions (Scheme 4.4.2.1). Accordingly, the requisite Si–O bond of the silyl ether precursor for RCM 4-60 was planned to construct
via a dehydrogenative coupling of alcohol 4-39 and hydrosilane 4-61 in which the Z-trisubstituted double bond would already be introduced. Based on our knowledge that alkoxyethyl-substituted alkynyl allylsilanes readily participate in allyl transfer–alcoholysis, installation of the Z-trisubstituted double bond was planned via an intramolecular allylation reaction of 4-63 in the presence of phenol. Subsequent displacement of phenoxide in 4-62 with hydride would give hydrosilane 4-61. Therefore, the necessary three-carbon unit C8–C10 of epoxyaldehyde 4-34 could be introduced at the later stage of the synthesis by the homologation of the allylic transposition product 4-58.

Scheme 4.4.2.1. Second Generation Approach for Amphidinolide V

The preparation of silane 4-61 was initiated by the merger of lithiated $p$-methoxyphenyl (PMP) ether\textsuperscript{15} 4-64 and methoxysilane 4-44 affording alkynyl allylsilane 4-63 (Scheme 4.4.2.2). Allyl transfer–alcoholysis of 4-63 with dry phenol provided phenoxy silane 4-62 as a single double bond isomer in 82\% yield. Initial attempts to reduce Si–O bond in 4-62 were unrewarding. Thus, treatment of 4-62 with DIBAL-H\textsuperscript{16} gave only recovered starting material, whereas LiAlH\textsubscript{4}\textsuperscript{17} afforded moderate yield of 4-61 only after extended reaction time. Boron-based reducing agents such as Super-hydride (LiBH\textsubscript{3}) delivered
silanol as a reaction product. After screening several metal hydride-based reducing agents, Red-Al was found to be the reagent of choice, inducing facile phenoxide displacement in less than 30 minutes furnishing silane 4-61 in 89% yield.

Scheme 4.4.2.2. Synthesis of Hydrosilane for Dehydrogenative Coupling

Preparation of allylic alcohol 4-39 for dehydrogenative coupling follows the same sequence of steps as for 4-51 (Scheme 4.4.2.3). Substrate homoallylic alcohol 4-43 was obtained in 95% enantiomeric purity by the catalytic asymmetric allylation procedure developed by Maruoka and coworkers.18 A base-induced alcoholysis of alkynylsilane 4-42 with 4-43 afforded monosubstituted silyl ether 4-41, which was then converted to cyclic siloxene 4-40 by ring-closing enyne metathesis with the Grubbs first-generation catalyst. Employment of the first-generation catalyst in this RCM of 4-41 was essential in order to avoid the formation of undesired 7-membered isomer (up to 25%) as it was observed in the presence of the second-generation catalyst. Subsequent ring cleavage of silacycle 4-40 with methyllithium delivered secondary alcohol 4-39 in 80% yield.

Scheme 4.4.2.3. Synthesis of Allylic Alcohol for Dehydrogenative Coupling
With the routes toward both partners secured, conditions for their coupling was then explored (Table 4.4.2.1). Bromination of silane 4-61 with NBS followed by reaction of the anticipated silyl bromide with alcohol 4-39 in the presence of amine base resulted in the formation of a complex mixture of products (entry 1). Consequently, transition metal-catalyzed dehydrogenative coupling of these substrates was investigated. Although a variety of metal complexes\textsuperscript{19} that would catalyze this transformation is available most of them are unsuitable due to potential side reactions, such as alkene isomerization, hydrogenation, and alkyne hydrosilylation. Moreover, considering the steric hindrance of starting silane and alcohol only catalysts of high activity would effect this transformation. For instance, an attempt to join 4-39 and 4-61 in the presence of [RuCl\textsubscript{2}(p-cymene)]\textsubscript{2} was unsuccessful, and the starting materials were recovered intact (entry 2). Searching for a promising catalyst possessing above mentioned properties we finally came across Xantphos-based complexes of Au\textsuperscript{20} and Cu\textsuperscript{21} recently described by Ito and Sawamura. However, no reaction occurred with in situ generated (Xantphos)AuCl catalyst upon heating up to 110 °C despite the reported broad reaction scope of this complex with sterically hindered silanes (entry 3). It has been shown that analogous (Xantphos)CuOt-Bu catalyst is more active than (Xantphos)AuCl. However, this sensitive complex readily undergoes hydrolysis and oxidation in the presence of trace amounts of moisture and air in the reaction medium. Therefore, we thought that in situ generation of (Xantphos)CuOt-Bu from CuCl, t-BuOLi and Xantphos ligand may offer a more convenient procedure. Unfortunately, treatment of CuCl, t-BuOLi and Xantphos in toluene followed by addition of substrates and heating the reaction mixture to 90 °C gave irreproducible results due to decomposition of the catalyst (entry 4). Gratifyingly, we found that easily accessible air-stable (Xantphos)CuCl catalyzed this transformation in the presence of a stoichiometric amount of t-BuOLi at 80 °C although variable amounts of inseparable t-Bu-siloxane were formed in the reaction (entry 5). To avoid the formation of inseparable t-Bu-siloxane byproduct, the effect of reaction temperature and base was next examined. Thus, dehydrogenative coupling at 60 °C required 30 hours for completion as oppose to 4 hours at 80 °C. Moreover, the product was obtained as an inseparable mixture contaminated with its double bond isomer (~20%) in addition to t-Bu-siloxane byproduct (entry 6). Changing the base to LiHMDS but keeping
reaction temperature at 80 °C afforded 4-60 in 71% yield after 24 h together with recovered starting materials (entry 7).

Table 4.4.2.1. Optimization Conditions for Hydrosilane Alcoholysis

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>(mol %)</th>
<th>Additives</th>
<th>(equiv)</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Time (h)</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NBS</td>
<td>110</td>
<td>–</td>
<td></td>
<td>CH₂Cl₂</td>
<td>25</td>
<td>–</td>
<td>–&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>[RuCl₂(p-cymene)]₂</td>
<td>5</td>
<td>–</td>
<td></td>
<td>CH₃CN</td>
<td>80</td>
<td>24</td>
<td>–&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>(Xantphos)AuCl</td>
<td>5</td>
<td></td>
<td>0.1, (1)</td>
<td>DCE</td>
<td>110</td>
<td>24</td>
<td>–&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>CuCl</td>
<td>5</td>
<td>Xantphos,</td>
<td>1</td>
<td>PhMe</td>
<td>90</td>
<td>12</td>
<td>54-74</td>
</tr>
<tr>
<td>5</td>
<td>(Xantphos)CuCl</td>
<td>5</td>
<td>'BuOLi</td>
<td>0.1, (1)</td>
<td>PhMe</td>
<td>80</td>
<td>4</td>
<td>71&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>(Xantphos)CuCl</td>
<td>5</td>
<td>'BuOLi</td>
<td>1</td>
<td>PhMe</td>
<td>60</td>
<td>30</td>
<td>80&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>(Xantphos)CuCl</td>
<td>5</td>
<td>LiHMDS</td>
<td>1</td>
<td>PhMe</td>
<td>80</td>
<td>24</td>
<td>71&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>(Xantphos)CuCl</td>
<td>5</td>
<td>NaHMDS</td>
<td>1</td>
<td>PhMe</td>
<td>80</td>
<td>5</td>
<td>66&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>9</td>
<td>(Xantphos)CuCl</td>
<td>5</td>
<td>KHMDS</td>
<td>1</td>
<td>PhMe</td>
<td>80</td>
<td>1</td>
<td>–&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>10</td>
<td>(Xantphos)CuCl</td>
<td>5</td>
<td>LiH</td>
<td>1</td>
<td>PhMe</td>
<td>80</td>
<td>36</td>
<td>–&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>11</td>
<td>(Xantphos)CuCl</td>
<td>5</td>
<td>'BuOLi</td>
<td>0.7</td>
<td>PhMe</td>
<td>80</td>
<td>5.5</td>
<td>97</td>
</tr>
</tbody>
</table>

[a] Isolated yield. [b] Complex mixture of products. [c] No reaction was observed, starting materials were recovered. [d] Variable amounts of t-Bu-siloxane was formed. [e] Mixture of double bond isomers was isolated. [f] Reaction did not go to completion. [g] Decomposition was observed. [h] Slow addition of 'BuOLi to the reaction mixture.

The same reaction with NaHMDS as a base was completed in 5 hours. However, product was isolated in reduced yield of 66% due to partial decomposition (entry 8). Furthermore, fast decomposition of reaction mixture was observed by changing countercation to potassium (entry 9). Additionally, generation of a stoichiometric amount of alkoxide by treating alcohol 4-39 with LiH followed by addition of silane 4-61 and (Xantphos)CuCl did not give any product after heating of reaction mixture for 36 h (entry 10).

With these unsatisfactory results we surmised that the formation of undesired siloxane in the reaction with
t-BuOLi could be minimized by slow addition of this base to the reaction medium. Gratifyingly, dehydrogenative coupling in the presence of catalytic amount of (Xantphos)CuCl with the slow addition of substoichiometric amount of t-BuOLi during 5.5 h afforded silyl ether 4-60 in 97% yield without any sign of the formation of t-Bu-siloxane byproduct (entry 11).

4.4.3. Rhenium-Catalyzed Allylic Transposition

With the development of a suitable protocol for the synthesis of silyl ether 4-60, our attention was focused on the subsequent RCM and a key allylic transposition step. Ring closure of 4-60 in the presence of the Grubbs second-generation catalyst and benzoquinone\(^{22}\) proceeded smoothly and delivered 8-membered siloxadiene 4-59 in 96% yield (Scheme 4.4.3.1).

![Scheme 4.4.3.1. Synthesis of Allylic Transposition Precursor](image)

Unfortunately, the allylic transposition of 4-59 was capricious, affording inconsistent results depending on the quality and preparation of Re\(_2\)O\(_7\) catalyst (Table 4.4.3.1). Application of the standard reaction conditions (Re\(_2\)O\(_7\), Et\(_2\)O, r.t., 0.5 h, see chapter 3 for details) for ring contraction of 4-58 afforded 6-membered siloxene 4-58 as an inseparable mixture of \(E/Z\)-isomers in 75:25 ratio (entry 1). We anticipated that lowering the reaction temperature should increase the stereoselectivity of the rearranged product. Hence, cooling the reaction mixture to 0 °C afforded 4-58 in an 81:19 \(E/Z\)-ratio after 2 h (entry 2). Further attempts to decrease the amount of unwanted isomer by performing the reaction below 0 °C resulted in incomplete conversions. The allylic transposition of 4-59 carried out at -7 °C has stopped at 95% conversion, and a 90:10 \(E/Z\)-ratio of 4-58 was observed after 6 h (entry 3). Prolonged reaction time did not improve the conversion and resulted in increased amount of (Z)-4-58. The allylic transposition performed at -25 °C gave only 40% conversion after 6 h due to the significantly decreased solubility of Re\(_2\)O\(_7\) in ether at this temperature (entry 4). Interestingly, the ring contraction with more soluble
Ph₃SiOReO₃ delivered 4-58 as a 1:1 mixture of double bond isomers (entry 5). Additionally, it has been found that the rate of rearrangement depends on the amount of residual perrhenic acid in the catalyst. Thus, Re₂O₇ delivered in closed bottle (Aldrich) was significantly more reactive than that received in sealed ampule (Alfa Aesar). Significant drawback of a more active catalyst is the irreproducibility of transposition as inconsistent results were obtained when different bottles were used. The color of these reagents is also different: pure Re₂O₇ is a yellow crystalline powder, however more reactive form from Aldrich is a greenish solid. Consequently, the allylic transposition with a yellow powder does not proceed below 0 °C. However, reproducible results with this catalyst were obtained by grinding Re₂O₇ to the fine powder and running the allylic transposition at 0 °C for 16 h. Under these reaction conditions 4-58 was obtained in 85% yield and an 85:15 E/Z-ratio on a gram scale (entry 6).

Table 4.4.3.1. Optimization of Ring-Contractive Allylic Transposition

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Catalyst (mol %)</th>
<th>T (°C)</th>
<th>Time (h)</th>
<th>E/Z ratio</th>
<th>Conversion (%)b</th>
<th>Yield (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Re₂O₇</td>
<td>5</td>
<td>25</td>
<td>0.5</td>
<td>75:25</td>
<td>100</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>Re₂O₇</td>
<td>5</td>
<td>0</td>
<td>2</td>
<td>81:19</td>
<td>100</td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td>Re₂O₇</td>
<td>5</td>
<td>-7</td>
<td>6</td>
<td>90:10</td>
<td>95</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>Re₂O₇</td>
<td>5</td>
<td>-25</td>
<td>6</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>Ph₃SiOReO₃</td>
<td>5</td>
<td>0</td>
<td>6</td>
<td>1:1</td>
<td>100</td>
<td>84</td>
</tr>
<tr>
<td>6</td>
<td>Re₂O₇c</td>
<td>10</td>
<td>0</td>
<td>16</td>
<td>85:15</td>
<td>100</td>
<td>85</td>
</tr>
</tbody>
</table>

[a] Isolated yield. [b] Conversion of starting material, determined from of ¹H NMR spectra of crude reaction mixture. [c] High quality Re₂O₇ was used.

4.4.4. Elaboration of Allylic Transposition Product to Epoxyaldehyde Synthetic Intermediate

Although the issues of catalyst reactivity and stereoselectivity for the allylic transposition were addressed, a new obstacle of PMP-ether cleavage suddenly came across; the oxidative deprotection of
4-58 was complicated due to the labile side chain bearing 1,3-diene subunit. Similarly, its reductive cleavage was prohibited by the presence of several conjugated functionalities. Lewis acid-catalyzed protocols were also unsuitable owing to the propensity of the side chain toward isomerization. Therefore, several oxidative protocols were examined (Table 4.4.4.1). The standard conditions employing CAN and NaHCO₃ afforded alcohol 4-64 in 38% yield based on recovered starting material (brsm) after 30 minutes at 0 °C (entry 1). Treatment of the reaction mixture with CAN for a longer period of time led to significant decomposition of starting material. However, the same reaction in the presence of 2-methyl-2-butene as a proton scavenger delivered free alcohol in 70% yield (brsm, entry 2). CAN immobilized on silica gel was less effective, affording product in reduced yield (entry 3).

**Table 4.4.4.1. Optimization of Conditions for PMP-ether Cleavage**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Reagent (equiv)</th>
<th>Additive</th>
<th>Additive (equiv)</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Time (h)</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CAN</td>
<td>2.5</td>
<td>NaHCO₃</td>
<td>8</td>
<td>Acetone/H₂O (9:1)</td>
<td>0</td>
<td>0.5</td>
<td>38&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>CAN</td>
<td>2.5</td>
<td></td>
<td>20</td>
<td>Acetone/H₂O (9:1)</td>
<td>0</td>
<td>0.5</td>
<td>70&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>CAN/SiO₂</td>
<td>2.5</td>
<td></td>
<td>20</td>
<td>Acetone/H₂O (9:1)</td>
<td>0</td>
<td>0.5</td>
<td>62&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>DDQ</td>
<td>1.3</td>
<td>pH = 7</td>
<td>20</td>
<td>DCM</td>
<td>0</td>
<td>0.5</td>
<td>–&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>PIFA</td>
<td>2.5</td>
<td>H₂O</td>
<td>10</td>
<td>CF₃CH₂OH/DCM</td>
<td>0</td>
<td>2</td>
<td>–&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>Ag(pic)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>5</td>
<td>H₂O</td>
<td>10</td>
<td>CF₃CH₂OH/DCM</td>
<td>0</td>
<td>2</td>
<td>–&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>CAN</td>
<td>2.5</td>
<td></td>
<td>20</td>
<td>Acetone/H₂O (9:1)</td>
<td>0</td>
<td>0.5</td>
<td>64&lt;sup&gt;b,d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yield. <sup>b</sup> Based on recovered starting material. <sup>c</sup> Decomposition of the reaction mixture. <sup>d</sup> Reaction on 1.5 mmol scale.

Oxidative cleavage with other oxidants such as DDQ, [bis(trifluoroacetoxy)iodo]benzene (PIFA) or Ag(II) picolinate resulted in decomposition of the substrate (entries 4-6). Based on these preliminary
results, CAN/2-methyl-2-butene combination was employed for carrying the material through this problematic step. Hence, alcohol **4-64** was reproducibly obtained in 64% yield (brsm) on a 1.5 mmol scale (entry 7).

Subsequent elaboration of **4-64** to allylic alcohol **4-34** via a five-step sequence was straightforward. Thus, IBX-mediated oxidation followed by Horner–Wadsworth–Emmons homologation afforded ester **4-65** as a single *E*-stereoisomer in 79% yield (Scheme 4.4.4.1). Consecutive DIBAL-H reduction and Sharpless asymmetric epoxidation\(^{27}\) delivered epoxyalcohol **4-67** as an inseparable mixture of diastereomers (88:12 *dr*). The formation of the observed diastereomers of **4-67** should primarily be the consequence of partial racemization of **4-58** during the allylic transposition (see chapter 3). Oxidation of epoxyalcohol **4-67** was best achieved under Parikh-Doering conditions,\(^{28}\) providing epoxyaldehyde **4-34** in 94% combined yield for 2 steps.

![Chemical reaction diagram]

**Scheme 4.4.4.1. Synthesis of Epoxyaldehyde**

Recognizing the potential difficulties of protodesilylation of unactivated C–Si bond of the 1,3-diene functionality at a later stage of the synthesis, an attempt to prepare desilylated epoxyaldehyde **4-68** was undertaken (Scheme 4.4.4.2). Thus, silyl group removal was achieved at an early stage of the synthetic sequence by treating cyclic siloxene **4-40** with a stoichiometric amount of AgF in a mixed solvent of HF-Py and MeOH at 0 °C to afford a quite unstable homoallylic alcohol **4-69**. Following dehydrogenative
coupling of 4-69 with silane 4-61 under optimized conditions delivered silyl ether 4-70. RCM of 4-70 in the presence of the Grubbs second-generation catalyst was inefficient due to the participation of an E-substituted double bond of 1,3-diene moiety in the metathesis event, leading to the alternative ring closure with the formation of 9-membered silacyclodiene 4-72. Consequently, the inseparable mixture of desired 8-membered product 4-71 and 4-72 was isolated with a 2:1 ratio in addition to other unidentifiable byproducts. Gratifyingly, selective formation of 4-71 was achieved by changing the catalyst to the Grubbs first-generation complex although 15 mol % loading was necessary for the reaction to be completed.

Scheme 4.4.4.2. Exploration of Synthetic Pathway with Intermediates Lacking Trimethylsilyl Group at the 1,3-Diene Moiety

Ring-contractive allylic transposition of obtained siloxadiene 4-71 was only possible upon addition of 2-methyl-2-butene to the reaction medium in order to reduce the acidity of Re₂O₇. Under these reaction conditions 6-membered siloxene 4-73 was formed in variable yields of 40–63%. However, reaction product undergoes fast decomposition if neat and it was not stable toward silica gel purification. Moreover, subsequent attempts to cleave PMP-ether of 4-73 met with failure. These findings indicate that trimethylsilyl group plays a critical role in effective protection of the 1,3-diene moiety from unwanted
metathesis and other side reactions along the synthetic sequence. Therefore, its removal was postponed to the penultimate stage of the synthesis as it was originally planned.

4.4.5. Preparation of the Building Block for Nucleophilic Addition to Epoxidealdehyde and Stability of Organometallic Nucleophiles

Having access to the requisite epoxidealdehyde, we next considered the synthesis of vinyl organometallic reagent for the subsequent nucleophilic addition. To this end, preparation of vinyl bromides bearing either protected carboxylic acid 4-79 or alcohol moiety 4-81 was investigated (Scheme 4.4.5.1). Thus, the copper mediated coupling of 4-pentyn-1-ol 4-75 with 2,3-dibromopropene 4-74 in the presence of tetrabutylammonium chloride afforded enyne 4-76, which was subsequently oxidized with Jones reagent to furnish carboxylic acid 4-77. Next, the 1,3-diene functionality of 4-78 was installed by enyne CM of 4-77 with ethylene in the presence of benzoquinone. Subsequent protection of carboxylic acid moiety with SEM afforded vinyl bromide 4-79.

\[
\begin{align*}
\text{Br} & \quad \text{Br} \quad \text{H}_2\text{C}=\text{CH}_2 \quad \text{K}_2\text{CO}_3, \text{CuI (1 equiv)} \quad \text{Bu}_4\text{NCl (0.5 equiv)} \quad \text{DMF, 50 °C, 20 h} \\
\text{4-74} & \quad \text{4-75} & \quad \text{Br} & \quad \text{4-76 (88%)} & \quad \text{Br} & \quad \text{4-77 (78%)} \\
\text{Br} & \quad \text{Br} & \quad \text{OH} & \quad \text{Br} & \quad \text{Br} & \quad \text{CO}_2\text{H} \\
\text{4-76} & \quad \text{4-78 (67%)} & \quad \text{SEMCl, Et}_3\text{N} \quad \text{THF, 0 °C} \\
\text{4-77 (quant)}
\end{align*}
\]

Scheme 4.4.5.1. Preparation of Building Blocks for Nucleophilic Addition to Epoxidealdehyde

For the preparation of triene 4-81, enyne 4-76 was reacted with ethylene catalyzed by the Grubbs second-generation catalyst and benzoquinone followed by TES-protection of primary alcohol 4-80.

At this point, the stability of vinyl lithium reagents generated by bromide to lithium exchange of the corresponding vinyl bromides was explored. Accordingly, vinyllithium species formed by treating vinyl
bromides with an appropriate amount of \( t \)-BuLi were kept cold for 30 minutes before subsequent protonation with methanol (Scheme 4.4.5.2). It was found that organometallic reagent derived either from triene carboxylic 4-78 or enyne carboxylic acid 4-77 did not yield the anticipated allyl substituted products. Moreover, complete decomposition of 4-78 was observed in less than 10 minutes after addition of three equivalents of \( t \)-BuLi. Similarly, metallation/protonation of protected carboxylic acid 4-79 gave unidentifiable mixture of products. However, vinyl bromide 4-80 possessing a free alcohol moiety delivered triene 4-82 quantitatively upon protonation of the reaction mixture. These findings suggest that the conversion of the alcohol moiety to the carboxylic acid should be carried out after the nucleophilic addition of a vinyl metal reagent to epoxyaldehyde in the synthetic plan.

\[ \text{Scheme 4.4.5.2. Investigation of Stability of Organometallic Nucleophiles} \]

To further explore the reactivity of vinyllithium species derived from protected alcohol 4-81, a test reaction with simple epoxyaldehyde 4-83 was examined (Scheme 4.4.5.3). Treatment of 4-81 with 2 equivalents of \( t \)-BuLi in ether for 10 minutes followed by addition of epoxyaldehyde 4-83 delivered a mixture of diastereomeric epoxyalcohols 4-84 in a 1:1 ratio. In addition a significant amount of byproduct 4-85 resulted from the protonation of vinyllithium species was isolated even though a rigorously dried solvent was used in the reaction.
Scheme 4.4.5.3. Addition of Vinyllithium Reagent to Model Epoxyaldehyde

Although mixed results from the addition of vinyllithium reagent with a model epoxyaldehyde was obtained the reaction between organometallic reagent derived from 4-81 and an advanced epoxyaldehyde intermediate was attempted (Scheme 4.4.5.4). To this end, 4-81 was treated with t-BuLi in ether at -78 °C and the resultant solution was added to a cold solution of epoxyaldehyde 4-34. To our disappointment, significant decomposition of epoxyaldehyde was observed, and epoxyalcohol 4-86 was isolated as a mixture of diastereomers in only 10% yield.

Scheme 4.4.5.4. Addition of Vinyllithium Reagent to Advanced Epoxyaldehyde

In order to improve the efficiency of nucleophilic addition step transmetallation of vinyllithium reagent to other organometallic species such as Grignard or vinylzinc reagents before addition to epoxyaldehyde was investigated. However, only protonated triene 4-85 was obtained in these trials along with recovered epoxyaldehyde. To satisfy our curiosity, oxidation/asymmetric reduction sequence for installation of syn-epohyalcohol functionality was investigated. Thus, 4-86 was oxidized under Parikh-
Doering conditions\textsuperscript{28} and the resultant ketone was subjected to a reduction with (S)-Me-CBS. Unfortunately, syn-epoxyalcohol 4-88 was obtained in low diastereomeric excess (2:1 \textit{dr}).

### 4.4.6. Third Generation Synthetic Approach

Over the course of previously described research on epoxyaldehyde additions, it became evident that a new strategy for the merger of two building blocks was necessary. In particular, requisite C7–C8 bond had to be constructed under essentially neutral reaction conditions. Moreover, a new route that would allow for the stereoselective incorporation of syn-epoxyalcohol subunit was needed since the additions\textsuperscript{7} to epoxyaldehyde 4-34 or reductions\textsuperscript{9} of epoxyketone 4-86 were problematic. Because of these limitations the following modifications in the synthetic plan were devised (Scheme 4.4.6.1).

![Scheme 4.4.6.1. Third Generation Approach for Amphidinolide V](image)

The syn-epoxyalcohol functionality of seco-acid 4-89 was envisaged to be accessed through a reductive opening of iodomethyl-substituted 1,3-diepoxide 4-90, which in turn could be derived from \(\alpha,\beta\)-unsaturated epoxyaldehyde 4-91. This sequence would secure the stereochemistry of the second epoxide
moiety via the Sharpless asymmetric epoxidation.\textsuperscript{27} The key \(\alpha,\beta\)-unsaturated epoxyaldehyde 4-91 was then planned to be prepared via a cross-aldol condensation of epoxyaldehyde 4-34 and donor aldehyde 4-92 bearing a 1,3-diene fragment. To implement this strategy, the efficient synthesis of 4-92 and mild conditions for its direct cross-aldol condensation with the counterpart aldehydes was needed.

