Tetrahedron 67 (2011) 6497–6512

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Development of a double allylboration reagent targeting 1,5-*syn*-(*E*)-diols: application to the synthesis of the C(23)–C(40) fragment of tetrafibricin

Philippe Nuhant, Jeremy Kister, Ricardo Lira, Achim Sorg, William R. Roush *

Departments of Chemistry, The Scripps Research Institute, Florida, 130 Scripps Way, Jupiter, FL 33458, USA

ARTICLE INFO

Article history:
Received 23 March 2011
Received in revised form 1 June 2011
Accepted 2 June 2011
Available online 13 June 2011

Keywords:
Studies on the synthesis of tetrafibricin
Double allylboration
Allene hydroboration
Kinetically controlled
Tetrabutylammonium allenyltrifluoroborate
Stereoselective synthesis of *syn*-1,5-*E*-diols

ABSTRACT

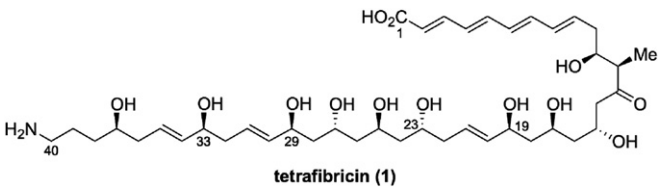
Interest in the synthesis of the C(23)–C(40) fragment **2** of tetrafibricin prompted us to develop a new method for the synthesis of 1,5-*syn*-(*E*)-diols. Toward this end, the kinetically controlled hydroboration of allenes **6**, **33**, *ent*-**39**, **42**, and **45** with the Soderquist borane **25R** were studied. Tetrabutylammonium allenyltrifluoroborate **45** gave superior results and was utilized in a double allylboration sequence with two different aldehydes to provide the targeted 1,5-*syn*-(*E*)-diols in generally high yields (72–98%), and with high enantioselectivity (>95% ee), diastereoselectivity (dr >20:1), and (*E*)/(*Z*) selectivity (>20:1). This new method was applied to the synthesis of the C(23)–C(40) fragment **2** of tetrafibricin.

1. Introduction

The 1,5-*syn*-(*E*)-diol substructure is found in a variety of natural products.[1] One of the strategies used to access 1,5-*syn*-(*E*)-diols, developed by Cossy and co-workers in their work on the total synthesis of tetrafibricin (Fig. 1), involves an iterative allyltitanation–cross metathesis-allyltitanation sequence.[2,3] This strategy provides the 1,5-*syn*-(*E*)-diol motif with good levels of diastereoselectivity. In 2004, Leighton published a method for synthesis of 1,5-*syn*-(*E*)-diols via a unique intramolecular alkyne silylformylation–allylsilylation reaction sequence that proceeds in modest yield and with modest diastereoselectivity.[4] A key sequence in Nicolaou's total synthesis of marinomycin A involved a Horner–Wadsworth–Emmons olefination and a *syn*-reduction of the carbonyl group that provided the 1,5-*syn*-(*E*)-diol unit with good diastereoselectivity.[5] In 2010, Friestad published a method for synthesis of the 1,5-(*E*)-diol unit of tetrafibricin involving the iterative Julia–Kociensky olefination of chiral aldehydes using a chiral α-silyloxy-γ-sulfononitrile.[6] As an alternative, we anticipated that use of a bifunctionalized allylmetal reagent could provide convenient, one-pot access to the 1,5-*syn*-(*E*)-diol motif.[7] Only a few chiral bifunctionalized allylmetal reagents have been reported that provide a high level of stereochemical control in such processes.[8]

Our group has developed several chiral 1,3-bifunctionalized allylborane reagents,[8c–e] and have successfully utilized these reagents in studies on the synthesis of polyhydroxylated natural products.[9]

We report herein the development of a new 1,3-bifunctionalized allylborane reagent that enables the targeted 1,5-*syn*-(*E*)-diol motif to be synthesized with excellent stereochemical control. We demonstrate the utility of this new method in the synthesis of the C(23)–C(40) fragment of tetrafibricin (**1**).



tetrafibricin (1)

Fig. 1. Tetrafibricin (**1**).

2. Background

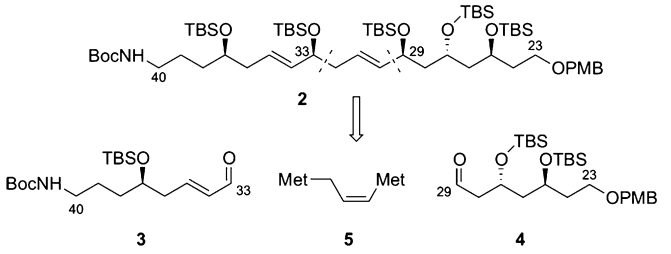
2.1. Studies on the synthesis of tetrafibricin

The present research was motivated by our interest in the synthesis of tetrafibricin, and especially the C(23)–C(40) fragment **2** (Scheme 1). Tetrafibricin (**1**) is a structurally unique natural

* Corresponding author. Tel.: +1 561 228 2450; fax: +1 561 228 3052; e-mail address: roush@scripps.edu (W.R. Roush).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.06.008

product isolated in 1993 from *Streptomyces neyagawaensis*.[10] It displays potent anti-aggregation properties against human platelets by blocking the glycoprotein (GP)IIb/IIIa receptor on the platelet surface, which is important for blood clotting.[11] The stereochemistry was assigned by Kishi based on ^{1}H NMR database technology, including NMR measurements in chiral solvents.[1b] The total synthesis of tetrafibricin has not yet been reported, which is necessary to confirm the relative stereochemistry assignment and to set the stage for biological structure-function studies. Our group reported the synthesis of the tetrafibricin C(1)–C(19) fragment,[12] and contributions from several other laboratories have also appeared.[2,6,13] We recently published a preliminary communication describing the synthesis of the C(23)–C(40) fragment **2**,[14] via the fragment coupling of **3** and **4** with a new bifunctional allylborane reagent. We provide herein the details of this effort, focusing on the studies leading to the development of the new double allylborating agent.



Scheme 1. Retrosynthetic analysis of the C(23)–C(40) fragment **2** of tetrafibricin.

2.2. The double allylboration reaction

In 2002 our group reported highly diastereo- and enantioselective syntheses of 1,5-*anti*-(*E*) (**10**) and 1,5-*syn*-(*Z*) (**15**) diols via a double allylboration sequence (Scheme 2).[8c]

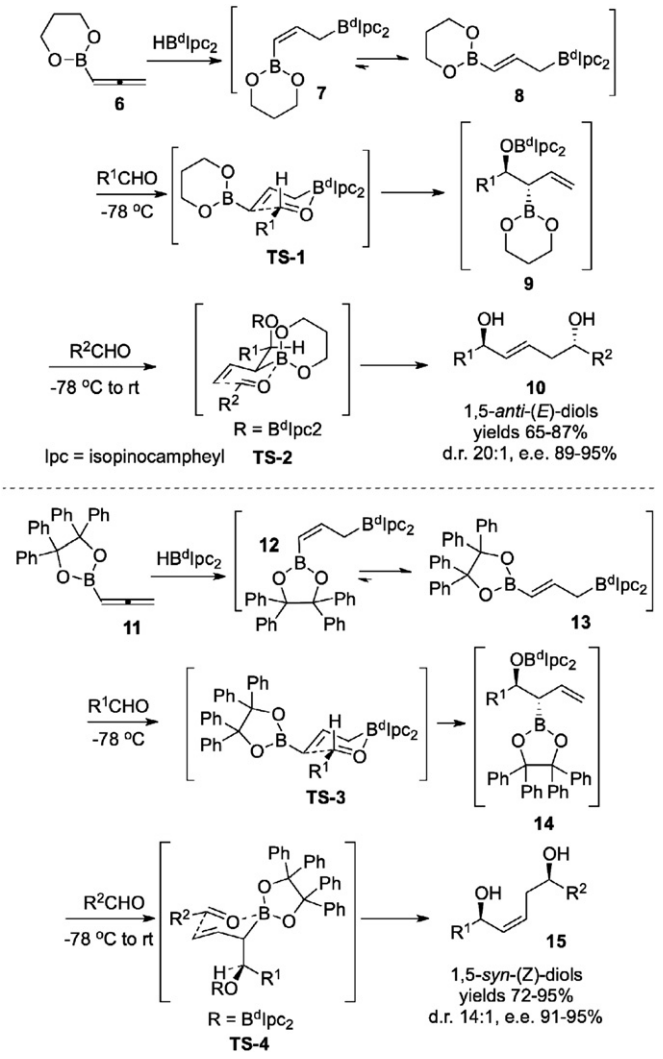
Hydroboration of allenes **6**[8c] and **11**[8c] using ^{D}diisopino-campheylborane (^{D}Ipc$_2$BH)[15] provides the kinetic hydroboration products **7** and **12**, which undergo rapid (*Z*) to (*E*) isomerization via a [1,3]-boratropic shifts[16] to give the observed (thermodynamic) allylboranes **8** and **13**.

The allylboration reaction of these reagents with aldehydes proceeds via chair-like transition states **TS-1** or **TS-3** to generate *anti*-β-alkoxyallylboronates **9** and **14**, respectively. Treatment of *anti*-β-alkoxyallylboronate **9** with a second aldehyde proceeds via the chair-like transition state **TS-2** with the methallylboronate α-substituent in a pseudo-equatorial position. This leads to the formation of the 1,5-*anti*-diol **10** with an intervening (*E*)-olefin. However, due to severe steric interactions the α-substituent in methallylboronate **14** occupies a pseudo-axial position in the second allylboration transition state **TS-4**, leading to the formation of the 1,5-*syn*-diol **15** with an embedded (*Z*)-olefin. Accordingly, we turned our efforts to the synthesis of the 1,5-*syn*-(*E*)-diol configuration, which is not accessible via these first-generation double allylboration reactions, but which is required for the synthesis of the C(23)–C(40) fragment of tetrafibricin.

3. Results and discussion

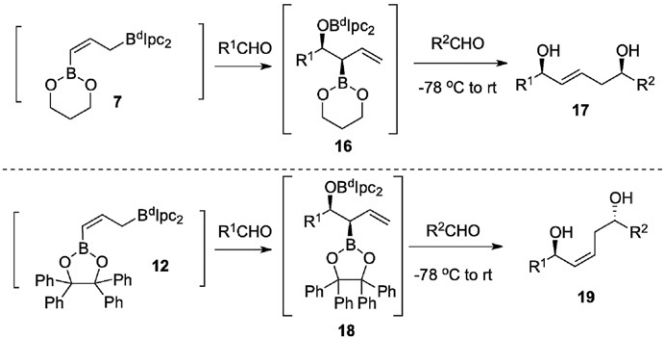
3.1. Initial attempts to extend the double allylboration reaction to the synthesis of 1,5-*syn*-(*E*)-diols 17 via kinetically controlled hydroboration of allenylboronates with Ipc$_2$BH

We anticipated that if the [1,3]-boratropic shifts[16] of **7** and **12** could be prevented by performing the hydroboration of **6** or **11** at low temperatures, we could access to the *syn*-β-alkoxyallylboronates **16**



Scheme 2. Synthesis of 1,5-*anti*-(*E*) **10** and 1,5-*syn*-(*Z*) **15** diols via the double allylboration reaction.

