



New synthetic strategies for the stereocontrolled synthesis of substituted ‘skipped’ diepoxides

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Dedicated to Professor Larry E. Overman on his receipt of the 2008 Tetrahedron Prize and in honor of his many important contributions to organic chemistry

ABSTRACT

This report describes a number of new synthetic approaches toward 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.

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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,¹ 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.² 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.³ 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**.⁴

Abbreviated skipped polyenes similar to **1** can be useful substrates for epoxidation and subsequent studies of biomimetic in vitro epoxide-opening cascades. Efficient epoxidation of such skipped polyenes would require a protocol that is reliably (*R,R*)- or (*S,S*)-selective for a wide variety of trans-disubstituted and

trisubstituted alkenes. The powerful Shi asymmetric epoxidation,⁵ 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 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.

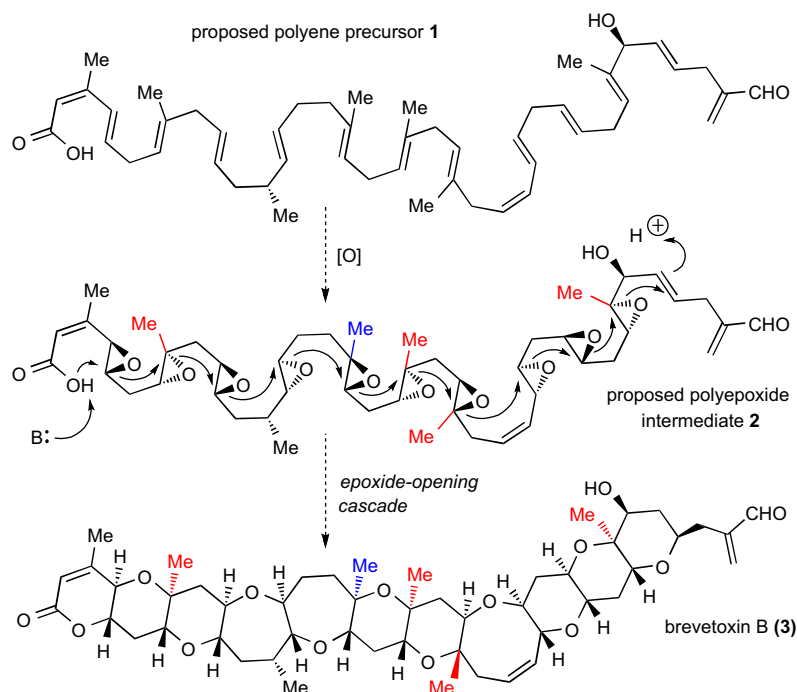
The difficulty of synthesizing highly substituted alkenes with careful stereo- and regiocontrol is well documented.⁶ Furthermore, the construction of skipped dienes can be additionally troublesome due to the rather delicate doubly allylic protons found in these compounds. The *pK_a* of 1,4-pentadiene (divinylmethane) in DMSO is approximately 35,⁷ making doubly allylic protons sensitive to strong base, and the same C–H bonds are also susceptible to hydrogen atom abstraction,⁸ which can lead to subsequent di- π -methane rearrangement.⁹ 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 polyenes¹⁰ and all-trans-disubstituted polyenes¹¹ 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 cascades of *endo*-selective epoxide openings (accompanied by concomitant protidesilylation in reactions of **5**)

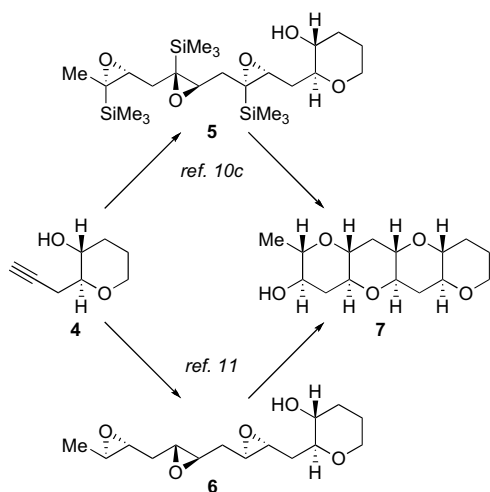
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Scheme 1. Nakanishi's proposed biosynthesis of brevetoxin B.