4.4.7. Development of a Proline-Mediated Direct Cross-Aldol Condensation of Aldehydes

Our efforts were first directed to the development of a direct cross-aldol condensation of two aldehydes. The main challenge of this transformation was the requirement of suppressing the cross-aldol reaction of both substrates, which otherwise would lead to the formation of \(\beta\)-hydroxycarbonyl compounds (aldols) as well as homo-aldol condensation of the donor aldehyde (Figure 4.4.7.1). In addition, the stereoselectivity of the resulting double bond had to be addressed. Although the direct organocatalytic cross-aldol reaction of two nonequivalent aldehydes is known,\textsuperscript{30} the direct cross-condensation to form \(\alpha,\beta\)-unsaturated aldehyde is limited to the reaction with formaldehyde.\textsuperscript{31} In general, \(\alpha,\beta\)-unsaturated carbonyl compounds, aldol condensation products, form as by-products in the organocatalytic aldol reaction. However, it has been recently proved by mechanistic investigations that in self-condensation of aliphatic aldehydes catalyzed by proline, a reversible aldol reaction competes with an irreversible aldol condensation pathway.\textsuperscript{32}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure4.4.7.1.png}
\caption{Competition between Aldol Reaction and Aldol Condensation}
\end{figure}

Moreover, mechanistic studies indicate that aldol condensations mediated by proline or secondary amines proceed via Knoevenagel–Mannich-type mechanism with second-order dependence of the
reaction rate on the catalyst concentration (Scheme 4.4.7.1).\textsuperscript{31b,32,33} In this mechanism, enamine derived from the donor aldehyde 4-95 reacts with iminium form of the acceptor aldehyde 4-96, generating adduct 4-97. Consecutive elimination of the secondary amine catalyst from this intermediate and hydrolysis of the resultant iminium intermediate 4-98 delivers condensation product 4-99. This mechanistic rationale suggests that the selective formation of $\alpha,\beta$-unsaturated aldehydes is possible under carefully tuned reaction conditions.

![Scheme 4.4.7.1. Knoevenagel–Mannich Mechanism of Aldol Condensation](image)

To achieve selective cross-condensation of two nonequivalent aldehydes, we decided to modify cross-aldol reaction conditions reported by the MacMillan group.\textsuperscript{30a} It is well-known that water plays an important role in aldol reaction assisting hydrolysis of oxazolidinone intermediates 4-100 formed in the catalytic cycle.\textsuperscript{34} The added water resulted in a net effect of an increased rate of aldol reaction and improved enantioselectivity. On the other hand, it has been demonstrated that oxazolidinones are important intermediates within the aldol reaction regime and they may participate in the reaction with electrophiles due to the existence of equilibrium with open iminium form.\textsuperscript{35} Therefore, removal of water
from the reaction medium should increase the amount of iminium ion (4-96) or corresponding oxazolidinone form (4-100) thus facilitating the condensation process.

Based on this idea, the reaction between hexanal and model epoxyaldehyde 4-83 in the presence of 4 Å molecular sieves (MS) with increased loading of L-proline was examined (Table 4.4.7.1). It was found that the addition of molecular sieves had a dramatic effect on the ratio between cross-alaldol and cross-condensation products. Thus, the slow addition of hexanal to epoxyaldehyde 4-83 and 10 mol % of the L-proline in the absence of MS (MacMillan conditions) afforded aldol product 4-101 (5:1 dr) with only a small amount of cross-condensation product 4-102a (entry 1). However, the reaction in the presence MS under otherwise identical conditions gave an equal amounts of 4-101 and 4-102a (entry 2). To our delight, reaction with 50 mol % of L-proline resulted in the formation of a condensation product as a major component of the reaction mixture (entry 3).

**Table 4.4.7.1. Optimization of Conditions for Direct Cross-Aldol Condensation**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Catalyst (mol %)</th>
<th>Additive</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Time (h)</th>
<th>Ratio(^a)</th>
<th>Yield (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L-Proline</td>
<td>10</td>
<td>–</td>
<td>DMF</td>
<td>0</td>
<td>20</td>
<td>11:89</td>
<td>11(^c)</td>
</tr>
<tr>
<td>2</td>
<td>L-Proline</td>
<td>10</td>
<td>MS</td>
<td>DMF</td>
<td>0</td>
<td>20</td>
<td>45:55</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>L-Proline</td>
<td>50</td>
<td>MS</td>
<td>DMF</td>
<td>0</td>
<td>4.5</td>
<td>90:10</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>L-Proline</td>
<td>100</td>
<td>MS</td>
<td>DMF</td>
<td>0</td>
<td>4.5</td>
<td>–</td>
<td>76</td>
</tr>
<tr>
<td>5</td>
<td>L-Proline</td>
<td>100</td>
<td>–</td>
<td>DMF</td>
<td>0</td>
<td>4.5</td>
<td>10:90</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>D-Proline</td>
<td>100</td>
<td>MS</td>
<td>DMF</td>
<td>0</td>
<td>4.5</td>
<td>–</td>
<td>71</td>
</tr>
<tr>
<td>7</td>
<td>L-Proline</td>
<td>100</td>
<td>MS</td>
<td>DMSO</td>
<td>20</td>
<td>4.5</td>
<td>–</td>
<td>60</td>
</tr>
<tr>
<td>8</td>
<td>L-Proline</td>
<td>30</td>
<td>MS</td>
<td>DMSO</td>
<td>20</td>
<td>14</td>
<td>–</td>
<td>59(^d)</td>
</tr>
</tbody>
</table>

[a] Determined from of \(^1\)H NMR spectra of crude reaction mixture. [b] Isolated yield. [c] Aldol 4-101 was also isolated in 55% yield due to its decomposition on silica gel. [d] Slow addition of aldehydes solution to the suspension of the catalyst.
Performing the reaction with a stoichiometric amount of L-proline gave 4-102a (single E-stereoisomer) as a sole product in 76% isolated yield (entry 4). Notably, the self-condensation of hexanal was not observed under these conditions. The same reaction in the absence of molecular sieves gave a similar result to that of the reaction with 10 mol % proline, providing 4-101 as a major product (entry 5). The stereochemistry of proline had negligible effect on the efficiency of the reaction. Thus, cross-condensation employing D-proline delivered \( \alpha,\beta \)-unsaturated aldehyde 4-102a only in slightly reduced yield (entry 6). Cross-condensation in the presence of other proteinogenic \( \alpha \)-amino acids was inefficient.

Performing the reaction in DMSO at 20 °C resulted in the formation of condensation product in 60% yield (entry 7). It has been found that proline strictly differentiate the reacting aldehydes by their electrophilicity difference,\(^{30k.m,n}\) thus, more electrophilic aldehydes participate as acceptor aldehydes whereas less electrophilic \( \alpha \)-unsubstituted aldehydes react solely as a donor component. Hence, in the presence of epoxyaldehyde less electrophilic hexanal reacts exclusively as a donor reaction partner and its homo-condensation was not observed until complete consumption of acceptor counterpart. This property of proline allowed developing catalytic variant of cross-aldol condensation. Thus, slow addition of a DMSO solution containing acceptor aldehyde 4-85 and donor aldehyde in a 1:1.4 ratio respectively to the DMSO suspension of L-proline over 14 hours afforded 4-102a in similar yield (entry 8). Importantly, under these reaction conditions homo-condensation product of hexanal was formed only in trace amounts. Due to the low cost of L-proline, further optimization of catalytic cross-condensation was not performed.

The generality of the direct cross-aldol condensation of two aldehydes was next explored (Table 4.4.7.2). Condensation reactions of 4-83 with \( \alpha \)-unsubstituted aliphatic aldehydes were generally efficient and afforded products with perfect \( E \)-selectivity. Thus, with propanal, \( \alpha,\beta \)-unsaturated epoxyaldehyde 4-102b was obtained in 73% yield (entry 2). However, \( \alpha \)-branched aliphatic aldehydes cannot be employed since they participate in aldol reaction catalyzed by proline only as an acceptor component due to the instability of the intermediate enamines.\(^{30k.m,n}\)
Table 4.4.7.2. Scope of Direct Cross-Aldol Condensation

![Reaction Scheme]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Donor</th>
<th>Product</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt; (%)</th>
<th>Entry</th>
<th>Donor</th>
<th>Product</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-93a</td>
<td>4-102a</td>
<td>76%</td>
<td>6</td>
<td>4-93f</td>
<td>4-102f</td>
<td>69%</td>
</tr>
<tr>
<td>2</td>
<td>4-93b</td>
<td>4-102b</td>
<td>73%</td>
<td>7</td>
<td>4-93g</td>
<td>4-102g</td>
<td>64%</td>
</tr>
<tr>
<td>3</td>
<td>4-93c</td>
<td>4-102c</td>
<td>71%°</td>
<td>8</td>
<td>4-93h</td>
<td>4-102h</td>
<td>69%</td>
</tr>
<tr>
<td>4</td>
<td>4-93d</td>
<td>4-102d</td>
<td>79%</td>
<td>9</td>
<td>4-93i</td>
<td>4-102i</td>
<td>78%</td>
</tr>
<tr>
<td>5</td>
<td>4-93e</td>
<td>4-102e</td>
<td>67%°</td>
<td>10</td>
<td>4-93j</td>
<td>4-102j</td>
<td>19%</td>
</tr>
</tbody>
</table>

[a] Conditions of cross-condensation with aldehydes as a donor component: 1 M solution of donor aldehyde (1–1.5 equiv) in DMF was slowly added via syringe pump to the suspension of acceptor aldehyde, L-proline (1 equiv) and 4 Å MS in DMF at 0 °C over 4.5 h. Conditions of cross-condensation with cyclic ketones as a donor component: 1 M solution of acceptor aldehyde (1 equiv) in DMSO was slowly added via syringe pump to the suspension of ketone (2 equiv), L-proline (1 equiv) and 4 Å MS in DMSO at r.t. over 4.5 h. [b] Isolated yield. [c] Reaction was run with 30 mol % of L-proline.
Moreover, acetaldehyde failed to afford any product due to excessive polymerization. Nevertheless, substitution of acetaldehyde with aromatic moieties (entry 3), or heteroatom functionalities (entries 4, 5) delivered corresponding enals 4-102c-e with good yields. Enal 4-102e was obtained as a single Z-isomer, whereas (Z)-4-102d was formed in 17.5:1 dr. In the case of protected glycolaldehyde (4-93h), a complex mixture of products was observed due to the participation of putative α,β-unsaturated aldehyde in the subsequent condensation. Triisopropylsilyl acetaldehyde (4-93i) underwent desilylation under the reaction conditions to form acetaldehyde, thus giving only polymerization products. Interestingly, reactions of phenylacetaldehyde (entry 3) and imide-protected glycine aldehyde (entry 5) were more efficient with a catalytic (30 mol %) amount of proline rather than under stoichiometric conditions. Due to the ability of proline to distinguish electrophilicity difference between aldehydes 30k,m,n 6-oxoheptanal can be utilized as a donor component (entry 6). In this case cross-condensation product was obtained as a single product in 69% yield despite the facile intramolecular homo-condensation of the ketoaldehyde in the absence of acceptor epoxyaldehyde.

The substrates scope was further explored with ketones as donor components as well as epoxyketones as acceptor coupling partners. Thus, condensation between 4-83 and cyclohexanone under standard conditions was not efficient and only aldol products were observed in the reaction mixture (~ 30%). Yet, under re-optimized conditions, which consist of slow addition of DMSO solution of an acceptor aldehyde to the suspension of ketone (2 equiv), L-proline (1 equiv) and 4 Å MS in DMSO at r.t., condensation product 4-102g was obtained in 64% yield (entry 7). Similarly, 6-membered enones 4-102h and 4-102i derived from tetrahydropyranone and N-methylpiperidone respectively were obtained in good yields (entries 8 and 9). The ring size of cyclic ketones significantly affects aldol condensation efficiency. Thus, reaction of cycloheptanone afforded enone 4-102j in low yield (entry 10). Moreover, condensation of cyclopentanone did not give any product due to decomposition, and linear ketones (4-93j-l) were unreactive. Additionally, 6-membered bicyclic ketones such as camphor (4-93m) or nopinone (4-93n) did not participate in this condensation reaction either. The lack of reactivity was also observed with
epoxyketones as an acceptor coupling partners. Therefore, as oppose to various aliphatic aldehydes, only substituted cyclohexanones can be employed as ketone donor components for direct cross-aldol condensation with epoxyaldehydes. In order to fully exploit the potential of this transformation more investigations are necessary.

4.4.8. Preparation of the Donor Aldehyde and cross-Aldol Condensation

In order to apply the newly developed direct cross-aldol condensation to the synthesis of amphidinolide V, we searched for a route to access a relatively simple donor aldehyde \textit{4-92}. Based on the original retosynthetic plan, the 1,3-diene functionality of this synthetic intermediate could be incorporated by enyne CM. Therefore, an efficient approach to internal alkyne precursor \textit{4-103} was necessary. Unfortunately, getting access to the target compound was elusive despite of considerable attempts (Scheme 4.4.8.1). The direct alkylation\textsuperscript{36} of terminal alkyne \textit{4-104} with a three-carbon containing building block alkyl bromide \textit{4-105} did not give any product as the bromide decomposed under the reaction conditions. Lewis acid-catalyzed conjugate addition\textsuperscript{37} of alkynyl silane \textit{4-106} to ethyl acrylate only returned the alkyne.

\textbf{Scheme 4.4.8.1.} Synthetic Attempts toward the Donor Aldehyde
On the other hand, allylation reactions\textsuperscript{38} of terminal alkyne 4-104 or its SEM-analog were efficient thus corresponding enynes 4-107 and 4-108 were prepared in good yield. Unfortunately, attempted functionalizations of the double bond in 4-107 via epoxidation–rearrangement, hydroboration–oxidation or CM with vinyl boronate\textsuperscript{39} or vinyl silane were fruitless. Similarly, decomposition was observed when 4-108 was subjected to an epoxidation–rearrangement sequence. Additionally, the malonic ester synthesis with propargyl bromide 4-109 was not possible due to instability of the bromide.

To overcome this challenge, a different route based on monosaponification of symmetrical diester 4-112 was developed (Scheme 4.4.8.2). Accordingly, condensation of dimethyl malonate with 1,4-dichloro-2-butyne 4-110 in the presence of K$_2$CO$_3$ afforded tetraester 4-111, which was subjected to the Krapcho\textsuperscript{40} decarboxylation conditions to give diester 4-112. Differentiation of two identical ester functional groups was realized as follows: treatment of 4-112 with 1 equivalent of potassium hydroxide in a methanol-water solution afforded monoacid 4-113 in 54% yield together with equal amounts of diacid and unreacted starting material, which was recycled. Acid 4-113 was then reduced to alcohol 4-114 with NaBH$_4$ through its hydroxybenzotriazole ester.\textsuperscript{41} Enyne CM of 4-114 with ethylene in the presence of benzoquinone\textsuperscript{22} delivered diene 4-115, which was oxidized to donor aldehyde 4-92 using the Parikh-Doering protocol.\textsuperscript{28}

\begin{center}
\includegraphics{Scheme_4.4.8.2.png}
\end{center}

\textbf{Scheme 4.4.8.2.} Preparation of the Donor Aldehyde
Next, direct cross-aldol condensation of 4-92 with acceptor epoxyaldehyde 4-34 was evaluated (Scheme 4.4.8.3). Thus, slow addition of a DMF solution of 4-92 (1.5 equiv, 1 M) via a syringe pump to the suspension of acceptor aldehyde, L-proline (1 equiv) and 4 Å MS in DMF at 0 °C afforded a separable mixture of cross-condensation products (E)-4-91 and (Z)-4-91 in 66% overall yield (E/Z = 12.5:1). Notably, self-condensation of 4-92 was not observed under these conditions.

![Scheme 4.4.8.3. Direct Cross-Condensation of Aldehydes](image)

### 4.4.9. Initial Approach for the Installation of syn-Epoxyalcohol and Macrolactonization

![Figure 4.4.9.1. Two Strategies for Epoxyalcohol Installation and Macrolactonization](image)

At this point, two tactics for elaborating α,β-unsaturated epoxyaldehyde (E)-4-91 to target molecule were considered. Thus, syn-epoxyalcohol moiety could be installed on an acyclic substrate before macrolactonization step, or alternatively, macrocyclization could precede the incorporation of
epoxyalcohol in the synthetic maneuver (Figure 4.4.9.1). The second strategy would require a selective desilylation of diphenylsilyl group in (E)-4-91 in the presence of trimethylsilyl substituent that protects the 1,3-diene moiety through the synthetic sequence (see section 4.4.4).

The implementation of the first approach commenced with the conversion of $\alpha,\beta$-unsaturated epoxyaldehyde (E)-4-91 to an advanced to iodomethyl substituted diepoxide 4-90 via a three-step sequence (Scheme 4.4.9.1). First, the aldehyde moiety was reduced with NaBH$_4$ and then the resultant allylic epoxyalcohol was subjected to the Sharpless asymmetric epoxidation to introduce the second epoxide moiety. Subsequent treatment of the epoxyalcohol with I$_2$/PPh$_3$ delivered 4-90 as a 4:1 mixture of diastereomers. Reductive opening of iododiepoxide was then examined under various conditions. Treatment of 4-90 with Zn/EtOH afforded a rearranged epoxyalcohol 4-89 together with iodohydrin resulting from the opening of the disubstituted epoxide functionality by ZnI$_2$ generated during the reaction in a 1:1 ratio. Analogously, exposure of 4-90 to PPh$_3$/I$_2$ in DMF delivered only iodohydrin as a reaction product. An attempt to close epoxide by treating the iodohydrin with NaH in THF was unsuccessful. Moreover, addition of $t$-BuLi to the diluted solution of diepoxide 4-90 in Et$_2$O at $–120$ °C delivered 4-89 and a $t$-Bu-ketone derived from nucleophilic addition $t$-BuLi on the ester moiety in a 1:2 ratio respectively. To prevent the undesired ketone formation, the methyl ester was saponified with 10 equivalents of Me$_3$SnOH in dichloroethane at 95 °C. The resulting acid was then subjected to the reaction with $t$-BuLi, delivering 4-89 as a sole product in 81% yield.

Once the requisite epoxyalcohol functionality was installed, specific tactics for macrolactonization were considered. Protection of C8 alcohol of 4-89 followed by desilylation to release C13 hydroxyl moiety was necessary for subsequent macrocyclization event. Alternatively, initial desilylation followed by macrolactonization of the acid diol could be explored. Since the rate of ring closure between C1 carboxylic acid and C13 alcohol (14-membered ring formation) is expected to be higher than the rate of C1–C8 macrolactonization (9-membered ring formation) we tested this possibility. Unfortunately, cleavage of both diphenylsilyl and trimethylsilyl groups by treating acid 4-89 with AgF in THF–MeOH–
H$_2$O solvent mixture$^{46}$ gave a complex mixture of products due to the instability of free acid under the reaction conditions. To solve this problem, 4-89 was first converted to methyl ester 4-118 by treating with TMSCHN$_2$ in CH$_2$Cl$_2$-MeOH.

**Scheme 4.4.9.1. Initial Approach for syn-Epoxylcohol Installation and Macrolactonization**

Exposure of 4-118 to AgF in THF–MeOH–H$_2$O solvent mixture delivered the intermediate diol albeit in low yield due to excessive decomposition. Subsequent saponification of methyl ester by treatment with Me$_3$SnOH$^{45}$ in dichloroethane at 95 °C furnished requisite acid diol 4-119. Unfortunately, the attempted ring closure by treating 4-119 with BOP-Cl$^{47}$ and DMAP afforded a mixture of two macrolactones in which 9-membered product 4-120 was formed as major component. Similar result was observed upon exposure of 4-117 to Yamaguchi macrolactonization$^{48}$ conditions, which provided the target molecule (−)-4-01, however, 9-membered lactone 4-120 as well as trichlorobenzoyl esters at C8 were also isolated.
Due to the limited success of macrolactonization with acid diol 4-119, the second tactic was investigated. Because of the sensitivity of synthetic intermediates to Brønsted and Lewis acidic conditions suitable protecting group that can be introduced and subsequently cleaved under neutral reaction conditions was planned. In the literature, azidomethylbenzoyl (AZMB) group\(^{49}\) has been successfully employed in carbohydrate and nucleoside synthesis, which seems to be ideal protecting group possessing the required properties for our system. It could be introduced in the target molecule under various esterification conditions and its cleavage could be affected under essentially mild conditions by treatment with Bu\(_3\)P in dioxane/water mixture. Hence, epoxyalcohol moiety of 4-118 was protected as AZMB-ester under Yamaguchi esterification conditions (Scheme 4.4.9.2). Subsequent desilylation and saponification with Me\(_3\)SnOH\(^{45}\) delivered seco-acid 4-122, which was subjected to Yamaguchi macrolactonization\(^{48}\) conditions to afford AZMB-protected amphidinolide V. Following treatment of 4-123 with Bu\(_3\)P in dioxane at room temperature induced reduction of the azido group, however, formation of the desired product via the elimination of isoindolinone was not observed. Further heating of the reaction mixture to 40 °C resulted in decomposition.

Scheme 4.4.9.2. Protection of syn-Epoxyalcohol and Macrolactonization
4.4.10. Macrolactonization and Completion of the Synthesis

Over the course of the previously described research on installation of syn-epoxyalcohol, its protection/deprotection, as well as the macrolactonization, it became evident that the epoxyalcohol moiety should be introduced after the macrolactonization event. Considering the low yield for the cleavage of both diphenylsilyl and trimethylsilyl groups in a single step, the selective removal of Ph₂Si-group liberating C13 alcohol moiety was required. This task was successfully achieved by treating \((E)-4-91\) with silver fluoride and \(\text{Et}_3\text{N} \cdot 3\text{HF}\), generating \(4-116\) in 77% yield (Scheme 4.4.10.1). Notably the integrity of the entire double bonds array and the epoxyaldehyde moiety remained unchanged under these conditions.

\[ \text{Scheme 4.4.10.1. Macrolactonization and Completion of the Synthesis} \]

At this point, saponification of the methyl ester in the presence of these sensitive functionalities was achieved by treating \(4-116\) with 10 equivalents of \(\text{Me}_3\text{SnOH}\) in dichloroethane at 100 °C for 2.5 h. The
quantitatively obtained sec-o-acid 4-124 was then subjected to the Yamaguchi macrolactonization conditions affording 61% combined yield of macrocyclic epimers along with 6% of a dimeric product. The undesired C13-epimer was separated at this stage, affording macrocycle 4-117 as a single isomer in 50% yield. After reduction of 4-117 with NaBH₄ in MeOH, an asymmetric epoxidation of allylic alcohol 4-125 delivered diepoxide 4-126 as a single diastereomer. Subsequent exposure of 4-126 to I₂/PPh₃ provided iododiepoxide 4-127. The reductive rearrangement of 4-127 was then accomplished by adding t-BuLi to a dilute solution (0.002 M) of 4-127 in Et₂O at –120 °C to afford syn-epoxyalcohol 4-128 in 80% yield. Notably, addition of t-BuLi to a more concentrated solution of iodide 4-127 delivered the desired product 4-128 in much lower yield due to the addition of t-BuLi with the lactone moiety. In comparison, exposure of 4-127 to lithium 4,4’-di-tert-butylbiphenylide (LDBB) in THF gave 4-128 in low yield due to excessive decomposition. The final removal of the trimethylsilyl group was accomplished with the aid of AgF in a solvent mixture of THF–MeOH–H₂O furnishing (–)-amphidinolide V ([α]D²⁵ = –12.6°, c = 0.8, CHCl₃). The spectroscopic data of the synthetic material are identical to those reported.

4.5. Summary

In conclusion, an asymmetric total synthesis of (–)-amphidinolide V has been accomplished in a longest linear sequence of 22 steps from commercially available starting materials with 3.3% overall yield. Synthetic approach illustrates the prowess of the silicon-tethered ring-closing enyne and diene metathesis as well as the allylic transposition of silyl ethers to enable stereoselective construction of 1,3- and 1,5-diene motifs. Moreover, the silicon tethers were utilized as efficient protecting groups along the synthesis whereby the number of unnecessary protecting group manipulations was reduced. Additionally, the direct proline-mediated cross-aldol condensation of two nonequivalent aldehydes has been developed. Employment of this method for cross-condensation of two advanced aldehyde intermediates allowed for the rapid construction of the crucial α,β-unsaturated epoxyaldehyde. This total synthesis demonstrates the potential utility of the newly developed synthetic methods described above for target oriented synthesis.
4.6. Experimental Details

4.6.1. Materials and Methods

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF) and diethyl ether (Et₂O) were dried by distillation from sodium and benzophenone. Methylene chloride (CH₂Cl₂), 1,2-dichloroethane (DCE), toluene (PhMe), triethylamine (Et₃N), acetonitrile (CH₃CN), dimethylformamide (DMF), and dimethylsulfoxide (DMSO), were dried by distillation from calcium hydride. All reactions were monitored by thin-layer chromatography using Silicycle silica gel 60 Å F-254 pre-coated plates (0.25 mm) and were visualized by UV, p-anisaldehyde, or KMnO₄ staining. Flash column chromatography was performed using silica gel 60 Å (32–63 mesh) purchased from Sorbent Technologies. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker Avance DRX-500 or Bruker AV-500 spectrometers. ¹H and ¹³C chemical shifts are referenced to internal solvent resonances (CHCl₃ ¹H, δ = 7.26; CDCl₃ ¹³C, δ = 77.0) and reported relative to SiMe₄; multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet), m (multiplet) and brs (broad signal). Coupling constants, J, are reported in Hertz. Electrospray ionization (ESI) mass spectra were recorded on a Micromass LCT equipped with a time-of-flight analyzer at the Mass Spectrometry Laboratory in the University of Illinois at Urbana-Champaign. Optical rotations were measured on a Jasco P-2000 polarimeter at the Illinois Institute of Technology using a 100 mm path-length cell at 589 nm.

