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## New synthetic strategies for the stereocontrolled synthesis of substituted “skipped” diepoxides

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### Abstract

This report describes a number of new synthetic approaches towards methyl-substituted mono- and diepoxy alcohols that serve as substrates for *endo*-selective epoxide-opening cascades. The key transformations involve the manipulation of alkynes. Highlighted are the directed methylmetalation of bishomopropargylic alcohols, the bromoallylation of alkynes, and Pd-catalyzed cross-coupling between an alkenyl boronate ester and allylic bromides.

### 1. Introduction

Skipped dienes, also known as 1,4- or homoconjugated dienes, are a key structural motif found in a number of important natural products, including several leukotrienes, the omega-3 fatty acids, insect pheromones,<sup>i</sup> and the macrolide amphidinolide A, among many others. Skipped polyene structures are also notable for their proposed intermediacy in the biosynthesis of ladder polyether natural products (such as brevetoxin B, **3**, Scheme 1).

These natural products, notorious for their acute toxicity and for the environmental destruction they wreak, have long fascinated organic chemists due to their intriguing mixture of structural complexity and stereochemical uniformity.<sup>ii</sup> It was Nakanishi who, nearly 25 years ago, advanced a concise proposal for the biosynthesis of brevetoxin B and other ladder polyethers, a synthesis that culminates in a cascade of regio- and stereospecific epoxide openings.<sup>iii</sup> The appeal of this hypothesis lies in its economy. *In vivo*, a single stereoselective epoxidase, chemoselective for *E* alkenes, acting on polyene **1** could generate all (*R,R*)-“skipped polyepoxide” **2**, which could in turn undergo an all-*endo* cascade of epoxide-opening cyclizations to afford brevetoxin B, **3**.<sup>iv</sup>

Abbreviated skipped polyenes similar to **1** can be useful substrates for epoxidation and subsequent studies of biomimetic *in vitro* epoxide-opening cascades. Construction of these polyepoxides requires a protocol that is reliably highly (*R,R*)- or (*S,S*)-selective for a wide variety of *trans*-disubstituted and trisubstituted alkenes. The powerful Shi asymmetric epoxidation,<sup>v</sup> in which the active catalyst is a chiral dioxirane generated *in situ* from a simple, fructose-derived ketone, has emerged as just such a method. If asymmetric epoxidations of this

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type are justifiably taken to be something of a “solved problem,” the stereocontrolled synthesis of the necessary *trans*-disubstituted and *E*-trisubstituted alkenes (and polyenes) then becomes the primary challenge.

The difficulty of synthesizing highly substituted alkenes with careful stereo- and regiocontrol is well documented.<sup>vi</sup> Furthermore, the construction of skipped dienes can be additionally troublesome due to the rather delicate doubly allylic protons found in these compounds. The  $pK_a$  of 1,4-pentadiene (divinylmethane) in DMSO is approximately 35,<sup>vii</sup> making doubly allylic protons sensitive to strong base, and the same C-H bonds are also susceptible to hydrogen atom abstraction,<sup>viii</sup> which can lead to subsequent di- $\Pi$ -methane rearrangement.<sup>ix</sup> Thus the synthesis of skipped dienes and polyenes must generally avoid very strong bases (such as alkylolithiums) and reagents that promote single electron processes.

### 1.1. Previous Work

Strategies for skipped polyenes previously explored in our group targeted the synthesis of trimethylsilyl (TMS)-substituted skipped polyenes<sup>x</sup> and all-*trans*-disubstituted polyenes<sup>xi</sup> from bishomopropargylic alcohol **4** (Scheme 2). These polyenes were then transformed into the polyepoxy alcohols **5** and **6**, respectively, with high diastereoselectivity via Shi epoxidation. Polyepoxy alcohols **5** and **6** then underwent *endo*-selective epoxide-opening cascades (accompanied by concomitant protodesilylation in reactions of **5**) to afford THP tetrad **7**, a characteristic structural subunit of the ladder polyether natural products.<sup>10,11</sup>

Versatile alkyne **4** was transformed into the skipped triene precursor to **5** via the copper-mediated cross-coupling of a propargyl nucleophile and a TMS-substituted alkenyl iodide.<sup>10c</sup> The all-*trans*-disubstituted triene precursor to **6** was obtained from dissolving metal reduction of a skipped triyne. Thus the two quite differently substituted triepoxides **5** and **6** could both be straightforwardly derived from common intermediate **4**, and both **5** and **6** cyclized to afford tetrad **7**.

It is notable that the ring junctions of **7** are all hydrogen-substituted. A cursory glance at the ladder polyether natural products reveals that methyl (Me) substituents are also frequently encountered at ring junctions (as in brevetoxin B (**3**, Scheme 1), which bears Me groups at five of its ten ring junctions). Methyl substituents also appear in **1** and **2**, Nakanishi's hypothesized polyepoxide and polyene precursors to brevetoxin B. The Me groups that decorate the trisubstituted epoxides of **2** are encountered both *distal* and *proximal* to the internal nucleophile.<sup>xii</sup> This point is critical, as the Me group can exert a rather powerful directing effect on the regioselectivity of epoxide opening, particularly under acidic activation.<sup>xiii</sup>

We recently reported that water overcomes methyl group directing effects in *endo*-selective epoxide-opening cyclizations to enable the rapid construction of fused tetrahydropyran (THP) bicycles and tricycles with the incorporation of angular Me groups.<sup>xiv</sup> In that report we described the effects of Me substitution in epoxide-opening reactions of diversely methyl-substituted mono- and diepoxy alcohols **8–12** (Scheme 3). The key propargylation and dissolving metal reactions used for diene and triene syntheses en route to **5** and **6** were unfortunately not readily amenable to the controlled incorporation of Me substituents into alkenes and skipped polyenes. We were therefore obligated to develop a number of new synthetic strategies for the synthesis of **8–12**. We herein describe these strategies for the stereo- and regiocontrolled synthesis of trisubstituted epoxides (and their trisubstituted alkene precursors). Two of the key transformations highlighted in this work, Thompson's directed methylmetalation of alkynes<sup>xv</sup> and Kaneda's haloallylation of alkynes,<sup>xvi</sup> have to our knowledge been rather infrequently used in total synthesis and related applications, but both methods have proved indispensable to our work. Furthermore, all of the syntheses detailed here

begin from common intermediate **4**. We believe that this work further emphasizes the utility and versatility of alkyne **4** as a synthetic platform.

## 2. Results and Discussion

### 2.1. Monoepoxide Syntheses

Bishomopropargylic alcohol **4** is prepared easily on a gram scale in five steps from 2,3-dihydropyran.<sup>xvii</sup> We began our exploration into new transformations of **4** by tackling the synthesis of monoepoxy alcohol **8**. Compound **8** bears a *proximal* methyl substituent and is therefore Me-substituted at both sides of the epoxide. Consequently, we planned to approach **8** via *syn*-selective 1,2-difunctionalization of alkyne **4** (or a protected derivative of **4**).

Repeated attempts at 1,2-difunctionalization of **4** and its TBS ether **13** via Negishi carbometalation<sup>xviii</sup> resulted either in very low or undetectable conversion under standard conditions (2 equiv AlMe<sub>3</sub> and 1 equiv Cp<sub>2</sub>ZrCl<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub> or 1,2-dichloroethane at room temperature) (Scheme 4). Heating above 30° C led only to the decomposition of starting material. Attempted methylaluminumation of **4** and **13** with the stoichiometric addition of water according to the modified protocol of Wipf and Lim<sup>xix</sup> likewise led to poor conversion and significant decomposition. Similarly, methylcupration<sup>xx</sup> of **13** was too slow to be practical. Thus the highly beguiling rapid, *syn*-stereoselective methylmetalation for the eventual 1,2-dimethylation of alkynes was unfortunately but a siren's song, leading only to failure in our early studies.

Other attempts at 1,2-difunctionalization of **13** via silylcupration and stannylcupration<sup>xxi</sup> were also unsuccessful, with low conversion observed in all cases and only stannylcupration<sup>xxii</sup> yielding even a trace of the desired adduct.

It appeared that **4** and **13** were relatively inert under standard *undirected* carbometalation and metallometalation conditions. In the case of **13**, the minimal alkyne reactivity may perhaps be due to the steric demand of the neighboring bulky silyl group in the lowest energy conformer of the molecule (alkyne and silyl ether both equatorial).

This inferred proximity could be turned to our advantage, however, in carbometalation *directed* by the free hydroxyl group in **4** (Scheme 4). Thompson's method for the directed methylmetalation of propargylic, homopropargylic, and bishomopropargylic alcohols with TiCl<sub>4</sub> and AlMe<sub>3</sub>,<sup>15</sup> recently used in the total synthesis of (–)-borrelidin by the Omura group,<sup>xxiii</sup> proved highly effective. Methylmetalation of **4**, I<sub>2</sub> treatment, and subsequent silyl protection afforded alkenyl iodide **16** in a modest 41% yield, but with >20:1 regio- and stereoselectivity.

Alkenyl iodide **16** could be transformed into epoxide-opening cyclization substrate **8** in three simple steps via Negishi coupling with dimethylzinc, Shi asymmetric epoxidation (Shi AE), and TBAF-induced deprotection of the TES ether (Scheme 5). The Shi asymmetric epoxidation step proceeded with considerably lower than is typically observed in Shi epoxidations of trisubstituted alkenes. We conjecture that this poor diastereoselectivity arises from a mismatched relationship between the chiral dioxirane epoxidation agent and the stereocenters of the neighboring THP ring. However, as we have not attempted epoxidation with the antipodal ketone catalyst (derived from expensive L-fructose), we cannot confirm this hypothesis.