to afford THP tetrad **7**, a characteristic structural subunit of the ladder polyether natural products.^{10,11}



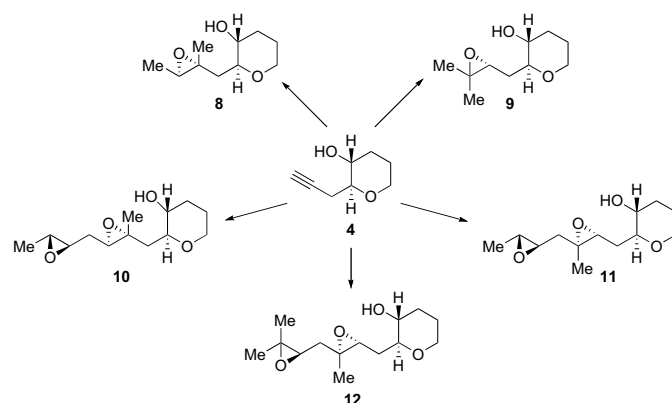
Scheme 2. Previous polyepoxy alcohol syntheses from common intermediate **4**.

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.^{10c} 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 5 of its 10 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.¹² 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.¹³

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.¹⁴ 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



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

work, Thompson's directed methylmetalation of alkynes¹⁵ and Kaneda's haloallylation of alkynes,¹⁶ 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.

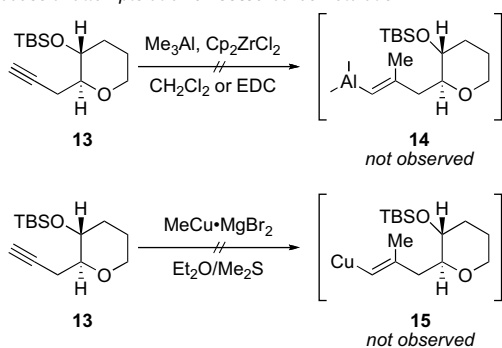
2. Results and discussion

2.1. Monoepoxide syntheses

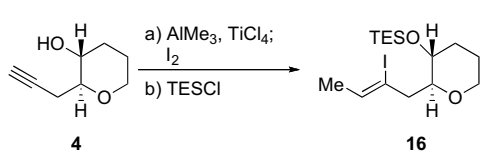
Bishomopropargylic alcohol **4** is prepared easily on a gram scale in five steps from 2,3-dihydropyran.¹⁷ We began our exploration into new transformations of **4** by tackling the synthesis of monoepoxy alcohol **8**. Compound **8** bears a *proximal* methyl substituent and is therefore Me-substituted 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 carbometalation¹⁸ resulted either in very low or undetectable conversion under standard conditions (2 equiv AlMe₃ and 1 equiv Cp₂ZrCl₂ in CH₂Cl₂ or 1,2-dichloroethane at room temperature) (Scheme 4). Heating above 30 °C led only to the decomposition of starting material. Attempted methylalumination of **4** and **13** with the stoichiometric addition of water according to the modified protocol of Wipf and Lim¹⁹ likewise led to poor conversion and significant decomposition. Similarly, methylcupration²⁰ 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.

unsuccessful attempts at *undirected* carbometalation:



successful *directed* carbometalation:



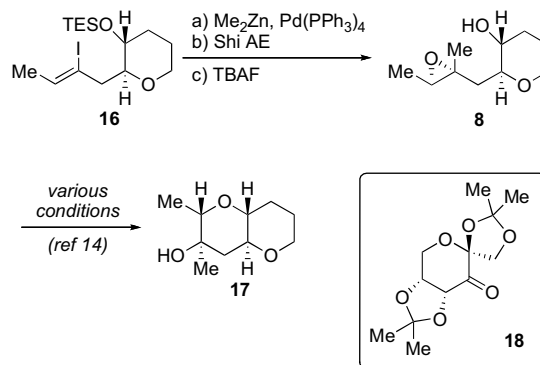
Scheme 4. Carbometalation studies of **4** and **13**: (a) AlMe₃, TiCl₄, CH₂Cl₂, –78 °C, 2 h; I₂, Et₂O; (b) TESCl, imid., DMF, 41% over two steps.