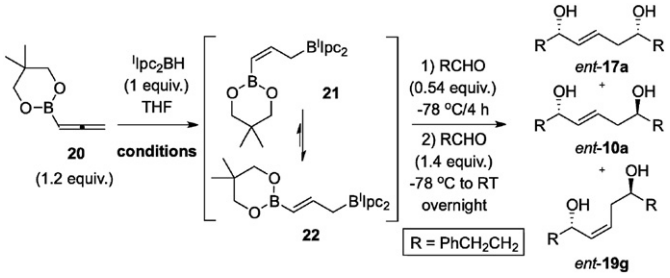
and **18**, respectively. If so, we expected (by analogy to transition states **TS-2** and **TS-4** in Scheme 2) that the subsequent allyboration of **16** or **18** would provide the 1,5-*syn*-(*E*)-diol **17** and 1,5-*anti*-(*Z*)-diol **19** with synthetically useful selectivity (Scheme 3).



Scheme 3. 1,5-*syn*-(*E*)-diol **17** and 1,5-*anti*-(*Z*)-diol **19**.

Accordingly, we attempted to generate (*Z*)-allylborane **21** via the kinetic hydroboration of allene **20** with ^{L}Ipc$_2$BH[15] under a range of reaction conditions (including variations of the solvent, reaction temperature, and time), including the use of Wilkinson's catalyst to

perform the hydroboration at low temperature.[17] However, when the reagent generated under these conditions was treated with hydrocinnamaldehyde at −78 °C, the targeted 1,5-*syn*-(*E*)-diol *ent*-**17a** was consistently the minor product and was not obtained with acceptable selectivity (Scheme 4 and Table 1).



Scheme 4. Studies of the kinetic hydroboration reaction of allene **20** with $^{L}Ipc_2BH$.

Table 1
Results of hydroboration–allylboration of allene **20** with $^{L}Ipc_2BH$[a]

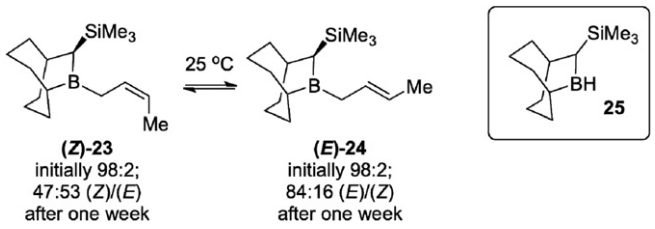
Entry	Catalyst	*T* (°C)	Time	Ratio *ent*-**17a**/*ent*-**10a**[b]/*ent*-**19g**[c]	Yield[d] (%)
1	None	−20	30 min	1:11:1	40
2	None	−30	1 h	1:6.2:0.8	36
3	$(Ph_3P)_3$ RhCl (5%)	−78	4 h	1:0.9:1.2	17

[a] Hydroboration reactions of **20** were performed in THF at the indicated temperatures and times. The resulting allylborane was then treated with hydrocinnamaldehyde as specified in Scheme 4 to give the indicated products.
[b] Product ratio determined by ^{13}C NMR analysis.
[c] Product ratio determined by ^{1}H NMR analysis.
[d] Isolated yields.

When the hydroboration reaction of **20** was performed at −20 °C for 30 min followed by treatment with hydrocinnamaldehyde at −78 °C, a mixture of the 1,5-*syn*-(*E*)-diol *ent*-**17a**, the 1,5-*anti*-(*E*)-diol diastereomer *ent*-**10a**, and the 1,5-*anti*-(*Z*)-diol **19g** were obtained with 1:11:1 selectivity, with favor of *ent*-**10a** predominating (entry 1, Table 1). This result can be explained by a rapid [1,3]-boratropic shift[16] that converts **21** to **22**. This isomerization also occurred rapidly at −30 °C (entry 2), as the hydroboration performed at this temperature resulted in a 1:6.2:0.8 mixture of products, again favoring the 1,5-*anti*-(*E*)-diol *ent*-**10a**. Allene hydroboration experiments performed using Wilkinson's catalyst at −78 °C (entry 3) gave a somewhat improved ratio of *ent*-**17a** to *ent*-**10a**, however the ratio these two diols was only ca. 1: 1, and a comparable amount of *ent*-**19g** was also obtained. These experiments were compromised by the poor solubility of $^{L}Ipc_2BH$ especially at low temperatures, resulting in incomplete conversion and poor overall yields.

3.2. Synthesis of 1,5-*anti*-(*Z*)-diols via the kinetically controlled hydroboration of 11 using Soderquist's borane

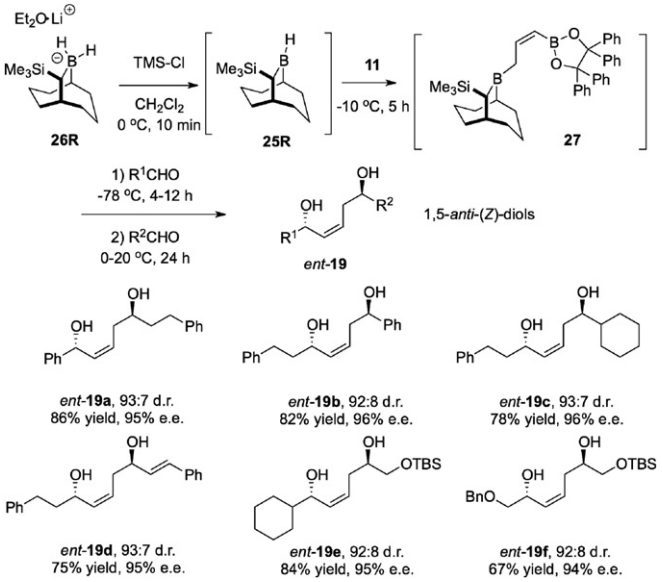
The inability to generate the bis-boryl reagent **21** with acceptable selectivity for use as a precursor to 1,5-*syn*-(*E*)-diols *ent*-**17a** prompted us to reevaluate our strategy. It was apparent from the results in Table 1 that we needed to identify a chiral dialkylborane for the allene hydroboration reaction such that the kinetic allylic borane products would undergo the 1,3-boratropic shift very slowly, if at all. Soderquist had published a series of papers in which allylboration reactions were performed with crotylboranes containing the 10-TMS-9-borabycyclo[3.3.2]decane auxiliary (TBBD).[18] These reagents demonstrated remarkable stability toward thermal isomerization:[19] the (*Z*)-crotyl-TBBD **23** isomer is reported to isomerize to (*E*)-crotyl-TBBD **24** with a half-life of approximately one week at room temperature (Scheme 5).



Scheme 5. *B*-Crotyl-10-TMS-9-borabyciclo[3.3.2]decanes (*Z*)-**23** and (*E*)-**24** undergo (*Z*) to (*E*) isomerization slowly at 25 °C in $CDCl_3$.

This observation suggested that it might be possible to slow the isomerization of **7** to **8**, or of **12** to **13** (Scheme 2) by replacing Ipc_2BH in the hydroboration step with the Soderquist borane, 10-TMS-9-borabyciclo[3.3.2]decane hydride (TBBD-H; **25**). If this hypothesis was confirmed, it would allow us to access the 1,5-*syn*-(*E*)-diol **17** starting from allene **6** and the 1,5-*anti*-(*Z*)-diol **19** starting from the allene **11** with the tetraphenylethylene glycol boronate ester.

We began by studying the hydroboration of allene **11** with the Soderquist borane **25**, en route to the 1,5-*anti*-(*Z*)-diol *ent*-**19**. The unstable TBBD-H **25R**[8d,20,21] was generated in situ from the borohydride **26R** (which we store in a glove box) by treatment with TMSCl. The resulting solution of borane **25R** was then treated with allene **11** at −10 °C for 5 h. At that point, the solution of in situ generated reagent **27** was subjected to a standard double allylboration protocol, involving treatment of **27** with an aldehyde (R^1CHO) at −78 °C typically for 4–12 h and then with a second aldehyde (R^2CHO) at 0 °C–20 °C for 12–24 h. Pleasingly, this protocol provided 1,5-*anti*-(*Z*)-diols *ent*-**19** in 67–86% yields, with ca. 12–13:1 diastereoselectivity and with 94–96% enantiomeric excess (% ee) (Scheme 6).[8d]

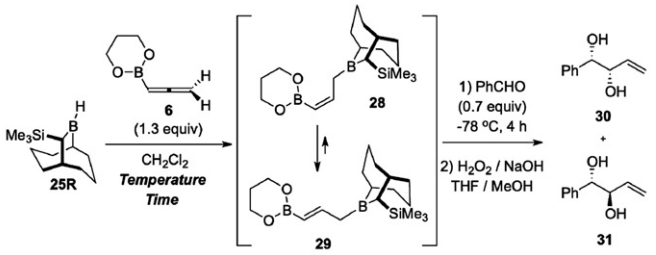


Scheme 6. Synthesis of 1,5-*anti*-(*Z*)-diols *ent*-**19a**–**f** using TBBD-H and allene **11**.

3.3. Studies of the kinetically controlled hydroboration of 2-allenyl-(1,3,2)-dioxaborinane 6 with the Soderquist borane

In view of the success demonstrated in Scheme 6 for the highly stereoselective synthesis of 1,5-*anti*-(*Z*)-diols *ent*-**19** via the kinetically controlled hydroboration of **11** using the Soderquist borane **25**,[8d] we attempted to extend this chemistry to the kinetically controlled hydroboration of allene **6**. Based on the examples summarized in Scheme 2 for reagent **8**,[8c] we expected that double allylborations of **28** (Scheme 7) would provide the targeted 1,5-*syn*-

(*E*)-diols *ent*-**17a** with synthetically useful selectivity, assuming that the hydroboration of **6** proceeded with kinetic control as demonstrated in Scheme 6 for **11**. Accordingly, studies of the hydroboration of **6** were initiated with the experiments summarized in Scheme 7. For these initial studies, the stereoselectivity of the hydroboration was assessed by subjecting the derived allylboranes **28**/**29** to an allylation–oxidation sequence with benzaldehyde, which provided **30** and its *anti* diastereomer **31**.