With epoxy alcohol **8** in hand, we turned to the synthesis of its isomer **9**, an epoxide-opening cyclization substrate that bears a *distal* Me substituent (located on the far side of the epoxide with respect to the alcohol). This Me group was appended via alkylation of a derivative of

alkyne **4** with iodomethane to afford bishomopropargylic alcohol **19** (Scheme 6). As the synthetic elaboration of internal alkyne **19** requires the incorporation of only one additional Me group, we initially attempted to perform a hydrometalation/methylation sequence on **19** and its silyl-protected derivatives with Schwartz's reagent, DIBAL, or 9-BBN, but observed in all cases low yield, poor regioselectivity, or both.

Instead of hydrometalation, standard Thompson carbometalation conditions (2.2 equiv  $\text{AlMe}_3$  and 1.1 equiv  $\text{TiCl}_4$  in  $\text{CH}_2\text{Cl}_2$  at  $-78^\circ$ ) proved best. Upon quenching with aqueous acid, carbometalation smoothly afforded trisubstituted alkene **20** in 70% yield (79% based on recovered starting material) and with no observable trace of undesired regio- or stereoisomers. Silyl protection, asymmetric epoxidation, and deprotection then provided distally Me-substituted epoxy alcohol **9**.

## 2.2. Diepoxide Syntheses

**2.2.1. Synthesis of Diepoxide 10**—In general, the alkenylmetal products of carbometalation are highly versatile and thus highly valuable, as they can be functionalized directly in a quenching operation with a variety of simple electrophiles (e.g.  $\text{H}^+$ ,  $\text{I}_2$ , a few highly electrophilic carbon electrophiles) or transmetalated to Pd or Cu and subsequently used as nucleophiles in conjugate addition and cross-coupling processes.<sup>xxiv</sup> Unfortunately, however, Thompson carbometalation involves delivery of the metal to the proximal end of alkynes **4** and **19** (and Me to the distal end). This regiochemistry precludes using transmetalation of the alkenylmetal and subsequent coupling for the construction of *linear* skipped dienes or polyenes.

For the assembly of the linear skipped dienes necessary for the synthesis of diepoxy alcohols **10**, **11**, and **12**, the development of new strategies became necessary. While terminal alkynes **4** and **13** were nearly inert to undirected *carbometalation* with Cu and Al/Zr systems, we elected to try these and closely related substrates in a catalytic *halopalladation* process. To our delight, halopalladation proved straightforward and efficient.

The palladium-catalyzed haloallylation of alkynes was discovered by Kaneda, Teranishi, and coworkers.<sup>16</sup> It has seen some use in recent years, with notable extensions of the method reported by the Rawal group<sup>xxv</sup> and a synthetic application described by Hoye and coworkers.<sup>xxvi</sup> It has proved invaluable to our own work. The method effects chloro- and bromoallylation of alkynes via the proposed mechanism shown in Scheme 7.<sup>16,xxvii</sup> The first step is regio- and *syn*-stereoselective alkyne halopalladation to afford alkenylpalladium halide **23**. After binding and 1,2 insertion of an allylic halide to give **24**,  $\beta$ -halide elimination gives diene **25**.

*Trans*-selective halocrotylation of **26**, the TBDPS ether of **4**, would provide direct access to the synthetically useful skipped diene **27** (Scheme 8), which bears the appropriate substitution at both the disubstituted and trisubstituted alkenes. This transformation proved problematic in practice. Bromocrotylation is not straightforward, as the requisite 3-bromo-1-butene is not commercially available and isomerizes to crotyl bromide at ambient temperature.<sup>xxviii</sup> Chlorocrotylation with 3-chloro-1-butene was successful, but the *E:Z* selectivity was only 1.7:1. Moreover, all attempts to effect the cross-coupling of the isomeric alkenyl chloride products with dimethylzinc via a  $\text{Pd}/\text{P}(\text{tBu})_3$  catalyst system<sup>xxix</sup> were unsuccessful.

We found more success with simple bromoallylation and subsequent homologation. Bromoallylation of **26** under conditions slightly modified from the original Kaneda conditions (dropwise addition of the alkyne to a room temperature solution of 5 mol%  $\text{PdCl}_2(\text{PhCN})_2$  in allyl bromide, with the addition of 5 equiv of  $\text{NaHCO}_3$ <sup>xxx</sup>) afforded diene **28** in 88% yield, with no trace of undesired regio- and stereoisomers (Scheme 9). Methylation of alkenyl

bromide **28** via Negishi coupling with dimethylzinc and a subsequent Shi asymmetric epoxidation chemoselective for the more electron-rich trisubstituted alkene provided epoxy alkene **29**. This monosubstituted alkene was readily and nearly quantitatively converted to the methylated disubstituted alkene via cross metathesis<sup>xxxii</sup> with *cis*-2-butenexxxii using the Hoveyda-Grubbs 2<sup>nd</sup> generation metathesis catalyst **31** (5 mol%),<sup>xxxiii</sup> in respectable 4.1:1 *E:Z* stereochemical purity. While a simple Me group is added in this reaction, cross metathesis is of course a versatile strategy that also makes possible the appendage of more complex epoxy alkenes for the eventual synthesis of longer epoxide chains.<sup>xxxiv</sup> Shi epoxidation of the resultant disubstituted alkene afforded the diepoxide in modest (2.7:1) overall dr, but we were able to improve this to better than 20:1 dr via preparative HPLC. The choice of TBDPS as silyl protecting group was in large part due its UV activity, which made detection on HPLC possible. Finally, cleavage of the silyl ether afforded diepoxy alcohol and epoxide-opening cascade substrate **10**.

**2.2.2. Synthesis of Diepoxide 11**—These results in hand, we were initially hopeful that Kaneda haloallylation could be extended to the synthesis of diepoxy alcohol cascade substrates **11** and **12**. Both of these substrates bear a Me substituent on the distal side (the *endo* site of attack) of the epoxide closer to the THP ring. Unfortunately, bromoallylation of internal alkyne **32** unexpectedly proceeded with a reversal of regioselectivity as compared to that observed with terminal alkyne **26** such that undesired regioisomer **33** predominated (Scheme 10).

Ultimately, for the synthesis of diepoxide **11**, we took recourse to the hydrometalation/cross-coupling strategy first investigated for the preparation of distally trisubstituted monoepoxide **9**. Hydrozirconation of **32** with Cp<sub>2</sub>Zr(H)Cl (Schwartz's reagent) proceeded in good yield, but the regioselectivity of addition across the alkyne was nearly 1:1, and separation of the resultant regioisomers after either iodinolysis of the C-Zr bond or transmetalation to Zn and quench with carbon electrophiles proved troublesome.

Uncatalyzed hydroboration of **32** with pinacolborane was so slow as to be entirely impractical, but the addition of catalytic quantities (0.1 equiv) of Cp<sub>2</sub>Zr(H)Cl and triethylamine according to the modification of Wang, et al.<sup>xxxv</sup> to the method developed by Pereira and Srebnik<sup>xxxvi</sup> improved the reaction rate (Scheme 11). However, even with Cp<sub>2</sub>Zr(H)Cl catalysis and upon heating the hydroboration reaction mixture to 60° for 28 h, conversion of starting alkyne **32** to pinacolates **35** and **36** was typically only 60–80%. While less than ideal, we found that these conditions represented a reasonable compromise, as longer reaction times and higher temperatures led to lower mass recovery. While poor conversion is a drawback of this transformation, unreacted **32** could be recovered and recycled. Furthermore, the stereochemistry of addition was cleanly *syn*, the regioselectivity was 2.0:1 in favor of the desired **35** over the undesired **36**, and, most important, the two regioisomeric pinacolate esters were readily separable by column chromatography.

After purification, alkenyl boronate ester **35** was cross-coupled with allyl bromide via Pd-catalyzed conditions adapted from those developed by Miyaura and coworkers.<sup>xxxvii</sup> The addition of 2 equivalents of water was found to improve the reaction rate substantially, presumably by effecting *in situ* hydrolysis of the boronate ester to the more reactive boronic acid. Bidentate bisphosphine ligands like dppe and the best ligand identified, dppf, were found to improve reaction rate as compared to those with monodentate ligands such as PPh<sub>3</sub>, PCy<sub>3</sub>, or Buchwald ligands.<sup>xxxviii</sup>

The crude diene was carried into Shi epoxidation (again chemoselective for the more electron-rich trisubstituted olefin over the monosubstituted) to afford epoxy alkene **37**. Cross metathesis of **37** with *cis*-2-butene again proceeded in excellent yield and good stereoselectivity (4.2:1 *E:Z*), and the resulting disubstituted alkene was subjected to another Shi epoxidation to afford

the diepoxide in disappointing 1.5:1 overall dr. The 1.5:1 mixture of diastereomers was enhanced to greater 9:1 diastereopurity via preparative HPLC, and final TBAF deprotection gave diepoxy alcohol and cascade substrate **11** in excellent yield.

**2.2.3. Synthesis of Diepoxide 12**—The synthesis of the third and final diepoxy alcohol cascade substrate **12**, which bears methyl substituents on both epoxides, intercepted the synthesis of **11** at alkenyl boronate ester **35** (Scheme 12). Cross coupling of **35** with prenyl bromide (rather than allyl) proceeded in similarly good 75% overall yield, but the coupling, which goes through an unsymmetrical  $\pi$ -allyl intermediate, resulted in a 2.5:1 mixture of the desired  $S_N2$  product **39** along with undesired  $S_N2'$  product **40**.

These diene isomers were inseparable by column chromatography, but Shi epoxidation proved chemoselective yet again, epoxidizing both trisubstituted alkenes in **39**, but leaving untouched the monosubstituted olefin in **40** to give a readily separable mixture of monoepoxide **41** and diepoxide **42** (65% yield based on **39**, 3.5:1 dr). The diastereopurity of **42** was improved via preparative HPLC, and samples of  $\geq 15:1$  dr were subjected to TBAF deprotection to afford diepoxy alcohol **12**.