Other attempts at 1,2-difunctionalization of **13** via silylcupration and stannylcupration²¹ were also unsuccessful, with low conversion observed in all cases and only stannylcupration²² 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 TiCl₄ and AlMe₃,¹⁵ recently used in the total synthesis of (–)-borrelidin by the Omura group,²³ proved highly effective. Methylmetalation of **4**, I₂ 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 diastereoselectivity 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.



Scheme 5. Synthesis of monoepoxy alcohol **8**: (a) Me₂Zn, Pd(PPh₃)₄, THF/PhMe, 85%; (b) chiral ketone **18**, Oxone, *n*-Bu₄NHSO₄, K₂CO₃, Na₂B₄O₇ buffer, DMM/MeCN, 0 °C, 71%, 2.8:1 dr; (c) TBAF, THF, 0 °C, 94%.

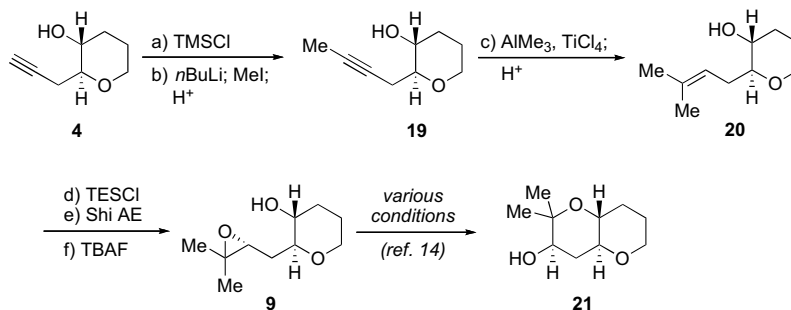
With epoxy alcohol **8** in hand, we turned to the synthesis of its isomer **9**, an epoxide-opening cyclization substrate that bears a *distal* Me substituent (located on the far side of the epoxide with respect to the alcohol). This Me group was appended via alkylation of a derivative of alkyne **4** 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 AlMe₃ and 1.1 equiv TiCl₄ in CH₂Cl₂ at –78 °C) proved best. Upon quenching with methanol, carbometalation smoothly afforded trisubstituted alkene **20** in 70% yield (79% based on recovered **19**) 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., H⁺, I₂, a few highly electrophilic carbon electrophiles) or transmetalated to Pd or Cu and subsequently used as



Scheme 6. Synthesis of monoepoxy alcohol **9**; (a) TMSCl, HMDS, pyridine, CH_2Cl_2 , 90%; (b) $n\text{-BuLi}$, Et_2O ; MeI; $\text{HCl}_{(\text{aq})}$, 88%; (c) AlMe_3 , TiCl_4 , CH_2Cl_2 , -78°C , 2 h, MeOH, 70% (79% based on recovered **19**); (d) TESCl, imid., DMF, 74%; (e) **18**, Oxone, $n\text{-Bu}_4\text{NHSO}_4$, K_2CO_3 , $\text{Na}_2\text{B}_4\text{O}_7$ buffer, DMM/MeCN, 0°C , 78%, 5.8:1 dr; (f) TBAF, THF, 0°C , 98%.

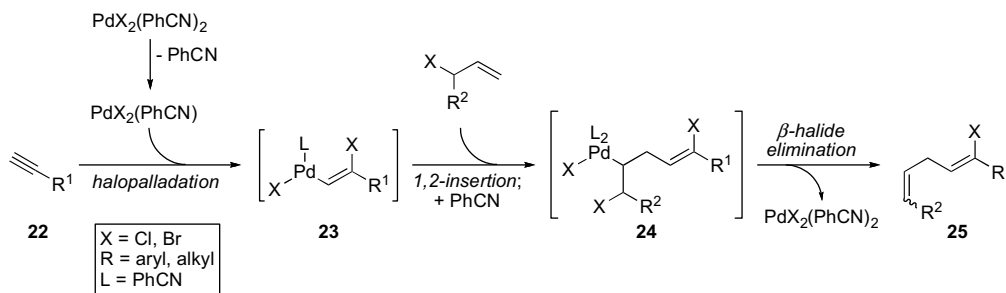
nucleophiles in conjugate addition and cross-coupling processes.²⁴ Unfortunately, however, Thompson carbometalation involves delivery of the metal to the proximal end of alkynes **4** and **19** (and Me to the distal end). This regiochemistry precludes using transmetalation of the alkenylmetal and subsequent 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 and co-workers.¹⁶ It has seen some use in recent years, with notable extensions of the method reported by the Rawal group²⁵ and a synthetic application described by Hoyer and Wang.²⁶ It has proved invaluable to our own work. The method effects chloro- and bromoallylation of alkynes via the proposed mecha-

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.²⁸ 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 $\text{Pd}/\text{P}(\text{t-Bu})_3$ catalyst system²⁹ were unsuccessful.