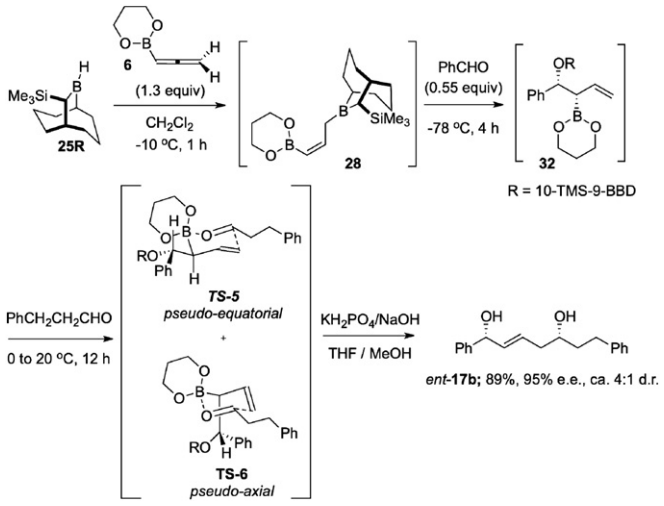
Entry	T (°C)	Time	Ratio **30:31** [a]	Yield [b]
1	-10	1 h	10:1	73%
2	-10	5 h	1.5:1	40%

[a] Determined by ^{1}H NMR analysis.
[b] Combined yield of isolated products.

Scheme 7. Hydroboration studies with TBBD-H **25R** and allene **6**.

Best results were obtained when the hydroboration reaction of **6** was performed at −10 °C for 1 h with the Soderquist borane **25R** (entry 1, Scheme 7). This resulted in the formation of *syn* diol **30** with 10:1 diastereoselectivity. However, increasing the reaction time from 1 h to 5 h led in an erosion of the diastereoselectivity, with the 1,2-*syn*-diol **30** being favored by only 1.5:1 over its *anti* diastereomer (entry 2). This result indicates that the [1,3]-boratropic rearrangement[16] of the kinetically formed (*Z*)-γ-boryl allylborane **28** occurs rapidly at −10 °C to give the thermodynamically favored (*E*)-γ-boryl allylborane **29**. Thus, control of the reaction time and temperature for the hydroboration reaction of **6** is crucial.

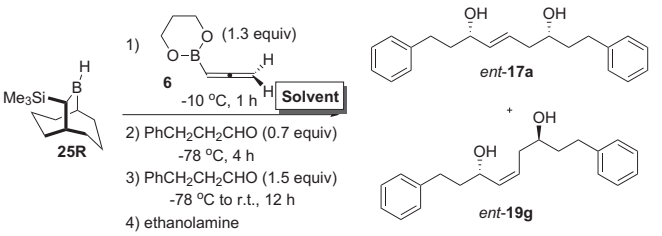
By using the conditions for the hydroboration of **6** defined in Scheme 7, we examined the double allylboration sequence of **28** using benzaldehyde and hydrocinnamaldehyde (Scheme 8). This experiment provided the targeted 1,5-*syn*-(*E*)-diol *ent*-**17b** as the major product in 95% ee, but as a ca. 4:1 mixture with the 1,5-*anti*-(*Z*)-isomer *ent*-**19a**.



Scheme 8. Double allylboration sequence using TBBD-H **25R**, allene **6**, benzaldehyde and hydrocinnamaldehyde.

This result (which is consistent with the results presented in Scheme 4) indicated that there was incomplete control of the transition states, with ca. 80% of the product (*ent*-**17b**) deriving from **TS-5**, and the remaining ca. 20% deriving from **TS-6**. While the reasons for the poor stereoselectivity of this transformation are not certain, it is conceivable that non-bonded interactions between the (1,3,2)-dioxaborinane unit and the group α to boron might destabilize **TS-5** compared to **TS-6**, which are diastereomeric to **TS-2** and **TS-4** in Scheme 2 (discounting the differences in the structures of the Ipc_2B—unit in **TS-2**/**TS-4** and the TBBD unit in **TS-5**/**TS-6**).

We attempted to improve the reaction diastereoselectivity by changing the reaction solvent and using hydrocinnamaldehyde as the substrate (Scheme 9). However, these experiments resulted in significant erosion of the reaction diastereoselectivity, compared to the results summarized in Scheme 8 for reactions performed in CH_2Cl_2.



Entry	Solvent	Ratio *ent*-**17a**:*ent*-**19g** [a]	Yield [b]
1	CH_2Cl_2	1.6:1	80%
2	Et_2O	1.7:1	60%
3	THF	1:1	30%
4	Toluene	1:1	77%

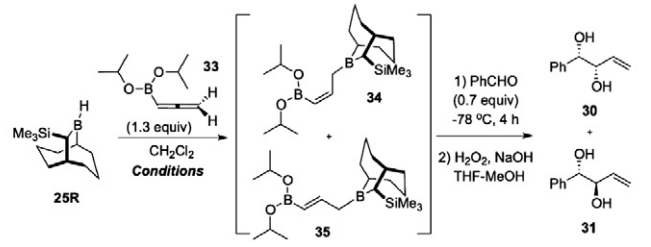
[a] Determined by ^{1}H NMR analysis.
[b] Isolated yields.

Scheme 9. Attempted optimization of the double allylboration sequence using TBBD-H **25R**, allene **6**, and hydrocinnamaldehyde.

These results prompted us to abandon studies of allene **6** as a precursor to the targeted 1,5-*syn*-(*E*)-diols *ent*-**17a**, and to explore other options for their synthesis.

3.4. Diisopropyl allenylboronate 33 as a possible precursor to 1,5-*syn*-(*E*)-diols *ent*-17a

In view of our speculation that non-bonded interactions involving the (1,3,2)-dioxaborinane unit of **32** might contribute to the destabilization of **TS-5** (Scheme 8), we decided to examine allenylboronate **33** with a conformationally flexible diisopropylboronate ester as the starting point for these experiments. The hydroboration reaction of **33** with the Soderquist borane **25R** was optimized by using an allylation–oxidation sequence with benzaldehyde similar to the one described with the allene **6** (Scheme 10).

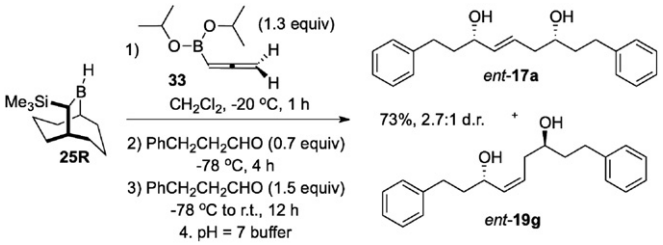


Entry	T (°C)	Time	Ratio **30:31** [a]
1	-10	1 h	5.3:1
2	-10	2 h	4.3:1
3	-20	1 h	8.0:1

[a] Determined by ^{1}H NMR analysis.

Scheme 10. Studies of the kinetic hydroboration of allene **33** with TBBD-H **25R**.

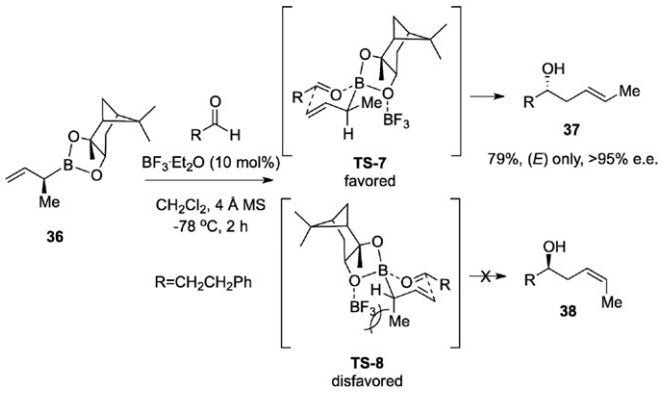
A 5.3:1 mixture of 1,2-*syn*-diol **30** and the 1,2-*anti* diastereomer **31** was obtained when the hydroboration of **33** with **25R** was performed at −10 °C for 1 h (entry 1, Scheme 10). Increasing the hydroboration time from 1 h to 2 h led to a slightly decreased diastereoselectivity (4.3:1 favoring **30**, entry 2). This result suggests that the [1,3]-boratropic rearrangement[16] of the kinetically formed (*Z*)-γ-boryl allylborane **34** to the (*E*)-γ-boryl allylborane **35** is competitive with the hydroboration at −10 °C. The optimal diastereoselectivity was obtained by performing the hydroboration at −20 °C for 1 h (entry 3). By using these optimized hydroboration conditions, the double allylboration sequence using hydrocinnamaldehyde leading to 1,5-*syn*-(*E*)-diol *ent*-**17a** was examined (Scheme 11). Unfortunately, the product was obtained with only 2.7:1 diastereoselectivity (ratio of *ent*-**17a**/*ent*-**19g**). Once again, it became necessary to explore alternative strategies to improve the diastereoselectivity of the second step of the double allylboration sequence leading to *ent*-**17a**.



Scheme 11. Double allylboration sequence using allene **33**, TBBD-H **25R**, and hydrocinnamaldehyde.

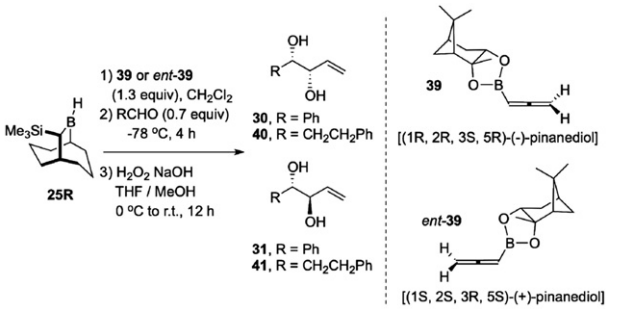
3.5. Studies of the kinetic hydroboration and allylboration reactions of pinanediol allenylboronates 39 and *ent*-39

An (*E*)-selective allylboration of aldehydes leading to (*E*)-5-hydroxy-2-pentenes **37** was developed in our laboratory (Scheme 12),[22] via the $BF_3{\cdot}OEt_2$ promoted reaction of the α-alkyl allylboronate **36** with aldehydes.[23] Of the two possible transition states, **TS-7** and **TS-8**, we suggested that the Lewis acid selectively coordinates with the most accessible α-face lone pair of electrons on the oxygen atom distal to the angular methyl group to minimize steric interactions. The alternative **TS-8**, in which the Lewis acid coordinates with the β-face oxygen non-bonded lone pair, is disfavored due to a 1,3-*syn*-pentane interaction between the pseudoaxial methyl group and the BF_3 unit.



Scheme 12. (*E*)-Selective Lewis acid mediated allylboration of the methallylboronate **36**.

These results suggested that an analogous strategy might be applicable to the synthesis of the targeted 1,5-*syn*-(*E*)-diols **17**. Thus, hydroboration of the pinanediol allenylboronates **39** or its enantiomer *ent*-**39** with TBBD-H **25R**, followed by double allylboration with the second allylboration step performed in the presence of a Lewis acid, was expected to proceed via a transition state similar to **TS-7** to give the targeted 1,5-*syn*-(*E*)-diols *ent*-**17a**. Accordingly, we optimized the hydroboration reaction by using an allylation–oxidation sequence with benzaldehyde (Scheme 13).