### 3. Conclusion

We have developed synthetic routes to trisubstituted mono- and diepoxides **8–12**, which serve as substrates in *endo*-selective epoxide-opening cyclizations and cascades. The longest of these routes (the synthesis of **11**) is eight steps from known homopropargylic alcohol **4**. We believe that these transformations highlight the remarkable versatility of common intermediate **4**. Further exploration into new methods for the stereocontrolled construction of skipped polyenes and epoxide chains is ongoing in our laboratory.

## 4. Experimental

### 4.1. General

Full experimental details for compounds **4**, **8–12**, **16–17**, **19–21**, **26**, **28–30**, **32**, **35**, **37–38**, and **42–43** are available in the Supporting Information to reference <sup>14</sup>.

All air-sensitive reactions were performed under an oxygen-free atmosphere of argon with rigid exclusion of moisture from reagents and glassware. Dichloromethane was either distilled from calcium hydride or purified via an SG Water USA solvent column system. Tetrahydrofuran (THF) and Et<sub>2</sub>O were either distilled from a blue solution of benzophenone ketyl or purified via an SG Water USA solvent column system. Triethylamine was purified via an SG Water USA solvent column system. Methyl iodide and allyl bromide were purified by filtration through basic alumina before use. K<sub>3</sub>PO<sub>4</sub> was oven-dried overnight before use. Chiral ketone **18**, used in Shi asymmetric epoxidation, was prepared from D-fructose according to the procedure of Vidal-Ferran and coworkers.<sup>xxxix</sup> All other reagents and solvents were used as obtained, without further purification.

### 4.2. Preparation of alkenyl iodide **16** by carbometalation

To a solution of bishomopropargylic alcohol **4** (265 mg, 1.89 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) at  $-78^\circ$  was added slowly a 2 M solution of AlMe<sub>3</sub> in hexanes (2.08 mL, 4.16 mmol). This solution was warmed for 3 min. by removing the flask from its cold bath to ensure complete deprotonation. After recooling to  $-78^\circ$ , a 1 M solution of TiCl<sub>4</sub> in CH<sub>2</sub>Cl<sub>2</sub> (2.08 mL, 2.08 mmol) was added dropwise. The solution was stirred 2 h. at  $-78^\circ$  and then quenched with a solution of I<sub>2</sub> (2.4 g, 9.45 mmol) in Et<sub>2</sub>O (20 mL). The reaction flask was then wrapped in foil and allowed to warm to room temperature for 10 h., at which point H<sub>2</sub>O (2 mL) was added. The quenched reaction solution was diluted with Et<sub>2</sub>O (100 mL) and washed with aqueous 3

M NaHSO<sub>3</sub> (40 mL) until the organic layer was colorless. The aqueous layer was extracted with Et<sub>2</sub>O (3 × 40 mL), and the combined organics were washed with sat. NaCl, dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. The crude alkenyl iodide was carried forward without purification; R<sub>f</sub> = 0.72 (50% EtOAc in hexanes), UV active.

Upon dissolution of this crude in DMF (1 mL), imidazole (322 mg, 4.73 mmol) and TESC1 (380 μL, 342 mg, 2.27 mmol) were added, and the solution was stirred 2 h. at room temperature. The reaction was applied directly to column of SiO<sub>2</sub> and chromatographed (2% EtOAc in hexanes) to afford **16** (310 mg, 0.78 mmol, 41% over 2 steps), which was isolated along with some silylated bishomopropargylic alcohol (43 mg, 0.17 mmol). R<sub>f</sub> of **16** = 0.60 (10% EtOAc in hexanes), UV active; [α]<sup>22</sup><sub>D</sub> = -19.2 (*c* = 4.0, CHCl<sub>3</sub>).

IR (thin film, NaCl) 2955, 2876, 1461, 1415, 1274, 1239, 1127, 1102, 1004 cm<sup>-1</sup>

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 5.64 (app qt, *J* = 6.3, 0.7 Hz, 1H), 3.90-3.85 (m, 1H), 3.39-3.28 (m, 3H), 3.04 (app d, *J* = 14.8 Hz, 1H), 2.41 (dd, *J* = 14.8, 9.1 Hz, 1H), 2.02 (m, 1H), 1.75 (d, *J* = 6.3 Hz, 3H), 1.68-1.62 (m, 2H), 1.54-1.44 (m, 1H), 0.96 (t, *J* = 7.9 Hz, 9H), 0.59 (q, *J* = 7.8 Hz, 6H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 131.5, 107.3, 81.3, 70.8, 68.1, 47.8, 33.8, 25.8, 22.5, 7.1, 5.3.

HR-MS (ESI) *m/z* calcd for C<sub>15</sub>H<sub>29</sub>IO<sub>2</sub>Si (M+Na)<sup>+</sup>: 419.0874, found 419.0893.

#### 4.3. Preparation of trisubstituted alkene **20** by carbometalation

To a of bishomopropargylic alcohol **19** in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at 0° was added slowly a 2 M solution of AlMe<sub>3</sub> in hexanes (0.96 mL, 1.93 mmol).<sup>S10</sup> This solution was stirred for 3 min. and then recooled to -78°. A 1 M solution of TiCl<sub>4</sub>, in CH<sub>2</sub>Cl<sub>2</sub> (0.96 mL, 0.96 mmol) was added dropwise. The solution was stirred 2 h. at -78° and then quenched with cold MeOH (1 mL), upon which the solution turned pale yellow. The solution was diluted with Et<sub>2</sub>O (10 mL) and washed with a saturated solution of Rochelle's salt (10 mL). The aqueous layer was extracted with Et<sub>2</sub>O (3 × 20 ml), dried over MgSO<sub>4</sub>, and concentrated *in vacuo*, and this crude product was purified by column chromatography (25% EtOAc in hexanes) to afford **20** as a colorless oil (105 mg, 0.62 mmol, 70%): R<sub>f</sub> = 0.38 (30% EtOAc in hexanes); [α]<sup>22</sup><sub>D</sub> = -19.4 (*c* = 1.2, CDCl<sub>3</sub>). Some unreacted **19** (16 mg, 0.10 mmol, 12%) was also recovered.

IR (thin film, NaCl) 3412, 2928, 2855, 1451, 1376, 1340, 1277, 1095, 1036, 944 cm<sup>-1</sup>

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 5.29 (app t, *J* = 7.0 Hz, 1H), 3.94-3.89 (m, 1H), 3.42-3.30 (m, 2H), 3.08 (ddd, *J* = 8.7, 7.2, 4.5 Hz, 1H), 2.52 (app dt, *J* = 15.0, 5.8 Hz, 1H), 2.24 (app dt, *J* = 15.0, 7.0 Hz, 1H), 2.10 (m, 1H), 1.73 (s, 3H), 1.72-1.64 (m, 5H), 1.40 (dddd, *J* = 17.4, 11.3, 6.3, 5.4 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 134.1, 120.5, 82.4, 70.9, 67.9, 32.8, 31.6, 26.1, 25.7, 18.2.

HR-MS (ESI) *m/z* calcd for C<sub>10</sub>H<sub>18</sub>O<sub>2</sub> (M+Na)<sup>+</sup>: 193.1199, found 193.1194.

#### 4.4. Preparation of alkenyl bromide **28** by bromoallylation

To PdCl<sub>2</sub>(PhCN)<sub>2</sub> (40 mg, 0.11 mmol) and NaHCO<sub>3</sub> (880 mg, 10.5 mmol) was added allyl bromide (9 mL, 105 mmol). The resulting solution was stirred 15 minutes at room temperature. Alkyne **26** (795 mg, 2.1 mmol) as a solution in THF (2 mL) was then added dropwise at ambient temperature via syringe pump over 90 min. After addition the reaction was stirred a further 30 min., directly concentrated *in vacuo*, and chromatographed (gradient 2% to 3% to 5% EtOAc in hexanes) to afford alkenyl bromide **28** (920 mg, 1.84 mmol, 88%): R<sub>f</sub> = 0.54 (10% EtOAc in hexanes); [α]<sup>22</sup><sub>D</sub> = -11.5 (*c* = 27.0, CDCl<sub>3</sub>).

**IR** (thin film, NaCl) 3072, 3011, 2933, 2858, 1639, 1472, 1428, 1362, 1218, 1127, 1103, 1048  $\text{cm}^{-1}$ .

**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.87 (app t,  $J = 8.4$  Hz, 4H), 7.56-7.46 (m, 6H), 5.92 (dddd,  $J = 16.5, 10.1, 6.2, 6.2$  Hz, 1H), 5.85 (app t,  $J = 6.8$  Hz, 1H), 5.22 (dd,  $J = 17.1, 1.7$  Hz, 1H), 5.13 (dd,  $J = 10.1, 1.5$  Hz, 1H), 3.92-3.87 (m, 1H), 3.71 (app td,  $J = 9.2, 1.5$  Hz, 1H), 3.55 (ddd,  $J = 10.2, 9.1, 4.6$  Hz, 1H), 3.39 (app td,  $J = 11.3, 2.7$  Hz, 1H), 3.32 (app d,  $J = 14.7$  Hz, 1H), 3.13-3.02 (m, 2H), 2.43 (dd,  $J = 14.8, 10.0$  Hz, 1H), 2.05-2.00 (m, 1H), 1.70-1.62 (m, 1H), 1.60-1.48 (m, 2H), 1.23 (s, 9H);  **$^{13}\text{C}$  NMR** (125 MHz,  $\text{CDCl}_3$ )  $\delta$  135.9, 135.9, 134.9, 134.3, 133.5, 129.9, 129.7, 127.8, 127.6, 126.0, 115.5, 80.0, 71.9, 67.6, 44.5, 35.8, 33.5, 27.1, 25.5, 19.3.