4.6.2. Experimental Procedures

**Characterization Data of Synthetic Intermediates for Amphidinolide V**

**Synthesis of Silane 4-61**

\[
\begin{align*}
\text{Br} & \quad \text{MeO} \quad \begin{array}{c}
\text{OH} \\
\text{K₂CO₃, DMF} \\
r.t., 12 \text{ h}
\end{array} \\
\rightarrow & \quad \text{PMPO\textsubscript{4-64}}
\end{align*}
\]

To a stirred suspension of 4-methoxyphenol (1.75 g, 14.1 mmol) and potassium carbonate (5.0 g, 36.2 mmol) in DMF (20 mL) was added propargyl bromide (1.9 mL, 16 mmol, 80% solution in toluene) and
the reaction mixture was stirred for 12 h at r.t. The reaction mixture was quenched with H₂O (200 mL) and extracted with Et₂O (3 x 50 mL). The combined extracts were washed with NaCl solution (10 wt. %, 2 x 50 mL), dried over MgSO₄, and solvent was removed under vacuum. The residue was purified by flash column chromatography (gradient elution 20:1 → 15:1 hexanes:EtOAc) to afford ether 4-64 (2.28 g, quantitative) as a yellow liquid. ¹H NMR (500 MHz, CDCl₃): δ 6.93 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 4.64 (d, J = 2.2 Hz, 2H), 3.77 (s, 3H), 2.51 (t, J = 2.4 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 154.5, 151.7, 116.1, 114.6, 78.9, 75.3, 56.6, 55.7. Both ¹H and ¹³C NMR spectra match the reported data.¹¹

To a solution of propargyl ether 4-64 (4.60 g, 28.4 mmol) in 100 mL of THF was added "BuLi (11.4 mL, 2.5 M in hexanes, 28.4 mmol) at −78 °C. The resultant solution was warmed to 0 °C and stirred for 30 min. It was then cooled to -30 °C and silane 4-44₁₀ (7.22 g, 28.4 mmol) was added. The reaction mixture was warmed to room temperature, stirred for 8 h, and quenched with saturated NH₄Cl solution. The reaction mixture was extracted with EtOAc (3 × 100 mL), combined extracts were dried over MgSO₄, and solvent was removed under vacuum. The residue was purified by flash column chromatography (gradient elution 100:1 → 50:1 hexanes:EtOAc) to afford alkynylsilane 4-63 (9.17 g, 84%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.64–7.57 (m, 4H), 7.44–7.39 (m, 2H), 7.39–7.33 (m, 4H), 7.00 (d, J = 9.0 Hz, 2H), 6.86 (d, J = 9.0 Hz, 2H), 5.86–5.75 (m, 1H), 4.98–4.87 (m, 2H), 4.77 (s, 2H), 3.79 (s, 3H), 2.16 (d, J = 7.7 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 154.5, 151.7, 134.9, 133.1, 132.7, 129.9, 127.9, 116.7, 115.3, 114.5, 104.8, 87.5, 57.7, 55.7, 21.8; HRMS (ESI) calcd for C₂₅H₂₅O₂Si [M+H]⁺: 385.1624, found 385.1627.
Anhydrous phenol was prepared by distillation from the benzene solution to remove the water/benzene azeotrope and the excess of benzene, followed by distillation of the residue under reduced pressure (bp = 85–86 °C / 20 mm). To a solution of alkynylsilane 4-63 (4.46 g, 11.6 mmol) and phenol (1.15 g, 12.18 mmol, 1.05 equiv) in 115 mL of DCE was added a pre-generated solution of Ph₃PAuSbF₆ (1 mol %), which was prepared by mixing stoichiometric amounts of Ph₃PAuCl (57.5 mg, 0.11 mmol) and AgSbF₆ (39.9 mg, 0.11 mmol) in DCE (1 mL) followed by filtration through a cotton plug to remove precipitated AgCl. The resultant brown solution was stirred at room temperature for 10 min and solvent was removed under reduced pressure. The crude product was purified by gravity column chromatography (gradient elution 100:1 → 35:1 hexanes:EtoAc) to afford vinyl silane 4-62 as a colorless oil (4.53 g, 82%). ¹H NMR (500 MHz, CDCl₃) δ 7.74–7.67 (m, 4H), 7.48–7.35 (m, 6H), 7.17 (t, J = 7.9 Hz, 2H), 6.94 (t, J = 7.3 Hz, 1H), 6.91–6.82 (m, 6H), 6.26 (s, 1H), 5.53–5.41 (m, 1H), 4.94–4.85 (m, 2H), 4.53 (s, 2H), 3.80 (s, 3H), 3.00 (d, J = 6.8 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 157.2, 154.9, 154.0, 152.6, 134.6, 134.8, 134.6, 130.1, 129.3, 128.0, 121.4, 119.9, 118.4, 117.2, 116.0, 114.6, 71.8, 55.7, 38.4; HRMS (ESI) calcd for C₃₁H₃₁O₃Si [M+H]⁺: 479.2042, found 479.2062.

To a solution of phenoxysilane 4-62 (4.53 g, 9.46 mmol) in 100 mL of Et₂O was added Red-Al (8.6 mL, 65 wt.%, 3.3 M in PhMe) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and quenched by addition of Na₂SO₄·10H₂O. The resultant mixture was stirred for additional 10 min and MgSO₄ was added. Formed suspension was stirred for 30 min, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (gradient elution 50:1 → 20:1 hexanes:EtoAc) to give silane 4-61 as a colorless oil (3.27 g, 89%). ¹H NMR (500 MHz, CDCl₃) δ 7.60–7.53 (m, 4H), 7.44–
7.32 (m, 6H), 6.92–6.81 (m, 4H), 6.11 (d, J = 5.5 Hz, 1H), 5.79–5.68 (m, 1H), 5.33 (d, J = 5.1 Hz, 1H),
5.09–4.99 (m, 2H), 4.53 (s, 2H), 3.79 (s, 3H), 3.09 (d, J = 7.0 Hz, 2H); \(^{13}\text{C NMR}\) (125 MHz, CDCl\(_3\)) \(\delta\)
155.3, 154.0, 152.7, 135.3, 135.0, 134.1, 129.6, 128.0, 118.7, 117.0, 115.9, 114.6, 72.2, 55.7, 37.7;
\textbf{HRMS} (ESI) calcd for C\(_{25}\)H\(_{27}\)O\(_2\)Si [M+H]\(^+\): 387.1780, found 387.1789.

\textbf{Synthesis of Allylic Alcohol 4-39}

\[
\begin{align*}
\text{Me}_2\text{SiCl}_2 & \xrightarrow{\text{propyne, } ^{n}\text{BuLi}} \text{Me}_2\text{SiMe} \_2 \text{Si} \\
\text{THF–Et}_2\text{O} & \xrightarrow{\text{Me}_2\text{SiCl}_2} \text{Me}_2\text{SiMe} \_2 \text{Si}
\end{align*}
\]

Dichlorodimethylsilane was redistilled from CaH\(_2\) prior to use. Propyne (bp = −23.2 °C) was condensed
in the round bottom flask at −78 °C to the 6.5 mL volume (4.59 g, 114.5 mmol). Precooled to −78 °C
THF–Et\(_2\)O mixture (1:1, V = 120 mL) was added to the reaction flask via cannula. Under vigorous
stirring \(^{n}\text{BuLi} (45.6 mL, 2.5 M in hexanes, 114 mmol) was slowly added to the resultant solution
producing white precipitate of lithium acetylide. The reaction mixture was slowly warmed to 0 °C and
stirred for 1 h. It was again cooled to −30 °C and dichlorodimethylsilane (4.67 mL, 5.0 g, 38.7 mmol) was
added. The reaction mixture was warmed to r.t. and then refluxed for additional 5 h. After this time the
reaction mixture was cooled to r.t. and quenched with saturated NH\(_4\)Cl solution. Layers were separated
and the aqueous layer was extracted with Et\(_2\)O (2 × 10 mL). Combined organic extracts were dried over
MgSO\(_4\) and solvent was removed under reduced pressure (cold rotavap bath). The crude material was
purified by vacuum distillation (bp = 80 °C / 20 mm) to give silane 4-42 as a colorless oil (4.82 g, 91%).
\(^1\text{H NMR}\) (500 MHz, CDCl\(_3\)) \(\delta\) 1.89 (s, 6H), 0.27 (s, 6H); \(^{13}\text{C NMR}\) (125 MHz, CDCl\(_3\)) \(\delta\) 103.9, 81.0, 5.0,
0.6. Both \(^1\text{H}\) and \(^{13}\text{C}\) NMR spectra match the reported data.\(^{52}\)
Alcohol 4-43 was prepared via modified reported method.\textsuperscript{55} For the efficiency of overall procedure commercial \(\text{Ag}_2\text{O}\) has to be rigorously dried by heating at 140 °C in high vacuum (0.5 mm) for 2 days (time is not optimized). After that \(\text{Ag}_2\text{O}\) can be stored in the glovebox.

**Preparation of the catalyst:** Solution of \((i-\text{PrO})_3\text{TiCl}\) (1.5 mL, 1 M in hexanes, 1.5 mmol) was diluted with 30 mL of freshly redistilled \(\text{CH}_2\text{Cl}_2\). To the resultant solution was added \(\text{Ag}_2\text{O}\) (173.8 mg, 0.75 mmol) and the reaction mixture was stirred for 7 h at room temperature under exclusion of light. After this time precipitate changed color from brown to grey. \((S)\)-BINOL (430 mg, 1.5 mmol) was then added and the reaction mixture was stirred for 2 h producing orange-red solution. At this point TLC analysis indicated only small amount (< 5%) of free \((S)\)-BINOL in the reaction mixture.

**Asymmetric allylation:** The generated solution of catalyst was cooled to –15 °C and trans-cinnamaldehyde (945 µL, 7.5 mmol) and allyltributyltin (2.6 mL, 8.3 mmol) were added sequentially. The reaction mixture was warmed to 0 °C and kept at this temperature for 2 days without stirring. The reaction mixture was quenched with saturated \(\text{NaHCO}_3\) solution and extracted with \(\text{CH}_2\text{Cl}_2\) (2 x 20 mL). Combined organic extracts were dried over \(\text{MgSO}_4\) and concentrated. The residue was purified by gravity column chromatography (gradient elution 15:1 → 5:1 hexanes:EtOAc) to afford alcohol 4-43 (1.24 g, 95%, >95% \(ee\)) as a colorless liquid. The enatiomeric excess of product was determined by derivatization with \((-\text{)-chloromenthoxypiphenylsilane according to the reported procedure.}\textsuperscript{54} \(\text{^1H NMR}\) (500 MHz, \(\text{CDCl}_3\)) \(\delta\) 7.41–7.37 (m, 2H), 7.35–7.30 (m, 2H), 7.27–7.22 (m, 1H), 6.62 (d, \(J = 15.9\) Hz, 1H), 6.25 (dd, \(J = 15.9\) Hz, \(J = 6.4\) Hz, 1H), 5.92–5.82 (m, 1H), 5.23–5.15 (m, 2H), 4.40–4.34 (m, 1H), 2.49–2.35 (m, 2H), 1.85–1.81 (m (OH), 1H); \(\text{^13C NMR}\) (125 MHz, \(\text{CDCl}_3\)) \(\delta\) 136.6, 134.0, 131.6, 130.3, 128.5, 127.6, 126.5, 118.5, 71.7, 42.0. Both \(\text{^1H}\) and \(\text{^13C}\) NMR spectra match the reported data.\textsuperscript{55}
Silane 4-42 (2.35 g, 17.22 mmol) and alcohol 4-43 (1.50 g, 8.61 mmol) were dissolved in hexanes–THF mixture (12:1, 150 mL). Sodium hydride (20.6 mg, 0.86 mmol) was added, and the reaction mixture was stirred at room temperature overnight. The solvent was evaporated on rotavapor and excess of silane was distilled from residue in cold trap (−78 °C) under high vacuum (0.4 mm Hg). The crude product was dissolved in hexanes (10 mL) and filtered through short layer of silica gel. The solvent was evaporated under reduced pressure to afford silyl ether 4-41 (2.24 g, 96%) as a pale yellow liquid. Product contained ~5% of inseparable symmetrical silaketal. ¹H NMR (500 MHz, CDCl₃) δ 7.41–7.37 (m, 2H), 7.34–7.29 (m, 2H), 7.26–7.21 (m, 1H), 6.56 (d, J = 15.9 Hz, 1H), 6.23 (dd, J = 15.9 Hz, J = 6.4 Hz, 1H), 5.92–5.81 (m, 1H), 5.14–5.06 (m, 2H), 4.53–4.47 (m, 1H), 2.49–2.35 (m, 2H), 1.89 (s, 3H), 0.28 (s, 3H), 0.25 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 137.0, 134.7, 131.9, 129.8, 128.5, 127.4, 126.5, 117.0, 103.6, 82.2, 73.9, 42.6, 4.8, 1.0, 0.8; HRMS (ESI) calcd for C₁₇H₂₂OSiNa [M+Na]⁺: 293.1338, found 293.1340.

To a solution of silyl ether 4-41 (2.23 g, 8.25 mmol) in 825 mL of CH₂Cl₂ (0.01 M) was added the Grubbs 1st generation catalyst (PCy₃)₂Cl₂Ru=CHPh (1.02 g, 1.23 mmol, 15 mol%). Ethylene was then passed through the solution for 25 min followed by argon for 30 min to remove excess of ethylene. The reaction mixture was refluxed at 55 °C for 12 h and solvent was evaporated under reduced pressure. The residue was quickly purified by flash column chromatography (50:1 hexanes:EtOAc) to afford red-brown liquid. In order to remove ruthenium by-products generated during the reaction the crude material was dissolved in 10 mL of CH₂Cl₂ and 1 mL of DMSO was added. Resultant solution was stirred at r.t. for 12 h and concentrated under reduced pressure. The residue was purified by gravity column chromatography (gradient elution 50:1 → 30:1 hexanes:EtOAc) to afford siloxene 4-40 (1.97 g, 88%) as a
yellow liquid. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.43–7.39 (m, 2H), 7.35–7.29 (m, 2H), 7.26–7.22 (m, 1H), 6.68–6.62 (m, 2H), 6.31 (dd, $J = 15.8$ Hz, $J = 5.9$ Hz, 1H), 4.99 (s, 1H), 4.83 (s, 1H), 4.60–4.55 (m, 1H), 2.51–2.37 (m, 2H), 1.91 (s, 3H), 0.40 (s, 3H), 0.38 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 144.5, 140.1, 139.7, 136.8, 131.6, 129.8, 128.4, 127.4, 126.5, 113.8, 71.3, 36.5, 20.8, 0.3, 0.1; HRMS (ESI) calcd for C$_{17}$H$_{23}$OSi [M+H]$^+$: 271.1518, found 271.1503.

To a solution of siloxene 4-40 (976 mg, 3.61 mmol) in 35 mL of THF was added MeLi (2.7 mL, 1.6 M in Et$_2$O, 4.33 mmol, 1.2 equiv) at −50 °C and the reaction mixture was stirred at this temperature for 1.5 h. The reaction mixture was quenched cold with MeOH followed by saturated NH$_4$Cl solution and extracted with EtOAc (3 x 10 mL). Combined organic extracts were dried over MgSO$_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (gradient elution 50:1 → 20:1 hexanes:EtOAc) to afford alcohol 4-39 (2.28 g, 80%) as a colorless liquid. [α]$^2_5$ = −5.8° (0.08, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.42–7.37 (m, 2H), 7.35–7.30 (m, 2H), 7.27–7.22 (m, 1H), 6.61 (d, $J = 16.0$ Hz, 1H), 6.25 (dd, $J = 16.0$ Hz, $J = 6.4$ Hz, 1H), 6.04 (t, $J = 7.4$ Hz, 1H), 4.71–4.67 (m, 1H), 4.50–4.48 (m, 1H), 4.40–4.33 (m, 1H), 2.57–2.35 (m, 2H), 1.78 (s, 3H), 1.77–1.72 (brs, 1H), 0.19 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 151.0, 149.0, 137.1, 136.7, 131.7, 130.4, 128.6, 127.7, 126.5, 109.5, 72.6, 39.7, 24.7, 0.6; HRMS (ESI) calcd for C$_{18}$H$_{27}$OSi [M+H]$^+$: 287.1831, found 287.1826.

Dehydrogenative Coupling and Synthesis of Epoxyaldehyde 4-34

Preparation of the catalyst. (Xantphos)CuCl was prepared analogously to the reported procedure for synthesis of (Xantphos)CuI.$^{57}$ To a suspension of dry CuCl (108.9 mg, 1.1 mmol) in CH$_2$Cl$_2$ (10 mL) was
added Xantphos (578.6 mg, 1.0 mmol) and resultant clear solution was stirred for 10 min. The solvent
was removed under vacuum and the precipitated solid was triturated in dry and degassed acetonitrile (3
mL). The suspension was vigorously stirred for 4 h and filtered using Schlenk filter funnel under Ar
atmosphere. The wet cake was washed with acetonitrile (3 x 5 mL) and dried under vacuum to afford an
off-white powder (631.8 mg, 93%). \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \( \delta \) 7.52 (d, \( J = 7.3 \text{ Hz} \), 2H), 7.45–7.37
(m, 8H), 7.32–7.25 (m, 4H), 7.24–7.18 (m, 8H), 7.08 (t, \( J = 7.7 \text{ Hz} \), 2H), 6.60–6.53 (m, 2H), 1.67 (s, 6H);
\textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \( \delta \) 154.5 (t, \( J = 6.0 \text{ Hz} \), 133.7 (t, \( J = 7.9 \text{ Hz} \), 133.1, 131.4 (t, \( J = 17.6 \text{ Hz} \),
129.7, 128.5 (t, \( J = 5.1 \text{ Hz} \), 126.6, 124.7, 119.9 (t, \( J = 13.9 \text{ Hz} \), 35.7, 28.3. An Ar-C cannot be identified
because of overlapping. Both \textsuperscript{1}H and \textsuperscript{13}C NMR spectra match the reported data.\textsuperscript{58}

**Dehydrogenative coupling:** To a solution of alcohol \textsuperscript{43}9 (1.0 g, 3.49 mmol) and silane \textsuperscript{46}1 (1.48 g,
3.84 mmol, 1.1 equiv) in 100 mL of toluene was added (Xantphos)CuCl (118.3 mg, 0.175 mmol, 5 mol
%) and the reaction flask was placed in the preheated to 85 °C oil bath. Solution of \( t \)-BuOLi (195.6 mg,
2.44 mmol, 0.7 equiv) in 30 mL of toluene was slowly added to the reaction mixture via syringe pump
over 5.5 h. After this time the reaction mixture was cooled to r.t. and quenched with saturated NH\textsubscript{4}Cl
solution. Layers were separated and water layer was extracted with EtOAc (3 x 10 mL). Combined
organic extracts were dried over MgSO\textsubscript{4}, concentrated under reduced pressure, and the residue was
quickly purified by flash column chromatography to afford pale yellow oil. In order to remove unreacted
silane \textsuperscript{46}1, it was converted to silanol\textsuperscript{59} as follows: the crude product was dissolved in 15 mL of CH\textsubscript{3}CN
and [RuCl\textsubscript{2}(p-cymene)]\textsubscript{2} (21.4 mg, 0.035 mmol, 10 mol % relative to excess of silane used) was added
followed by addition of 100 \( \mu \text{L} \) of H\textsubscript{2}O. The reaction mixture was heated to 80 °C and stirred for 2 h. The
reaction mixture was then cooled to r.t. and solvent was evaporated under vacuum. The residue was
purified by gravity column chromatography (gradient elution 150:1 \( \rightarrow \) 50:1 hexanes:EtOAc) to afford
silyl ether \textsuperscript{46}0 (2.27 g, 97%) as a colorless oil. \([\alpha]^{25}_D = -28.5^\circ \) (0.97, CHCl\textsubscript{3}); \textsuperscript{1}H NMR (500 MHz,
CDCl\textsubscript{3}) \( \delta \) 7.66–7.61 (m, 4H), 7.43–7.31 (m, 6H), 7.30–7.25 (m, 2H), 7.24–7.19 (m, 3H), 6.86–6.79 (m,
4H), 6.29 (d, \( J = 15.9 \text{ Hz} \), 1H), 6.19 (d, \( J = 1.5 \text{ Hz} \), 1H), 6.13 (ddd, \( J = 15.9 \text{ Hz} \), \( J = 7.1 \text{ Hz} \), \( J = 1.3 \text{ Hz} \),
1H), 6.02 (dt, $J = 7.3$ Hz, $J = 1.3$ Hz, 1H), 5.56–5.47 (m, 1H), 4.92–4.84 (m, 2H), 4.66 (s, 1H), 4.49–4.41 (m, 4H), 3.78 (s, 3H), 2.97 (d, $J = 7.0$ Hz, 2H), 2.61–2.53 (m, 1H), 2.50–2.42 (m, 1H), 1.74 (s, 3H), 0.13 (d, $J = 1.4$ Hz, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 155.8, 153.9, 152.7, 151.2, 147.0, 138.0, 136.9, 135.9, 135.7, 135.12, 135.05, 134.92, 132.0, 130.3, 129.79, 129.75, 128.4, 127.8, 127.4, 126.4, 120.1, 117.0, 115.9, 114.5, 109.3, 74.8, 72.0, 55.7, 40.3, 38.3, 24.7, 0.5; HRMS (ESI) calcd for C$_{43}$H$_{50}$O$_3$Si$_2$Na [M+Na]$^+$: 693.3196, found 693.3188.

![Chemical structure](image)

To a solution of vinyl silane 4-60 (1.59 g, 2.37 mmol) in CH$_2$Cl$_2$ (475 mL, 0.005 M) were added the Grubbs 2nd generation catalyst (SImes)(PCy$_3$)$_2$Ru=CHPh (100.5 mg, 0.118 mmol, 5 mol%) and 1,4-benzoquinone (51.2 mg, 0.47 mmol, 20 mol%). The reaction mixture was refluxed at 40 °C for 12 h and then concentrated under reduced pressure. The residue was purified by gravity column chromatography (gradient elution 150:1 → 50:1 hexanes:EtOAc) to afford eight-membered siloxacycle 4-59 as a colorless oil (1.29 g, 96%). $\left[\alpha\right]_D^{25} = +10.2^\circ$ (0.93, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.67–7.62 (m, 2H), 7.58–7.53 (m, 2H), 7.43–7.31 (m, 6H), 6.94–6.90 (m, 2H), 6.89–6.84 (m, 2H), 6.14 (s, 1H), 6.07 (t, $J = 7.3$ Hz, 1H), 5.90–5.83 (m, 1H), 5.51 (dd, $J = 11.0$ Hz, $J = 4.8$ Hz, 1H), 4.72–4.69 (m, 1H), 4.61–4.56 (m, 3H), 4.51 (d, $J = 1.8$ Hz, 1H), 3.80 (s, 3H), 3.61 (dd, $J = 13.0$ Hz, $J = 8.4$ Hz, 1H), 2.86 (dd, $J = 13.0$ Hz, $J = 9.1$ Hz, 1H), 2.62–2.55 (m, 1H), 2.50–2.43 (m, 1H), 1.79 (s, 3H), 0.16 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 157.6, 154.0, 152.7, 151.2, 147.0, 138.6, 136.1, 135.1, 134.6, 134.1, 130.6, 129.9, 129.6, 127.8, 127.6, 121.1, 116.0, 114.6, 109.3, 73.9, 71.7, 55.7, 40.0, 30.6, 24.7, 0.6; HRMS (ESI) calcd for C$_{35}$H$_{43}$O$_3$Si$_2$ [M+H]$^+$: 567.2751, found 567.2753.
Commercial rhenium(VII) oxide was grounded to the fine powder in the glovebox prior to reaction. Eight-membered cyclic siloxadiene 4-59 (1.5 g, 2.65 mmol) was dissolved in ether (17.6 mL, 0.15 M) inside of the glovebox and solution was cooled to -20 °C. Rhenium(VII) oxide (128.2 mg, 0.26 mmol, 10 mol %) was added and the reaction flask was sealed. The reaction flask was taken out of the glovebox and placed into an insulated box filled with ice. The reaction mixture was stirred at 0 °C for 16 h and quenched with Et$_3$N (0.5 mL). The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (gradient elution 50:1 → 15:1 hexanes:EtOAc) to yield six-membered siloxene 4-58 as a yellow oil (1.28 g, 85%). Siloxene 4-58 was obtained as inseparable mixture of double bond isomers (E/Z = 85:15). The major isomer is designated by (*), the minor isomer is denoted by (†). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.67–7.61 (m, 2H*, 2H†), 7.61–7.56 (m, 2H*, 2H†), 7.48–7.32 (m, 6H*, 6H†), 6.92–6.82 (m, 4H*, 4H†), 6.23 (s, 1H*, 1H†), 5.97 (t, $J = 7.5$ Hz, 1H*), 5.82–5.72 (m, 1H*, 1H†), 5.71–5.61 (m, 1H*, 2H†), 4.86 (s, 1H†), 4.70 (s, 1H*), 4.68–4.62 (m, 1H*, 1H†), 4.55–4.46 (m, 3H*, 2H†), 4.42 (s, 1H†), 3.79 (s, 3H*, 3H†), 2.93–2.87 (m, 2H*), 2.87–2.82 (m, 2H†), 2.45 (ddd, $J = 17.2$ Hz, $J = 10.1$ Hz, $J = 1.2$ Hz, 1H*, 1H†), 2.34 (dd, $J = 17.2$ Hz, $J = 2.7$ Hz, 1H*, 1H†), 1.79 (s, 3H*), 1.76 (s, 3H†), 0.18 (s, 9H*), 0.10 (s, 9H†); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 155.9, 154.0, 152.6, 151.0, 146.2, 139.4, 135.7†, 135.1, 134.9, 134.7, 134.5, 132.6, 132.2†, 130.1, 130.0, 129.9†, 129.5, 127.9, 127.8, 118.0, 115.9, 114.6, 110.3†, 109.4, 73.6, 72.4, 55.7, 36.7, 34.4, 32.7†, 24.7, 24.4†, 0.5, -1.5†; HRMS (ESI) calcd for C$_{35}$H$_{43}$O$_3$Si$_2$ [M+H]$^+$: 567.2751, found 567.2751.
To a solution of siloxene 4-58 (1.0 g, 1.76 mmol) in acetone–H₂O mixture (25 mL, 9:1) were added 2-methyl-2-butene (3.74 mL, 20 equiv) and CAN (2.9 g, 5.29 mmol, 3 equiv) sequentially at 0 °C. The reaction mixture was stirred for 20 min and quenched with Et₃N (3 mL). The solvent was evaporated under reduced pressure and the residue was dissolved in CH₂Cl₂ (15 mL). The solution was dried over MgSO₄ and concentrated under vacuum. Crude reaction mixture was purified by flash column chromatography (gradient elution 30:1 → 5:1 hexanes:EtOAc) to afford alcohol 4-64 (427 mg, 53%) as a yellow oil and recovered starting material (179 mg) which was re-subjected to the reaction conditions (BORSM 64%). Alcohol 4-64 was obtained as inseparable mixture of double bond isomers formed during allylic transposition step. The major isomer is designated by (*), the minor isomer is denoted by (†).