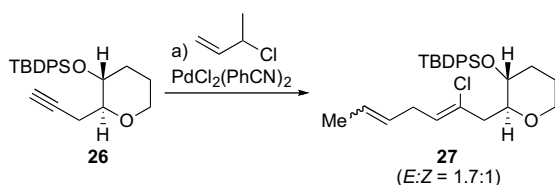
We found more success with simple bromoallylation and subsequent homologation. Bromoallylation of **26** under conditions slightly modified from the original Kaneda conditions (dropwise addition of the alkyne to a room temperature solution of 5 mol % $\text{PdCl}_2(\text{PhCN})_2$ in allyl bromide, with the addition of 5 equiv of NaHCO_3 ³⁰) 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 mono-substituted alkene was readily and nearly quantitatively converted



Scheme 7. The mechanism for haloallylation proposed by Kaneda and co-workers.

nism shown in Scheme 7.^{16,27} The first step is regioselective and *syn*-stereoselective alkyne halopalladation to afford alkenylpalladium halide **23**. After binding and 1,2 insertion of an allylic halide to give **24**, β -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

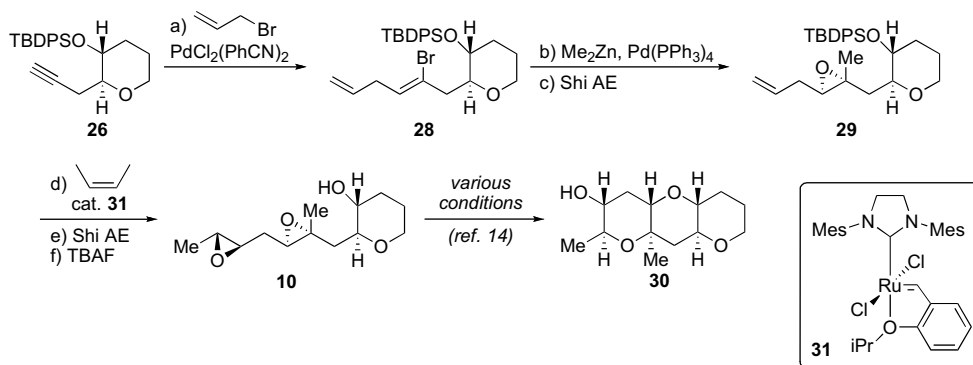


Scheme 8. Chlorocrotylation of alkyne **26**; (a) 3-chloro-1-butene, $\text{PdCl}_2(\text{PhCN})_2$, NaHCO_3 , THF, 87%, 1.7:1 *E/Z*.

to the methylated disubstituted alkene via cross metathesis³¹ with *cis*-2-butene³² using the Hoveyda–Grubbs second generation metathesis catalyst **31** (5 mol %),³³ 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.³⁴ 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**

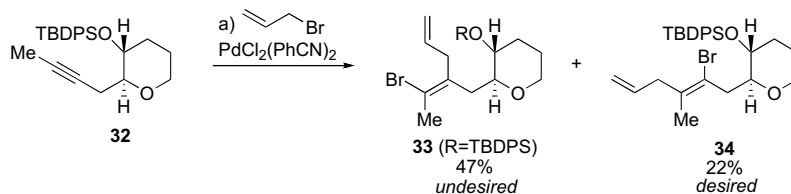
These results in hand, we were initially hopeful that Kaneda haloallylation could be extended to the synthesis of diepoxy alcohol cascade substrates **11** and **12**. Both of these substrates bear a Me



Scheme 9. Synthesis of diepoxide **10**; (a) allyl bromide, $\text{PdCl}_2(\text{PhCN})_2$, NaHCO_3 , rt, 88%; (b) Me_2Zn , $\text{Pd}(\text{PPh}_3)_4$, THF/PhMe; (c) **18**, Oxone, $n\text{-Bu}_4\text{NHSO}_4$, K_2CO_3 , $\text{Na}_2\text{B}_4\text{O}_7$ buffer, DMM/MeCN, 0°C , 48% over two steps, 4:1 dr; (d) *cis*-2-butene, Hoveyda–Grubbs second generation catalyst **31**, CH_2Cl_2 , 4.1:1 *E/Z*; (e) **18**, Oxone, $n\text{-Bu}_4\text{NHSO}_4$, K_2CO_3 , $\text{Na}_2\text{B}_4\text{O}_7$ buffer, DMM/MeCN, 0°C , 90% over two steps, 2.7:1 overall dr; (f) TBAF, THF, 98%.