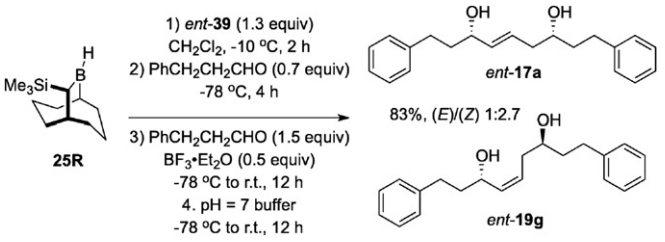


Entry	R	Allene	T (°C)	Time	*syn*:*anti* [a]	Yield [b]
1	Ph	**39**	0	2 h	**30**:**31** (3.2:1)	<30% (96% e.e.) [c]
2	Ph	*ent*-**39**	0	2 h	**30**:**31** (3.2:1)	48% (97% e.e.) [c]
3	Ph	*ent*-**39**	0	40 min	**30**:**31** (8.1:1)	ND
4	Ph	*ent*-**39**	-10	1 h	**30**:**31** (12:1)	ND
5	Ph	*ent*-**39**	-10	2 h	**30**:**31** (8.1:1)	ND
6	CH_2CH_2Ph	*ent*-**39**	-10	2 h	**40**:**41** (7.3:1)	85%

[a] Determined by ^1H NMR analysis.
[b] Isolated yields (ND = not determined).
[c] Determined by Mosher ester analysis.

Scheme 13. Studies of the hydroboration–allylboration reactions of allenes **39** and *ent*-**39**.

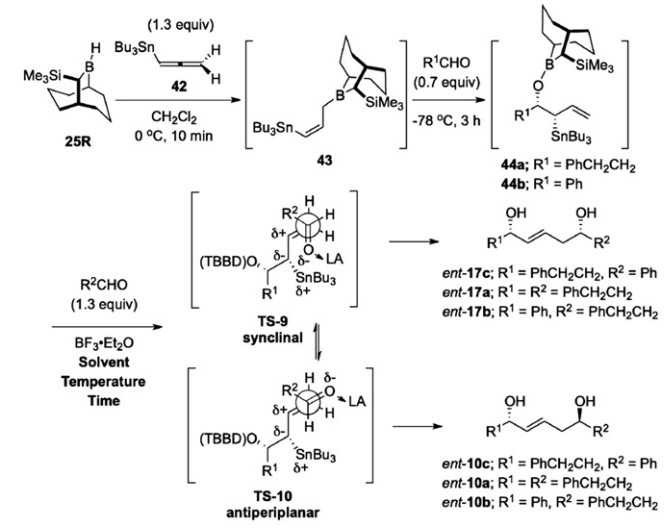
The hydroboration reaction of allene **39** with borane **25R** at 0 °C for 2 h resulted in the formation of **30** in less than 30% yield and with a diastereoselectivity of 3.2:1, but with excellent enantioselectivity (96% ee) (entry 1, Scheme 13). The same reaction was performed, switching the allene **39** for its enantiomer *ent*-**39** to determine if there is a double diasteroselection[24] component to the selectivity of the allylation reaction. This experiment led to the formation of the diol **30** with 48% yield, 3.2:1 diastereoselectivity and 97% ee (entry 2). These results showed that the chirality of the pinanediol moiety does not affect the stereoselectivity of the steps leading to diol **30**. Decreasing the reaction time from 2 h to 40 min led to an improvement of the diastereoselectivity, 8.1:1 in favor of the 1,2-*syn*-diol **30** (entry 3). Performing the hydroboration reaction at −10 °C for 1 h resulted in an increase in the diastereoselectivity of the overall reaction process leading to **30** (12:1) (entry 4). However, increasing the reaction time from 1 h to 2 h resulted in a lower selectivity (8.1:1) (entry 5). Use of hydrocinnamaldehyde in the allylboration sequence gave diol **40** in 85% yield with a diastereoselectivity of 7.3:1 (entry 6). Unfortunately, when these optimized hydroboration conditions were applied in a double allylboration sequence using hydrocinnamaldehyde and $BF_3{\cdot}Et_2O$ during the second allylboration reaction, the 1,5-*syn*-(*E*)-diol *ent*-**17a** and 1,5-*anti*-(*Z*)-diol *ent*-**19g** were obtained in 83% yield but with a disappointing 2.7:1 ratio favoring the (*Z*)-diol *ent*-**19g** (Scheme 14). Attempts to increase the selectivity of the double allylboration reaction by performing the second allylboration in the presence of other Lewis or Brønsted acids ($TiCl_4$, $SnCl_4$, Et_2AlCl, BCl_3, TfOH, TFA, $Sc(OTf)_3$) were unsuccessful.



Scheme 14. Double allylboration sequence using allene *ent*-**39**, TBBD-H **25R**, and hydrocinnamaldehyde.

3.6. Studies of double allylmetallation reactions starting with allenyltributylstannane 42

Although double allylboration reactions starting with allenylboronates **6**, **20**, **33**, and **39** by using the Sodequist borane **25R** failed to provide 1,5-*syn*-(*E*)-diol *ent*-**17** with acceptable diastereoselectivity, the hydroboration step proved to be efficient and kinetically controlled for formation of the required (*Z*)-allylic borane species. Accordingly, we decided to explore the use of **25R** as a hydroborating reagent with other allenes that could be employed as precursors to the targeted 1,5-*syn*-(*E*)-diols. In particular, we were attracted to the use of allenylstannane **42** since the Lewis acid mediated reactions of allylstannanes with aldehydes are well established.[25] With the aim of employing *syn*-β-alkoxyallylstannanes **44a** and **44b** as double allylmetallation intermediates, our attention turned to the hydroboration of the readily available allenylstannane **42**[26] with **25R**, which would provide the kinetic (*Z*)-bimetallic allylborane **43**. This intermediate was expected to undergo an allylboration reaction with an aldehyde to provide **44a** or **44b**, which could react with a second aldehyde in the presence of Lewis acid. Two transition states **TS-9** and **TS-10** could be envisioned for the second allylation step. The synclinal transition state[25d] **TS-9** would provide the desired 1,5-*syn*-(*E*)-diol *ent*-**17a**, *ent*-**17c** or *ent*-**17b**. Alternatively, the antiperiplanar transition state[25] **TS-10** would give the undesired 1,5-*anti*-(*E*)-diol *ent*-**10a**, *ent*-**10c** or *ent*-**10b**, depending on the aldehydes employed (Scheme 15).



Entry	Solvent A/B	T (°C)	Time	Ratio *ent*-**17c**:*ent*-**10c** [a]	Yield [b]
1	CH_2Cl_2	-78	4 h	4:1	81% (94% e.e.)[c]
2	Et_2O	-78	4 h	>15:1	2%
3	Toluene	-78	4 h	2:1	40%

[a] Determined by ^{1}H NMR analysis.
[b] Isolated yields.
[c] Determined by Mosher ester analysis.

Scheme 15. Double allylmetallation sequence involving allenylstannane **42**.

We first studied the hydroboration of **42** with the Soderquist borane **25R** by using an allylboration sequence with hydrocinnamaldehyde. This provided the unstable *syn*-β-alkoxyallylstannane **44a** with >4:1 selectivity when the hydroboration reaction was performed in dichloromethane at 0 °C for 1 h. In order to confirm the stereochemistry of **44a**, we performed a subsequent allylstannation of **44a** with benzaldehyde in presence of $BF_3\cdot Et_2O$ at −78 °C for 4 h, which resulted in the formation of a 4:1 mixture of the 1,5-*syn*-(*E*)-diol *ent*-**17c** and 1,5-*anti*-(*E*)-diol *ent*-**10c** in 81% yield; the enantiomeric purity of *ent*-**17c** was 94% ee (Mosher analysis). In an attempt to improve the diastereoselectivity, we examined the influence of the solvent on the reaction. When the hydroboration reaction of **42** was performed in Et_2O, product *ent*-**17c** was obtained in only 2% yield, but with >15:1 diastereoselectivity. When the reaction was made in toluene, we obtained a 2:1 mixture of *ent*-**17c** and *ent*-**10c** in 40% yield (entry 3, Scheme 15). We also examined other Lewis acids, such as $Ti(OiPr)_4$/*S*-Binol,[27] $Yb(OTf)_3$,[28] $ZnBr_2$, AgOTf/*S*-Binap,[29] $FeCl_3$ to improve the selectivity of the second allylstannation reaction, but without success. These experiments resulted either in no reaction, degradation or Peterson type elimination[30] of the *syn*-β-alkoxyallylstannane **44a**.

Attempts to improve the reaction diastereoselectivity by performing the second allylation at lower temperatures met with some success. When the second allylation reaction of **44a** was performed at 0 °C, we obtained allylation products in 72% yield but with diminished selectivity (2:1 in favor of *ent*-**17c**, entry 1, Table 2). However, performing the second allylation reaction at −90 °C (entry 2) enabled us to obtain the 1,5-diol products in 81% yield, with slightly better selectivity (5:1). Further reductions of the reaction temperature, to −110 °C, required that we use a co-solvent such as Et_2O or pentane that does not freeze at this temperature. Use of Et_2O as the co-solvent led to improvement in the selectivity (11:1) but the yield was only 30% (entry 3). Use of pentane as co-solvent provided *ent*-**17c** in 66% yield and 10:1 selectivity (entry 4). Because of the difficulty maintaining the cold bath at such a low temperature for a long period, we ran the reaction in a mixture of dichloromethane and pentane (1:3) at −78 °C for 3 h and were pleased to find that the 1,5-*syn*-(*E*)-diol *ent*-**17c** was produced in 73% yield with 6:1 selectivity (entry 5). Investigations by Keck and Denmark suggest that a synclinal arrangement of the π-systems (C=O and C=C) in the transition state (comparable to **TS-9**) is favored as this allows stabilization of the transition state through frontier orbital interactions and minimization of charge transfer[31] thus, performing the reactions at low temperatures in non-polar solvent systems might accentuate these effects. Further reduction of the solvent polarity by increasing the ratio of pentane/dichloromethane to 4:1 at −78 °C provided 1,5-*syn*-(*E*)-diol *ent*-**17c** with 7:1 ds (entry 6).