**¹H NMR** (500 MHz, CDCl₃) δ 7.67–7.63 (m, 2H*, 2H†), 7.63–7.59 (m, 2H*, 2H†), 7.47–7.33 (m, 6H*, 6H†), 6.14 (d, J = 2.0 Hz, 1H*, 1H†), 5.96 (t, J = 7.5 Hz, 1H*), 5.82–5.71 (m, 1H*, 1H†), 5.69–5.59 (m, 1H*, 2H†), 4.86 (dd, J = 2.3 Hz, J = 1.4 Hz, 1H†), 4.69 (dd, J = 2.5 Hz, J = 1.4 Hz, 1H*), 4.65–4.58 (m, 1H*, 1H†), 4.50 (d, J = 1.8 Hz, 1H*), 4.41 (d, J = 1.5 Hz, 1H†), 4.13 (s, 2H*, 2H†), 2.92–2.87 (m, 2H*), 2.87–2.82 (m, 2H†), 2.36 (ddd, J =17.2 Hz, J =10.3 Hz, J = 2.1 Hz, 1H*, 1H†), 2.19 (dd, J =17.2 Hz, J =2.6 Hz, 1H*, 1H†), 1.78 (s, 3H*), 1.75 (s, 3H†), 1.74–1.66 (brs, 1H*, 1H†), 0.17 (s, 9H*), 0.09 (s, 9H†);

**¹³C NMR** (125 MHz, CDCl₃) δ 160.1, 151.0, 146.2, 139.4, 135.7†, 135.3, 134.8, 134.7, 134.6, 132.6, 132.2†, 130.1, 130.0, 129.9†, 129.4, 127.9, 127.8, 114.3, 110.3†, 109.3, 72.5, 67.7, 36.8, 34.4, 32.6†, 24.7, 24.4†, 0.5, -1.5†; **HRMS** (ESI) calcd for C₂₈H₃₇O₂Si₂ [M+H]⁺: 461.2332, found 461.2325.
Oxidation: To a solution of alcohol 4-64 (2.09 g, 4.54 mmol) in 15 mL of DMSO was added IBX (2.54 g 9.08 mmol, 2 equiv) at r.t. and the reaction mixture was stirred for 1 h. After this time the reaction mixture was cooled to 0 °C and diluted with Et₂O (30 mL) and NaCl solution (10 wt. %, 50 mL). After separation of layers organic extract was washed with NaCl solution (10 wt. %, 3 x 10 mL) and combined aqueous phase was extracted with Et₂O (1 x 15 mL). Ether extracts were dried over MgSO₄ and concentrated under reduced pressure to give crude aldehyde as a colorless oil.

Olefination: To a solution of triethyl phosphonoacetate (1.82 mL, 9.08 mmol) in 25 mL of THF was added NaHMDS (1.67 g, 9.08 mmol) at 0 °C and the reaction mixture was stirred for 30 min. The reaction mixture was cooled to –78 °C and transferred to a cold (~78 °C) solution of crude aldehyde in 50 mL of THF via cannula. The reaction mixture was slowly warmed to 0 °C over 3 h and quenched with saturated NH₄Cl solution. The crude product was extracted with CH₂Cl₂ (3 x 20 mL), combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (gradient elution 50:1 → 30:1 hexanes:EtOAc) to afford ester 4-65 (1.9 g, 79%) as a pale yellow oil. Ester 4-65 was obtained as inseparable mixture of double bond isomers formed during allylic transposition step. The major isomer is designated by (*), the minor isomer is denoted by (†). ¹H NMR (500 MHz, CDCl₃) δ 7.67–7.62 (m, 2H*, 2H†), 7.60–7.56 (m, 2H*, 2H†), 7.49–7.34 (m, 7H*, 7H†), 6.48 (s, 1H*, 1H†), 6.03–5.94 (m, 2H*, 1H†), 5.84–5.72 (m, 1H*, 1H†), 5.71–5.61 (m, 1H*, 2H†), 4.86 (dd, J = 2.2 Hz, J = 1.5 Hz, 1H†), 4.69 (dd, J = 2.5 Hz, J = 1.4 Hz, 1H*), 4.68–4.61 (m, 1H*, 1H†), 4.50 (d, J = 1.8 Hz, 1H*), 4.41 (d, J = 1.5 Hz, 1H†), 4.24 (q, J = 7.1 Hz, 2H*, 2H†), 2.93–2.88 (m, 2H*), 2.88–2.83 (m, 2H†), 2.57–2.46 (m, 2H*, 2H†), 1.79 (s, 3H*), 1.76 (s, 3H†), 1.31 (t, J = 7.2 Hz, 3H*, 3H†), 0.18 (s, 9H*), 0.09 (s, 9H†); ¹³C NMR (125 MHz, CDCl₃) δ 166.9, 153.2, 151.0, 147.9, 146.4, 145.8†, 139.2, 135.6†, 134.9, 134.7, 134.2, 133.6, 132.5, 132.3, 131.9†, 130.5, 130.3, 130.2†,
To a solution of ester 4-65 (1.9 g, 3.59 mmol) in 30 mL of THF was added DIBAL-H (9 mL, 1 M in toluene, 8.99 mmol, 2.5 equiv) at -78 °C. The reaction mixture was warmed to -50 °C and stirred at this temperature for 1.5 h. After this time the reaction mixture was quenched with MeOH followed by saturated solution of sodium potassium tartrate (20 mL). The reaction mixture was stirred at r.t. for 30 min and extracted with EtOAc (3 x 15 mL). Combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (gradient elution 10:1 → 3:1 hexanes:EtOAc) to afford alcohol 4-66 (1.59 g, 91%) as a colorless oil. Alcohol 4-66 was obtained as inseparable mixture of double bond isomers formed during allylic transposition step. The major isomer is designated by (*), the minor isomer is denoted by (†).

**1H NMR** (500 MHz, CDCl₃) δ 7.68–7.63 (m, 2H*, 2H†), 7.62–7.57 (m, 2H*, 2H†), 7.48–7.32 (m, 6H*, 6H†), 6.41 (d, J = 16.0 Hz, 1H*, 1H†), 6.05 (s, 1H*, 1H†), 6.02–5.93 (m, 2H*, 1H†), 5.82–5.62 (m, 2H*, 3H†), 4.86 (dd, J = 2.3 Hz, J = 1.4 Hz, 1H†), 4.69 (dd, J = 2.5 Hz, J = 1.4 Hz, 1H*), 4.66–4.59 (m, 1H*, 1H†), 4.50 (d, J = 1.8 Hz, 1H*), 4.41 (d, J = 1.5 Hz, 1H†), 4.31–4.21 (m, 2H*, 2H†), 2.93–2.87 (m, 2H*), 2.87–2.82 (m, 2H†), 2.55 (dd, J = 17.1 Hz, J = 2.8 Hz, 1H*, 1H†), 2.47 (ddd, J = 17.1 Hz, J = 10.0 Hz, J = 1.5 Hz, 1H*, 1H†), 1.79 (s, 3H*), 1.76 (s, 3H†), 1.49–1.43 (brs, 1H*, 1H†), 0.18 (s, 9H*), 0.09 (s, 9H†); **13C NMR** (125 MHz, CDCl₃) δ 154.7, 151.0, 146.2, 139.4, 135.8, 135.1, 134.9, 134.7, 134.5, 132.7, 132.3†, 130.2, 130.1, 130.0†, 129.5, 128.8, 128.0, 127.8, 123.4, 110.3†, 109.4, 72.6, 63.4, 36.0, 34.4, 32.7†, 24.7, 24.4†, 0.5, -1.5†; **HRMS** (ESI) calcd for C₃₀H₃₅O₂Si₂ [M+H]+: 487.2489, found 487.2477.
Epoxidation: To a suspension of activated molecular sieves (MS 4Å) in CH$_2$Cl$_2$ (750 mg in 8 mL) and (–)-d-DIPT (57.7 mg, 0.246 mmol, 15 mol %) was added Ti(i-PrO)$_4$ (48.5 µL, 0.164 mmol, 10 mol %) at 0 °C. The reaction mixture was cooled to –20 °C and solution of t-BuOOH (480 µL, 5.5 M in decane, 1.6 equiv) was added. The reaction mixture was stirred at –20 °C for 30 min and transferred to a cold (-20 °C) suspension of alcohol 4-66 (800 mg, 1.64 mmol) and MS (750 mg) in 8.5 mL of CH$_2$Cl$_2$ via a cannula. The reaction flask was sealed and the reaction mixture was kept at –20 °C in freezer for 12 h without stirring. After this time the reaction mixture was filtered through a pad of celite, quenched with FeSO$_4$ solution (30 wt. %), and extracted with EtOAc (3 x 20 mL). The combined organic extracts were concentrated under reduced pressure and the residue was purified by flash column chromatography (gradient elution 5:1 → 3:1 hexanes:EtOAc) to yield epoxyalcohol 4-67 (844 mg) as a mixture with (–)-d-DIPT. Epoxyalcohol 4-67 was obtained as inseparable mixture of double bond diastereomers and epimers at the allylic ether stereogenic center. The minor isomers are denoted by (†). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.66–7.61 (m, 2H), 7.61–7.56 (m, 2H), 7.48–7.33 (m, 6H), 6.31 (d, $J = 1.8$ Hz, 1H†), 6.25 (d, $J = 1.8$ Hz, 1H), 5.94 (t, $J = 7.5$ Hz, 1H), 5.81–5.69 (m, 1H), 5.68–5.56 (m, 1H), 4.85 (s, 1H†), 4.69 (s, 1H), 4.65–4.55 (m, 1H), 4.49 (d, $J = 1.7$ Hz, 1H), 4.41 (s, 1H†), 4.02–3.94 (m, 1H), 3.77–3.68 (m, 1H), 3.53 (d, $J = 1.8$ Hz, 1H†), 3.50 (d, $J = 1.7$ Hz, 1H), 3.19 (dt, $J = 4.1$ Hz, $J = 2.1$ Hz, 1H†), 3.10 (dt, $J = 4.2$ Hz, $J = 2.3$ Hz, 1H), 2.91–2.85 (m, 2H), 2.85–2.81 (m, 2H†), 2.35 (ddd, $J = 17.4$ Hz, $J = 9.8$ Hz, $J = 2.0$ Hz, 1H), 2.23 (ddd, $J = 13.7$ Hz, $J = 12.0$ Hz, $J = 2.8$ Hz, 1H†), 2.17 (dd, $J = 17.4$ Hz, $J = 2.7$ Hz, 1H), 1.83–1.76 (m, 4H), 1.75 (s, 3H†), 0.17 (s, 9H), 0.08 (s, 9H†); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 155.5, 151.0, 146.3, 145.8†, 139.3, 135.6†, 134.8, 134.6, 134.3, 132.4, 132.0†, 130.2, 130.1, 129.7, 129.5†, 128.0, 127.9, 122.3†, 119.9, 110.3†, 109.4, 72.7†, 72.6, 72.4†, 61.2, 59.1, 58.8†, 58.2, 57.8†,
35.1, 34.3, 34.0†, 32.6†, 24.7, 24.4†, 0.5, -1.5†; HRMS (ESI) calcd for C$_{30}$H$_{39}$O$_3$Si$_2$ [M+H]$^+$: 503.2438, found 503.2430.

**Oxidation:** To a solution of crude epoxyalcohol 4-67, DMSO (2.3 mL, 32.9 mmol 20 equiv), and Et$_3$N (2.3 mL, 16.4 mmol, 10 equiv) in 7 mL of CH$_2$Cl$_2$ was added SO$_3$•Py (1.3 g, 8.22 mmol, 5 equiv) at 0 °C. The reaction mixture was warmed to 10 °C, stirred at this temperature for 3 h, and quenched with H$_2$O (15 mL). EtOAc (40 mL) was then added to the reaction mixture. After separation of layers organic extract was washed with NaCl solution (10 wt.%, 3 x 10 mL) and combined aqueous phase was extracted with EtOAc (1 x 10 mL). The EtOAc extracts were dried over MgSO$_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (gradient elution 10:1 → 3:1 hexanes:EtOAc) to yield epoxyaldehyde 4-34 (773 mg, 94%) as a pale yellow oil. Epoxyaldehyde 4-34 was obtained as inseparable mixture of double bond diastereomers and epimers at the allylic ether stereogenic center. The minor isomers are denoted by (†). $^1$H NMR (500 MHz, CDCl$_3$) δ 9.12 (d, $J$ = 6.1 Hz, 1H), 7.67–7.54 (m, 4H), 7.50–7.33 (m, 6H), 6.43 (s, 1H†), 6.37 (d, $J$ = 1.8 Hz, 1H), 5.93 (t, $J$ = 7.5 Hz, 1H), 5.83–5.70 (m, 1H), 5.67–5.56 (m, 1H), 4.85 (s, 1H†), 4.69 (s, 1H), 4.65–4.55 (m, 1H), 4.49 (s, 1H), 4.40 (s, 1H†), 3.77 (d, $J$ = 1.5 Hz, 1H†), 3.73 (d, $J$ = 1.3 Hz, 1H), 3.43 (dd, $J$ = 6.1 Hz, $J$ = 1.8 Hz, 1H†), 3.35 (dd, $J$ = 6.1 Hz, $J$ = 1.7 Hz, 1H), 2.92–2.85 (m, 2H), 2.85–2.81 (m, 2H†), 2.35 (ddd, $J$ = 17.4 Hz, $J$ = 9.8 Hz, $J$ = 2.1 Hz, 1H), 2.19 (d, $J$ = 5.8 Hz, 2H†), 2.11 (dd, $J$ = 17.4 Hz, $J$ = 2.7 Hz, 1H), 1.78 (s, 3H), 1.75 (s, 3H†), 0.17 (s, 9H), 0.09 (s, 9H†); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 197.0, 152.5, 151.0, 146.4, 139.1, 135.5†, 134.8, 134.6, 134.3, 133.7, 132.0, 131.6†, 130.44, 130.35, 130.0, 129.8†, 128.1, 128.0, 125.3†, 123.2, 110.3†, 109.4, 72.6†, 72.5, 72.3†, 59.5, 59.3†, 58.9, 58.5†, 34.6, 34.3, 33.6†, 32.6†, 24.7, 24.4†, 0.5, -1.5†; HRMS (ESI) calcd for C$_{30}$H$_{37}$O$_3$Si$_2$ [M+H]$^+$: 501.2281, found 501.2279.
Synthesis of Donor Aldehyde 4-92

To a solution of 1,4-dichloro-2-butyne 4-110 (2.5 g, 2.0 mL, 20.3 mmol) and dimethyl malonate (23.2 mL, 203 mmol, 10 equiv) in THF–DMF mixture (150 mL 1:1) was added K₂CO₃ (14.0 g, 101.6 mmol, 5 equiv) and the reaction mixture was refluxed for 12 h. After this time the reaction mixture was cooled to r.t., quenched with saturated NH₄Cl solution (100 mL), and diluted with H₂O (200 mL). After separation of layers organic extract was washed with NaCl solution (10 wt. %, 3 x 50 mL) and combined aqueous phase was extracted with EtOAc (2 x 20 mL). EtOAc extracts were dried over MgSO₄ and concentrated under reduced pressure. Excess of malonate was distilled off under high vacuum and the residue was purified by flash column chromatography (gradient elution 5:1 → 3:1 hexanes:EtOAc) to yield tetraester 4-111 (4.77 g, 75%) as a white solid. ¹H NMR (500 MHz, CDCl₃): δ 3.75 (s, 12H), 3.45 (t, J = 7.7 Hz, 2H), 2.65 (d, J = 7.7 Hz, 4H); ¹³C NMR (125 MHz, CDCl₃) δ 168.3, 77.9, 52.7, 51.2, 18.8. HRMS (ESI) calcd for C₁₄H₁₉O₈ [M+H]+: 315.1080, found 315.1068.

To a solution of tetraester 4-111 (4.77 g, 15.2 mmol) in 130 mL of DMSO were added NaCN (1.86 g, 38.0 mmol, 2.5 equiv) and H₂O (820 µL, 45.6 mmol, 3 equiv) and the reaction flask was placed in the preheated to 110 °C oil bath. The reaction mixture was stirred at this temperature for 4 h and cooled to r.t. The reaction mixture was quenched with saturated NH₄Cl solution (100 mL), diluted with H₂O (250 mL), and extracted with EtOAc (3 x 50 mL). Combined organic extracts were washed with NaCl solution (10 wt.%, 3 x 50 mL) and combined aqueous phase was extracted with EtOAc (2 x 15 mL). EtOAc extracts were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by gravity column chromatography (gradient elution 15:1 → 3:1 hexanes:EtOAc) to yield diester 4-112 (1.69 g,
56%, white solid) and monodecarboxylated triester (1.42 g, 37%, off white solid). Triester was resubjected to the reaction conditions to yield additional 633 mg of the product. Combined yield is 2.32 g, 77%. Reaction can be performed without isolation of intermediate triester, however, yield of the product decreased to 64%. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 3.68 (s, 6H), 2.51–2.41 (m, 8H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 172.4, 79.0, 51.7, 33.7, 14.7. HRMS (ESI) calcd for C$_{10}$H$_{15}$O$_4$ [M+H]$^+$: 199.0970, found 199.0979.

To a solution of diester 4-112 (1.64 g, 8.25 mmol) in MeOH–H$_2$O mixture (120 mL, 2:1) was added KOH (462.9 mg, 8.25 mmol, 1 equiv) at 0 °C and the reaction mixture was stirred at r.t. for 12 h. After this time MeOH was removed under vacuum and water layer was saturated with NaCl. The reaction mixture was extracted with EtOAc (5 x 30 mL) to separate unreacted starting material and potassium salt of monoacid 4-113 (organic phase) from potassium salt of diacid (aqueous phase). Combined organic extracts were acidified with 3 M HCl, dried over MgSO$_4$, and solvent was removed under reduced pressure. The residue was purified by flash column chromatography (gradient elution 10:1 → 1:5 hexanes:EtOAc) to afford monoacid 4-113 (819 mg, 54%, 70% BORSM, white solid) and recovered starting material (380.6 mg, 23%, off white solid) which was resubjected to the reaction conditions. The water solution of potassium salt of diacid was acidified with 3 M HCl end extracted with EtOAc (5 x 30 mL). Combined organic extracts were dried over MgSO$_4$ and concentrated under reduced pressure to afford diacid (304.2 mg 22%) as a white powder which was recovered. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 3.69 (s, 3H), 2.58–2.41 (m, 8H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 177.7, 172.5, 79.2, 78.7, 51.7, 33.63, 33.58, 14.7, 14.4. HRMS (ESI) calcd for C$_9$H$_{12}$O$_4$Na [M+Na]$^+$: 207.0633, found 207.0642.
To a solution of acid 4-113 (1.04 g, 5.67 mmol) and i-Pr₂NEt (1.18 mL, 6.8 mmol, 1.2 equiv) in 30 mL of THF was added (benzotriazol-1-ylx)tris(dimethylamino)phosphonium hexafluorophosphate (BOP, 2.76 g, 6.23 mmol, 1.1 equiv) and the reaction mixture was stirred for 30 min. The reaction mixture was then cooled to 0 °C and NaBH₄ (536 mg, 14.16 mmol, 2.5 equiv) was added. After stirring at r.t. for 1 h the reaction mixture was quenched with saturated NH₄Cl and extracted with EtOAc (3 x 20 mL). Combined organic extracts were dried over MgSO₄ and solvent was removed under reduced pressure. The residue was purified by flash column chromatography (gradient elution 5:1 → 1:1 hexanes:EtOAc) to afford alcohol 4-114 (906 mg, 94%) as a colorless liquid. ³¹H NMR (500 MHz, CDCl₃): δ 3.71–3.63 (m, 5H), 2.50–2.38 (m, 4H), 2.24–2.13 (m, 3H), 2.71–1.63 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 172.6, 80.2, 78.6, 61.5, 51.6, 33.7, 31.4, 15.2, 14.6. HRMS (ESI) calcd for C₉H₁₅O₃ [M+H]⁺: 171.1021, found 171.1018.

Alcohol 4-114 (1.12 g, 6.56 mmol) was dissolved in 80 mL of CH₂Cl₂ in a 500 mL Schlenk tube and Grubbs 2nd generation catalyst (SImes)(PCy₃)Cl₂Ru=CHPh (556.6 mg, 0.656 mmol, 10 mol %) and 1,4-benzoquinone (141.7 mg, 1.31 mmol, 20 mol %) were added. Ethylene gas was then passed through the solution for 15 min and additional 2 atm (30 psi) of ethylene were introduced. Schlenk tube was sealed and placed in the preheated to 50 °C oil bath. After stirring at 50 °C for 12 h the reaction mixture was cooled to r.t. and concentrated under reduced pressure. The residue was purified by flash column chromatography (gradient elution 10:1 → 2:1 hexanes:EtOAc) to give alcohol 4-115 as a green liquid (992 mg, 76%) and its aldehyde (126.3 mg, 10%, green liquid). ¹H NMR (500 MHz, CDCl₃): δ 5.11 (s, 1H), 5.10 (s, 1H), 4.99 (s, 1H), 4.97 (s, 1H), 3.68–3.63 (m, 5H), 2.58 (dd, J = 9.0 Hz, J = 6.3 Hz, 2H),
2.47 (dd, $J = 9.0$ Hz, $J = 6.3$ Hz, 2H), 2.33 (dt, $J = 7.6$ Hz, $J = 0.9$ Hz, 2H), 1.74–1.67 (m, 2H); 13C NMR (125 MHz, CDCl$_3$) δ 173.7, 146.4, 145.7, 112.5, 112.3, 62.5, 51.6, 33.3, 31.4, 30.3, 29.3. HRMS (ESI) calcd for C$_{11}$H$_{19}$O$_3$ [M+H]$^+$: 199.1334, found 199.1341.

To a solution of alcohol 4-115 (271 mg, 1.37 mmol), DMSO (1.0 mL, 13.7 mmol 10 equiv), and Et$_3$N (1.9 mL, 13.7 mmol, 10 equiv) in 10 mL of CH$_2$Cl$_2$ was added solution of SO$_3$•Py (1.09 g, 6.83 mmol, 5 equiv) in 1 mL of DMSO at 0 ºC. The reaction mixture was slowly warmed to r.t. over 2 h and quenched with H$_2$O (10 mL). EtOAc (40 mL) was then added to the reaction mixture, and after separation of layers organic extract was washed with NaCl solution (10 wt. %, 3 x 10 mL). The combined aqueous phase was extracted with EtOAc (1 x 10 mL), organic extracts were dried over MgSO$_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (gradient elution 15:1 → 10:1 hexanes:EtOAc) to afford aldehyde 4-92 (212 mg, 79%) as a colorless liquid. 1H NMR (500 MHz, CDCl$_3$): 9.75 (s, 1H), 5.11 (s, 1H), 5.07 (s, 1H), 5.00–4.97 (m, 2H), 3.64 (s, 3H), δ 2.60–2.53 (m, 6H), 2.47–2.41 (m, 2H); 13C NMR (125 MHz, CDCl$_3$) δ 201.7, 173.4, 145.4, 145.0, 112.9, 112.7, 51.5, 42.6, 33.1, 29.1, 26.3. HRMS (ESI) calcd for C$_{11}$H$_{16}$O$_3$Na [M+Na]$^+$: 219.0997, found 219.0999.

Cross-Aldol Condensation and Final Elaboration

To a solution of acceptor aldehyde 4-34 (681 mg, 1.36 mmol) in 680 µL of DMF (2 M) were added activated molecular sieves (MS, 4Å, 680 mg) and L-proline (156.6 mg, 1.36 mmol) and the reaction mixture was cooled to 0 ºC. Under vigorous stirring solution of donor aldehyde 4-92 (400 mg, 2.04
mmol) in DMF (2 mL, 1.0 M) was added to the reaction mixture over 24 h at 0 °C via syringe pump. After completed addition the reaction mixture was stirred for additional 3 h and resultant orange-red suspension was diluted with EtOAc and filtered through a pad of celite. Collected filtrate was washed with NaCl solution (10 wt. %, 3 x 15 mL) and combined aqueous phase was extracted with EtOAc (1 x 10 mL). Combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by gravity column chromatography (gradient elution 25:1 → 10:1 hexanes:EtOAc) to afford epoxyaldehyde (E)-4-91 (554 mg, 60%, colorless oil) and its Z-isomer (54,5 mg, 6%, colorless oil). Epoxyaldehyde (E)-4-91 was isolated as inseparable mixture of double bond diastereomers and epimers at the allylic ether stereogenic center. The minor isomers are denoted by (†).

For (E)-4-91: **¹H NMR** (500 MHz, CDCl₃) δ 9.47 (s, 1H), 9.46 (s, 1H†), 7.67–7.54 (m, 4H), 7.48–7.32 (m, 6H), 6.34 (d, J = 1.8 Hz, 1H†), 6.29–6.23 (m, 2H), 5.93 (t, J = 7.5 Hz, 1H), 5.82–5.69 (m, 1H), 5.68–5.56 (m, 1H), 5.15–5.11 (m, 2H), 4.99 (s, 1H), 4.97 (s, 1H†), 4.84 (s, 1H†), 4.83 (s, 1H†), 4.81 (s, 1H), 4.78 (s, 1H†), 4.68 (d, J = 2.4 Hz, J = 1.3 Hz, 1H), 4.64–4.54 (m, 1H), 4.48 (d, J = 1.54 Hz, 1H), 4.40 (s, 1H†), 3.66–3.59 (m, 4H), 3.55 (d, J = 1.5 Hz, 1H†), 3.51 (d, J = 1.5 Hz, 1H), 3.41 (d, J = 16.1 Hz, 1H), 3.25 (d, J = 16.1 Hz, 1H), 2.91–2.85 (m, 2H), 2.85–2.81 (m, 2H†), 2.58–2.52 (m, 2H), 2.43–2.38 (m, 2H), 2.33 (ddd, J = 17.4 Hz, J = 9.9 Hz, J = 2.2 Hz, 1H), 2.15 (dd, J = 17.4 Hz, J = 2.7 Hz, 1H), 1.77 (s, 3H), 1.74 (s, 3H†), 0.16 (s, 9H), 0.08 (s, 9H†); **¹³C NMR** (125 MHz, CDCl₃) δ 192.6, 173.3, 154.2, 151.0, 150.2, 146.4, 145.7, 144.2, 143.5, 139.2, 134.8, 134.6, 134.0, 132.2, 130.4, 130.3, 129.8, 128.0, 127.9, 123.3†, 121.0, 113.2, 112.9, 110.3†, 109.4, 72.5, 62.7, 55.4, 54.2†, 51.5, 35.1, 34.3, 33.9†, 33.1, 32.6†, 29.4, 28.2, 24.7, 24.4†, 0.5, -1.5†; **HRMS** (ESI) calcd for C₄₁H₅₁O₅Si₂ [M+H]⁺: 679.3275, found 679.3266.