**HR-MS** (ESI)  $m/z$  calcd for  $\text{C}_{27}\text{H}_{35}\text{BrO}_2\text{Si}$  ( $\text{M}+\text{Na}$ ) $^+$ : 521.1482, found 521.1489.

#### 4.5. Preparation of alkenyl boronate ester **35** by hydroboration

Alkyne **32** (616 mg, 1.56 mmol) was added to a dry, cooled sealed tube. The tube was pumped under high vacuum and then backfilled with argon three times. Pinacolborane (287  $\mu\text{L}$ , 253 mg, 1.98 mmol) was added, followed by  $\text{Et}_3\text{N}$  (22  $\mu\text{L}$ , 16 mg, 0.16 mmol) and Schwartz's reagent (41 mg, 0.16 mmol). The resulting slurry was heated to  $60^\circ$  and stirred vigorously for 28 h. while protected from light. After cooling, the crude reaction mixture was filtered through a short pad of  $\text{SiO}_2$  (100%  $\text{Et}_2\text{O}$ ) and concentrated *in vacuo* to a heavy oil containing a 2:1 mixture of pinacolate **35** ( $R_f = 0.36$ , 10%  $\text{EtOAc}$  in hexanes) and its regioisomer **36** ( $R_f = 0.38$ , 10%  $\text{EtOAc}$  in hexanes), along with unreacted **32**, traces of a proton quench product, and borate and other impurities. These were separated via careful column chromatography (gradient 3% to 5%  $\text{EtOAc}$  in hexanes) to afford **35** (235 mg, 0.45 mmol, 29% (39% based on recovered **32**) in >20:1 regioisomeric purity along with unreacted **32** (163 mg, 26%):  $[\alpha]_D^{22} = -2.1$  ( $c = 1.9$ ,  $\text{CDCl}_3$ ).

**IR** (thin film, NaCl) 3072, 2932, 2246, 1632, 1472, 1428, 1371, 1301, 1103  $\text{cm}^{-1}$

**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.71-7.67 (m, 4H), 7.45-7.36 (m, 6H), 6.43 (app tq,  $J = 6.4, 1.5$  Hz, 1H), 3.81-3.76 (m, 1H), 3.45-3.39 (m, 1H), 3.30-3.24 (m, 2H), 2.81-2.75 (m, 1H), 2.08-2.00 (m, 1H), 1.82-1.77 (m, 1H), 1.63 (d,  $J = 1.5$  Hz, 3H), 1.49-1.38 (m, 3H), 1.27 (app s, 12H), 1.04 (s, 9H);  **$^{13}\text{C}$  NMR** (125 MHz,  $\text{CDCl}_3$ )  $\delta$  143.43, 136.1, 136.1, 134.9, 133.9, 129.9, 129.7, 127.9, 127.6, 83.3, 82.4, 72.6, 67.9, 33.6, 32.1, 27.2, 25.8, 25.1, 25.0, 19.5, 14.5 (no signal was observed for the boron-bound carbon).

**HR-MS** (ESI)  $m/z$  calcd for  $\text{C}_{31}\text{H}_{46}\text{BO}_4\text{Si}$  ( $\text{M}+\text{Na}$ ) $^+$ : 543.3089, found 543.3089.

#### 4.6. Preparation of diepoxide **42** by Pd-catalyzed cross-coupling and Shi AE

[1, 1'-Bis(diphenylphosphino)ferrocene] dichloropalladium(II) ( $\text{PdCl}_2(\text{dppf})$ ) (73 mg, 0.10 mmol) was added to a flame-dried, cooled sealed tube.  $\text{K}_3\text{PO}_4$  (1.83 g, 8.63 mmol) was added, and the tube was pumped under high vacuum and backfilled with argon three times. Alkenyl boronate **35** (600 mg, 1.15 mmol) was then added as a solution in dry THF (2 mL). The mixture was allowed to stir under Ar for 5 min. Degassed water (42 mg, 42  $\mu\text{L}$ , 2.3 mmol, degassed via sparging) was then added, followed immediately by prenyl bromide (859 mg, 666  $\mu\text{L}$ , 5.76 mmol). The sealed tub was capped, and the slurry was heated to  $80^\circ$  and stirred vigorously for 42 h. After cooling and dilution with  $\text{Et}_2\text{O}$  (5 mL), the crude product was filtered through  $\text{SiO}_2$  (washed with  $\text{Et}_2\text{O}$ ) and concentrated *in vacuo* to yield a 2.5:1 mixture of **39** and **40**. These inseparable diene isomers were purified away from phosphine and other impurities via column chromatography (gradient 2% to 3%  $\text{EtOAc}$  in hexanes) to give a 2.5:1 mixture of **39:40** (400 mg, 0.86 mmol, 75% combined yield,  $R_f = 0.63$ , 10%  $\text{EtOAc}$  in hexanes). This mixture was carried forward into Shi epoxidation without further purification.



To this mixture (400 mg, 0.86 mmol) in 2:1 v/v DMM:MeCN (23.2 mL) was added a 0.05 M solution of  $\text{Na}_2\text{B}_4\text{O}_7 \cdot 10\text{H}_2\text{O}$  in  $4 \times 10^{-4}$   $\text{Na}_2\text{EDTA}$  (15.5 mL),  $n\text{Bu}_4\text{HSO}_4$  (75 mg, 0.22 mmol), and chiral ketone **18** (222 mg, 0.86 mmol). This biphasic mixture was stirred vigorously at 0°. To this mixture was added, simultaneously over 30 min. via syringe pump, a solution of Oxone (1.06 g, 1.73 mmol) in  $4 \times 10^{-4}$   $\text{Na}_2\text{EDTA}$  (7.75 mL) and a 0.89 M solution of  $\text{K}_2\text{CO}_3$  (7.75 mL, 6.9 mmol). After the  $\text{K}_2\text{CO}_3$  and Oxone solutions had been added, the resulting mixture was stirred an additional 20 min., at which point it was diluted with EtOAc (25 mL). The aqueous layer was extracted with EtOAc ( $3 \times 25$  mL), and the combined organics were washed with sat. NaCl, dried over  $\text{MgSO}_4$ , and concentrated *in vacuo* to provide desired diepoxide **42** and diastereomers. **40** was partially oxidized under these conditions to monoepoxide **41** ( $R_f = 0.77$ , 20% EtOAc in hexanes. Column chromatography (15% EtOAc in hexanes) afforded diepoxide **42** in 3.5:1 overall dr as a colorless oil (276 mg, 0.56 mmol, 65% (49% yield over 2 steps),  $R_f = 0.54$  (20% EtOAc in hexanes)) contaminated with a small quantity of ketone **18**. Diepoxide **42** was further purified via preparative HPLC (Supelco SUPELCOSIL LC-SI 20 mm achiral  $\text{SiO}_2$  column, 5  $\mu\text{m}$  particle size; 99.5:0.5 hexanes:iPrOH, 20 mL/min.;  $t_R$  of desired diastereomer = 11.9 min.) to afford **42** free of **20** and in 15:1 to 20:1 overall dr (depending on batch):  $[\alpha]^{22}_D$  for a sample in 20:1 dr =  $-7.5$  ( $c = 3.3$ ,  $\text{CDCl}_3$ ).

**IR** (thin film, NaCl) 3072, 2958, 2930, 2857, 1590, 1472, 1462, 1428, 1379, 1102  $\text{cm}^{-1}$

**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.71-7.66 (m, 4H), 7.46-7.41 (m, 2H), 7.40-7.36 (m, 4H), 3.85-3.80 (m, 1H), 3.43 (ddd,  $J = 9.3, 4.8, 4.5$  Hz, 1H), 3.29 (app td,  $J = 9.3, 2.5$  Hz, 1H), 2.93 (app t,  $J = 6.1$  Hz, 1H), 2.89 (app t,  $J = 6.0$  Hz, 1H), 2.11 (ddd,  $J = 14.4, 6.4, 2.7$  Hz, 1H), 1.85-1.80 (m, 1H), 1.77-1.73 (m, 2H), 1.60 (ddd,  $J = 14.9, 9.5, 5.8$  Hz, 1H), 1.51-1.39 (m, 3H), 1.33 (app s, 6H), 1.27 (s, 3H), 1.04 (s, 9H);  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  136.1, 136.1, 134.7, 133.6, 130.0, 129.8, 127.9, 127.7, 81.4, 72.5, 67.9, 61.3, 61.2, 58.8, 58.0, 38.2, 33.5, 31.8, 27.2, 25.6, 24.9, 19.5, 19.0, 17.3.

**HR-MS** (ESI)  $m/z$  calcd for  $\text{C}_{30}\text{H}_{42}\text{O}_4\text{Si}$  ( $\text{M}+\text{Na}$ ) $^+$ : 517.2745, found 517.2751.