Table 2
Attempts to optimize the second allylboration reaction of **44a** and **44b** with benzaldehyde or hydrocinnamaldehyde and $BF_3\cdot Et_2O$ as per Scheme 15

Entry	Solvent	*T* (°C), time	Product ratio [a]	Yield [b] (%)
1	CH_2Cl_2	0, 4 h	*ent*-**17c**/*ent*-**10c** (2:1)	72
2	CH_2Cl_2	−90, 3 h	*ent*-**17c**/*ent*-**10c** (5:1)	81
3	CH_2Cl_2/Et_2O (1/2)	−110, 3 h	*ent*-**17c**/*ent*-**10c** (11:1)	30
4	CH_2Cl_2/Pent (1/3)	−110, 2.5 h	*ent*-**17c**/*ent*-**10c** (10:1)	66
5	CH_2Cl_2/Pent (1/3)	−78, 3 h	*ent*-**17c**/*ent*-**10c** (6:1)	73
6	CH_2Cl_2/Pent (1/4)	−78, 4.25 h	*ent*-**17c**/*ent*-**10c** (7:1)	81
7	CH_2Cl_2/Pent (1/4)	−78, 4.25 h	*ent*-**17a**/*ent*-**10a** (7:1)	57
8	CH_2Cl_2/Pent (1/4)	−78, 4.25 h	*ent*-**17b**/*ent*-**10b** (4:1)	51 (93% ee) [c]

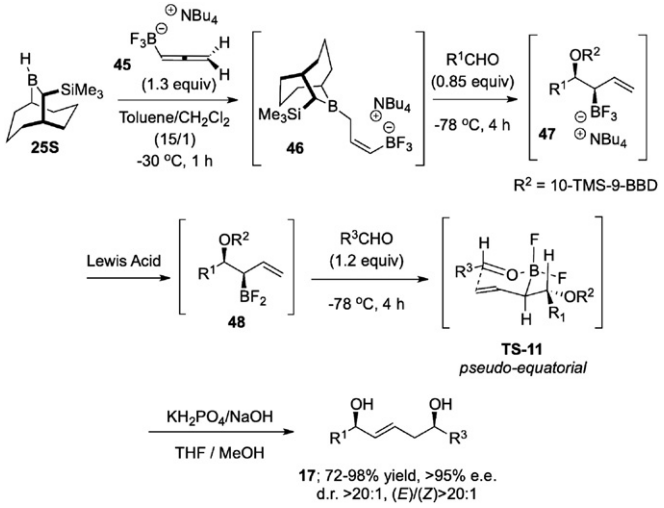
[a] Determined by ^{1}H NMR analysis.
[b] Isolated yields.
[c] Determined by Mosher ester analysis.

Similar diastereoselectivity but a lower yield (57%) was obtained when hydrocinnamaldehyde was used instead of benzaldehyde (compound *ent*-**17a** and *ent*-**10a**, entry 7). However, when benzaldehyde was used for first allylboration, followed by use of

hydrocinnamaldehyde in the second allylstannation step, using the same conditions described as above, a 51% yield of a 4:1 mixture of 1,5-*syn*-(*E*)-diol *ent*-**17b** and 1,5-*anti*-(*E*)-diol *ent*-**10b** was obtained favoring of *ent*-**17b** (93% ee; entry 8). While these results were encouraging, we sought a significantly more stereoselective method for synthesis of the targeted 1,5-*syn*-(*E*)-diols.

3.7. Development of the double allylborating agent 46 starting from tetrabutylammonium allenyltrifluoroborate 45

We were intrigued by several publications from Batey's laboratory, who reported allylation and crotylation of aldehydes using potassium allyl and crotyltrifluoroborates.[32] These data stimulated the idea that it should be possible to generate a double allylborating reagent, specifically the (*Z*)-γ-boryl allyltrifluoroborate **46**, via the kinetically controlled hydroboration of tetrabutylammonium allenyltrifluoroborate **45** with the Soderquist borane, **25S** (Scheme 16). Based on the Batey precedent, it was expected that allylic trifluoroborate **47** could be converted to allylboron difluoride **48** upon treatment with an appropriate Lewis acid. Further, and most importantly, it was anticipated that **48** would undergo aldehyde allylboration reactions with much greater stereoselectivity than with **32** previously studied (Scheme 8), owing to the smaller size of the difluoroborane unit of **48** compared to the (1,3,2)-dioxaborinane unit in **32** (e.g., compare **TS-11** for **48** with **TS-5** for **32**).

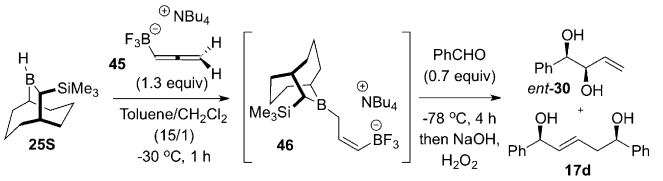


Scheme 16. Synthesis of 1,5-*syn*-(*E*)-diols **17** from allenyltrifluoroborate **45**.

Studies of the hydroboration of **45** commenced with the experiments summarized in Table 3. Initially, the hydroboration of allene **45** (1.3 equiv) was performed with the Soderquist borane, **25S**, at 0 °C for 1 h. The solution was cooled to −78 °C and then benzaldehyde (0.7 equiv) was added. The reaction was maintained at −78 °C for 4 h, then was worked up oxidatively. This provided 1,2-*syn*-diol *ent*-**30** as a 5.7:1 mixture of diastereomers, along with the unexpected (*E*)-1,5-*syn*-diol **17d** (Table 3, entry 1). The formation of **17d** suggested that allylboron difluoride **48** was forming during the reaction.

A significant improvement of the product diastereoselectivity (16:1) was realized by performing the hydroboration at −10 °C for 1 h (entry 2), suggesting that the rate of boratropic isomerization of **46** can be controlled by keeping the reaction temperature below −10 °C. However, *ent*-**30** and **17d** were still formed in ca. 3:1 ratio. Attempts to reduce any residual benzaldehyde, by addition of DIBAL prior to the oxidative workup did not eliminate **17d** as a reaction product (entry 3), suggesting that **17d** is formed during the allylboration reaction at −78 °C and not during workup. The best

Table 3
Hydroboration of allene **45** and allylboration reactions of the derived reagent **46**



Entry	Solvent	Hydroboration temp/time	Yield (%) of *ent*-**30**[a] (*syn*/*anti*)[b]	Ratio *ent*-**30**/**17d**[c]
1	CH_2Cl_2	0 °C/1 h	39 (5.7:1)	3.0:1
2	CH_2Cl_2	−10 °C/1 h	38 (16:1)	2.9:1
3[d]	CH_2Cl_2	−10 °C/1 h	39 (12:1)	3.3:1
4	CH_2Cl_2	−10 °C/3 h	41 (5.1:1)	3.2:1
5	CH_2Cl_2	−30 °C/1 h	52 (>20:1)	3.7:1
6	CH_2Cl_2	−30 °C/3 h	52 (>20:1)	4.3:1
7	Et_2O/CH_2Cl_2[e]	−30 °C/1 h	50 (>20:1)	7.1:1
8	Toluene/THF[f]	−30 °C/1 h	51 (>20:1)	>30:1
9	Toluene/CH_2Cl_2[g]	−30 °C/1 h	87[h] (>20:1)	>30:1

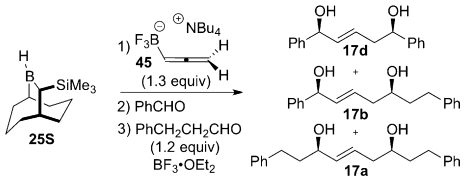
[a] Isolated yields.
[b] Determined by ^1H NMR analysis.
[c] Determined after isolation of *ent*-**30** and **17d**.
[d] Dibal-H (2 equiv) added before the oxidation step.
[e] Et_2O/CH_2Cl_2 (2:1).
[f] Toluene/THF (2:1).
[g] Toluene/CH_2Cl_2 (15:1).
[h] Compound *ent*-**30** obtained in 97% ee, determined by Mosher ester analysis.

diastereoselectivity for *ent*-**30** (>20:1) was obtained from experiments in which the hydroboration reaction was run at −30 °C (entries 5 and 6), which suggested that under these conditions the [1,3]-boratropic isomerization of **46** to the corresponding (*E*)-isomer is essentially suppressed. Examination of the reaction in other solvents led to the discovery that the competitive abstraction of fluoride ion from **47** to give **48** (the precursor to **17d**) could also be suppressed (entries 7, 8, and 9). Best results were obtained (entry 9) when the hydroboration/allylboration sequence was performed in a 15:1 mixture of toluene and CH_2Cl_2 (CH_2Cl_2 is needed owing to the poor solubility properties of **45** in toluene). Under these conditions, the 1,2-*syn*-diol *ent*-**30** was obtained in 87% yield, with 97% ee, and >20:1 dr after oxidative workup. These data demonstrate that **46** is obtained with very high stereoselectivity via the kinetically controlled hydroboration of **45**, and also that the first allylboration reaction provides the intermediate β-alkoxyallyltrifluoroborate **47** with excellent stereochemical control.

Next, we applied these optimized reaction conditions to the double allylboration reaction leading to the targeted 1,5-*syn*-(*E*)-diols **17** (Table 4). This next phase of the reaction development was facilitated by addition of $BF_3{\cdot}OEt_2$ to the intermediate β-alkoxyallyltrifluoroborate **47**.[33] This smoothly generated the allylic boron difluoride intermediate **48**, which reacted with the second aldehyde to give the targeted 1,5-*syn*-diol **17**. The amount of the aldehyde used in the first allylboration reaction proved to be important for avoiding the homo-coupling double allylboration products **17d** (deriving from the first aldehyde) and **17a** (deriving from the second aldehyde). Optimized reaction conditions (Table 4, entry 2) were found by using 1.3 equiv of the allene **45**, 0.85 equiv of the first aldehyde, 1.5 equiv of $BF_3{\cdot}Et_2O$ and 1.2 equiv of second aldehyde. This combination provided the 1,5-*syn*-diol-(*E*) **17** in 73% yield, with excellent enantioselectivity (>95% ee), diastereoselectivity (dr>20:1), and (*E*)/(*Z*) ratio (>20:1).

By using these optimized reaction conditions (Table 4, entry 2), a series of double allylboration reactions were performed to demonstrate the scope and utility of this new procedure (see Scheme 17). These results demonstrate that the long-sought 1,5-*syn*-(*E*)-

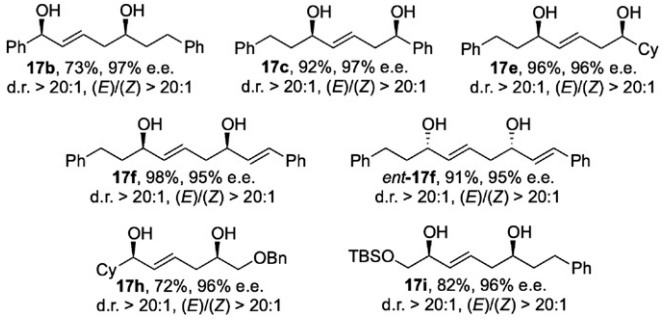
Table 4
Optimization of the double allylboration reaction of **46** generated by the hydroboration of allene **45**[a]



Entry	PhCHO (equiv)	$BF_3 \cdot OEt_2$ (equiv)	Yield[b] (%) **17b**	Ratio[c] (*E*)/(*Z*)	Ratio **17d**/**17b**/**17a**[c]
1	0.75	1.5	60	>20:1	0:89:11
2	0.85	1.5	73	>20:1	0:100[d]:0
3	0.95	1.5	51	>20:1	8:92:0
4[e]	0.85	1.5	30	6:1	0:100:0
5[f]	0.85	—	77	6:1	0:100:0

[a] Reaction conditions: solvent: toluene/CH_2Cl_2; hydroboration: −30 °C, 1 h; first allylboration: −78 °C, 4 h; second allylboration: −78 °C, 4 h; workup: pH 7 buffer (KH_2PO_4/NaOH).
[b] Isolated yields.
[c] Determined by ^1H NMR analysis.
[d] Compound **17b** obtained with >20:1 dr and 97% ee, determined by Mosher ester analysis.
[e] Second allylboration: 0 °C, 2 h.
[f] Second allylboration: −78 to 20 °C, 12 h.