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**. Hydrometalation of **32** with $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$ (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.

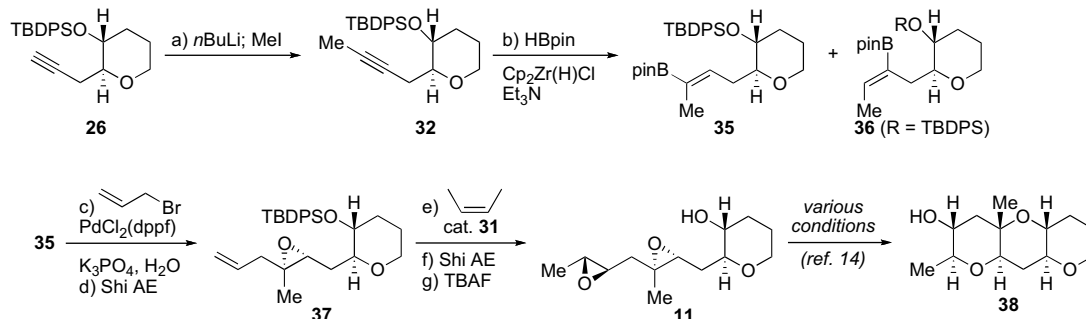


Scheme 10. Bromoallylation of internal alkyne **32**; (a) allyl bromide, $\text{PdCl}_2(\text{PhCN})_2$, NaHCO_3 , THF, 69%, 2.2:1 **33/34** regioselectivity.

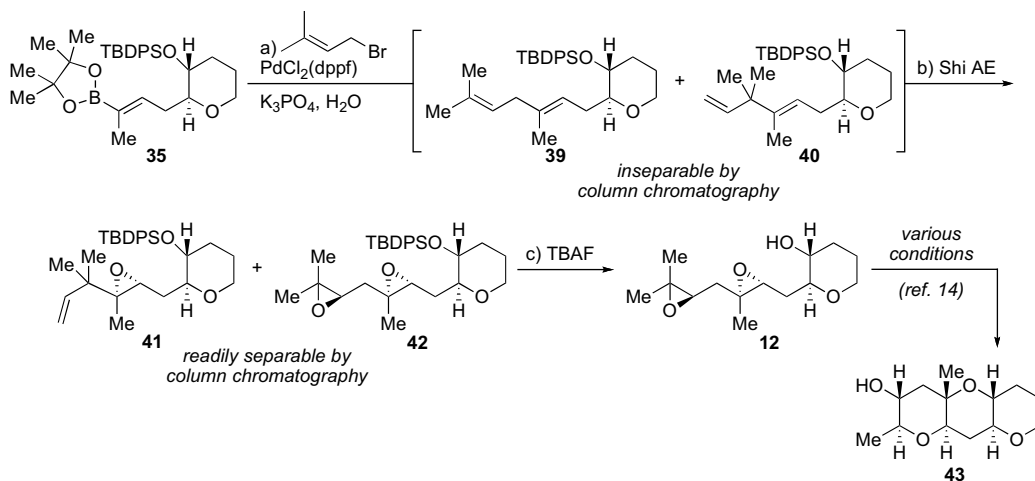
Uncatalyzed hydroboration of **32** with pinacolborane was so slow as to be entirely impractical, but the addition of catalytic quantities (0.1 equiv) of $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$ and triethylamine according to the modification of Wang and co-workers³⁵ to the method developed by Pereira and Srebnik³⁶ improved the reaction rate (Scheme 11). However, even with $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$ catalysis and upon heating the hydroboration reaction mixture to 60°C 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 co-workers.³⁷ The addition of 2 equiv of water was found to improve the reaction rate substantially, pre-