## Acknowledgments

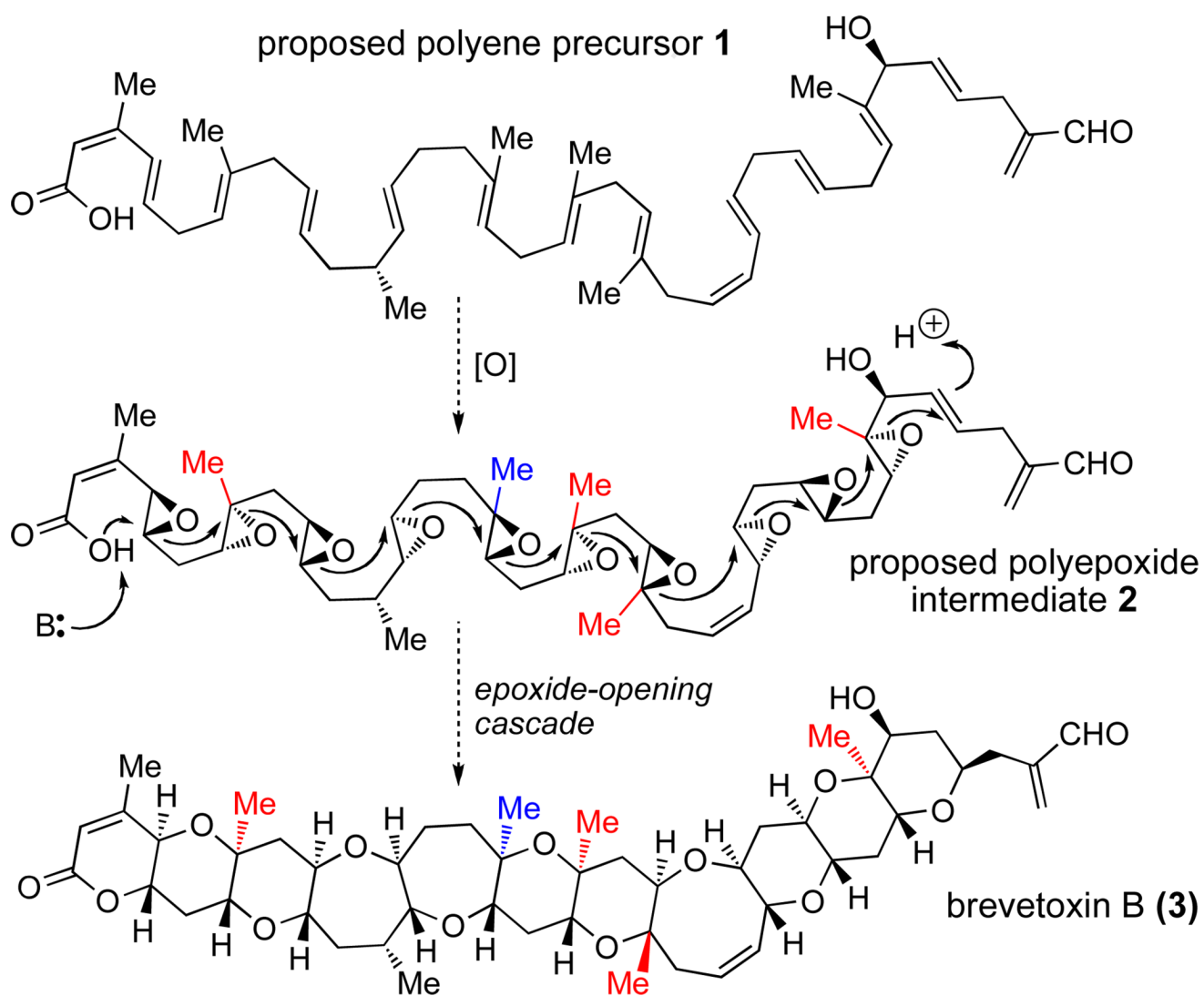
This work was supported by the NIGMS (GM72566). C.J.M. thanks the George Büchi Summer Graduate Fellowship for fellowship support. Li Li (MIT) acquired HR-MS data. We are grateful also to Dr. Jeffery A. Byers, Aaron van Dyke, Ivan Vilotijevic, and Brian S. Underwood (all of MIT) for many helpful discussions. Without their insights this work would not have been possible.

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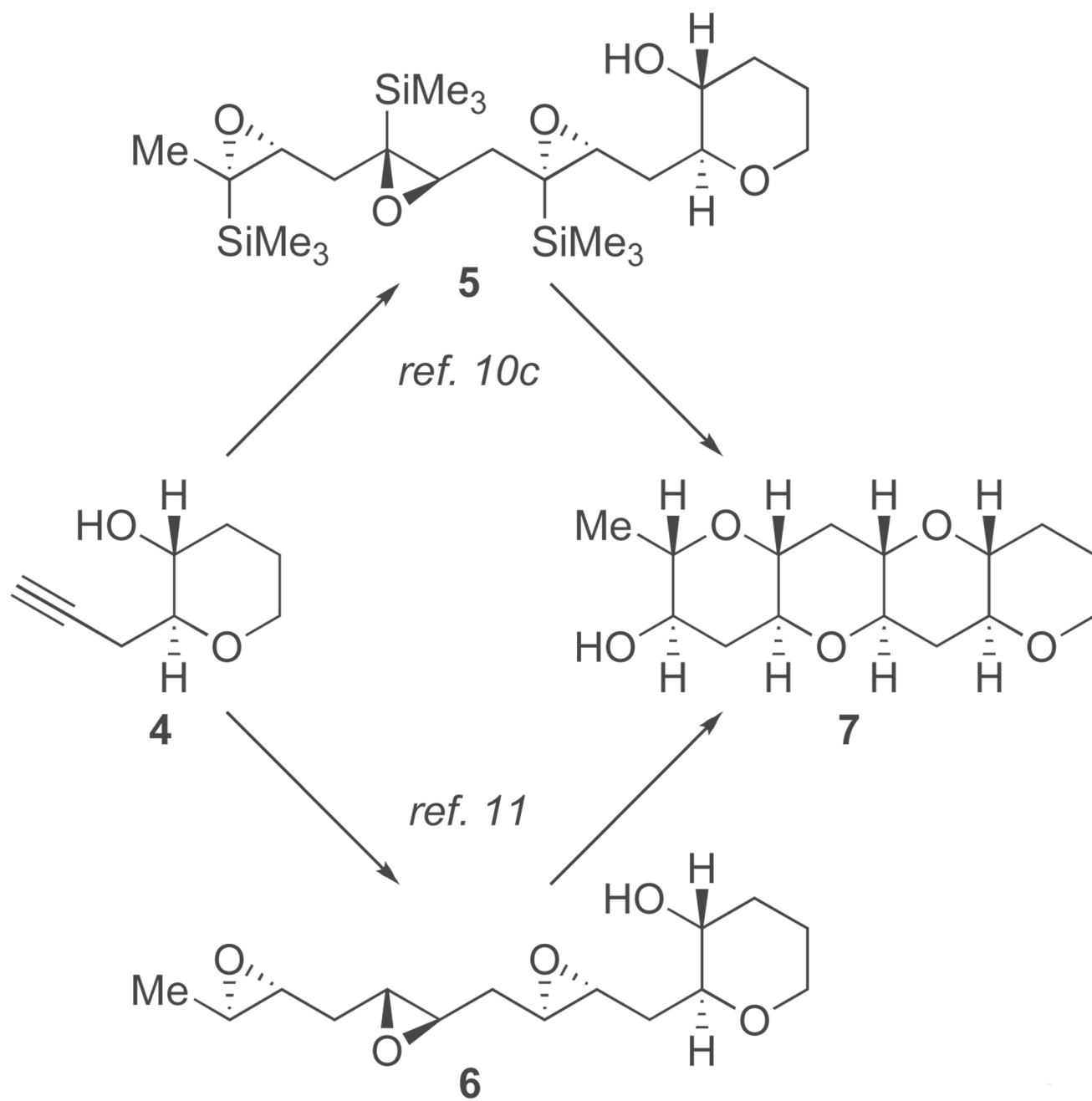
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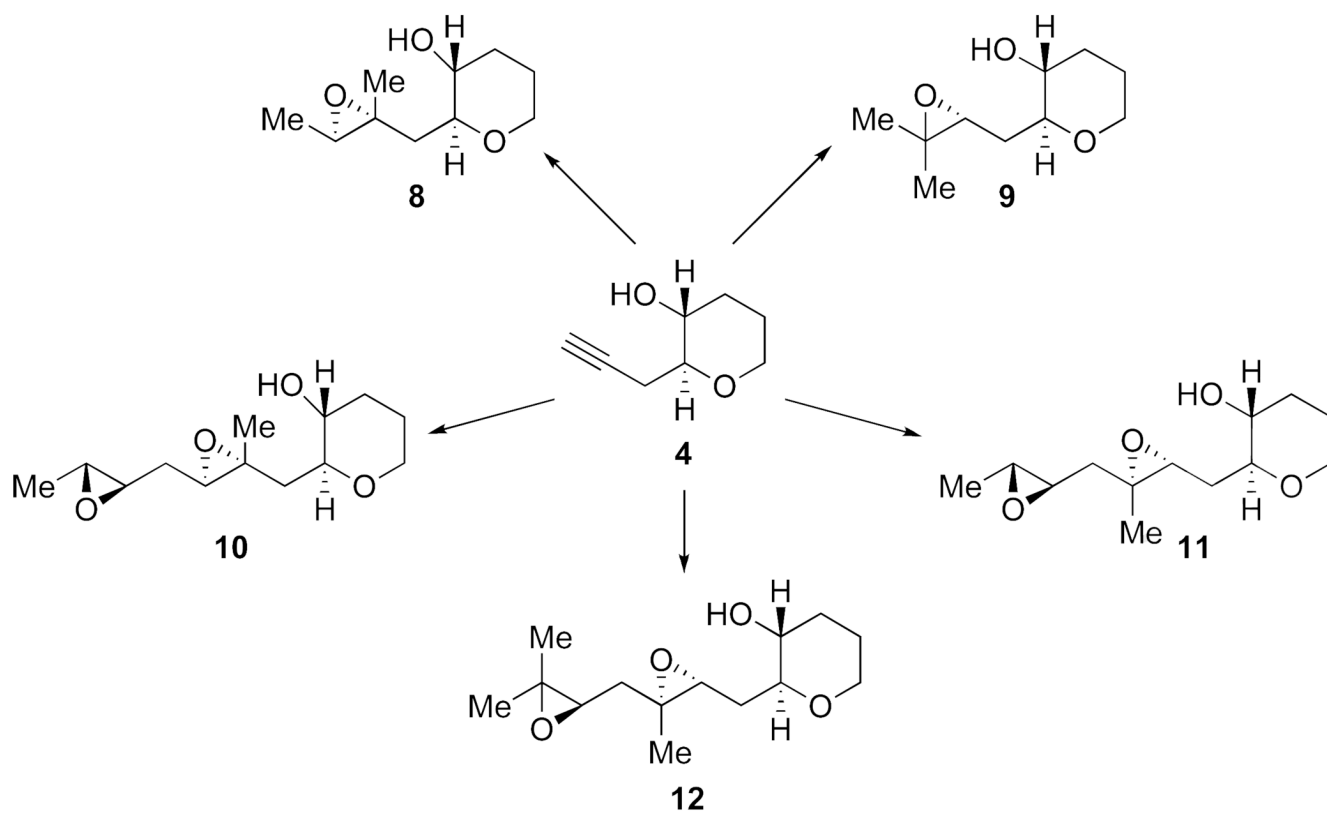
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**Scheme 1.**  
Nakanishi's proposed biosynthesis of brevetoxin B.