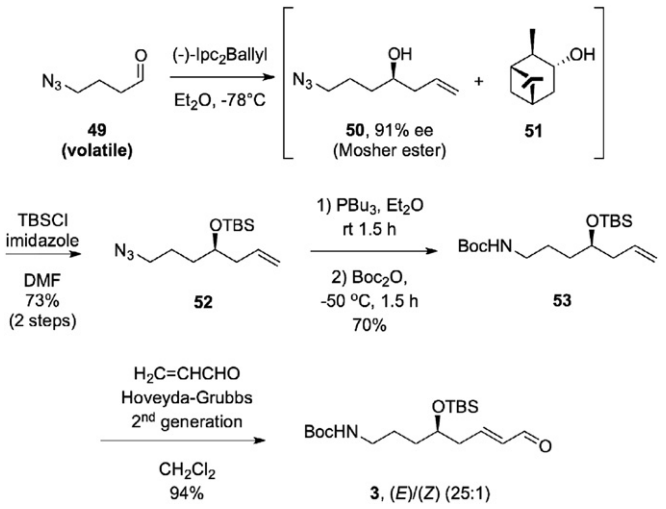
diols **17** are obtained in 72–98% yields, >95% ee, >20:1 dr, and with >20:1 (*E*)/(*Z*) selectivity. Thus, use of the allenyltrifluoroborate **45** in combination with the Soderquist borane provides an efficient, highly stereoselective synthesis of the 1,5-*syn*-(*E*)-diols illustrated by the structures in Scheme 17.



Scheme 17. 1,5-*syn*-(*E*)-Diols synthesized by using the optimal reaction Conditions. All experiments were performed by using the conditions defined in entry 2 of Table 4.

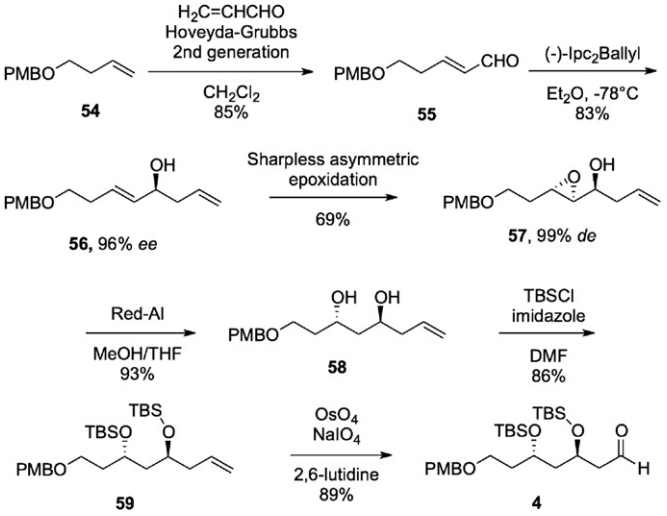
3.8. Application of the new double allylboration procedure to the synthesis of the C(23)–C(40) fragment of tetrafibricin

The original objective of this methodology development project was the synthesis of a double allylboration reagent that would facilitate the stereoselective synthesis of the C(23)–C(40) fragment of tetrafibricin. As we presented in Scheme 1, we envisioned that this fragment could be assembled from aldehydes **3** and **4** by a double allylboration sequence. The synthesis of aldehyde **3** (Scheme 18) started from the known 4-azidobutanal[34] **49**, which was subjected to an allylboration reaction with Brown's (−)-di(isopinocampheyl) allylborane reagent.[35] This provided secondary alcohol **50** as an inseparable mixture with isopinocampheol, **51**. This mixture was treated with TBSCl and imidazole which provided the TBS ether **51** in 73% yield over the two steps. The enantiomeric purity of alcohol **50** was determined to be 91% ee, by application of the Mosher ester analysis.[36] This analysis also enabled us to confirm the absolute stereochemistry of **50**. Reduction of the azide by treatment with Bu_3P in wet diethyl ether, followed by protection of the primary amine as a *tert*-butyl carbamate (Boc) provided **53** in 70% yield.[37] The cross olefin metathesis[38] of **53** with acrolein and using the second-generation Grubbs–Hoveyda catalyst[39] gave aldehyde **3** in 94% yield ((*E*)/(*Z*)=25:1). Aldehyde **3** corresponds to the C(33)–C(40) fragment of tetrafibricin (Scheme 18).



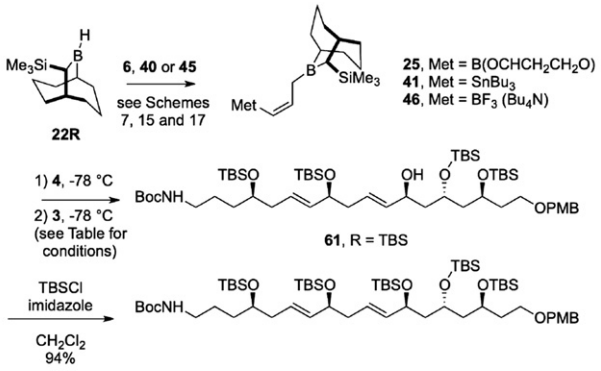
Scheme 18. Synthesis of aldehyde **3**.

The synthesis of aldehyde **4** began with cross-metathesis between readily available olefin **54**[40] and acrolein in the presence of Grubbs–Hoveyda second-generation catalyst.[39] This reaction provided the unsaturated aldehyde **55** in 85% yield. Subjection of **55** to a Brown allylboration[35] using (−)-di(isopinocampheyl)-allylborane afforded alcohol **56** in 83% yield and 96% ee as verified by Mosher ester analysis.[36] Asymmetric epoxidation of alcohol **56** under the standard Sharpless epoxidation conditions[41] delivered epoxy alcohol **57** in 69% yield as a single diastereomer. Reduction of the epoxide using Red-Al in the presence of MeOH[42] provided *anti*-1,3-diol **58**, the stereochemistry of which was verified by ^{13}C NMR analysis of the derived acetonide according to Rychnovsky's method.[43] Protection of the diol in **58** with TBSCl and imidazole gave **59**. Finally oxidative cleavage of the vinyl group of **59** by using Jin's protocol (OsO_4/$NaIO_4$/2,6-lutidine)[44] provided aldehyde **4**, which corresponds to the C(23)–C(29) fragment of tetrafibricin (Scheme 19).



Scheme 19. Synthesis of aldehyde **4**.

Studies performed on the coupling of aldehyde fragments **3** and **4** to give the targeted tetrafibricin intermediate **2** are summarized in Scheme 20. Initial studies were performed using reagent **28** generated from allene **6** as described in Scheme 7. Use of **28** in this double allyboration sequence (using the conditions defined in Scheme 8) provided **60** in 67% yield, but as an inseparable 6:1 mixture of diastereomers (entry 1, Scheme 20). When reagent **43**, generated from allene **42** as described in Scheme 15 was used, the double allylmetalation product **60** was obtained in 24% yield as an inseparable 4:1 mixture of diastereomers (entry 2, Scheme 20).



Entry [a]	Allene	**60** (*E*)/(*Z*) [e]	**60** d.r. [f]	Yield [g]
1 [b]	**6**	70:30	6:1	67%
2 [c]	**42**	>20:1	4:1	24%
3 [d]	**45**	>20:1	>20:1	83%

[a] The requisite allylboranes **28**, **43** and **21** were generated and the first allylboration step performed as described in **Schemes 7-8**, **15**, and **17**, respectively.

[b] The second allylboration step for the synthesis starting with **28** was performed at -78 °C in CH_2Cl_2.

[c] The second allylmetallation step for the synthesis starting with **43** was performed at -78 °C in CH_2Cl_2 in the presence of BF_3•OEt_2.

[d] The second allylboration step for the synthesis starting with **46** was performed at -78 °C in a 15:1 toluene- CH_2Cl_2 solvent mixture.

[e] Determined by ^1H NMR and ^{13}C NMR analysis.

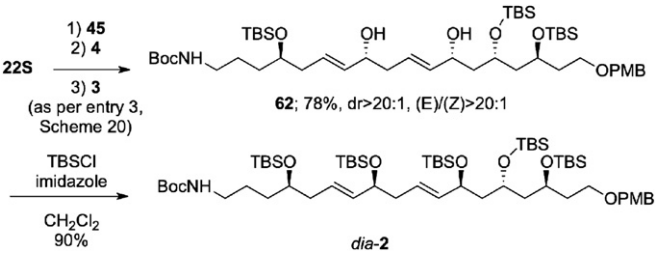
[f] Determined by ^1H NMR and ^{13}C NMR analysis and absolute configuration by Mosher ester analysis.

[g] Isolated yields of **2** and its diastereomer.

Scheme 20. Synthesis of the C(23)–C(40) fragment **2** of tetrafibricin.

Fortunately, excellent results were obtained when the double allylboration coupling of aldehydes **4** and **3** was performed using reagent **46** generated from allenyltrifluoroborate **45** (entry 3, Scheme 20). This reaction provided **60** in 83% yield, with exceptional diastereoselectivity (>20:1) and (*E*)/(*Z*) ratio (>20:1). The stereochemistry of the two hydroxyl groups in **45** were confirmed by using the Mosher method.[36] This result demonstrates that the fragment assembly reaction using reagent **46** is compatible with protecting groups such as silyl ethers, PMB ethers, and acid labile Boc carbamates. Treatment of **60** with TBSCl and imidazole furnished the tetrafibricin C(23)–C(40) fragment **2** in 94% yield. Furthermore, replacement of **25R** by **25S** in the hydroboration reaction of allene **45** allowed the diastereomeric 1,5-diol **62** to be obtained in comparable yield and stereoselectivity (Scheme 21).

In comparison with other methods[2–7] described in the literature for synthesis of 1,5-diol units, our double allylboration procedure is



Scheme 21. Synthesis of the diastereomer **62**.

highly convergent and has a high degree of stereochemical generality. In fact, the synthesis of several different diastereoisomers of a 1,5-diol system can now be achieved simply by changing the nature of the borane reagent (10-TMS-9-BBD-H or Ipc_2BH) or the monosubstituted allene used to synthesize the double allylboration reagent (e.g., see Schemes 2, **6**, **17**, **20**, and **21**). Thus, we expect that our method will prove useful for the synthesis and confirmation of the relative and absolute stereochemistry of 1,5-diol units found in other natural products.

4. Conclusion

In summary, we have developed an efficient and highly diastereoselective double allyboration reaction sequence starting from the hydroboration of tetrabutylammonium allenyltrifluoroborate **45** and the Soderquist borane, TBBD-H **25**. This method has enabled us to synthesize the C(23)–C(40) fragment **2** of tetrafibricin and its C(29)–C(33) diastereoisomer **62** with very high stereoselectivity. Further progress toward the completion of the total synthesis of tetrafibricin **1** will be reported in due course.