For (Z)-4-91: **¹H NMR** (500 MHz, CDCl₃) δ 10.2 (s, 1H), 7.66–7.54 (m, 4H), 7.48–7.33 (m, 6H), 6.35 (s, 1H†), 6.28 (d, J = 1.8 Hz, 1H), 5.98 (d, J = 8.5 Hz, 1H), 5.93 (t, J = 7.6 Hz, 1H), 5.83–5.70 (m, 1H), 5.69–5.56 (m, 1H), 5.30 (s, 1H), 5.04–4.95 (m, 3H), 4.84 (s, 1H†), 4.68 (s, 1H), 4.66–4.55 (m, 1H), 4.48 (s, 1H), 4.40 (s, 1H†), 4.17 (dd, J = 8.4 Hz, J = 1.3 Hz, 1H†), 4.06 (dd, J = 8.4 Hz, J = 1.4 Hz, 1H), 3.67
(s, 3H), 3.66 (s, 3H†), 3.45 (d, \( J = 1.5 \) Hz, 1H†), 3.41 (d, \( J = 1.1 \) Hz, 1H), 3.29–3.18 (m, 2H), 2.93–2.85 (m, 2H), 2.85–2.80 (m, 2H†), 2.62–2.56 (m, 2H), 2.52–2.45 (m, 2H), 2.38 (ddd, \( J = 17.4 \) Hz, \( J = 9.9 \) Hz, \( J = 1.9 \) Hz, 1H), 2.26–2.22 (m, 2H†), 2.18 (dd, \( J = 17.4 \) Hz, \( J = 2.6 \) Hz, 1H), 1.77 (s, 3H), 1.74 (s, 3H†), 0.16 (s, 9H), 0.08 (s, 9H†); \(^{13}C\) NMR (125 MHz, CDCl\(_3\)) \( \delta \) 189.7, 173.4, 154.3, 151.0, 146.4, 144.5, 143.6, 143.2, 142.7, 139.2, 134.8, 134.6, 134.0, 132.2, 131.8, 130.3, 130.2, 129.8, 128.0, 127.9, 123.3†, 121.0, 115.7, 113.7, 110.3†, 109.4, 72.5, 63.0, 53.9, 51.6, 35.2, 34.3, 33.7, 33.2, 32.6†, 29.7†, 28.9, 24.7, 24.4†, 0.5, -1.5†.

To a solution of silyl ether \((E)-4-91\) (277 mg, 0.41 mmol) in 15 mL of THF were added Et\(_3\)N•3HF (332 \( \mu \)L, 2.05 mmol, 5 equiv) and AgF (207 mg, 1.63 mmol, 4 equiv) and the reaction mixture was stirred for 30 min under exclusion of light. The reaction mixture was quenched with saturated NaHCO\(_3\) solution and extracted with EtOAc (3 x 10 mL). Combined organic extracts were dried over MgSO\(_4\) and concentrated under reduced pressure. The residue was purified by flash column chromatography (gradient elution 10:1 → 2:1 hexanes:EtOAc) to afford alcohol \(4-116\) (157.2 mg, 77%) as a colorless oil. Diastereomers of \(4-116\) were partially separable at this stage and after gravity column chromatography (gradient elution 5:1 → 2:1 hexanes:EtOAc) were isolated 2 fractions: diastereomeric mixture (101.2 mg) and clean alcohol \(25\) as inseparable mixture of double bond isomers formed during allylic transposition step. The major isomer is designated by (*), the minor isomer is denoted by (†). \(^1H\) NMR (500 MHz, CDCl\(_3\)) \( \delta \) 9.46 (s, 1H*, 1H†), 6.25 (d, \( J = 8.5 \) Hz, 1H*, 1H†), 5.90 (t, \( J = 7.5 \) Hz, 1H*), 5.71–5.58 (m, 1H*, 2H†), 5.53–5.42 (m, 1H*, 1H†), 5.30 (s, 1H*, 1H†), 5.15 (s, 2H*, 2H†), 5.12 (s, 1H*, 1H†), 5.00 (s, 1H*, 1H†), 4.83 (dd, \( J = 2.2 \) Hz, \( J = 1.5 \) Hz, 1H†), 4.80 (s, 1H*, 1H†), 4.67 (dd, \( J = 2.4 \) Hz, \( J = 1.3 \) Hz, 1H*), 4.46 (d, \( J = 1.8 \) Hz, 1H*), 4.38 (d, \( J = 1.5 \) Hz, 1H†), 4.21–4.13 (m, 1H*, 1H†), 3.65 (s, 3H*, 3H†), 3.61 (dd, \( J = 8.5 \) Hz, \( J = 1.8 \) Hz, 1H*), 3.60 (s, 1H*, 1H†), 3.56 (s, 3H*, 3H†), 3.52 (d, \( J = 1.5 \) Hz, 1H†), 3.05–3.00 (m, 2H), 2.65–2.60 (m, 2H), 2.54–2.46 (m, 2H), 2.38 (ddd, \( J = 17.4 \) Hz, \( J = 9.9 \) Hz, \( J = 1.9 \) Hz, 1H), 2.26–2.22 (m, 2H†), 2.18 (dd, \( J = 17.4 \) Hz, \( J = 2.6 \) Hz, 1H), 1.76 (s, 3H), 1.74 (s, 3H†), 0.16 (s, 9H), 0.08 (s, 9H†).
2.0 Hz, 1H*, 1H†), 3.49 (d, J = 1.8 Hz, 1H*, 1H†), 3.39 (d, J = 16.1 Hz, 1H*, 1H†), 3.25 (d, J = 16.1 Hz, 1H*, 1H†), 2.88–2.82 (m, 2H*), 2.82–2.78 (m, 2H†), 2.62–2.55 (m, 2H*, 2H†), 2.46 (dd, J = 8.7 Hz, J = 6.4 Hz, 2H*, 2H†), 2.29–2.22 (m, 1H*, 1H†), 2.22–2.08 (m, 2H*, 2H†), 1.76 (s, 3H*), 1.73 (s, 3H†), 0.15 (s, 9H*), 0.06 (s, 9H†); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 192.7, 173.5, 150.9, 150.5, 146.6, 145.6, 144.1, 143.2, 140.6, 139.0, 135.4†, 132.8, 132.4†, 130.6†, 130.1, 116.8, 113.0, 112.8, 110.3†, 109.4, 71.7, 61.7, 55.6, 51.6, 39.9, 34.3, 33.1, 32.6†, 29.3, 28.1, 24.6, 24.4†, 0.5, -1.5†; HRMS (ESI) calcd for C\(_{29}\)H\(_{43}\)O\(_5\)Si \([\text{M+H}]^+\): 499.2880, found 499.2884.

In a Schlenk tube (2 mL) Me\(_3\)SnOH (181 mg, 1.0 mmol, 10 equiv) was added to a solution of methyl ester 4-116 (50 mg, 0.1 mmol) in 400 \(\mu\)L of DCE. Schlenk tube was sealed and placed in the preheated to 100 °C oil bath. The reaction mixture was stirred at this temperature for 2.5 h and cooled to r.t. The resultant yellow suspension was concentrated under reduced pressure and the residue was purified by flash column chromatography (gradient elution 4:1 → 1:3 hexanes:EtOAc) to afford seco-acid 4-124 (48.5 mg, quantitative) as a colorless oil. seco-Acid 4-124 was isolated as inseparable mixture of double bond isomers formed during allylic transposition step. The major isomer is designated by (*), the minor isomer is denoted by (†). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 9.46 (s, 1H*, 1H†), 6.25 (d, J = 8.5 Hz, 1H*, 1H†), 5.90 (t, J = 7.6 Hz, 1H*), 5.71–5.58 (m, 1H*, 2H†), 5.53–5.42 (m, 1H*, 1H†), 5.31 (s, 1H*, 1H†), 5.17 (s, 1H*, 1H†), 5.15 (s, 1H*, 1H†), 5.13 (s, 1H*, 1H†), 5.03 (s, 1H*, 1H†), 4.83 (dd, J = 2.6 Hz, J = 1.5 Hz, 1H†), 4.81 (s, 1H*, 1H†), 4.67 (dd, J = 2.6 Hz, J = 1.5 Hz, 1H*), 4.47 (d, J = 1.8 Hz, 1H*), 4.39 (d, J = 1.5 Hz, 1H†), 4.23–4.16 (m, 1H*, 1H†), 3.64 (dd, J = 8.5 Hz, J = 2.0 Hz, 1H*, 1H†), 3.49 (d, J = 1.5 Hz, 1H*, 1H†), 3.38 (d, J = 16.1 Hz, 1H*, 1H†), 3.27 (d, J = 16.1 Hz, 1H*, 1H†), 2.89–2.83 (m, 2H*), 2.83–2.78 (m, 2H†), 2.63–2.56 (m, 2H*, 2H†), 2.53–2.46 (m, 2H*, 2H†), 2.29–2.18 (m, 2H*, 2H†), 1.76 (s, 3H*), 1.73 (s, 3H†), 0.15 (s, 9H*), 0.07 (s, 9H†); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 192.8,
To a solution of seco-acid 4-124 (199 mg, 0.41 mmol) in 3 mL of THF were added \(t\)-Pr\(_2\)NEt (572 \(\mu\)L, 3.28 mmol, 8 equiv) and Cl\(_3\)C\(_6\)H\(_2\)COCl (256 \(\mu\)L, 1.64 mmol, 4 equiv) and the reaction mixture was stirred at r.t. for 2 h. After this time pale yellow solution was added dropwise to a solution of DMAP (501.6 mg, 4.1 mmol, 10 equiv) in 205 mL of toluene (0.002 M) producing a white precipitate. The reaction mixture was stirred for 8 h and concentrated under reduced pressure. The residue was purified by flash column chromatography (gradient elution 5:1 \rightarrow 3:1 hexanes:EtOAc) to afford mixture of epimeric macrolactones (118.0 mg, 61%) and dimeric macrolide (23 mg, 6%). Macrolactones were separated by gravity column chromatography (gradient elution 15:1 \rightarrow 5:1 hexanes:EtOAc) to give 4-117 (96.3 mg, 50%, colorless oil) and C\(_{13}\)-epi-4-117 (21.4 mg, 11%, colorless oil). Macrolactone 4-117 was isolated as inseparable mixture of double bond isomers formed during allylic transposition step. The major isomer is designated by (*), the minor isomer is denoted by (†). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 9.46 (s, 1H*, 1H†), 6.12 (d, \(J = 8.6\) Hz, 1H*, 1H†), 5.88 (t, \(J = 7.6\) Hz, 1H*), 5.77–5.67 (m, 1H*, 1H†), 5.58 (t, \(J = 7.0\) Hz, 1H†), 5.41–5.34 (m, 1H*, 1H†), 5.32–5.25 (m, 2H*, 2H†), 5.13–5.07 (m, 3H*, 3H†), 5.00–4.96 (m, 2H*, 2H†), 4.83 (dd, \(J = 2.4\) Hz, \(J = 1.3\) Hz, 1H†), 4.67 (dd, \(J = 2.4\) Hz, \(J = 1.3\) Hz, 1H*), 4.46 (d, \(J = 1.5\) Hz, 1H*), 4.37 (d, \(J = 1.5\) Hz, 1H†), 3.65–3.58 (m, 2H*, 2H†), 3.40 (d, \(J = 1.5\) Hz, 1H*, 1H†), 3.12 (d, \(J = 15.0\) Hz, 1H*, 1H†), 2.88–2.76 (m, 3H*, 3H†), 2.54–2.40 (m, 3H*, 3H†), 2.36 (dd, \(J = 14.6\) Hz, \(J = 9.1\) Hz, 1H*, 1H†), 2.22–2.13 (m, 1H*, 1H†), 1.76 (s, 3H*), 1.72 (s, 3H†), 0.14 (s, 9H*), 0.07 (s, 9H†); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 193.0, 172.5, 150.9, 150.0, 147.0, 146.0, 145.3, 144.3, 140.5, 138.4, 134.9†, 132.9†, 132.5,
To a solution of aldehyde 4-117 (135 mg, 0.24 mmol) in 5 mL of MeOH was added NaBH₄ (11 mg, 0.24 mmol, 1 equiv) at 0 °C and the reaction mixture was stirred for 2 min. The reaction mixture was quenched with saturated NH₄Cl solution and extracted with EtOAc (3 x 10 mL). Combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (gradient elution 5:1 → 3:1 hexanes:EtOAc) to afford alcohol 4-125 (124.0 mg 91%) as a colorless oil. Alcohol 4-125 was isolated as inseparable mixture of double bond isomers formed during allylic transposition step. The major isomer is designated by (*), the minor isomer is denoted by (†).

$^1$H NMR (500 MHz, CDCl₃) δ 5.89 (t, $J = 7.5$ Hz, 1H*), 5.79–5.67 (m, 1H*, 1H†), 5.60 (t, $J = 7.0$ Hz, 1H†), 5.47–5.34 (m, 1H*, 1H†), 5.31 (d, $J = 8.7$ Hz, 1H*, 1H†), 5.29–5.20 (m, 2H*, 2H†), 5.16 (s, 1H*, 1H†), 5.08 (s, 1H*, 1H†), 5.03 (s, 1H*, 1H†), 4.99 (s, 1H*, 1H†), 4.87 (s, 1H*, 1H†), 4.83 (dd, $J = 2.2$ Hz, $J = 1.5$ Hz, 1H†), 4.68 (dd, $J = 2.4$ Hz, $J = 1.3$ Hz, 1H*), 4.47 (d, $J = 1.8$ Hz, 1H*), 4.38 (d, $J = 1.5$ Hz, 1H†), 4.11–4.01 (m, 2H*, 2H†), 3.46–3.37 (m, 2H*, 2H†), 3.25 (d, $J = 1.8$ Hz, 1H*, 1H†), 2.97 (d, $J = 15.0$ Hz, 1H*, 1H†), 2.88–2.83 (m, 2H*), 2.83–2.78 (m, 2H†), 2.61–2.47 (m, 3H*, 3H†), 2.43–2.34 (m, 2H*, 2H†), 2.31 (dd, $J = 14.4$ Hz, $J = 9.4$ Hz, 1H*, 1H†), 1.76 (s, 3H*), 1.72 (s, 3H†), 1.70–1.54 (brs, 1H*, 1H†), 0.14 (s, 9H*), 0.07 (s, 9H†); $^{13}$C NMR (125 MHz, CDCl₃) δ 172.1, 150.9, 147.4, 146.9, 145.8, 144.0, 141.3, 138.5, 135.0†, 132.7†, 132.3, 128.6, 128.2†, 123.8, 115.1, 114.4, 113.0, 110.3†, 109.4, 75.7, 65.9, 61.3, 58.4, 38.0, 34.17, 34.14, 33.5, 32.6†, 29.7, 24.6, 24.3†, 0.4, -1.5†; HRMS (ESI) calcd for C₂₈H₄₅O₅Si [M+H]^+: 469.2774, found 469.2768.
Alcohol **C13-epi-125** was obtained by reduction of aldehyde **C13-epi-124** with NaBH₄ as it described for 4-117. Alcohol **C13-epi-125** was isolated as inseparable mixture of double bond isomers formed during allylic transposition step. The major isomer is designated by (*), the minor isomer is denoted by (†). **¹H NMR** (500 MHz, CDCl₃) δ 5.90 (t, J = 7.5 Hz, 1H*), 5.82–5.71 (m, 1H*, 1H†), 5.60 (t, J = 7.0 Hz, 1H†), 5.47–5.38 (m, 2H*, 2H†), 5.38–5.30 (m, 1H*, 1H†), 5.29–5.23 (m, 2H*, 2H†), 5.22 (s, 1H*, 1H†), 5.05 (s, 1H*, 1H†), 5.03 (s, 1H*, 1H†), 4.83 (s, 1H*, 2H†), 4.68 (dd, J = 2.6 Hz, J = 1.5 Hz, 1H*), 4.48 (d, J = 1.5 Hz, 1H*), 4.38 (d, J = 1.5 Hz, 1H†), 4.07–3.92 (m, 3H*, 3H†), 3.60 (d, J = 14.9 Hz, 1H*, 1H†), 3.32 (d, J = 1.8 Hz, 1H*, 1H†), 2.99 (d, J = 14.9 Hz, 1H*, 1H†), 2.89–2.83 (m, 2H*, 2H†), 2.83–2.79 (m, 2H†), 2.52–2.30 (m, 3H*, 3H†), 2.26–2.15 (m, 2H*, 2H†), 2.09 (ddd, J = 14.9 Hz, J = 11.2 Hz, J = 1.2 Hz, 1H*, 1H†), 1.77 (s, 3H*), 1.73 (s, 3H†), 1.56–1.36 (brs, 1H*, 1H†), 0.15 (s, 9H*), 0.08 (s, 9H†); **¹³C NMR** (125 MHz, CDCl₃) δ 172.0, 150.9, 147.5, 147.0, 145.8, 143.0, 141.4, 138.5, 134.9†, 132.9†, 132.5, 128.7, 128.3†, 123.9, 118.7, 116.6, 114.0, 110.4†, 109.4, 75.8, 65.5, 62.2, 53.6, 34.8, 34.6, 34.2, 32.6†, 32.1, 31.5, 24.7, 24.4†, 0.5, -1.5†; **HRMS** (ESI) calcd for C₂₈H₄₁O₄Si [M+H]+: 469.2774, found 469.2767.

**Epoxidation:** To a suspension of activated molecular sieves (MS 4Å) in CH₂Cl₂ (100 mg in 6 mL) and (−)-d-DIPT (21.0 mg, 0.090 mmol) was added Ti(i-PrO)₄ (17.6 µL, 0.060 mmol) at 0 °C. The reaction mixture was cooled to −20 °C and solution of t-BuOOH (174 µL, 5.5 M in decane, 0.96 mmol) was added. The reaction mixture was stirred at −20 °C for 30 min and 2 mL of resultant suspension was added.
to a cold (−20 °C) suspension of alcohol 4-125 (70 mg, 0.149 mmol) and MS (100 mg) in 1 mL of CH₂Cl₂ via syringe. The reaction flask was sealed and the reaction mixture was kept at −20 °C in freezer for 12 h without stirring. After this time the reaction mixture was filtered through a pad of celite. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography (gradient elution 10:1 → 2:1 hexanes:EtOAc) to yield diepoxide 4-126 (74 mg) as an inseparable mixture with (−)-d-DIPT. Diepoxide 4-126 was obtained as an inseparable mixture of double bond isomers formed during allylic transposition step. The major isomer is designated by (*), the minor isomer is denoted by (†).

**1H NMR** (500 MHz, CDCl₃) δ 5.88 (t, J = 7.6 Hz, 1H*), 5.76–5.65 (m, 1H*, 1H†), 5.58 (t, J = 7.0 Hz, 1H†), 5.42–5.32 (m, 1H*, 1H†), 5.28–5.21 (m, 2H*, 2H†), 5.17 (s, 1H*, 1H†), 5.10 (s, 1H*, 1H†), 5.04 (s, 1H*, 1H†), 4.99 (s, 1H*, 1H†), 4.95 (s, 1H*, 1H†), 4.83 (s, 1H†), 4.67 (dd, J = 2.4 Hz, J = 1.3 Hz, 1H*). 4.46 (d, J = 1.1 Hz, 1H*), 4.37 (d, J = 1.5 Hz, 1H†), 3.83 (dd, J = 1.5 Hz, J = 1.1 Hz, 1H†). 3.72 (dd, J = 12.7 Hz, J = 8.4 Hz, 1H*, 1H†), 3.39 (d, J = 1.8 Hz, 1H*, 1H†), 3.02 (d, J = 6.8 Hz, 1H*, 1H†), 2.91–2.81 (m, 4H*, 2H†), 2.81–2.77 (m, 2H†), 2.73–2.64 (m, 1H*, 1H†), 2.56–2.48 (m, 1H*, 1H†), 2.48–2.34 (m, 4H*, 4H†), 2.30 (dd, J = 14.7 Hz, J = 8.9 Hz, 1H*, 1H†), 1.87–1.80 (brs, 1H*, 1H†), 1.76 (s, 3H*), 1.71 (s, 3H†), 0.14 (s, 9H*), 0.07 (s, 9H†); **13C NMR** (125 MHz, CDCl₃) δ 172.1, 150.9, 147.7, 147.0, 143.3, 139.7, 138.5, 134.9†, 132.8†, 132.4, 128.6, 128.2†, 117.2, 114.7, 113.6, 110.3†, 109.4, 73.1, 63.4, 62.6, 59.6, 58.3, 57.4, 37.4, 34.6, 34.2, 33.6, 32.5†, 29.6, 24.6, 24.3†, 0.4, -1.5†; **HRMS** (ESI) calcd for C₂₈H₄₁O₅Si [M+H]+: 485.2723, found 485.2715.

**Iodination:** To a solution of crude epoxyalcohol 4-126 in 7 mL of CH₂Cl₂ were added PPh₃ (156.3 mg, 0.60 mmol, 4 equiv) and imidazole (71 mg, 1.04 mmol, 7 equiv) and the reaction mixture was cooled to 0 °C. Iodine (151.3 mg, 0.60 mmol, 4 equiv) was then added and the reaction mixture was warmed to r.t. and stirred under exclusion of light for 1.5 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography (gradient elution 20:1 → 10:1 hexanes:EtOAc) to yield iododiepoxide 4-127 (75.8 mg, 85% over 2 steps) as a colorless oil. Iododiepoxide 4-127 was obtained as inseparable mixture of double bond isomers formed during allylic
transposition step. The major isomer is designated by (*), the minor isomer is denoted by (†).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.88 (t, $J = 7.5$ Hz, 1H*), 5.76–5.64 (m, 1H*, 1H†), 5.59 (t, $J = 7.0$ Hz, 1H†), 5.45–5.32 (m, 1H*, 1H†), 5.31–5.23 (m, 2H*, 2H†), 5.22 (s, 1H*, 1H†), 5.10 (s, 2H*, 2H†), 5.03 (s, 1H*, 1H†), 4.97 (s, 1H*, 1H†), 4.83 (s, 1H†), 4.68 (s, 1H*), 4.47 (d, $J = 1.8$ Hz, 1H*), 4.37 (d, $J = 1.1$ Hz, 1H†), 3.57 (d, $J = 10.4$ Hz, 1H*, 1H†), 3.40 (d, $J = 1.8$ Hz, 1H*, 1H†), 3.19–3.11 (m, 2H*, 2H†), 2.99 (d, $J = 5.8$ Hz, 1H*, 1H†), 2.89–2.77 (m, 3H*, 3H†), 2.72–2.63 (m, 1H*, 1H†), 2.57–2.50 (m, 1H*, 1H†), 2.46–2.33 (m, 4H*, 4H†), 2.29 (dd, $J = 14.7$ Hz, $J = 7.9$ Hz, 1H*, 1H†), 1.76 (s, 3H*), 1.72 (s, 3H†), 0.14 (s, 9H*), 0.07 (s, 9H†);

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 172.0, 151.0, 147.4, 147.0, 143.3, 139.4, 138.5, 134.9†, 132.8†, 132.4, 128.5, 128.1†, 117.7, 115.1, 113.8, 110.3†, 109.4, 73.3, 66.4, 61.0, 58.2, 57.5, 36.9, 35.6, 34.2, 33.6, 32.5†, 29.9, 24.7, 24.4†, 11.9, 0.5, -1.5†; HRMS (ESI) calcd for C$_{28}$H$_{40}$O$_4$SiI [M+H]$^+$: 595.1741, found 595.1749.

To a solution of epoxyiodide 4-127 (36 mg, 0.061 mmol) in 30 mL of Et$_2$O (0.002 M) was added t-BuLi (71 µL, 1.7 M in pentane, 0.12 mmol, 2 equiv) at −120 ºC (Trapp mixture: THF/Et$_2$O/pentane = 4:1:1) and the reaction mixture was stirred for 2 min. The reaction mixture was quenched cold with MeOH followed by saturated NH$_4$Cl solution at 0 ºC and extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over MgSO$_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (gradient elution 10:1 → 3:1 hexanes:EtOAc) to afford alcohol 4-128 (22.7 mg 80%) as a colorless oil and recovered starting material (3.5 mg). Alcohol 4-128 was obtained as inseparable mixture of double bond isomers formed during allylic transposition step. The major isomer is designated by (*), the minor isomer is denoted by (†).
(s, 1H*, 1H†), 5.08 (s, 1H*, 1H†), 4.92 (s, 1H*, 1H†), 4.83 (s, 1H†), 4.67 (dd, J = 2.2 Hz, J = 1.5 Hz, 1H*), 4.47 (d, J = 1.5 Hz, 1H*), 4.37 (d, J = 1.5 Hz, 1H†), 4.04–3.98 (m, 1H*, 1H†), 3.46 (d, J = 1.2 Hz, 1H*, 1H†), 3.25 (d, J = 16.2 Hz, 1H*, 1H†), 3.10 (d, J = 16.2 Hz, 1H*, 1H†), 2.88–2.77 (m, 3H*, 3H†), 2.76–2.69 (m, 1H*, 1H†), 2.67–2.58 (m, 1H*, 1H†), 2.50–2.34 (m, 4H*, 4H†), 2.22 (d, J = 5.5 Hz, 1H*, 1H† (OH)), 1.76 (s, 3H*), 1.72 (s, 3H†), 0.17 (s, 9H*), 0.07 (s, 9H†); 13C NMR (125 MHz, CDCl3) δ 171.9, 150.9, 146.9, 144.9, 144.6, 142.1, 140.7, 138.6, 135.0†, 132.9†, 132.6, 127.7, 127.3†, 115.2, 114.86, 114.82, 114.0, 110.3†, 109.4, 74.4, 71.4, 63.2, 58.0, 39.2, 39.1, 34.2, 33.7, 32.5†, 30.5, 24.7, 24.4†, 0.5, -1.5†; HRMS (ESI) calcd for C28H41O4Si [M+H]+: 469.2774, found 469.2777.