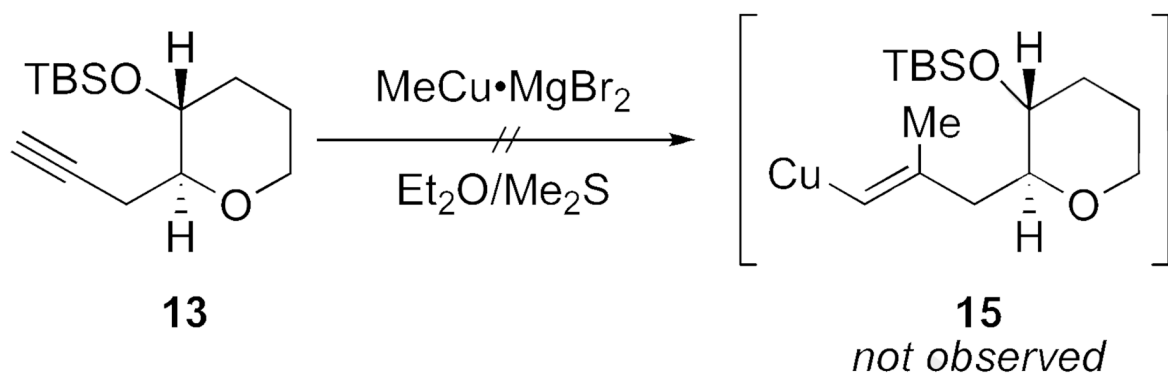
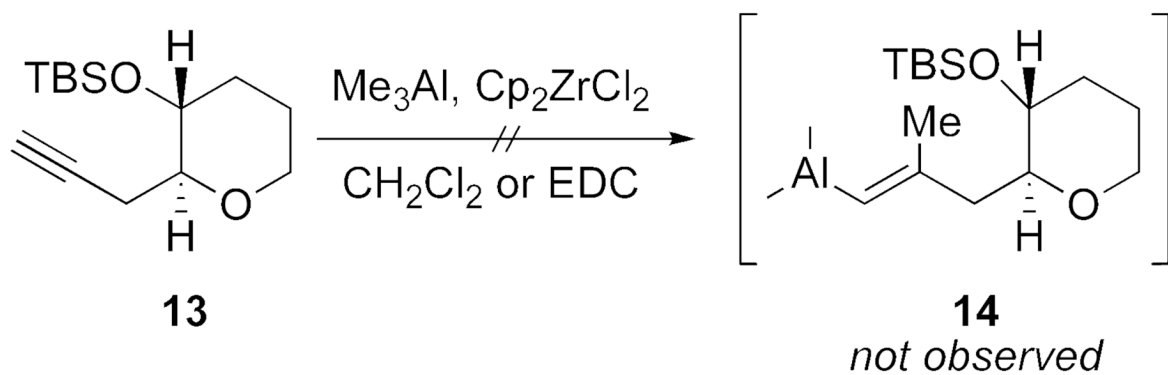


**Scheme 2.**  
Previous polyepoxy alcohol syntheses from common intermediate 4.

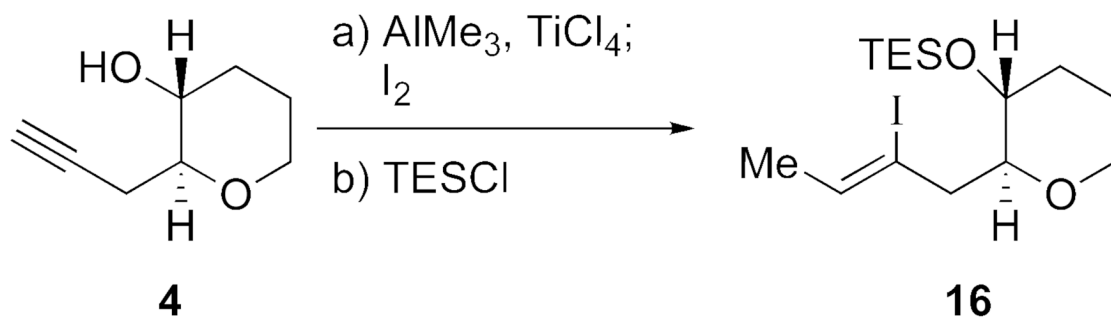


**Scheme 3.**  
Mono- and diepoxy alcohols synthesized from bishomopropargylic alcohol 4.

unsuccessful attempts at **undirected** carbometalation:

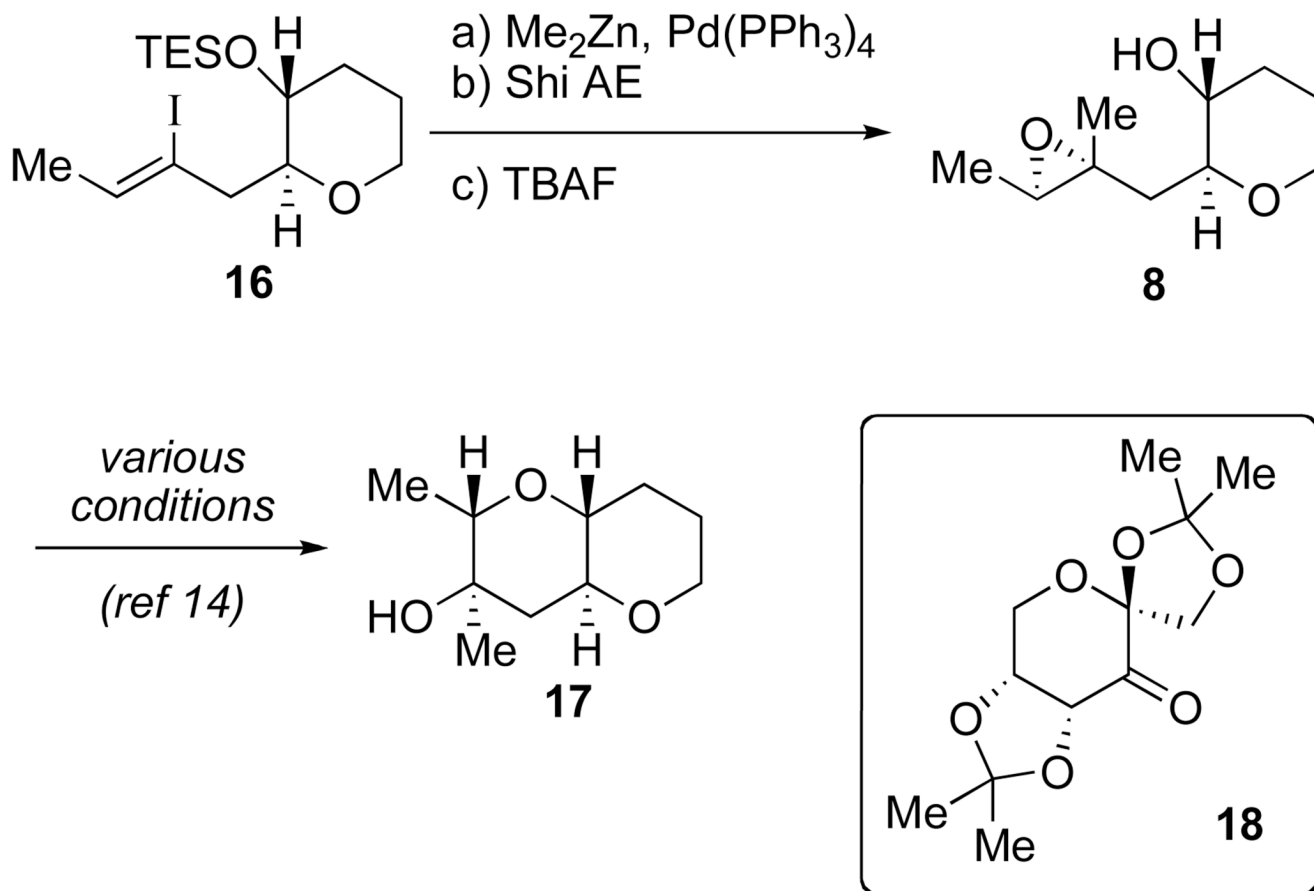


successful **directed** carbometalation:



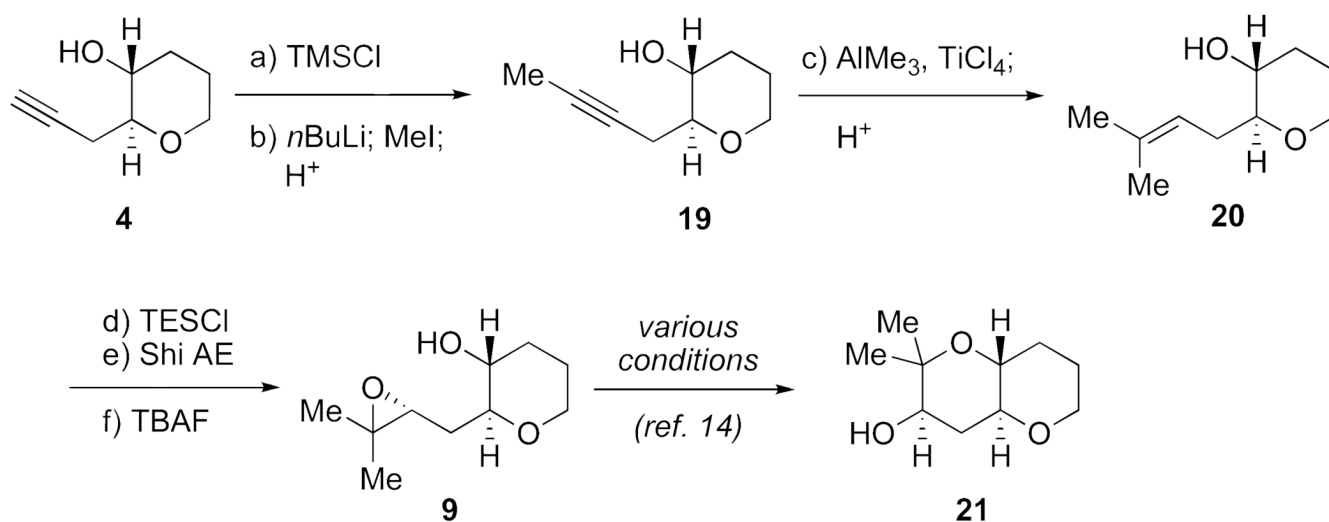
**Scheme 4.**

Carbometalation studies of **4** and **13**. a)  $\text{AlMe}_3$ ,  $\text{TiCl}_4$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ$ , 2 h.;  $\text{I}_2$ ,  $\text{Et}_2\text{O}$ ; b)  $\text{TESCl}$ , imid., DMF, 41% over 2 steps (45% brsm).

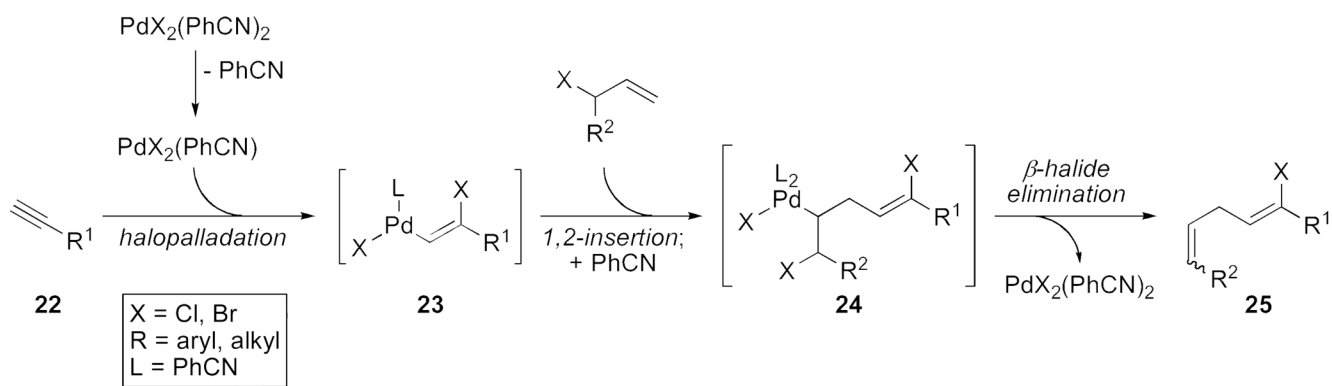
**Scheme 5.**

Synthesis of monoepoxy alcohol **8**. a)  $\text{Me}_2\text{Zn}$ ,  $\text{Pd}(\text{PPh}_3)_4$ , THF/PhMe, 85%; b) chiral ketone **18**, Oxone,  $n\text{Bu}_4\text{NHSO}_4$ ,  $\text{K}_2\text{CO}_3$ ,  $\text{Na}_2\text{B}_4\text{O}_7$  buffer, DMM/MeCN,  $0^\circ$ , 71%, 2.8:1 dr; c) TBAF, THF,  $0^\circ$ , 94%.

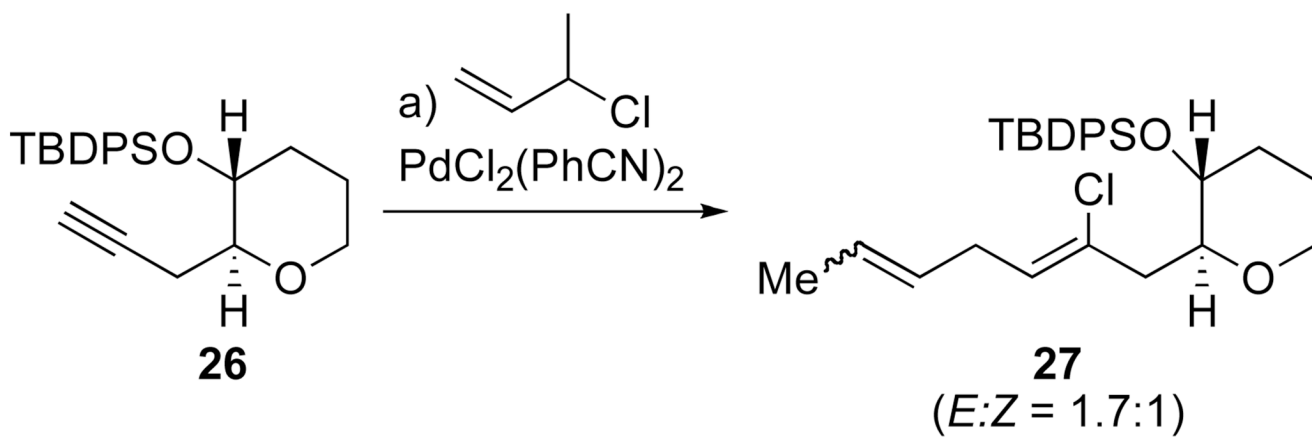


**Scheme 6.**

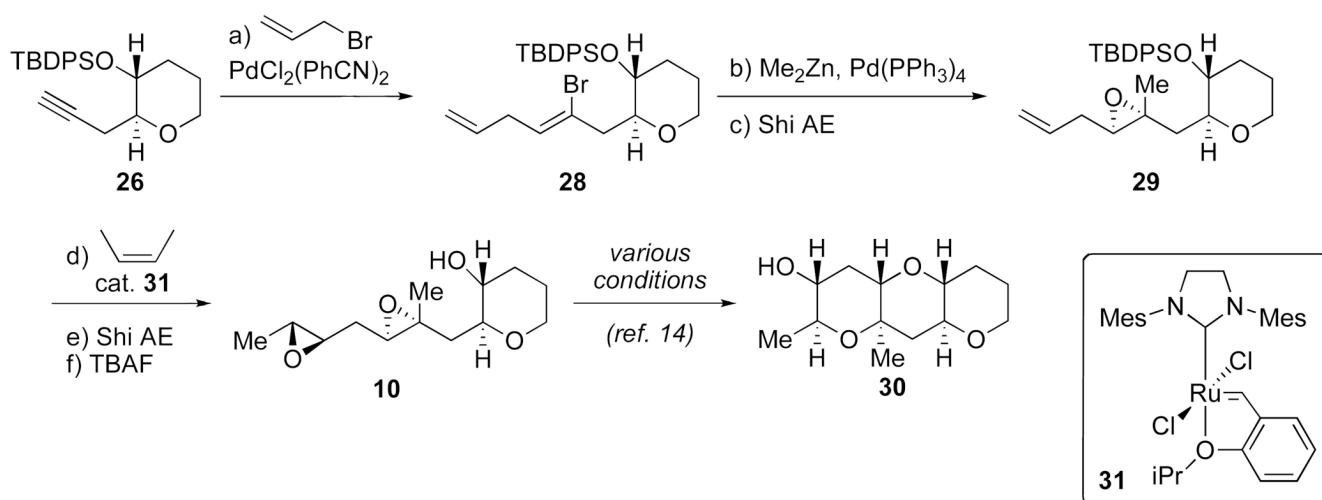
Synthesis of monoepoxy alcohol **9** a) TMSCl, HMDS, pyridine,  $\text{CH}_2\text{Cl}_2$ , 90%; b)  $n\text{BuLi}$ ,  $\text{Et}_2\text{O}$ ; MeI;  $\text{HCl}_{(\text{aq})}$ , 88%; c)  $\text{AlMe}_3$ ,  $\text{TiCl}_4$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ$ , 2 h.; MeOH, 70% (79% brsm); d) TESCl, imid., DMF, 74%; e) **18**, Oxone,  $n\text{Bu}_4\text{NHSO}_4$ ,  $\text{K}_2\text{CO}_3$ ,  $\text{Na}_2\text{B}_4\text{O}_7$  buffer, DMM/MeCN,  $0^\circ$ , 78%, 5.8:1 dr; f) TBAF, THF,  $0^\circ$ , 98%.