5. Experimental section

5.1. General

Tetrahydrofuran, dichloromethane, diethyl ether, and toluene were purified by passing through a solvent column of activated alumina (A-1). Hexanes, acetonitrile and trimethylsilyl chloride were purified by distillation from calcium hydride. Anhydrous pentane and methanol were purchased from Aldrich Chemical Company. All commercially available aldehydes were purified by vacuum distillation before use. Unless indicated otherwise, other commercially available reagents were used as received without purification. Unless otherwise indicated, all reactions were conducted under an atmosphere of argon using flamed-dried or oven-dried (140 °C) glassware. Standard techniques for handling air-sensitive compounds were also employed for all operations. Celite 545® was dried at 140 °C for at least 12 h prior to use. Removal of solvents was accomplished on a rotary evaporator at reduced pressure. Reaction mixtures were maintained at low temperature by using a Thermo NESLAB CB-60 cold bath. Enantiomeric excess and absolute configurations of all new alcohol products were determined by using the Mosher[36] method.

^1H NMR spectra were recorded on a Bruker spectrometer at 400 MHz. ^{13}C NMR spectra were recorded on a Bruker spectrometer at 100 MHz. The proton signal for non-deuterated solvent (δ 7.24 ppm for $CHCl_3$) was used as an internal reference for ^1H NMR spectra. For ^{13}C NMR spectra, chemical shifts are reported relative to the δ 77.24 ppm resonance of $CDCl_3$. Infrared (IR) spectra were recorded as thin films using CH_2Cl_2 as the solvent or neat on a Perkin–Elmer Spectrum 1000 FTIR. Optical rotations were measured on a Rudolph Autopol IV polarimeter using a quartz cell with 1 mL capacity and a 1 dm path length. Melting points were

determined on a Mel-Temp II hot stage melting point apparatus and are uncorrected. High-resolution mass spectra were recorded on a spectrometer at the University of Florida Mass Spectrometry Laboratory.

Analytical thin layer chromatography (TLC) was performed on Kieselgel 60 F_{254} glass plates precoated with a 0.25 mm thickness of silica gel. TLC plates were visualized with UV light and/or by staining with cerium molybdate (5 g $Ce(SO_4)_2$, 25 g $(NH_4)Mo_7O_{24}\cdot 4H_2O$, 450 mL H_2O, 50 mL H_2SO_4). Preparative thin layer chromatography (TLC) was performed on Kieselgel 60 F_{254} glass plates precoated with a 0.5 mm thickness of silica gel. Column chromatography was generally performed according to the method of Still[45] using Kieselgel 60 (230–400 mesh) silica gel.

5.2. Procedure for the preparation of the allenyl boronic esters (6, 20, and *ent*-39)

Freshly distilled trimethyl borate (21.7 mL, 196 mmol) was added to a round bottom flask containing 150 mL of ether placed in a −78 °C cold bath. A 0 °C solution of allenylmagnesium bromide (1 M in ether, 196 mmol) was added via syringe or cannula at a rate as to keep the internal reaction temperature below −65 °C. A white precipitate formed during this addition. The reaction mixture was stirred 3 h at −78 °C, then was warmed to 0 °C over 1 h and stirred at 0 °C for an additional hour. Aqueous HCl (2 M, 392 mmol) was added via an addition funnel. This mixture was stirred for 1 h and then the organic layer was separated using a separatory funnel. The aqueous layer was washed with ether (2×200 mL) and the combined organic phases were dried over Na_2SO_4 for 30 min. The solution was filtered under nitrogen and solvent removed in vacuo until ~250 mL of solvent remained (the rotary evaporator was flushed and backfilled using an argon balloon). The appropriate diol (137 mmol) was added to the flask and reaction stirred for 24 h at room temperature, at which time 10 g of $MgSO_4$ was added and the mixture stirred for an additional 18 h at room temperature. The reaction was filtered under nitrogen using a coarse fritted funnel and solvent removed in vacuo using argon to backfill the rotary evaporator.

*5.2.1. 2-Allenyl-1,3,2-dioxaborinane (**6**).* The remaining clear yellow oil was distilled under vacuum (bp 20 mm Hg, 81–82 °C) to yield 76% of **6** as a clear colorless oil. The oil was transferred to small vials and stored under nitrogen in a desiccator in a −20 °C freezer. This material could be used neat over several months without decomposition. Spectroscopic data obtained for **6** matched that reported in the literature.[8a]

*5.2.2. 2-Allenyl-5,5-dimethyl-1,3,2-dioxaborinane (**20**).* The remaining clear yellow oil was distilled under vacuum (bp 46–48 °C/0.5 mbar) to yield 69% of **20** as a clear colorless oil. The oil was transferred to small vials and stored under nitrogen within a desiccator in a −20 °C freezer and could be used neat over several months without decomposition: IR (neat) 2963, 2935, 2889, 1936, 1479, 1426, 1379, 1350, 1331, 1259, 1227, 1184, 1088, 1009, 870, 814, 681, 666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.83 (t, J=6.9 Hz, 1H), 4.61 (d, J=7.0 Hz, 2H), 3.66 (s, 4H), 0.98 (s, 6H); ^{13}C (100 MHz, $CDCl_3$) δ 217.9, 72.5, 69.7, 31.8, 21.8; HRMS (ESI) calcd for $C_8H_{13}BO_2$ ($M+Na^+$) 175.0906, found 175.0908.

*5.2.3. Pinanediol allenylboronate (ent-**39**).* Purified by flash column chromatography (96/4: hexanes/EtOAc); $[\alpha]_D^{26}$ +10.4 (*c* 0.52, $CHCl_3$); IR (neat) 2971, 2918, 1937, 1423, 1368, 1203, 1189 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 4.94 (t, J=6.9 Hz, 1H), 4.65 (d, J=6.9 Hz, 2H), 4.34 (dd, J=8.7, 2.0 Hz, 1H), 2.39–2.30 (m, 1H), 2.29–2.17 (m, 1H), 2.64–2.54 (dd, J=6.0, 5.0 Hz, 1H), 1.94–1.87 (m, 2H), 1.42 (s, 3H), 1.29 (s, 3H), 1.17 (d, J=11.0 Hz, 1H), 0.85 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 219.2, 86.4, 78.4, 70.2, 51.5, 39.7, 38.4, 35.6, 28.8, 27.3, 26.7, 24.2; HRMS (ESI) calcd for $C_{13}H_{19}BO_2$ $[M+Na]^+$ 241.1376, found 241.1380.

*5.2.4. N,N,N-Tributylbutan-1-aminium trifluoro(propa-1,2-dien-1-yl) borate (**45**).* An established procedure[46] for synthesis of allylic trifluoroborate tetrabutylammonium salts was modified for preparation of allene **8**. A 1 M aqueous solution of tetrabutylammonium hydroxide (20.0 mL, 20.0 mmol, 1 equiv) was added to a suspension of the known potassium allenyltrifluoroborate[47] (2.92 g, 20.0 mmol, 1 equiv) in CH_2Cl_2 (30 mL). The reaction was stirred at room for 30 min. The reaction mixture was then diluted with CH_2Cl_2 (20 mL), the organic layer was separated, dried over Mg_2SO_4, filtrated, and concentrated in vacuo to afford tetrabutylammonium allenyltrifluoroborate **45** (5.81 g, 83%) as a hygroscopic colorless solid which was stored in the glove box. IR (neat) 2963, 2936, 2876, 1930, 1473, 1382, 1248, 1071, 996, 968, 882, 795, 739, 600 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 4.76 (br s, 1H), 4.09–4.06 (m, 2H), 3.18–3.14 (m, 8H), 1.61–1.53 (m, 8H), 1.38 (sextuplet, J=7.3 Hz, 8H), 0.95 (t, J=7.3 Hz, 12H); ^{13}C (100 MHz, $CDCl_3$) δ 210.6 (q, J=4.3 Hz), 86.8 (br s), 65.6, 58.6, 24.0, 19.8, 13.8; ^{19}F (376 MHz, $CDCl_3$) δ −137.1 (d, J=48 Hz); HRMS (ESI) calcd for $C_3H_3BF_3$ $[M-NBu_4]^-$ 107.0280, found 107.0286.

*5.2.5. Lithium B-H$_2$-(10R)-trimethylsilyl-9-borabicyclo[3.3.2] decane diethyl etherate (**26**).* Soderquist's literature procedure was modified as follows: a solution of ethyl acetate (0.488 mL, 5.00 mmol, 0.5 equiv) in Et_2O (4.5 mL) was added dropwise (0.5 mL/min) to a 1 M solution of $LiAlH_4$ in Et_2O (10.0 mL, 10.0 mmol, 1 equiv). The resulting suspension of lithium monoethoxyaluminium hydride was stirred at 20 °C for 1 h (white precipitate). The reaction mixture was cooled to 0 °C and a solution of (−)-*B*-methoxy-10*R*-trimethylsilyl-9-borabicyclo[3.3.2.]decane (2.38 g, 10.0 mmol, 1 equiv) **64R**[21] in Et_2O (20 mL) was added dropwise (1 mL/min). The reaction was stirred at 0 °C for 1 h then was allowed to reach room temperature. The suspension was filtered (fritted funnel with Celite) with care taken to prevent exposure of the borohydride to the open atmosphere. The solid dialkoxyalane was washed with Et_2O (3×10 mL). The combined washings and supernatant were concentrated in vacuo to afford mono-diethyl etherate **26** as a white solid, which was dried under high vacuum for at least 12 h. The known borohydride **26** can be stored without decomposition in a glove box. ^1H (400 MHz, $CDCl_3$) δ 3.67 (q, J=7.1 Hz, 4H), 2.37 (s, 1H), 1.66–1.37 (m, 13H), 1.29 (t, J=7.1 Hz, 6H), 0.91 (s, 1H), 0.45 (br s, 1H), 0.00 (s, 1H), −0.07 (s, 9H); ^{13}C (100 MHz, $CDCl_3$) δ 66.5, 37.3, 35.5, 34.8, 33.3, 33.0, 24.2, 23.4, 14.8, −0.1.