To a solution of vinyl silane 4-128 (18 mg, 0.038 mmol) in 900 μL of THF–MeOH–H2O mixture (10:9:1) was added AgF (24.4 mg, 0.19 mmol, 5 equiv) and the reaction mixture was stirred at r.t. for 3 h under exclusion of light. After this time TLC analysis indicated ~80% conversion. The reaction mixture was quenched with a saturated NaHCO3 solution and extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over MgSO4 and concentrated under reduced pressure. The residue was purified by gravity column chromatography (gradient elution 7:1 → 5:1 hexanes:EtOAc) to give Amphidinolide V (9.5 mg, 62%) as a colorless oil and recovered starting material (~1 mg). [α]25D = -12.6° (0.8, CHCl3); 1H NMR (500 MHz, CDCl3) δ 6.12 (d, J = 15.6 Hz, 1H), 5.77–5.67 (m, 1H), 5.59 (dt, J = 15.6 Hz, J = 6.7 Hz, 1H), 5.47 (s, 1H), 5.46–5.39 (m, 2H), 5.23 (s, 1H), 5.19 (s, 1H), 5.16 (s, 1H), 5.13 (s, 1H), 5.10 (s, 1H), 5.08 (s, 1H), 4.93 (s, 1H), 4.89 (s, 2H), 4.03–3.97 (m, 1H), 3.46 (d, J = 1.2 Hz, 1H), 3.25 (d, J = 16.2 Hz, 1H), 3.10 (d, J = 16.2 Hz, 1H), 2.86–2.78 (m, 3H), 2.77–2.70 (m, 1H), 2.67–2.59 (m, 1H), 2.51–2.35 (m, 4H), 2.30–2.21 (brs, 1H), 1.83 (s, 3H); 13C NMR (125 MHz, CDCl3) δ 171.9, 144.9, 144.6, 142.1, 141.8, 140.7, 134.1, 132.0, 128.0, 127.4, 115.13, 115.08, 114.8 (2x), 114.0, 74.3, 71.4, 63.3, 57.9, 39.13, 39.07, 35.1, 33.7, 30.5, 18.6; HRMS (ESI) calcd for C25H33O4 [M+H]+: 397.2379, found 397.2377.
Spectroscopic Data for (–)-Amphidinolide V

**Table 4.6.2.1.** Comparison of Spectroscopic Data of Synthetic Material with the Reported\(^1\) for (–)-Amphidinolide V\(^2\)

<table>
<thead>
<tr>
<th>(^1)H NMR data (δ (ppm), multiplicity, (J) (Hz), #H)</th>
<th>(^13)C NMR data (δ, ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reported</td>
<td>Synthetic</td>
</tr>
<tr>
<td>6.12 (d, 15.6, 1H)</td>
<td>6.12 (d, 15.6, 1H)</td>
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<tr>
<td>5.77–5.67 (m, 1H)</td>
<td>5.77–5.67 (m, 1H)</td>
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<tr>
<td>5.60 (dt, 15.6, 6.7, 1H)</td>
<td>5.59 (dt, 15.6, 6.7, 1H)</td>
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<tr>
<td>5.46 (s, 1H)</td>
<td>5.47 (s, 1H)</td>
</tr>
<tr>
<td>5.45–5.43 (m, 1H)</td>
<td>5.46–5.39 (m, 2H)</td>
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<tr>
<td>5.43–5.40 (m, 1H)</td>
<td>5.43–5.39 (m, 2H)</td>
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<tr>
<td>5.24 (s, 1H)</td>
<td>5.23 (s, 1H)</td>
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<td>5.19 (s, 1H)</td>
<td>5.19 (s, 1H)</td>
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<td>5.16 (s, 1H)</td>
<td>5.16 (s, 1H)</td>
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<td>5.13 (s, 1H)</td>
<td>5.13 (s, 1H)</td>
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<tr>
<td>5.10 (s, 1H)</td>
<td>5.10 (s, 1H)</td>
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<tr>
<td>5.08 (s, 1H)</td>
<td>5.08 (s, 1H)</td>
</tr>
<tr>
<td>4.93 (s, 1H)</td>
<td>4.93 (s, 1H)</td>
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<tr>
<td>4.89 (s, 2H)</td>
<td>4.89 (s, 2H)</td>
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<tr>
<td>4.00 (dd, 5.8, 5.4, 1H)</td>
<td>4.03–3.97 (m, 1H)</td>
</tr>
<tr>
<td>3.46 (brs, 1H)</td>
<td>3.46 (d, 1.2, 1H)</td>
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<tr>
<td>3.25 (d, 16.4, 1H)</td>
<td>3.25 (d, 16.2, 1H)</td>
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<tr>
<td>3.11 (d, 16.4, 1H)</td>
<td>3.10 (d, 16.2, 1H)</td>
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<tr>
<td>2.85–2.82 (m, 2H)</td>
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<td>2.47–2.43 (m, 2H)</td>
<td>2.51–2.35 (m, 4H)</td>
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<tr>
<td>2.41–2.39 (m, 2H)</td>
<td>2.51–2.35 (m, 4H)</td>
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<tr>
<td>2.12 (d, 5.4, 1H, OH)</td>
<td>2.30–2.21 (brs, 1H)</td>
</tr>
<tr>
<td>1.83 (s, 3H)</td>
<td>1.83 (s, 3H)</td>
</tr>
</tbody>
</table>

[a] Solvent CDCl\(_3\), data for synthetic material referenced to 7.26 (\(^1\)H NMR) and 77.0 (\(^13\)C NMR)
(--)-Amphidinolide V

Spectrum reproduced from:

Fürstner, A.; Larionov, O.; Flügge, S. Angew. Chem., Int. Ed. 2007, 46, 5545–5548
(-)-Amphidinolide V

Spectrum reproduced from:

**Characterization Data of Synthetic Intermediates in Other Routes:**

To a solution of ethyl iodoacrylate (E-4-46\(^{13}\)) (546 mg, 2.42 mmol, 1.2 equiv) in Et\(_3\)N (10 mL) were added (Ph\(_3\)P)\(_2\)PdCl\(_2\) (14.1 mg, 0.02 mmol, 1 mol %) and CuI (7.7 mg, 0.04 mmol, 2 mol %). Resultant yellow suspension was heated to 50 °C and stirred until palladium complex was dissolved (~20 min). To the above solution was added alkyne 4-45\(^{10}\) (500 mg, 2.01 mmol) and the reaction mixture was stirred for 15 min at 50 °C. The reaction mixture was then cooled to room temperature. The precipitates formed during the reaction were filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (gradient elution 100:1 → 75:1 hexanes:EtOAc) to afford silane 4-46 (662.8 mg, 95%) as a colorless oil.

**\(^{1}H\) NMR (500 MHz, CDCl\(_3\))** δ 7.70–7.58 (m, 4H), 7.47–7.34 (m, 6H), 6.85 (d, J = 15.9 Hz, 1H), 6.38 (d, J = 15.9 Hz, 1H), 5.91–5.79 (m, 1H), 5.03–4.90 (m, 2H), 4.24 (q, J = 7.1 Hz, 2H), 2.21 (d, J = 7.8 Hz, 2H), 1.31 (t, J = 7.1 Hz, 3H); **\(^{13}C\) NMR (125 MHz, CDCl\(_3\))** δ 165.5, 134.9, 132.8, 132.5, 132.4, 130.1, 128.0, 124.4, 115.6, 105.0, 99.3, 60.9, 21.7, 14.8; **HRMS (ESI)** calcd for C\(_{22}\)H\(_{23}\)O\(_2\)Si [M+H]\(^{+}\): 347.1467, found 347.1476.

### Reduction:

To a solution of ester 4-47 (642.8 mg, 1.86 mmol) in 20 mL of THF was added DIBAL-H (5.6 mL, 1 M in hexanes, 5.57 mmol, 3 equiv) at -78 °C. The reaction mixture was warmed to -50 °C and stirred at this temperature for 20 min. After this time the reaction mixture was quenched cold with MeOH, warmed to r.t., and diluted with saturated solution of sodium potassium tartrate (20 mL). The reaction mixture was stirred for 30 min and extracted with EtOAc (3 x 15 mL). Combined organic extracts were dried over MgSO\(_4\) and concentrated under reduced pressure. The residue was purified by
flash column chromatography (gradient elution 10:1 → 3:1 hexanes:EtOAc) to afford alcohol S1 (558.5 mg, 99%) as a colorless oil. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.74–7.62 (m, 4H), 7.47–7.34 (m, 6H), 6.45 (dt, \(J = 16.0\) Hz, \(J = 5.0\) Hz, 1H), 5.96–5.82 (m, 2H), 5.04–4.90 (m, 2H), 4.25 (dd, \(J = 4.7\) Hz, \(J = 1.5\) Hz, 2H), 2.21 (d, \(J = 7.8\) Hz, 2H), 1.78–1.58 (brs, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 144.2, 134.9, 133.6, 133.0, 129.8, 127.9, 115.2, 110.0, 107.1, 89.9, 62.8, 22.0; HRMS (ESI) calcd for C\(_{20}\)H\(_{20}\)OSiNa [M+Na\(^+\)]: 327.1181, found 327.1178.

**Esterification:** To a solution of alcohol S1 (50.0 mg, 0.164 mmol), pyridine (133 \(\mu\)L, 1.64 mmol, 10 equiv), and DMAP (~ 5 mg) in 5 mL of CH\(_2\)Cl\(_2\) was added Ac\(_2\)O (108 \(\mu\)L, 1.15 mmol, 7 equiv) and the reaction mixture was stirred at r.t. for 30 min. After this time solution was concentrated and the residue was purified by flash column chromatography (gradient elution 30:1 → 20:1 hexanes:EtOAc) to afford acetate 4-38 (56.9 mg, quantitative) as a colorless oil. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.68–7.59 (m, 4H), 7.44–7.33 (m, 6H), 6.34 (dt, \(J = 16.0\) Hz, \(J = 5.8\) Hz, 1H), 5.92–5.79 (m, 2H), 4.99–4.89 (m, 2H), 4.64 (d, \(J = 5.1\) Hz, 2H), 2.17 (d, \(J = 7.8\) Hz, 2H), 2.10 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 170.4, 138.6, 134.9, 133.4, 132.8, 129.9, 127.9, 115.3, 112.9, 106.3, 90.9, 63.7, 21.9, 20.8; HRMS (ESI) calcd for C\(_{22}\)H\(_{20}\)O\(_2\)SiNa [M+Na\(^+\)]: 369.1287, found 369.1292.

\(p\)-Methoxybenzyl trichloroacetimidate was prepared according to the literature procedure.\(^{60}\) To a solution of alcohol S1 (50.0 mg, 0.164 mmol) and \(p\)-methoxybenzyl trichloroacetimidate (0.246 mmol, 1 M in toluene 1.5 equiv) in toluene (5 mL) was added La(OTf)\(_3\) and the reaction mixture was heated to 40 \(^\circ\)C and stirred at this temperature for 30 min. The reaction mixture was then concentrated under reduced pressure and the residue was purified by flash column chromatography (25:1 hexanes:EtOAc) to afford PMB-ether 4-55c (60.7 mg, 87%) as a colorless oil. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.71–7.64 (m, 4H), 7.46–7.35 (m, 6H), 7.33–7.27 (m, 2H), 6.94–6.89 (m, 2H), 6.41 (dt, \(J = 16.1\) Hz, \(J = 5.4\) Hz, 1H), 5.97–
5.83 (m, 2H), 5.03–4.90 (m, 2H), 4.50 (s, 2H), 4.10 (dd, J = 5.3 Hz, J = 1.8 Hz, 2H), 3.83 (s, 3H), 2.23–2.17 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 159.3, 142.0, 134.9, 133.6, 132.9, 130.0, 129.8, 129.3, 127.9, 115.2, 113.8, 111.1, 107.2, 89.6, 72.1, 69.3, 55.2, 22.0.

To a solution of alcohol S1 (50.0 mg, 0.164 mmol), p-methoxyphenol (61.2 mg, 0.493 mmol, 3 equiv) and triphenylphosphine (107.5 mg, 0.41 mmol, 2.5 equiv) in THF (5 mL) at 50 °C was added a solution of DIAD (81 µL, 0.41 mmol, 2.5 equiv) in THF (2 mL) dropwise over 1 h. THF was then removed in vacuum and the residue was purified by flash column chromatography (30:1 hexanes:EtOAc) to give PMP-ether 4-55d (46.3 mg, 69%) as a colorless oil. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.72–7.64 (m, 4H), 7.46–7.36 (m, 6H), 6.90–6.83 (m, 4H), 6.50 (dt, J = 16.0 Hz, J = 5.0 Hz, 1H), 6.01 (d, J = 16.0 Hz, 1H), 5.93–5.83 (m, 1H), 5.03–4.92 (m, 2H), 4.58 (dd, J = 4.9 Hz, J = 1.5 Hz, 2H), 3.79 (s, 3H), 2.21 (d, J = 7.8 Hz, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 154.1, 152.4, 140.4, 134.9, 133.5, 132.9, 129.8, 127.9, 115.7, 115.2, 114.7, 111.6, 106.8, 90.3, 68.1, 55.7, 22.0.

To a solution of alcohol S1 (50.0 mg, 0.164 mmol), $^3$Pr$_2$NEt (129 µL, 0.739 mmol, 4.5 equiv) and Bu$_4$NI (66.7 mg, 0.180 mmol, 1.1 equiv) in CH$_2$Cl$_2$ (5 mL) was added SEMCl (58 µL, 0.328 mmol, 2 equiv) at r.t. and the reaction mixture was stirred overnight. After this time solution was concentrated and the residue was purified by flash column chromatography (30:1 hexanes:EtOAc) to give SEM-ether 4-55c (51.9 mg, 73%) as a colorless oil. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.71–7.63 (m, 4H), 7.46–7.34 (m, 6H), 6.39 (dt, J = 16.0 Hz, J = 5.3 Hz, 1H), 5.94–5.81 (m, 2H), 5.01–4.90 (m, 2H), 4.71 (s, 2H), 4.17 (dd, J = 5.3 Hz, J = 1.8 Hz, 2H), 3.69–3.62 (m, 2H), 2.19 (d, J = 7.9 Hz, 2H), 1.01–0.93 (m, 2H), 0.05 (s, 9H); $^{13}$C
NMR (125 MHz, CDCl₃) δ 141.7, 134.9, 133.6, 132.9, 129.8, 127.9, 115.2, 111.1, 107.1, 94.3, 89.6, 66.8, 65.3, 22.0, 18.1, -1.4.

Silane 4-42 (364.5 mg, 2.67 mmol, 2 equiv) and alcohol 4-48 (150.0 mg, 1.34 mmol) were dissolved in hexanes–THF mixture (2.5:1, 14 mL). Sodium hydride (5.3 mg, 60% in oil, 0.134 mmol, 10 mol %) was added, and the reaction mixture was stirred at r.t. for 4 h. The reaction mixture was then filtered through a short layer of silica gel. The solvent was evaporated under reduced pressure to afford a mixture of silyl ether 4-49 and unreacted silane 4-42 (363.1 mg, 1.18:1) as a colorless liquid. Yield of 4-49 is 84% based on 1.18:1 ratio of compounds. For 4-49: ¹H NMR (500 MHz, CDCl₃) δ 5.86–5.74 (m, 1H), 5.66–5.56 (m, 1H), 5.50–5.42 (m, 1H), 5.09–5.00 (m, 2H), 4.28–4.21 (m, 1H), 2.38–2.21 (m, 2H), 1.89 (s, 3H), 1.71–1.66 (m, 3H), 0.22 (s, 3H), 0.20 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 135.1, 133.4, 126.0, 116.6, 103.2, 82.4, 73.9, 42.5, 17.6, 4.7, 0.94, 0.86.

Crude mixture of silyl ether 4-49 and 4-42 (192.0 mg, 0.59 mmol, 1.18:1) was dissolved in 60 mL of CH₂Cl₂ (0.01 M) and the Grubbs 2nd generation catalyst (SImes)(PC₅)₂Ru=CHPh (37.8 mg, 0.044 mmol, 7.5 mol %) was added. The reaction mixture was refluxed at 45 °C for 12 h and solvent was evaporated under reduced pressure. The residue was purified by gravity column chromatography (250:1 hexanes:EtOAc) to afford siloxene 4-50 (94.1 mg, 76%) as a colorless liquid. For 4-50: ¹H NMR (500 MHz, CDCl₃) δ 6.58 (dd, J = 6.2 Hz, J = 2.7 Hz, 1H), 5.75–5.66 (m, 1H), 5.61–5.53 (m, 1H), 4.93 (s, 1H), 4.77 (s, 1H), 4.34–4.28 (m, 1H), 2.40–2.31 (m, 1H), 2.31–2.23 (m, 1H), 1.86 (s, 3H), 1.70 (d, J = 6.4 Hz, 3H), 0.33 (s, 3H), 0.31 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 144.6, 140.0, 139.9, 133.5, 126.6, 113.6, 71.5, 36.5, 20.8, 17.7, 0.3, 0.1.
To a solution of siloxene 4-50 (174 mg, 0.835 mmol) in 20 mL of THF was added MeLi (334 μL, 3.0 M in diethoxymethane, 1.0 mmol, 1.2 equiv) at −50 °C and resultant yellow solution was stirred at this temperature for 15 min. The reaction mixture was quenched cold with MeOH followed by a saturated NH₄Cl solution. The reaction mixture was warmed to r.t. and extracted with EtOAc (3 x 10 mL). Combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (gradient elution 25:1 → 10:1 hexanes:EtOAc) to afford alcohol 4-51 (139.4 mg, 74%) as a colorless liquid. 

1H NMR (500 MHz, CDCl₃) δ 5.97 (t, J = 7.5 Hz, 1H), 5.68 (dq, J = 12.9 Hz, J = 6.4 Hz, 1H), 5.56–5.46 (m, 1H), 4.68 (s, 1H), 4.47 (s, 1H), 4.15–4.07 (m, 1H), 2.46–2.29 (m, 2H), 1.76 (s, 3H), 1.70 (d, J = 6.4 Hz, 3H), 1.61–1.49 (brs, 1H), 0.17 (s, 9H); 13C NMR (125 MHz, CDCl₃) δ 151.1, 148.4, 137.5, 133.5, 127.0, 109.4, 72.7, 39.6, 24.7, 17.6, 0.5; HRMS (EI) calcd for C₁₃H₂₄O₅Si [M]+: 224.15965, found 224.16002.

To a solution of silane 4-51 (37.5 mg, 0.167 mmol) in 5 mL of THF was added TBAF (334 μL, 1.0 M in THF, 0.334 mmol, 2 equiv). The reaction mixture was heated to 70 °C and stirred at this temperature for 1 h. It was then cooled to r.t. and quenched with a saturated NH₄Cl solution. The reaction mixture was extracted with EtOAc (3 x 10 mL), the combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (gradient elution 15:1 → 10:1 hexanes:EtOAc) to afford alcohol 4-52 (22.4 mg, 88%) as a colorless liquid. 

1H NMR (500 MHz, CDCl₃) δ 6.22 (d, J = 15.7 Hz, 1H), 5.74–5.57 (m, 2H), 5.56–5.46 (m, 1H), 4.91 (s, 2H), 4.17–4.06 (m, 1H), 2.43–2.25 (m, 2H), 1.84 (s, 3H), 1.75–1.62 (m, 4H); 13C NMR (125 MHz, CDCl₃) δ 141.8, 136.1, 133.4, 126.9, 125.8, 115.4, 72.2, 41.0, 18.6, 17.6.
To a solution of alkynylsilane 4-47 (752.7 mg, 2.17 mmol) and phenol (204.4 mg, 2.17 mmol, 1 equiv) in 65 mL of DCE was added a pre-generated solution of Ph$_3$PAuF$_6$ (3 mol %), which was prepared by mixing stoichiometric amounts of Ph$_3$PAuCl (32.3 mg, 0.065 mmol) and AgSbF$_6$ (22.4 mg, 0.11 mmol) in DCE (3 mL) followed by filtration through a cotton plug to remove precipitated AgCl. The resultant brown solution was stirred at r.t. for 40 min and quenched with Et$_3$N (50 μL). The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (gradient elution 50:1 → 10:1 hexanes:EtOAc) to afford vinyl silane 4-57 as a colorless oil (611.9 mg, 64%). Silane 4-57 was obtained as inseparable mixture of double bond isomers (4:1 Z/E). The major isomer is designated by (*) and the minor isomer is denoted by (†).$^1$H NMR (500 MHz, CDCl$_3$) δ 7.75 (d, J = 15.8 Hz, 1H†), 7.73–7.63 (m, 4H*, 4H†), 7.50–7.36 (m, 6H*, 6H†), 7.33 (d, J = 15.9 Hz, 1H*), 7.20–7.11 (m, 2H*, 2H†), 6.96–6.90 (m, 1H*, 1H†), 6.89–6.80 (m, 2H*, 2H†), 6.46 (s, 1H*), 6.34 (s, 1H†), 6.00 (d, J = 15.9 Hz, 1H*), 5.94 (d, J = 15.8 Hz, 1H†), 5.92–5.80 (m, 1H†), 5.51–5.39 (m, 1H*), 5.14–5.04 (m, 2H†), 4.89–4.77 (m, 2H*), 4.22 (q, J = 7.1 Hz, 2H*), 4.11 (q, J = 7.1 Hz, 2H†), 3.14 (d, J = 6.2 Hz, 2H*, 2H†), 1.30 (t, J = 7.1 Hz, 3H*), 1.20 (t, J = 7.1 Hz, 3H†); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 166.9, 154.63†, 154.58, 147.8, 143.9, 134.9, 134.7†, 134.5, 134.1†, 133.9, 132.7, 130.4, 130.3†, 129.4, 129.3†, 128.1, 121.7, 121.1†, 120.5, 120.0†, 119.8, 117.4†, 116.7, 60.5, 60.3†, 39.8†, 36.7, 14.3, 14.2†.

To a solution of siloxene 4-40 (1.33 g, 4.91 mmol) in 40 mL of MeOH were added HF•Py (358 μL, 19.7 mmol, 4 equiv) and AgF (623.5 mg, 4.91 mmol, 4 equiv) at 0 °C, and the reaction mixture was stirred for 20 min under exclusion of light. The reaction mixture was quenched with saturated NaHCO$_3$ solution and extracted with EtOAc (3 x 20 mL). Combined organic extracts were dried over MgSO$_4$ and
concentrated under reduced pressure. The residue was purified by fast gravity column chromatography (gradient elution 50:1 → 20:1 hexanes:EtOAc) to afford alcohol 4-69 (875.0 mg, 83%) as a pale yellow oil. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.42–7.37 (m, 2H), 7.36–7.30 (m, 2H), 7.29–7.23 (m, 1H), 6.62 (d, $J$ = 15.7 Hz, 1H), 6.32–6.22 (m, 2H), 5.70 (ddd, $J$ = 15.4 Hz, $J$ = 7.6 Hz, $J$ = 7.3 Hz, 1H), 4.95 (s, 2H), 4.41–4.34 (m, 1H), 2.55–2.40 (m, 2H), 1.95 (s, 1H, OH), 1.87 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 141.7, 136.6, 136.4, 131.7, 130.3, 128.5, 127.6, 126.4, 125.3, 115.6, 72.1, 41.0, 18.6; HRMS (ESI) calcd for C$_{15}$H$_{16}$ONa [M+Na]$^+$: 237.1255, found 237.1261.