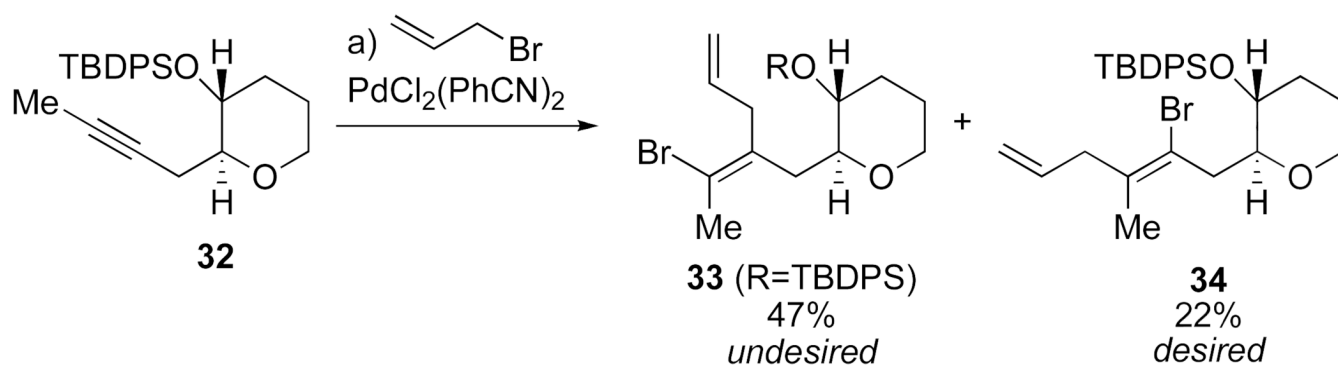
**Scheme 7.**  
The mechanism for haloallylation proposed by Kaneda et al.



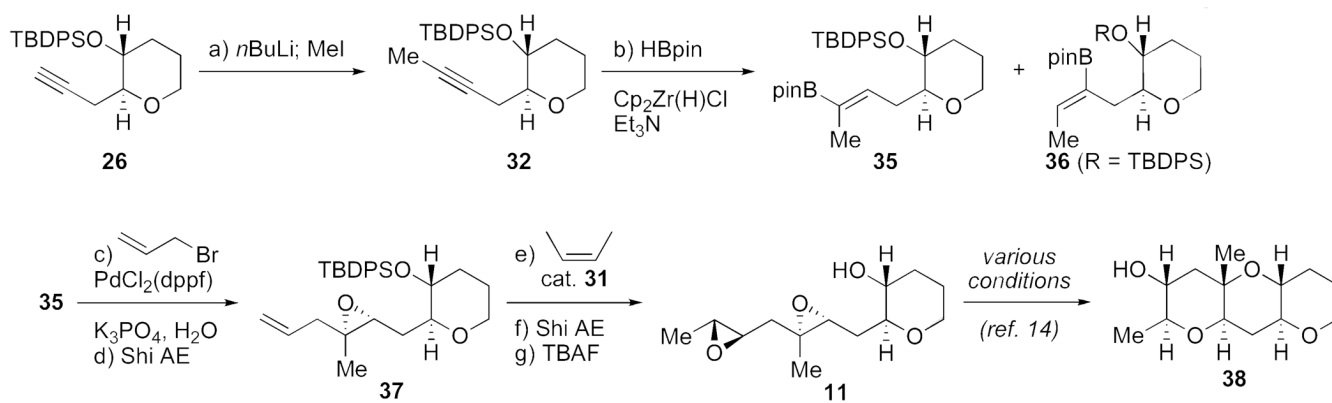
**Scheme 8.**  
Chlorocrotylation of alkyne **26**. a) 3-chloro-1-butene,  $\text{PdCl}_2(\text{PhCN})_2$ ,  $\text{NaHCO}_3$ , THF, 87%,  
1.7:1 *E:Z*

**Scheme 9.**

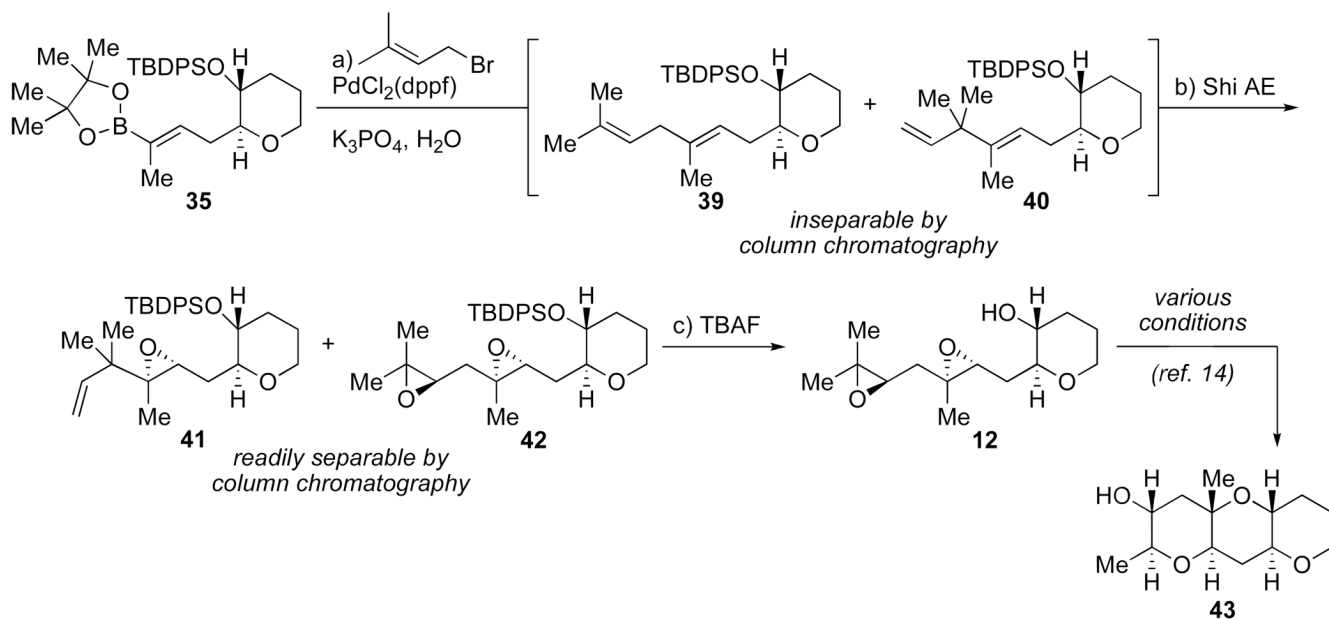
Synthesis of diepoxide **10**. a) allyl bromide,  $\text{PdCl}_2(\text{PhCN})_2$ ,  $\text{NaHCO}_3$ , rt, 88%; b)  $\text{Me}_2\text{Zn}$ ,  $\text{Pd}(\text{PPh}_3)_4$ , THF/PhMe; c) **18**, Oxone,  $n\text{Bu}_4\text{NHSO}_4$ ,  $\text{K}_2\text{CO}_3$ ,  $\text{Na}_2\text{B}_4\text{O}_7$  buffer, DMM/MeCN,  $0^\circ$ , 48% over 2 steps, 4:1 dr; d) *cis*-2-butene, Hoveyda-Grubbs 2<sup>nd</sup> gen. catalyst **31**,  $\text{CH}_2\text{Cl}_2$ , 4.1:1 *E:Z*; e) **18**, Oxone,  $n\text{Bu}_4\text{NHSO}_4$ ,  $\text{K}_2\text{CO}_3$ ,  $\text{Na}_2\text{B}_4\text{O}_7$  buffer, DMM/MeCN,  $0^\circ$ , 90% over 2 steps, 2.7:1 overall dr; f) TBAF, THF, 98%.

**Scheme 10.**

Bromoallylation of internal alkyne **32** a) allyl bromide,  $\text{PdCl}_2(\text{PhCN})_2$ ,  $\text{NaHCO}_3$ , THF, **69%**, 2.2:1 **33:34** regioselectivity.

**Scheme 11.**

Synthesis of diepoxy alcohol **11**. a) *n*BuLi, THF; MeI, 99%; b) HBpin, Cp<sub>2</sub>Zr(H)Cl, Et<sub>3</sub>N, 60°, 44% (2.0:1 mixture of regioisomers **35** and **36**, 60% brsm); c) allyl bromide, PdCl<sub>2</sub>(dppf), K<sub>3</sub>PO<sub>4</sub>, H<sub>2</sub>O, THF; d) **18**, Oxone, *n*Bu<sub>4</sub>NHSO<sub>4</sub>, K<sub>2</sub>CO<sub>3</sub>, Na<sub>2</sub>B<sub>4</sub>O<sub>7</sub> buffer, DMM/MeCN, 0°, 53% over 2 steps, 3:1 dr; e) *cis*-2-butene, catalyst **31**, CH<sub>2</sub>Cl<sub>2</sub>, 4.2:1 *E:Z*; f) **18**, Oxone, *n*Bu<sub>4</sub>NHSO<sub>4</sub>, K<sub>2</sub>CO<sub>3</sub>, Na<sub>2</sub>B<sub>4</sub>O<sub>7</sub> buffer, DMM/MeCN, 0°, 85% over 2 steps, 1.5:1 overall dr; g) TBAF, THF, 95%.

**Scheme 12.**

Synthesis of diepoxy alcohol **12** a) prenyl bromide,  $\text{PdCl}_2(\text{dppf})$ ,  $\text{K}_3\text{PO}_4$ ,  $\text{H}_2\text{O}$ , THF, 75%, 2.5:1 **39:40**; b) **18**, Oxone,  $n\text{Bu}_4\text{NHSO}_4$ ,  $\text{K}_2\text{CO}_3$ ,  $\text{Na}_2\text{B}_4\text{O}_7$  buffer, DMM/MeCN,  $0^\circ$ , 65% (yield of **42** based on **39**), 3.5:1 dr; c) TBAF, THF, 92%.