Scheme 11. Synthesis of diepoxy alcohol **11**; (a) $n\text{-BuLi}$, THF, MeI, 99%; (b) HBpin, $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$, Et_3N , 60°C , 44% (2.0:1 mixture of regioisomers **35** and **36**, 60% based on recovered **32**); (c) allyl bromide, $\text{PdCl}_2(\text{dppf})$, K_3PO_4 , H_2O , THF; (d) **18**, Oxone, $n\text{-Bu}_4\text{NHSO}_4$, K_2CO_3 , $\text{Na}_2\text{B}_4\text{O}_7$ buffer, DMM/MeCN, 0°C , 53% over two steps, 3:1 dr; (e) *cis*-2-butene, catalyst **31**, CH_2Cl_2 , 4.2:1 *E/Z*; (f) **18**, Oxone, $n\text{-Bu}_4\text{NHSO}_4$, K_2CO_3 , $\text{Na}_2\text{B}_4\text{O}_7$ buffer, DMM/MeCN, 0°C , 85% over two steps, 1.5:1 overall dr; (g) TBAF, THF, 95%.



Scheme 12. Synthesis of diepoxy alcohol **12**; (a) prenyl bromide, $\text{PdCl}_2(\text{dppf})$, K_3PO_4 , H_2O , THF, 75%, 2.5:1 **39/40**; (b) **18**, Oxone, $n\text{-Bu}_4\text{NHSO}_4$, K_2CO_3 , $\text{Na}_2\text{B}_4\text{O}_7$ buffer, DMM/MeCN, 0°C , 65% (yield of **42** based on **39**), 3.5:1 dr; (c) TBAF, THF, 92%.

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 π -allyl intermediate, resulted in a 2.5:1 mixture of the desired $\text{S}_{\text{N}}2$ product **39** along with undesired $\text{S}_{\text{N}}2'$ 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 Supplementary data to Ref. 14.

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) was 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. Allyl bromide was purified by filtration through basic alumina before use. K_3PO_4 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 co-workers.³⁹ All other reagents and solvents were used as obtained, without further purification.

4.2. Preparation of alkenyl iodide **16** by carbometallation

To a solution of bishomopropargylic alcohol **4** (265 mg, 1.89 mmol) in CH_2Cl_2 (20 mL) at -78°C was added slowly a 2 M solution of AlMe_3 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°C , a 1 M solution of TiCl_4 in CH_2Cl_2 (2.08 mL, 2.08 mmol) was added dropwise. The solution was stirred 2 h at -78°C and then quenched with a solution of I_2 (2.4 g, 9.45 mmol) in Et_2O (20 mL). The reaction flask was then wrapped in foil and allowed to warm to room temperature for 10 h., at which point H_2O (2 mL) was added. The quenched reaction solution was diluted with Et_2O (100 mL) and washed with aqueous 3 M NaHSO_3 (40 mL) until the organic layer was colorless. The aqueous layer was extracted with Et_2O (3×40 mL), and the combined organics were washed with satd NaCl, dried over MgSO_4 , and concentrated in vacuo. The crude alkenyl iodide was carried forward without purification; $R_f = 0.72$ (50% EtOAc in hexanes), UV active.

Upon dissolution of this crude in DMF (1 mL), imidazole (322 mg, 4.73 mmol) and TESCl (380 μL , 342 mg, 2.27 mmol) were added, and the solution was stirred 2 h at room temperature. The reaction mixture was applied directly to column of SiO_2 and chromatographed (2% EtOAc in hexanes) to afford **16** (310 mg, 0.78 mmol, 41% over two steps), which was isolated along with some silylated bishomopropargylic alcohol (43 mg, 0.17 mmol). R_f of **16** = 0.60 (10% EtOAc in hexanes), UV active; $[\alpha]_D^{22} -19.2$ (*c* 4.0, CHCl_3).

IR (thin film, NaCl) 2955, 2876, 1461, 1415, 1274, 1239, 1127, 1102, 1004 cm^{-1} .

^1H NMR (500 MHz, CDCl_3) 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); ^{13}C NMR (125 MHz, CDCl_3) δ 131.5, 107.3, 81.3, 70.8, 68.1, 47.8, 33.8, 25.8, 22.5, 7.1, 5.3.