To a solution of alcohol 4-69 (850.0 mg, 3.97 mmol) and silane 4-61 (1.69 g, 4.36 mmol, 1.1 equiv) in 100 mL of toluene was added (Xanthphos)CuCl (134.4 mg, 0.198 mmol, 5 mol %) and the reaction flask was placed in the preheated to 80 °C oil bath. A solution of t-BuOLi (190.6 mg, 2.38 mmol, 0.6 equiv) in 30 mL of toluene was slowly added to the reaction mixture via syringe pump over 4 h. After this time the reaction mixture was cooled to r.t. and quenched with saturated NH$_4$Cl solution. Layers were separated and water layer was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over MgSO$_4$, concentrated under reduced pressure, and the residue was quickly purified by flash column chromatography to afford pale yellow oil. In order to remove unreacted silane 4-61, it was converted to silanol$^{59}$ as follows: the crude product was dissolved in 15 mL of CH$_3$CN and [RuCl$_2$(p-cymene)]$_2$ (23.9 mg, 0.039 mmol, 10 mol % relative to excess of silane used) was added followed by addition of 100 μL of H$_2$O. The reaction mixture was heated to 80 °C and stirred for 2 h. The reaction mixture was then cooled to r.t. and solvent was evaporated under vacuum. The residue was purified by gravity column chromatography (gradient elution 150:1 → 50:1 hexanes:EtOAc) to afford silyl ether 4-70 (2.14 g, 90%) as a colorless oil. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.69–7.61 (m, 4H), 7.45–7.32 (m, 6H), 7.32–7.20 (m, 5H), 6.89–6.80 (m, 4H), 6.30 (d, $J$ = 15.9 Hz, 1H), 6.20–6.12 (m, 3H), 5.65 (ddd, $J$ = 15.2 Hz, $J$ = 7.5 Hz,
\[ J = 7.3 \text{ Hz}, \ 1\text{H}), \ 5.59–5.48 \text{ (m, 1H), 4.95–4.84 \text{ (m, 4H), 4.55–4.42 \text{ (m, 3H), 3.78 \text{ (s, 3H), 2.99 \text{ (d, \( J = 6.9 \text{ Hz}, \ 2\text{H), 2.53–2.38 \text{ (m, 2H), 1.79 \text{ (s, 3H); 1}^3\text{C NMR (125 MHz, CDCl}_3) \delta 155.8, 153.9, 152.7, 142.0, 136.9, 135.8, 135.7, 135.4, 135.09, 135.0, 132.0, 130.3, 129.79, 129.76, 128.4, 127.8, 127.4, 126.5, 126.1, 120.1, 117.0, 115.9, 114.8, 114.5, 74.7, 72.0, 55.7, 41.6, 38.3, 18.6; HRMS (ESI) calcd for C\text{40}H\text{42}O\text{3}Si \text{Na} [\text{M+Na}^+]: 621.2801, \text{ found } 621.2801. \]

To a solution of vinyl silane 4-70 (1.62 g, 2.71 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (545 mL, 0.005 M) were added the Grubbs 1\textsuperscript{st} generation catalyst (PC\textsubscript{y}\textsubscript{3})\textsubscript{2}Ru=CHPh (334.6 mg, 0.406 mmol, 15 mol \%) and 1,4-benzoquinone (58.6 mg, 0.542 mmol, 20 mol \%). The reaction mixture was refluxed at 40 °C for 12 h and then concentrated under reduced pressure. The residue was purified by gravity column chromatography (gradient elution 150:1 → 50:1 hexanes:EtOAc) to afford eight-membered siloxacycle 4-71 as a colorless oil (1.15 g, 86%). \(^1\text{H NMR (500 MHz, CDCl}_3) \delta 7.68–7.64 \text{ (m, 2H), 7.59–7.54 \text{ (m, 2H), 7.44–7.33 \text{ (m, 6H), 6.95–6.91 \text{ (m, 2H), 6.90–6.85 \text{ (m, 2H), 6.25 \text{ (d, \( J = 15.7 \text{ Hz}, 1\text{H), 6.18–6.14 \text{ (m, 1H), 5.92–5.84 \text{ (m, 1H), 5.79–5.71 \text{ (m, 1H), 5.53 \text{ (dd, \( J = 10.9 \text{ Hz, } J = 4.9 \text{ Hz, 1H), 4.96–4.91 \text{ (m, 2H), 4.65–4.57 \text{ (m, 3H), 3.81 \text{ (s, 3H), 3.55 \text{ (dd, \( J = 13.0 \text{ Hz, } J = 8.1 \text{ Hz, 1H), 2.91 \text{ (dd, \( J = 13.0 \text{ Hz, } J = 9.3 \text{ Hz, 1H), 2.58–2.49 \text{ (m, 1H), 2.49–2.41 \text{ (m, 1H), 1.87 \text{ (s, 3H); 1}^3\text{C NMR (125 MHz, CDCl}_3) \delta 157.5, 154.0, 152.7, 142.0, 136.1, 135.3, 135.2, 135.0, 134.6, 134.1, 130.7, 129.8, 129.6, 127.8, 127.7, 126.6, 121.1, 116.0, 114.8, 114.6, 73.8, 71.2, 55.7, 41.2, 30.6, 18.6; HRMS (ESI) calcd for C\text{32}H\text{35}O\text{3}Si [\text{M+H}^+]: 495.2355, \text{ found } 495.2359. \]
Commercial rhenium(VII) oxide was grounded to the fine powder in the glovebox prior to reaction. A solution of siloxadiene 4-71 (100.9 mg, 0.204 mmol) and 2-methyl-2-butene (216 μL, 2.04 mmol, 10 equiv) in ether (1.4 mL, 0.15 M) was cooled to -20 °C inside of the glovebox. Rhenium(VII) oxide (9.9 mg, 0.02 mmol, 10 mol %) was added and the reaction flask was sealed. The reaction flask was taken out of the glovebox and placed into an insulated box filled with ice. The reaction mixture was stirred at 0 °C for 6 h and then quenched with Et₃N (50 μL). The solvent was evaporated under reduced pressure and the residue was dissolved in 30:1 hexanes:EtOAc mixture. Product was quickly purified by passing the solution through a short layer of silica gel to yield six-membered siloxene 4-73 as a colorless oil (63.0 mg, 63%). Isolated compound decomposes upon long exposure to silicagel as well as upon storage. ¹H NMR (500 MHz, CDCl₃) δ 7.69–7.65 (m, 2H), 7.63–7.58 (m, 2H), 7.50–7.40 (m, 4H), 7.40–7.35 (m, 2H), 6.94–6.89 (m, 2H), 6.89–6.84 (m, 2H), 6.28–6.24 (m, 1H), 6.19 (d, J = 15.6 Hz, 1H), 5.84 (ddt, J = 15.2 Hz, J = 6.3 Hz, J = 0.9 Hz, 1H), 5.74–5.65 (m, 2H), 4.93 (s, 2H), 4.72–4.65 (m, 1H), 4.56–4.49 (m, 2H), 3.80 (s, 3H), 2.92–2.87 (m, 2H), 2.48 (ddt, J = 17.3 Hz, J = 10.1 Hz, J = 2.1 Hz, 1H), 2.37 (dd, J = 17.4 Hz, J = 2.8 Hz, 1H), 1.88 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 156.0, 154.0, 152.6, 141.9, 135.1, 134.8, 134.6, 134.4, 133.9, 132.7, 130.1, 130.0, 129.2, 128.0, 127.9, 127.8, 118.1, 115.9, 114.9, 114.6, 73.6, 72.4, 55.7, 36.7, 35.2, 18.6; HRMS (ESI) calcd for C₃₂H₃₅O₃Si[M+H]^+: 495.2355, found 495.2354.

To a 100 mL Schlenk tube were added CuI (1.58 g, 8.32 mmol, 1 equiv), dry Bu₄NCl (1.16 g, 4.16 mmol, 0.5 equiv), and dry K₂CO₃ (2.30 g, 16.6 mmol, 2 equiv) under Ar atmosphere. DMF (25 mL) was then introduced to the reaction vessel followed by addition of 4-pentyn-1-ol (774 μL, 8.32 mmol) and 2,3-dibromopropene (1.22 mL, 12.5 mmol, 1.5 equiv). The Schlenk tube was sealed and the reaction mixture
was stirred at 50 °C for 20 h. After this time the reaction mixture was cooled to r.t., quenched with saturated NH₄Cl solution (100 mL), and diluted with EtOAc (30 mL). After separation of layers aqueous phase was extracted with EtOAc (2 x 20 mL). The EtOAc extracts were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (gradient elution 10:1 → 2:1 hexanes:EtOAc) to yield bromide 4-76 (1.48 g, 88%) as a yellow oil. 

\[ ^1H \text{ NMR} (500 \text{ MHz, CDCl}_3): \delta 5.96–5.91 \text{ (m, 1H), 5.53–5.49 (m, 1H), 3.75 (t, } J = 6.2 \text{ Hz, 2H), 3.33–3.27 (m, 2H), 2.36–2.27 \text{ (m, 2H), 1.80–1.71 (m, 2H), 1.71–1.58 (brs, 1H, OH); } ^{13}C \text{ NMR} (125 \text{ MHz, CDCl}_3) \delta 128.0, 117.5, 83.3, 75.7, 61.7, 31.9, 31.3, 15.3; \text{ HRMS (EI) calcd for C}_{8}\text{H}_{10}\text{BrO[M-H]}^+: 200.99150, \text{ found 200.99004.} \]

\[
\begin{align*}
\text{Br} & \quad \text{Jones (5 equiv)} \quad 0 \text{°C, 0.5 h} \\
\text{4-76} & \quad \text{Br} \quad \text{CO}_2\text{H} \\
\end{align*}
\]

To a solution of alcohol 4-76 (1.0 g, 4.92 mmol) in acetone (450 mL, 0.01 M) was added Jones reagent (9.5 mL, 2.6 M, 24.6 mmol, 5 equiv) dropwise at 0 °C. The reaction mixture was stirred for 20 min and excess of Jones reagent was quenched with isopropanol. The reaction mixture was filtered through a pad of celite and concentrated under reduced pressure. The residue was dissolved in CH₂Cl₂ (30 mL) and extracted with saturated Na₂CO₃ solution (3 x 10 mL). Combined aqueous phase was acidified to pH = 2 with 3 M HCl and extracted with CH₂Cl₂ (3 x 30 mL). Combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure to give acid 4-77 (835 mg, 78%) as a white solid. 

\[ ^1H \text{ NMR} (500 \text{ MHz, CDCl}_3): \delta 5.97–5.92 \text{ (m, 1H), 5.53–5.49 (m, 1H), 3.32–3.26 (m, 2H), 2.63–2.56 (m, 2H), 2.55–2.49 (m, 2H); } ^{13}C \text{ NMR} (125 \text{ MHz, CDCl}_3) \delta 178.4, 127.6, 117.6, 81.8, 76.2, 33.4, 31.7, 14.4; \text{ HRMS (ESI) calcd for C}_{8}\text{H}_{9}\text{O}_{2}\text{BrNa[M+Na]}^+: 238.9684, \text{ found 238.9679.} \]
**Enyne CM:** Acid 4-77 (800 mg, 3.69 mmol) was dissolved in 80 mL of CH₂Cl₂ in a 500 mL Schlenk tube and the Grubbs 2nd generation catalyst (SiMes)(PCy₃)Cl₂Ru=CHR (312.9 mg, 0.369 mmol, 10 mol %) and 1,4-benzoquinone (79.7 mg, 0.737 mmol, 20 mol %) were added. Ethylene gas was then passed through the solution for 15 min and additional 2 atm (30 psi) of ethylene were introduced. Schlenk tube was sealed and placed in the preheated to 50 °C oil bath. After stirring at 50 °C for 12 h the reaction mixture was cooled to r.t. and concentrated under reduced pressure. The residue was purified by flash column chromatography (gradient elution 15:1 → 1:1 hexanes:EtOAc) to give crude acid as a brown liquid. It was dissolved in CH₂Cl₂ (30 mL) and extracted with saturated Na₂CO₃ solution (3 x 10 mL). The combined aqueous phase was acidified to pH = 2 with 3 M HCl and extracted with CH₂Cl₂ (3 x 30 mL). The combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure to give acid 4-78 (601.5 mg, 67%) as a pale yellow oil. ¹H NMR (500 MHz, CDCl₃): δ 5.63–5.59 (m, 1H), 5.52–5.48 (m, 1H), 5.33 (s, 1H), 5.17 (s, 1H), 5.14 (s, 1H), 5.05 (s, 1H), 3.39 (s, 2H), 2.66–2.59 (m, 2H), 2.59–2.52 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 179.5, 144.1, 142.2, 131.4, 118.3, 116.0, 113.7, 46.4, 33.1, 28.7; HRMS (ESI) calcd for C₁₀H₁₆O₂BrNa [M+Na]⁺: 266.9997, found 266.9996.

**Protection:** To a solution of acid 4-78 (50.0 mg, 0.20 mmol) and Et₃N (85 μL, 0.612 mmol, 3 equiv) in THF (5 mL) was added SEMCl (47 μL, 0.265 mmol, 1.3 equiv) at 0 °C and the reaction mixture was stirred for 1 h. After this time solution was concentrated and the residue was purified by flash column chromatography (gradient elution 20:1 → 10:1 hexanes:EtOAc) to give SEM-ester 4-79 (76.6 mg, quantitative) as a colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 5.61–5.59 (m, 1H), 5.51–5.48 (m, 1H), 5.33 (s, 1H), 5.28 (s, 2H), 5.15 (s, 1H), 5.12 (s, 1H), 5.03 (s, 1H), 3.73–3.67 (m, 2H), 3.38 (s, 2H), 2.65–2.59 (m, 2H), 2.57–2.51 (m, 2H), 0.98–0.93 (m, 2H), 0.02 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 172.7, 144.4, 142.2, 131.4, 118.2, 116.0, 113.5, 88.9, 67.8, 46.3, 33.4, 28.8, 18.0, -1.5.
Enyne CM: Alcohol 4-76 (700 mg, 3.45 mmol) was dissolved in 70 mL of CH₂Cl₂ in a 500 mL Schlenk tube and the Grubbs 2nd generation catalyst (SiMes)(PCy₃)₂Ru=CHPh (292.6 mg, 0.345 mmol, 10 mol %) and 1,4-benzoquinone (74.5 mg, 0.689 mmol, 20 mol %) were added. Ethylene gas was then passed through the solution for 15 min and additional 2 atm (30 psi) of ethylene were introduced. The Schlenk tube was sealed and placed in the preheated to 50 °C oil bath. After stirring at 50 °C for 12 h the reaction mixture was cooled to r.t. and concentrated under reduced pressure. The residue was purified by flash column chromatography (gradient elution 15:1 → 3:1 hexanes:EtOAc) to give triene 4-80 (565.7 mg, 71%) as a pale yellow oil. ¹H NMR (500 MHz, CDCl₃): δ 5.58–5.61 (m, 1H), 5.50–5.48 (m, 1H), 5.33 (s, 1H), 5.12 (s, 1H), 5.10 (s, 1H), 5.01 (s, 1H), 3.65 (t, J = 6.4 Hz, 2H), 3.38 (s, 2H), 2.35 (t, J = 7.7 Hz, 2H), 1.77–1.70 (m, 2H), 1.69–1.62 (brs, 1H, OH); ¹³C NMR (125 MHz, CDCl₃) δ 145.6, 142.6, 131.6, 118.1, 115.8, 113.1, 62.4, 46.3, 31.4, 30.2.

Protection: To a solution of alcohol 4-80 (376 mg, 1.63 mmol), and imidazole (221.5 mg, 2.25 mmol, 2 equiv) in DMF (15 mL) was added TESCl (328 μL, 1.95 mmol, 1.2 equiv) at 0 °C and the reaction mixture was warmed to r.t. and stirred for 30 min. The reaction mixture was then quenched with water and extracted with hexanes (3 x 20 mL). Combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by fast flash column chromatography (gradient elution 100:1 → 25:1 hexanes:EtOAc) to afford silyl ether 4-81 (526.6 mg, 94%) as a pale yellow oil. ¹H NMR (500 MHz, CDCl₃): δ 5.62–5.59 (m, 1H), 5.51–5.48 (m, 1H), 5.34 (s, 1H), 5.12 (s, 2H), 5.09 (s, 1H), 5.00 (s, 1H), 3.63 (t, J = 6.4 Hz, 2H), 3.38 (s, 2H), 2.35–2.30 (m, 2H), 1.75–1.67 (m, 2H), 0.96 (t, J = 8.0 Hz, 9H), 0.60 (q, J = 8.0 Hz, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 145.9, 142.8, 131.7, 118.0, 115.7, 112.9, 62.4, 46.4, 31.7, 30.2, 6.8, 4.4.
To a solution of vinyl bromide 4-81 (191.6 mg, 0.555 mmol, 1.2 equiv) in Et₂O (10 mL) was added t-BuLi (653 μL, 1.7 M in pentane, 1.11 mmol, 2.4 equiv) at −78 °C and the reaction mixture was stirred for 5 min. Solution of epoxyaldehyde 4-83 (100.0 mg, 0.462 mmol) in 5 mL of Et₂O was then added. The reaction mixture was stirred for 30 min at -50 °C and warmed to 0 °C. It was then quenched with saturated NH₄Cl solution (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (gradient elution 25:1 → 10:1 hexanes:EtOAc) to afford epoxyalcohol 4-84 (131.9 mg, 59%, 1:1 dr) as a colorless oil and triene 4-85 (59.1 mg, 40%) as a colorless liquid. Diastereomers of 4-84 were partially separable by gravity column chromatography (gradient elution 25:1 → 10:1 hexanes:EtOAc) thus 3 fractions were isolated: diastereomeric mixture (49.5 mg), less polar diastereomer (55.8 mg), and more polar diastereomer (26.6 mg). For less polar diastereomer: ¹H NMR (500 MHz, CDCl₃): δ 5.31–5.27 (m, 2H), 5.12 (s, 1H), 5.07 (s, 2H), 4.99 (s, 1H), 4.96 (s, 1H), 4.08 (dd, J = 11.6 Hz, J = 5.6 Hz, 1H), 4.03–3.98 (m, 1H), 3.74 (dd, J = 11.6 Hz, J = 6.6 Hz, 1H), 3.62 (t, J = 6.5 Hz, 2H), 3.21–3.15 (m, 2H), 3.12–3.04 (m, 2H), 2.78 (d, J = 2.5 Hz, 1H, OH), 2.35–2.29 (m, 2H), 1.75–1.67 (m, 2H), 0.96 (t, J = 8.0 Hz, 9H), 0.92 (s, 9H), 0.60 (q, J = 8.0 Hz, 6H), 0.12 (s, 3H), 0.11 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 146.60, 146.57, 144.3, 114.8, 112.7, 112.2, 71.7, 62.5, 62.1, 58.2, 55.2, 37.3, 31.8, 30.3, 25.8, 18.3, 6.8, 4.5, -5.3, -5.5. For more polar diastereomer: ¹H NMR (500 MHz, CDCl₃): δ 5.30 (s, 1H), 5.23 (s, 1H), 5.09 (s, 1H), 5.05 (s, 2H), 4.99 (s, 1H), 4.97 (s, 1H), 4.01 (dd, J = 7.2 Hz, J = 3.3 Hz, 1H), 3.85 (dd, J = 11.9 Hz, J = 4.2 Hz, 1H), 3.74 (dd, J = 11.9 Hz, J = 6.1 Hz, 1H), 3.63 (t, J = 6.4 Hz, 2H), 3.22 (dt, J = 6.1 Hz, J = 4.3 Hz, 1H), 3.15 (d, J = 16.4 Hz, 1H), 3.11 (dd, J = 7.4 Hz, J = 4.4 Hz, 1H), 3.03 (d, J = 16.4 Hz, 1H), 3.35–3.29 (m, 2H), 2.19 (d, J = 3.8 Hz, 1H, OH), 1.74–1.66 (m, 2H),
0.96 (t, \(J = 7.9\) Hz, 9H), 0.90 (s, 9H), 0.60 (q, \(J = 7.9\) Hz, 6H), 0.09 (s, 3H), 0.07 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 146.5, 145.9, 144.0, 114.9, 113.6, 112.7, 72.0, 62.5, 61.5, 59.4, 58.2, 37.2, 31.9, 30.3, 25.8, 18.3, 6.8, 4.4, -5.3, -5.4.

Aldehyde (E)-4-91 was used crude as it is inseparable from donor aldehyde after cross-condensation step (5:1 mixture). To a solution of aldehyde (E)-4-91 (178.9 mg, 0.249 mmol) in 5 mL of MeOH was added NaBH\(_4\) (10 mg, 0.261 mmol, 1.05 equiv) at 0 °C and the reaction mixture was stirred for 5 min. The reaction mixture was quenched with a saturated NH\(_4\)Cl solution and extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over MgSO\(_4\) and concentrated under reduced pressure. The residue was purified by flash column chromatography (gradient elution 5:1 → 2:1 hexanes:EtOAc) to afford alcohol S2 (110.0 mg 58% yield, based on \(^1\)H NMR) as an inseparable mixture with alcohol derived from donor aldehyde. Alcohol S2 was isolated as inseparable mixture of double bond isomers formed during allylic transposition step. The major isomer is designated by (*), the minor isomer is denoted by (†).\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.65–7.55 (m, 4H*, 4H†), 7.46–7.32 (m, 6H*, 6H†), 6.27 (d, \(J = 1.7\) Hz, 1H†), 6.20 (d, \(J = 2.0\) Hz, 1H*), 5.93 (t, \(J = 7.5\) Hz, 1H*), 5.80–5.69 (m, 1H*, 2H†), 5.67–5.57 (m, 1H*, 1H†), 5.40 (d, \(J = 8.5\) Hz, 1H*, 1H†), 5.22 (s, 1H*, 1H†), 5.16 (s, 1H*, 1H†), 5.05 (s, 1H*, 1H†), 5.00 (s, 1H*, 1H†), 4.85–4.83 (m, 1H†), 4.70–4.67 (m, 1H*), 4.63–4.55 (m, 1H*, 1H†), 4.50–4.46 (m, 1H*), 4.41–4.39 (m, 1H†), 4.04 (s, 2H*, 2H†), 3.65 (s, 3H*, 3H†), 3.52 (dd, \(J = 8.6\) Hz, \(J = 1.9\) Hz, 1H†), 3.40 (dd, \(J = 8.5\) Hz, \(J = 1.9\) Hz, 1H*, 2H†), 3.36 (d, \(J = 1.5\) Hz, 1H*), 3.18 (s, 2H*, 2H†), 2.91–2.85 (m, 2H*), 2.85–2.80 (m, 2H†), 2.63–2.57 (m, 2H*, 2H†), 2.51–2.44 (m, 2H*, 2H†), 2.37–2.29 (m, 1H*, 1H†), 2.24–2.14 (m, 1H*, 1H†), 1.77 (s, 3H*), 1.74 (s, 3H†), 0.16 (s, 9H*), 0.08 (s, 9H†); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 173.4, 155.8†, 155.7, 151.0, 146.2, 145.8, 144.1, 143.1, 139.3, 135.6†, 135.0,
134.8, 134.6, 134.3, 132.4, 132.0†, 130.2, 130.1, 129.6, 129.5†, 127.9, 127.8, 123.8, 121.2†, 118.8, 113.6, 113.0, 110.3†, 109.3, 72.6†, 72.5, 65.7, 63.1†, 62.5, 56.0, 54.6†, 51.6, 35.3, 34.3, 34.2†, 33.2, 32.9, 32.6†, 29.4, 24.7, 24.4†, 0.5, -1.5†; HRMS (ESI) calcd for C₄₁H₅₃O₅Si₂ [M+H]+: 681.3432, found 681.3433.

### Epoxidation:

To a suspension of activated molecular sieves (MS 4Å) in CH₂Cl₂ (100 mg in 6 mL) and (−)-D-DIPT (17.1 mg, 0.073 mmol) was added Ti(i-PrO)₄ (14.4 μL, 0.049 mmol) at 0 °C. The reaction mixture was cooled to −20 °C and solution of t-BuOOH (141 μL, 5.5 M in decane, 0.774 mmol) was added. The reaction mixture was stirred at -20 °C for 30 min and 2 mL of resultant suspension was added to a cold (−20 °C) suspension of crude alcohol S2 (110 mg, ~0.162 mmol) and MS (100 mg) in 1 mL of CH₂Cl₂ via syringe. The reaction flask was sealed and the reaction mixture was kept at −20 °C in freezer for 12 h without stirring. After this time the reaction mixture was filtered through a pad of celite. To the filtrate was added FeSO₄ solution (10 wt. %, 10 mL) and the reaction mixture was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure to give crude diepoxide S3 (137.9 mg, 88% yield based on ¹H NMR) as inseparable mixture with (−)-D-DIPT and alcohol derived from epoxyaldehyde.

### Iodination:

To a solution of crude epoxyalcohol S3 (121.5 mg) in 7 mL of CH₂Cl₂ were added PPh₃ (91.4 mg, 0.349 mmol) and imidazole (41.5 mg, 0.610 mmol) and the reaction mixture was cooled to 0 °C. Iodine (88.5 mg, 0.349 mmol) was then added and the reaction mixture was warmed to r.t. and stirred
under exclusion of light for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography (gradient elution 20:1 → 7:1 hexanes:EtOAc) to yield iododiepoxide 4-90 (79.4 mg, 73% yield based on \textsuperscript{1}H NMR) as a colorless oil. Iododiepoxide 4-90 was obtained as inseparable mixture of diastereomers. Minor isomers are denoted by (†).\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 7.66–7.54 (m, 4H), 7.49–7.32 (m, 6H), 6.35 (d, \(J = 1.8\) Hz, 1H†), 6.33 (s, 1H†), 6.27 (d, \(J = 1.8\) Hz, 1H), 5.94 (t, \(J = 7.5\) Hz, 1H), 5.81–5.69 (m, 1H), 5.68–5.56 (m, 1H), 5.37 (s, 1H†), 5.32 (s, 1H), 5.30 (s, 1H), 5.28 (s, 1H†), 5.26 (s, 1H†), 5.23 (s, 1H), 5.05 (s, 1H), 4.87–4.83 (m, 1H†), 4.71–4.67 (m, 1H), 4.64–4.55 (m, 1H), 4.50–4.47 (m, 1H), 4.42–4.39 (m, 1H†), 3.67 (s, 3H), 3.54 (d, \(J = 1.5\) Hz, 1H†), 3.52–3.47 (m, 1H†), 3.44 (s, 1H), 3.30 (d, \(J = 10.1\) Hz, 1H), 3.27 (d, \(J = 10.3\) Hz, 1H†), 3.14 (dd, \(J = 10.3\) Hz, \(J = 1.4\) Hz, 1H†), 3.06 (d, \(J = 10.1\) Hz, 1H), 3.02–2.80 (m, 6H), 2.66–2.58 (m, 2H), 2.53–2.45 (m, 2H), 2.33 (ddd, \(J = 17.3\) Hz, \(J = 9.9\) Hz, \(J = 2.0\) Hz, 1H), 2.21–2.10 (m, 1H), 1.78 (s, 3H), 1.74 (s, 3H†), 0.17 (s, 9H), 0.08 (s, 9H†); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) 173.3, 154.5, 151.0, 146.3, 145.8†, 145.5†, 145.3, 142.0, 141.5†, 139.2, 135.6†, 134.8, 134.6, 134.1, 132.2, 131.8†, 130.3, 130.2, 129.8, 129.6†, 128.0, 127.9, 122.7†, 120.5, 120.4†, 116.0†, 115.7, 114.4, 114.1†, 110.3†, 109.4, 72.6†, 72.5, 72.4†, 64.3†, 64.2, 64.0†, 62.2, 60.3†, 59.9†, 58.6†, 58.0, 56.1†, 55.8, 54.9†, 54.5†, 51.6, 35.0, 34.3, 34.0†, 33.9, 33.1, 32.6†, 29.1, 24.7, 24.4†, 9.4, 9.1†, 0.5, -1.5†; HRMS (ESI) calcd for C\textsubscript{41}H\textsubscript{52}IO\textsubscript{3}Si\textsubscript{2} [M+H]\textsuperscript{+}: 807.2398, found 807.2391.

In a Schlenk tube (2 mL) Me\textsubscript{3}SnOH (112 mg, 0.62 mmol, 10 equiv) was added to a solution of methyl ester 4-90 (50 mg, 0.062 mmol) in 500 \(\mu\)L of DCE. The Schlenk tube was sealed and placed in the preheated to 95 °C oil bath. The reaction mixture was stirred at this temperature for 3 h and cooled to r.t. The resultant yellow suspension was concentrated under reduced pressure and the residue was purified by
flash column chromatography (gradient elution 5:1 → 1:1 hexanes:EtOAc) to afford seco-acid S4 (48.5 mg, quantitative) as a colorless oil. Acid S4 was obtained as inseparable mixture of diastereomers. Minor isomers are denoted by (†). \(^1\)H NMR (500 MHz, CDCl\(_3\)) δ 7.65–7.53 (m, 4H), 7.48–7.33 (m, 6H), 6.35 (d, \(J = 1.4\) Hz, 1H†), 6.32 (s, 1H†), 6.26 (d, \(J = 1.6\) Hz, 1H), 5.93 (t, \(J = 7.5\) Hz, 1H), 5.80–5.69 (m, 1H), 5.66–5.55 (m, 1H), 5.36 (s, 1H†), 5.31 (s, 2H), 5.30–5.27 (m, 2H†), 5.24 (s, 1H), 5.06 (s, 1H), 4.85–4.82 (m, 1H†), 4.70–4.66 (m, 1H), 4.63–4.53 (m, 1H), 4.49–4.46 (m, 1H), 4.41–4.38 (m, 1H†), 3.54 (s, 1H†), 3.51–3.47 (m, 1H†), 3.43 (s, 1H), 3.30 (d, \(J = 10.1\) Hz, 1H), 3.27 (d, \(J = 10.3\) Hz, 1H†), 3.13 (d, \(J = 10.2\) Hz, 1H†), 3.04 (d, \(J = 10.1\) Hz, 1H), 3.00–2.80 (m, 6H), 2.66–2.57 (m, 2H), 2.56–2.49 (m, 2H), 2.32 (ddd, \(J = 17.2\) Hz, \(J = 9.8\) Hz, \(J = 1.7\) Hz, 1H), 2.20–2.09 (m, 1H), 1.77 (s, 3H), 1.74 (s, 3H†), 0.16 (s, 9H), 0.08 (s, 9H†); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) δ 178.7, 154.5, 151.0, 147.6†, 146.3, 145.8†, 145.1†, 145.0, 142.0, 141.4†, 139.2, 135.6†, 134.8, 134.6, 134.0, 132.2, 131.8†, 130.3, 130.2, 129.8, 129.6†, 128.0, 127.9, 122.8†, 120.6, 116.1†, 115.8, 114.6, 114.2†, 110.3†, 109.4, 72.6†, 72.5, 72.4†, 64.1, 64.0†, 62.2, 60.4†, 59.9†, 58.6†, 58.0, 56.1†, 55.7, 54.9†, 35.1†, 35.0, 34.3, 34.0†, 33.9, 33.0, 32.6†, 28.7, 24.7, 24.4†, 9.3, 9.1†, 0.5, -1.5†; HRMS (ESI) calcd for C\(_{40}\)H\(_{50}\)O\(_3\)Si\(_2\) [M+H]\(^+\): 793.2242, found 793.2239.

To a solution of epoxyiodide S4 (50 mg, 0.064 mmol) in 3 mL of Et\(_2\)O (0.02 M) was added \(t\)-BuLi (76 μL, 1.7 M in pentane, 0.128 mmol, 2 equiv) at −120 °C (Trapp mixture: THF/Et\(_2\)O/pentane = 4:1:1) and the reaction mixture was stirred for 2 min. The reaction mixture was quenched cold with MeOH followed by saturated NH\(_4\)Cl solution at 0 °C and extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over MgSO\(_4\) and concentrated under reduced pressure. The residue was purified by flash column chromatography (gradient elution 2:1 → 1:1 hexanes:EtOAc) to afford acid alcohol 4-89 (34.3 mg, 81%) as a colorless oil. Acid alcohol 4-89 was obtained as an inseparable mixture
of diastereomers. Minor isomers are denoted by (†). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.66–7.55 (m, 4H), 7.48–7.32 (m, 6H), 6.31 (s, 1H†), 6.24 (d, \(J = 1.8\) Hz, 1H), 5.93 (t, \(J = 7.5\) Hz, 1H), 5.80–5.70 (m, 1H), 5.67–5.56 (m, 1H), 5.31–5.25 (m, 2H), 5.24–5.21 (m, 2H†), 5.14 (s, 1H), 5.12 (s, 1H†), 5.10 (s, 1H), 5.07 (s, 1H†), 5.01 (s, 1H), 4.99 (s, 1H†), 4.94 (s, 1H†), 4.86–4.82 (m, 1H†), 4.71–4.66 (m, 1H), 4.63–4.54 (m, 1H), 4.50–4.47 (m, 1H), 4.42–4.38 (m, 1H†), 4.37 (d, \(J = 3.0\) Hz, 1H†), 4.35 (d, \(J = 3.0\) Hz, 1H†), 4.07 (d, \(J = 4.3\) Hz, 1H), 3.63 (d, \(J = 1.7\) Hz, 1H†), 3.59 (d, \(J = 1.6\) Hz, 1H†), 3.52 (d, \(J = 1.7\) Hz, 1H†), 3.48 (d, \(J = 1.7\) Hz, 1H), 3.17 (d, \(J = 16.3\) Hz, 1H), 3.10–2.99 (m, 2H), 2.91–2.85 (m, 2H), 2.85–2.79 (m, 2H†), 2.65–2.47 (m, 4H), 2.34 (ddd, \(J = 17.3\) Hz, \(J = 9.9\) Hz, \(J = 1.9\) Hz, 1H), 2.23–2.11 (m, 1H), 1.77 (s, 3H), 1.73 (s, 3H†), 0.16 (s, 9H), 0.08 (s, 9H†); \(^1\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 178.5, 155.3†, 155.1, 151.0, 146.3, 145.9, 144.8, 144.6†, 143.5, 139.3, 135.6†, 134.8, 134.6, 134.2, 132.3, 131.9†, 130.3, 130.2, 129.7, 129.5†, 128.0, 127.9, 120.1, 119.6†, 115.2, 114.2†, 113.9, 113.6, 110.3†, 109.4, 72.9, 72.7†, 72.6, 72.4†, 71.3†, 61.3, 61.0†, 59.6†, 59.0, 37.8, 37.3†, 37.2†, 35.1, 34.3, 34.1†, 33.1, 32.6†, 29.7†, 28.7, 24.7, 24.4†, 0.5, -1.5†; HRMS (ESI) calcd for C\(_{40}\)H\(_{51}\)O\(_5\)Si\(_2\) [M+H]\(^+\): 667.3275, found 667.3290.

To a solution of acid \(\mathbf{4-89}\) (30 mg, 0.045 mmol) in 5 mL of CH\(_2\)Cl\(_2\)–MeOH mixture (3:2) was added TMSCHN\(_2\) (34 \(\mu\)L, 2 M in Et\(_2\)O, 0.067 mmol, 1.5 equiv) at r.t. The reaction mixture was stirred for 5 min and concentrated under reduced pressure. The residue was purified by flash column chromatography (gradient elution: 10:1 → 3:1 hexanes:EtOAc) to afford methyl ester \(\mathbf{4-118}\) (28.0 mg 92%) as a colorless oil. Ester \(\mathbf{4-118}\) was obtained as an inseparable mixture of diastereomers. Minor isomers are denoted by (†). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.65–7.55 (m, 4H), 7.48–7.33 (m, 6H), 6.31 (s, 1H†), 6.24 (d, \(J = 1.9\) Hz, 1H), 5.93 (t, \(J = 7.5\) Hz, 1H), 5.80–5.69 (m, 1H), 5.67–5.56 (m, 1H), 5.30–5.25 (m, 2H), 5.24–5.21 (m, 2H†), 5.12 (s, 1H), 5.09 (s, 1H), 5.09–5.06 (m, 2H†), 5.01 (s, 1H), 4.99 (s, 1H†), 4.97 (s, 1H), 4.92 (s,
1H†), 4.86–4.82 (m, 1H†), 4.70–4.67 (m, 1H), 4.63–4.54 (m, 1H), 4.50–4.47 (m, 1H), 4.41–4.38 (m, 1H†), 4.37–4.33 (m, 2H†), 4.10–4.03 (m, 1H), 3.67 (s, 3H†), 3.66 (s, 3H), 3.62 (d, J = 1.8 Hz, 1H†), 3.58 (d, J = 1.7 Hz, 1H†), 3.52–3.50 (m, 1H†), 3.47 (d, J = 1.8 Hz, 1H), 3.17 (d, J = 16.2 Hz, 1H), 3.09–2.99 (m, 2H), 2.91–2.85 (m, 2H), 2.85–2.80 (m, 2H†), 2.64–2.55 (m, 2H), 2.51–2.45 (m, 2H), 2.34 (ddt, J = 17.3 Hz, J = 9.9 Hz, J = 2.0 Hz, 1H), 2.23–2.10 (m, 1H), 1.77 (s, 3H), 1.74 (s, 3H†), 0.16 (s, 9H), 0.08 (s, 9H†); 13C NMR (125 MHz, CDCl₃) δ 173.5, 155.4†, 155.2, 151.0, 146.3, 146.0, 145.8†, 145.3†, 145.1, 144.9†, 143.6, 139.3, 135.6†, 134.8, 134.6, 134.2, 132.3, 131.9†, 130.3, 130.2, 129.7, 129.5†, 128.0, 127.9, 122.1†, 120.0, 119.6†, 115.3†, 115.22†, 115.15, 114.2†, 113.8, 113.6†, 113.5, 110.3†, 109.4, 72.9, 72.7, 72.6, 72.4†, 71.4†, 71.3†, 61.3, 61.0†, 59.6†, 58.9, 58.2†, 57.6†, 51.6, 37.9, 37.4†, 37.3†, 35.2†, 35.1, 34.4, 34.1†, 33.2, 32.6†, 29.7†, 29.1, 24.7, 24.4†, 0.5, -1.5†; HRMS (ESI) calcd for C₄₃H₅₃O₅Si₂ [M+H]^+: 681.3432, found 681.3428.

To a solution of ester 4-118 (11 mg, 0.018 mmol) in 600 µL of THF–MeOH–H₂O mixture (10:9:1) was added AgF (10.2 mg, 0.081 mmol, 5 equiv) and the reaction mixture was stirred at r.t. for 2 h under exclusion of light. The reaction mixture was quenched saturated NaHCO₃ solution and extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (gradient elution 5:1 → 1:1 hexanes:EtOAc) to give diol S₅ (1.7 mg, 26%) as a colorless oil. 1H NMR (500 MHz, CDCl₃) δ 6.15 (d, J = 15.6 Hz, 1H), 5.72 (ddt, J = 15.2 Hz, J = 6.3 Hz, J = 0.7 Hz, 1H), 5.63 (dt, J = 15.6 Hz, J = 6.8 Hz, 1H), 5.51 (ddt, J = 15.3 Hz, J = 6.7 Hz, J = 1.3 Hz, 1H), 5.31 (s, 1H), 5.28 (s, 1H), 5.26 (s, 1H), 5.13 (s, 2H), 5.08 (s, 1H), 5.02–4.96 (m, 2H), 4.89 (s, 2H), 4.22–4.15 (m, 1H), 4.09–4.03 (m, 1H), 3.67 (s, 3H), 3.46 (d, J = 2.2 Hz, 1H), 3.16 (d, J = 16.2 Hz, 1H), 3.11–3.02 (m, 2H), 2.88–2.82 (m, 2H), 2.64–2.57 (m, 2H),
Representative Procedure for Direct Cross-Aldol Condensation of Epoxyaldehydes and Acceptor Aldehydes with Stoichiometric Amount of Proline:

To a solution of acceptor aldehyde 4-83 (50 mg, 0.231 mmol) in 230 μL of DMF (1 M) were added activated molecular sieves (MS, 4Å, 100 mg) and L-proline (26.6 mg, 0.231 mmol, 1 equiv) and the reaction mixture was cooled to 0 °C. Under vigorous stirring solution of donor aldehyde (34 μL, 0.277 mmol, 1.2 equiv) in DMF (250 μL, 1.1 M) was added to the reaction mixture over 4.5 h at 0 °C via a syringe pump. After completion of the addition, the reaction mixture was stirred for additional 1 h and resultant suspension was diluted with EtOAc and filtered through a pad of celite. The collected filtrate was washed with NaCl solution (10 wt. %, 3 x 10 mL) and combined aqueous phase was extracted with EtOAc (1 x 10 mL). The combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (gradient elution 50:1 → 20:1 hexanes:EtOAc) to afford epoxyaldehyde 4-102a (52.6 mg, 76%) as a colorless liquid. ^1H NMR (500 MHz, CDCl₃) δ 9.41 (s, 1H), 6.23 (d, J = 8.0 Hz, 1H), 3.86–3.76 (m, 3H), 3.47–3.42 (m, 1H), 2.47–2.28 (m, 2H), 1.45–1.28 (m, 4H), 0.94–0.86 (m, 12H), 0.09 (s, 3H), 0.07 (s, 3H); ^13C NMR (125 MHz, CDCl₃) δ 193.4, 147.9, 146.1, 61.5, 59.6, 52.5, 31.1, 25.8, 24.0, 22.6, 18.3, 13.8, -5.3, -5.4; HRMS (ESI) calcd for C₁₆H₃₁O₃Si [M+H]⁺: 299.2042, found 299.2049.
Procedure for Direct Cross-Aldol Condensation of Epoxyaldehydes and Acceptor Aldehydes with Catalytic Amount of Proline:

Under vigorous stirring to a suspension of L-proline (8.0 mg, 0.069 mmol, 30 mol %) and activated molecular sieves (MS, 4Å, 100 mg) in 250 μL of DMSO was added 230 μL of a DMSO solution (1.0 M) containing acceptor aldehyde 4-83 (50 mg, 0.231 mmol) and donor aldehyde (39 μL, 0.323 mmol, 1.4 equiv) over 4.5 h at 20 °C via a syringe pump. After completing the addition, the reaction mixture was stirred for additional 1 h and resultant suspension was diluted with EtOAc and filtered through a pad of celite. The collected filtrate was washed with an NaCl solution (10 wt. %, 3 x 10 mL) and the combined aqueous phase was extracted with EtOAc (1 x 10 mL). The combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (gradient elution 50:1 → 20:1 hexanes:EtOAc) to afford epoxyaldehyde 4-102a (42.8 mg, 62%) as a colorless liquid.

Colorless liquid (73% yield); \(^1H\) NMR (500 MHz, CDCl₃) \(\delta\) 9.43 (s, 1H), 6.29–6.26 (m, 1H), 3.86–3.74 (m, 3H), 3.45–3.41 (m, 1H), 1.89 (d, \(J = 1.2\) Hz, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); \(^13C\) NMR (125 MHz, CDCl₃) \(\delta\) 193.6, 145.8, 143.1, 61.5, 59.4, 52.6, 25.8, 18.3, 9.6, -5.3, -5.4; HRMS (ESI) calcd for C₁₃H₂₅O₃Si [M+H]⁺: 257.1573, found 257.1566.

Reaction was run with 30 mol % of L-Pro. Yellow oil (71% yield); \(^1H\) NMR (500 MHz, CDCl₃) \(\delta\) 9.67 (s, 1H), 7.47–7.37 (m, 3H), 7.32–7.28 (m, 2H), 6.53 (d, \(J = 8.1\) Hz, 1H), 3.97 (dd, \(J = 11.7\) Hz, \(J = 5.1\) Hz, 1H), 3.88 (dd, \(J = 11.7\) Hz, \(J = 5.1\) Hz,
Donor aldehyde for condensation was obtained according to literature procedure.\textsuperscript{62}

Epoxyaldehyde 4-102d (yellow oil, 79\% yield) was isolated as inseparable mixture of double bond isomers, $dr = 17.5:1$. The minor isomer is designated by (†).\textsuperscript{1H}

\textbf{NMR} (500 MHz, CDCl$_3$) $\delta$ 9.92 (s, 1H†), 9.43 (s, 1H), 7.33–7.21 (m, 5H), 6.99 (d, $J = 7.8$ Hz, 1H), 6.05 (d, $J = 7.2$ Hz, 1H†), 4.21 (dd, $J = 7.2$ Hz, $J = 4.4$ Hz, 1H†), 4.18 (dd, $J = 7.8$ Hz, $J = 4.5$ Hz, 1H), 3.85 (dd, $J = 12.3$ Hz, $J = 3.2$ Hz, 1H), 3.84 (dd, $J = 7.2$ Hz, $J = 5.1$ Hz, 1H), 3.66 (dd, $J = 7.2$ Hz, $J = 4.6$ Hz, 1H), 3.44–3.40 (m, 1H), 0.92 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); \textbf{13C NMR} (125 MHz, CDCl$_3$) $\delta$ 185.5, 165.9, 148.0, 134.7, 134.6, 131.9, 124.1, 61.2, 60.4, 52.3, 25.8, 18.3, −5.3, −5.4; \textbf{HRMS} (ESI) calcd for C$_{20}$H$_{26}$NO$_5$Si [M+H]$^+$: 388.1580, found 388.1587.

Donor aldehyde for condensation was obtained according to literature procedure.\textsuperscript{63}

Cross-condensation was run with 30 mol \% of L-Pro. Epoxyaldehyde 4-102e was obtained as a pale yellow oil (67\% yield); \textsuperscript{1H NMR} (500 MHz, CDCl$_3$) $\delta$ 9.49 (s, 1H), 7.95–7.90 (m, 2H), 7.82–7.77 (m, 2H), 7.01 (d, $J = 7.2$ Hz, 1H), 4.05 (dd, $J = 12.3$ Hz, $J = 3.2$ Hz, 1H), 3.84 (dd, $J = 12.3$ Hz, $J = 5.1$ Hz, 1H), 3.66 (dd, $J = 7.2$ Hz, $J = 4.6$ Hz, 1H), 3.44–3.40 (m, 1H), 0.92 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); \textbf{13C NMR} (125 MHz, CDCl$_3$) $\delta$ 185.5, 165.9, 148.0, 134.7, 134.6, 131.9, 124.1, 61.2, 60.4, 52.3, 25.8, 18.3, −5.3, −5.4; \textbf{HRMS} (ESI) calcd for C$_{20}$H$_{26}$NO$_5$Si [M+H]$^+$: 388.1580, found 388.1587.

Donor aldehyde for condensation was obtained by ozonolysis of 1-methyl-1-cyclohexene. Epoxyaldehyde 4-102f was obtained as a pale yellow oil (69\% yield); \textsuperscript{1H NMR} (500 MHz, CDCl$_3$) $\delta$ 9.39 (s, 1H), 6.28 (d, $J = 8.1$ Hz, 1H), 3.88 (dd, $J = 8.1$ Hz, $J = 4.4$ Hz, 1H), 3.85–3.77 (m, 2H), 3.47–3.42 (m, 1H), 2.45 (t, $J = 7.0$ Hz, 2H), 2.43–2.30 (m, 2H), 2.12 (s, 3H), 1.71–1.62 (m, 2H), 0.88 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); \textbf{13C NMR} (125 MHz,
Representative Procedure for Direct Cross-Aldol Condensation of Epoxyaldehydes and Ketones with Stoichiometric Amount of Proline:

To a solution of cyclohexanone (48 μL, 0.462 mmol, 2 equiv) in 250 μL of DMSO were added activated molecular sieves (MS, 4Å, 100 mg) and L-proline (26.6 mg, 0.231 mmol, 1 equiv). Under vigorous stirring solution of epoxyaldehyde 4-83 (50 mg, 0.231 mmol) in 230 μL of DMSO (1.0 M) was added to the reaction mixture over 4.5 h via syringe pump. After completing the addition, the reaction mixture was stirred for additional 2 h and resultant suspension was diluted with EtOAc and filtered through a pad of celite. The collected filtrate was washed with an NaCl solution (10 wt. %, 3 x 10 mL) and combined aqueous phase was extracted with EtOAc (1 x 10 mL). The combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (gradient elution 20:1 → 5:1 hexanes:EtOAc) to afford epoxyaldehyde 4-102g (43.7 mg, 64%) as a pale yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 6.32–6.26 (m, 1H), 3.76–3.71 (m, 2H), 3.61 (dd, J = 8.0 Hz, J = 4.4 Hz, 1H), 3.36–3.31 (m, 1H), 2.80–2.70 (m, 1H), 2.63–2.53 (m, 1H), 2.45 (t, J = 6.6 Hz, 2H), 1.94–1.83 (m, 2H), 1.83–1.74 (m, 2H), 0.88 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 199.5, 141.5, 131.0, 61.9, 59.2, 52.4, 40.1, 27.2, 25.8, 23.4, 23.2, 18.3, -5.3, -5.4; HRMS (ESI) calcd for C₁₆H₂₉O₃Si [M+H]+: 297.1886, found 297.1885.

Pale yellow oil (69% yield); ¹H NMR (500 MHz, CDCl₃) δ 6.51–6.47 (m, 1H), 4.77 (dd, J = 15.3 Hz, J = 2.0 Hz, 1H), 4.63 (dd, J = 15.3 Hz, J = 1.9 Hz, 1H), 4.06–3.95 (m, 2H), 3.76–3.66 (m, 2H), 3.50 (dd, J = 7.4 Hz, J = 4.4 Hz, 1H), 3.37–3.31 (m, 1H), 2.67–2.54 (m, 2H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 194.2,
137.9, 131.3, 67.1, 65.3, 61.6, 59.0, 51.9, 39.6, 25.8, 18.2, -5.3, -5.4; HRMS (ESI) calcd for C_{15}H_{27}O_{4}Si [M+H]^+: 299.1679, found 299.1676.

Yellow oil (78% yield); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 6.42–6.38 (m, 1H), 3.75–3.67 (m, 2H), 3.58–3.52 (m, 2H), 3.45–3.39 (m, 1H), 3.36–3.31 (m, 1H), 2.79–2.69 (m, 2H), 2.64–2.52 (m, 2H), 2.43 (s, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 195.8, 137.7, 131.4, 61.8, 59.2, 56.0, 52.5, 52.1, 46.0, 38.9, 25.8, 18.2, -5.3, -5.4; HRMS (ESI) calcd for C_{16}H_{30}NO_{3}Si [M+H]^+: 312.1995, found 312.1987.

Pale yellow oil (19% yield); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 6.28 (d, \(J = 7.9\) Hz, 1H), 3.74 (d, \(J = 5.3\) Hz, 2H), 3.66 (dd, \(J = 7.9\) Hz, \(J = 4.4\) Hz, 1H), 3.35–3.30 (m, 1H), 2.65–2.51 (m, 4H), 1.82–1.65 (m, 6H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 203.0, 145.8, 131.2, 61.9, 59.2, 52.5, 42.9, 31.2, 29.7, 27.7, 25.8, 25.2, 18.3, -5.3, -5.4; HRMS (ESI) calcd for C_{17}H_{31}O_{3}Si [M+H]^+: 311.2042, found 311.2050.
4.7. References


Appendix I

Selected NMR Spectra for Part I
Appendix II

Selected NMR Spectra for Part II
OH

2-119a OH
trans-2-120a (less polar isomer)

+ cis-2-120a (more polar isomer)

Chemical Shift (ppm)

9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0

Chemical Shift (ppm)

10.57 6.11 2.01 2.00

Chemical Shift (ppm)

192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0 -8
cis-2-120a
(more polar isomer)
trans-2-120b (less polar isomer) + cis-2-120b (more polar isomer)

(2:1:1)
trans-2-120b
(less polar isomer)
cis-2-120b
(more polar isomer)
trans-2'-120d
(less polar isomer)

(2.7:1)

cis-2'-120d
(more polar isomer)
trans-2-120d
(less polar isomer)
cis-2-120d
(more polar isomer)
Chemical Shift (ppm)

\[
\begin{array}{c}
7.22 \\
5.99 \\
4.0, 3.9, 3.8 \\
1.19, 1.00 \\
\end{array}
\]

**trans-2-120e**
(less polar isomer)

**cis-2-120e**
(more polar isomer)

(1:2:1)
trans-2-120e
(less polar isomer)
c/s-2-120e
(more polar isomer)
trans-2-120h
(less polar isomer)

+ cis-2-120h
(more polar isomer)

Chemical Shift (ppm)

2.99
1.30

(2.3:1)
trans-2-120h
(less polar isomer)
After one week:

![Chemical shift spectrum after one week]

After a month:

![Chemical shift spectrum after a month]
cis-2-120J
(less polar isomer)

trans-2-120J
(more polar isomer)

(2.3:1)
c/s-2-120j
(less polar isomer)
After one week:

![Chemical Shift Spectrum (9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0)](image1)

After two weeks:

![Chemical Shift Spectrum (9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0)](image2)

After a month:

![Chemical Shift Spectrum (9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0)](image3)
trans-2-120j
(more polar isomer)
After one week:

After two weeks:

After a month:
Appendix III

Selected NMR Spectra for Part III
3-279f
C_{5}H_{11} Ph_{2}

3-279i

PPM

158.577
141.087
136.613
135.729
135.077
129.552
127.649
120.418
116.311
114.209
74.760
42.770
31.777
26.465
24.558
22.591
14.052
3-280j
enantiomer

racemate
C₃H₁₁
OH
\[\text{racemic}\]

C₂H₁₁
OH
\[79\% \text{ ee}\]

Retention Time

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Appendix IV

Selected NMR Spectra for Part IV
enantiomer

\[
\text{Ph} - \text{OH} + \text{Ph}_2\text{SiCl} \xrightarrow{\text{DMAP}} \text{Ph}_2\text{SiO} - \text{Ph}
\]

racemate

\[
\text{Ph} - \text{OH} + \text{Ph}_2\text{SiCl} \xrightarrow{\text{DMAP}} \text{Ph}_2\text{SiO} - \text{Ph}
\]
Chemical Shift (ppm)

Ph\(\text{O}\)\text{Si}Me

\(\text{Ph}\text{O}\)\text{Si}Me

\(- 5\%\)
Chemical Shift (ppm)
2.09
0.50
1.21
0.37
3.91
0.16
1.21
0.16
1.26
1.00
1.18
5.17
7.64
2.49

192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0

-1.47
134.65
134.86
135.14
139.38
146.20
151.00
152.61
154.03
155.93
enantiomer

\[
\text{Ph}_2\text{Si}O\overset{82.18}{\text{OH}}\text{SiMe}_3
\]

\[
\text{Ti(O^t\text{Pr})}_4, (-)-\text{DIPT} \rightarrow \text{Ph}_2\text{Si}O\overset{82.18}{\text{OH}}\text{SiMe}_3
\]

\[
\text{MS, DCM, } -20 \degree C \rightarrow \text{4-67, 88:12 d.r. SiMe}_3
\]

racemate

\[
\text{Ph}_2\text{Si}O\overset{82.18}{\text{OH}}\text{SiMe}_3
\]

\[
\text{Ti(O^t\text{Pr})}_4, (-)-\text{DIPT} \rightarrow \text{Ph}_2\text{Si}O\overset{82.18}{\text{OH}}\text{SiMe}_3
\]

\[
\text{MS, DCM, } -20 \degree C \rightarrow \text{rac-4-66, SiMe}_3
\]
(E)-4-91, 82.18 d.r.

nOe

Chemical Shift (ppm)

Chemical Shift (ppm)
(E)-4-91, 82:18 d.r.
(Z)-4-91
4:1 d.r.

Chemical Shift (ppm)

nOe

Ha

Hb
4-116, 82:18 d.r.
Chemical Shift (ppm)

0.70 2.46 0.46 2.03 0.45 0.98 0.24 0.96 0.24 2.40 2.46 1.29 4.89

Chemical Shift (ppm)

14.15 14.25 36.67 39.80 60.29 60.52 76.74 77.25 116.74 117.37 119.83 120.49 121.68 128.08 130.42 132.71 133.87 134.90 143.94 147.80 154.58 154.63 166.92
4-84 (top diastereomer)
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