HRMS (ESI) m/z calcd for $\text{C}_{15}\text{H}_{29}\text{IO}_2\text{Si}$ ($\text{M}+\text{Na}$) $^+$: 419.0874, found: 419.0893.

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

To a of bishomopropargylic alcohol **19** in CH_2Cl_2 (10 mL) at 0°C was added slowly a 2 M solution of AlMe_3 in hexanes (0.96 mL, 1.93 mmol). This solution was stirred for 3 min and then recooled to -78°C . A 1 M solution of TiCl_4 in CH_2Cl_2 (0.96 mL, 0.96 mmol) was added dropwise. The solution was stirred 2 h at -78°C and then quenched with cold MeOH (1 mL), upon which the solution turned pale yellow. The solution was diluted with Et_2O (10 mL) and washed with a saturated solution of Rochelle's salt (10 mL). The aqueous layer was extracted with Et_2O (3×20 mL), dried over MgSO_4 , 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%); $R_f=0.38$ (30% EtOAc in hexanes); $[\alpha]_D^{22}-19.4$ (c 1.2, CDCl_3). 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^{-1} .

^1H NMR (500 MHz, CDCl_3) 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); ^{13}C NMR (100 MHz, CDCl_3) δ 134.1, 120.5, 82.4, 70.9, 67.9, 32.8, 31.6, 26.1, 25.7, 18.2.

HRMS (ESI) m/z calcd for $\text{C}_{10}\text{H}_{18}\text{O}_2$ ($\text{M}+\text{Na}$) $^+$: 193.1199, found: 193.1194.

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

To $\text{PdCl}_2(\text{PhCN})_2$ (40 mg, 0.11 mmol) and NaHCO_3 (880 mg, 10.5 mmol) was added allyl bromide (9 mL, 105 mmol). The resulting solution was stirred 15 min 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 mixture 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%); $R_f=0.54$ (10% EtOAc in hexanes); $[\alpha]_D^{22}-11.5$ (c 27.0, CDCl_3).

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

^1H NMR (500 MHz, CDCl_3) δ 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}C NMR (125 MHz, CDCl_3) δ 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.

HRMS (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 μL , 253 mg, 1.98 mmol) was added, followed by Et_3N (22 μL , 16 mg, 0.16 mmol)

and Schwartz's reagent (41 mg, 0.16 mmol). The resulting slurry was heated to 60°C and stirred vigorously for 28 h while protected from light. After cooling, the crude reaction mixture was filtered through a short pad of SiO_2 (100% Et_2O) and concentrated in vacuo to a heavy oil containing a 2:1 mixture of pinacolate **35** ($R_f=0.36$, 10% EtOAc in hexanes) and its regioisomer **36** ($R_f=0.38$, 10% 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% 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, CDCl_3).

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

^1H NMR (500 MHz, CDCl_3) δ 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}C NMR (125 MHz, CDCl_3) δ 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).

HRMS (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. K_3PO_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 μL , 2.3 mmol, degassed via sparging) was then added, followed immediately by prenol bromide (859 mg, 666 μL , 5.76 mmol). The sealed tube was capped, and the slurry was heated to 80°C and stirred vigorously for 42 h. After cooling and dilution with Et_2O (5 mL), the crude product was filtered through SiO_2 (washed with Et_2O) 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% 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% 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 4×10^{-4} Na_2EDTA (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°C . To this mixture was added, simultaneously over 30 min via syringe pump, a solution of Oxone (1.06 g, 1.73 mmol) in 4×10^{-4} Na_2EDTA (7.75 mL) and a 0.89 M solution of K_2CO_3 (7.75 mL, 6.9 mmol). After the K_2CO_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 (3×25 mL), and the combined organics were washed with satd NaCl, dried over MgSO_4 , and concentrated in vacuo to provide desired diepoxide **42** and diastereomers. Compound **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 two 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 SiO_2 column, 5 μm particle size; 99.5:0.5 hexanes/

i-PrOH, 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); $[\alpha]_D^{22}$ (for a sample in 20:1 dr) -7.5 (c 3.3, $CDCl_3$).

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

1H NMR (500 MHz, $CDCl_3$) δ 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}C NMR (100 MHz, $CDCl_3$) δ 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.

HRMS (ESI) m/z calcd for $C_{30}H_{42}O_4Si$ ($M+Na$) $^+$: 517.2745, found: 517.2751.

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