5.3. Procedure for titration of the borohydride 26

To a solution of borohydride **26** (0.073 g, 0.250 mmol, 1 equiv) in Et_2O (1.0 mL) at 0 °C was added TMSCl (0.048 mL, 0.375 mmol, 1.5 equiv). The reaction mixture was stirred at 0 °C for 10 min before 4-methoxybenzaldehyde (0.121 mL, 1.0 mmol, 4 equiv) was added. The reaction mixture was stirred at 20 °C for 3 h then acetic acid (0.286 mL, 5.00 mmol, 20 equiv) was added and the mixture was stirred for an additional 4 h. The solvent was removed under reduced pressure (rotary evaporator) and the residue was analyzed by ^1H NMR spectroscopy. The yield of in situ generated **25** was determined from the integrations of the methoxy groups of 4-methoxybenzyl alcohol (**Int1**) and 4-methoxybenzaldehyde (**Int2**). The titration reaction was run simultaneously in two different flasks. The average yields were generally in the range of 90–93%.

$$\text{Yield} = \frac{\left(\dfrac{\mathbf{Int1}}{\mathbf{Int1}+\mathbf{Int2}}\right)\times \eta_{\text{aldehyde}}}{\eta_{\text{borohydride}}}$$

5.4. Procedure A. Synthesis of 1,5-diols *ent*-17a and *ent*-10a from the hydroboration reaction of allene 20 with $^{L}Ipc_2BH$

$^{L}Ipc_2BH$ (287 mg, 1.0 mmol) was weighed in a glove box into a round bottom flask containing a stir bar (Note: the crystalline Ipc_2BH should be crushed and pulverized with a glass rod prior to use in order to ensure efficient hydroboration). The flask was capped with a rubber septum and removed from the glove box and placed in bath at the appropriate reaction temperature (Table 1). THF (2 mL) was added to the flask followed by the allenyl boronic ester **20** (148 mg, 1.0 mmol) as a solution in THF (1 mL). For hydroboration reaction time and temperatures, see Table 1. After the hydroboration reaction was terminated, the reaction mixture was cooled to −78 °C. Distilled hydrocinnamaldehyde (71 μL, 0.54 mmol) was added dropwise via a microliter syringe. The flask was stirred at −78 °C for 4 h and then additional hydrocinnamaldehyde (184 μL, 1.40 mmol) was added dropwise via microliter syringe. The reaction was stirred an additional 2 h. The flask was then removed from the −78 °C bath and allowed to warm to room temperature and stirred overnight. The reaction mixture was cooled in an ice bath and 1 mL of 3 M NaOH solution was added dropwise followed by 0.4 mL of a 50% H_2O_2 solution. This mixture was stirred for 4 h at room temperature at which time it was diluted with 40 mL of CH_2Cl_2 and 20 mL of a saturated aqueous solution of $NaHCO_3$ and 5 mL of a saturated aqueous solution of NaCl. The organic layer was separated and the aqueous washed with CH_2Cl_2 (2×10 mL). The combined organic extracts were dried over Na_2SO_4, then filtered and the solvent removed in vacuo. The crude products were then purified by flash chromatography.

5.5. Procedure B. Synthesis of 1,2-diols 30 and 40 from allenes 6, 33, 39, and *ent*-39

To a 0 °C solution of borohydride **25R**[21] (81 mg, 0.250 mmol, 1 equiv, considering a 90% yield for the conversion of borohydride **26R** to borane **25R** based on the borane **25R** titration[8d]) in CH_2Cl_2 (0.5 mL) was added TMSCl (32 μL, 0.250 mmol, 1 equiv). The reaction mixture was stirred for 10 min, then was cooled to −78 °C and a solution of allene **6**, **33**, or **39** (0.325 mmol, 1.3 equiv) in CH_2Cl_2 (1.0 mL) was added dropwise. For hydroboration reaction times and temperatures, see Schemes 7, **10**, and **13**. The resulting reaction mixture was then cooled to −78 °C and a solution of benzaldehyde or hydrocinnamaldehyde (0.175 mmol, 0.7 equiv) in CH_2Cl_2 (0.3 mL) was added. The mixture was stirred for 4 h at −78 °C, then an aqueous 3 N NaOH solution (0.25 mL) and aqueous 50% H_2O_2 (0.1 mL) were added follow by THF (1 mL) and MeOH (0.5 mL). This mixture was then stirred at 20 °C for 12 h. The biphasic mixture was poured into saturated aqueous NH_4Cl, and the crude product was extracted with ethyl acetate (3×). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude products were then purified by flash chromatography.

5.6. Procedure C. Synthesis of 1,5-diols *ent*-17a, *ent*-17b, *ent*-19g from allenes 6, 33, and 39

To a 0 °C solution of borohydride **25R** (81.0 mg, 0.250 mmol, 1 equiv, considering a 90% yield for the conversion of borohydride **26R** to borane **25R** based on the borane **25R** titration[8d]) in CH_2Cl_2 (0.5 mL) was added TMSCl (32 μL, 0.250 mmol, 1 equiv). The reaction mixture was stirred for 10 min, then was cooled to −78 °C and a solution of allene **6**, **33**, or **39** (0.325 mmol, 1.3 equiv) in CH_2Cl_2 (1.0 mL) was added dropwise. For hydroboration reaction times and temperature, see Schemes 8, **11**, **14** for optimal conditions. The resulting clear reaction mixture was then cooled to −78 °C and benzaldehyde or hydrocinnamaldehyde (0.175 mmol, 0.7 equiv) was added. The mixture was stirred at −78 °C for 4 h, then a second aldehyde (0.375 mmol, 1.5 equiv) (followed by $BF_3{\cdot}OEt_2$ (0.125 mmol, 0.5 equiv) if using allene **39** was added and the reaction mixture was stirred for an additional 4 h. The reactions were quenched by using one of three general methods: (1) addition of ethanolamine (75 μL, 1.25 mmol, 5 equiv); (2) addition of aqueous 3 N NaOH solution (0.25 mL); and aqueous 50% H_2O_2 (0.1 mL); or (3) by addition of a pH 7 buffer solution (KH_2PO_4/NaOH) (1 mL) followed by THF (1.5 mL) and MeOH (0.5 mL). In the latter procedure, additional THF (1 mL) and MeOH (0.5 mL) were added, and the mixture was stirred at 20 °C for 12 h. The reaction mixture was then poured into saturated aqueous NH_4Cl, and the crude product was extracted with ethyl acetate (3×). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude products were then purified by flash chromatography.

5.7. Procedure D. Synthesis of 1,5-diols *ent*-17a, *ent*-17b, *ent*-17c from allene 42

To a 0 °C solution of borohydride **25R** (81 mg, 0.250 mmol, 1 equiv, considering a 90% yield for the conversion of borohydride **26R** to borane **25R** based on the borane **25R** titration[8d]) in CH_2Cl_2 (0.5 mL) was added TMSCl (32.0 μL, 0.250 mmol, 1 equiv). The reaction mixture was stirred for 10 min, then was cooled to 0 °C. At this point, a solution of allenyltributylstannane **42** (80% purity from Sigma–Aldrich, 121 μL, 0.325 mmol, 1.3 equiv) in CH_2Cl_2 (1.0 mL) was added and the reaction mixture was stirred for 1 h. The mixture was cooled to −78 °C and hydrocinnamaldehyde or benzaldehyde (0.175 mmol, 0.7 equiv) was added. After 3 h, the reaction was diluted with pentane (see Table 2) and a second aldehyde (0.325 mmol, 1.3 equiv) was added followed by $BF_3{\cdot}OEt_2$ (46 μL, 0.375 mmol, 1.5 equiv) and the reaction was stirred for an additional 4.25 h. Ethanolamine (75 μL, 1.25 mmol, 5 equiv) was added and the reaction mixture was allowed to reach 20 °C and stirred for 12 h. The mixture was poured into saturated aqueous NH_4Cl solution (20 mL) and the crude product was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO4, filtered, and concentrated under reduced pressure. The crude products were then purified by flash chromatography.

5.8. Procedure E. Synthesis of 1,5-diols 17 and *ent*-17 from allene 45

To a 0 °C solution of borohydride **25** (81.0 mg, 0.250 mmol, 1 equiv, considering a 90% yield for the conversion of borohydride **26** to borane **25** based on the borane **25** titration[8d]) in toluene (0.5 mL) was added TMSCl (32.0 μL, 0.250 mmol, 1 equiv). The reaction mixture was stirred for 10 min, then was cooled to −78 °C and a solution of allene **45** (0.114 g, 0.325 mmol, 1.3 equiv) in toluene (1 mL)/CH_2Cl_2 (0.1 mL) was added dropwise. The viscous mixture was stirred at −30 °C for 1 h. The resulting clear reaction mixture was then cooled to −78 °C and a solution of the first aldehyde (0.213 mmol, 0.85 equiv) in CH_2Cl_2 (0.25 mL) was added. After 4 h, a solution of the second aldehyde (0.300 mmol, 1.2 equiv) in CH_2Cl_2 (0.25 mL) followed by $BF_3{\cdot}OEt_2$ (47.0 μL, 0.375 mmol, 1.5 equiv) were added. The reaction mixture was stirred for an additional 4 h at −78 °C. A pH 7 buffer solution (KH_2PO_4/NaOH) (1 mL) followed by THF (1.5 mL) and MeOH (0.5 mL) were then added to the mixture, which was stirred at 20 °C for 24 h. The biphasic mixture was poured into saturated aqueous NH_4Cl solution, and the crude product was extracted with ethyl acetate (3×). The combined organic layers were washed with brine, dried over

$MgSO_4$, filtered, and concentrated under reduced pressure. The crude products were then purified by flash chromatography.

*5.8.1. (3R,4E,7S)-1,9-diphenylnon-4-ene-3,7-diol (**17a**).* $[\alpha]_D^{25}$ −6.4 (*c* 0.64, $CHCl_3$); ee 96%; IR (neat) 3347, 3084, 3061, 3025, 2924, 2857, 1668, 1602, 1495, 1454, 1312, 1051, 1030, 971, 923, 746, 698 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 7.35–7.18 (m, 10H), 5.72–5.57 (m, 2H), 4.11 (q, *J*=6.8 Hz, 1H), 3.72–3.62 (m, 1H), 2.85–2.65 (m, 4H), 2.34–2.13 (m, 2H), 1.84–1.67 (m, 4H); ^{13}C (100 MHz, $CDCl_3$) δ 142.0, 141.9, 136.5, 128.45, 128.41, 127.6, 125.88, 125.87, 72.1, 70.3, 40.5, 38.8, 38.6, 32.0, 31.8; HRMS (ESI) calcd for $C_{21}H_{26}O_2Na$ $[M+Na]^+$ 333.1831, found 333.1825.

*5.8.2. (3S,4E,7R)-1,9-Diphenylnon-4-ene-3,7-diol (ent-**17a**).* $[\alpha]_D^{25}$ +6.4 (*c* 0.64, $CHCl_3$); ^1H NMR, ^{13}C NMR and IR and HRMS data were identical to **17a**.

*5.8.3. (3S,4E,7S)-1,9-Diphenylnon-4-ene-3,7-diol (ent-**10a**).* $[\alpha]_D^{24}$ −12.8 (*c* 1.0, $CHCl_3$); IR (thin film) 3350, 3026, 2928, 1603, 1495, 1454, 1051 cm^{-1}; ^1H (500 MHz, $CDCl_3$) δ 7.35–7.18 (m, 10H), 5.70 (dt, *J*=15.0, 7.0, 7.0 Hz, 1H), 5.63 (dd, *J*=15.0, 6.0 Hz, 1 H), 4.11 (q, *J*=6.8 Hz, 1H), 3.72–3.62 (m, 1H), 2.85–2.65 (m, 4H), 2.34–2.13 (m, 2H), 1.84–1.67 (m, 4H); ^{13}C (125 MHz, $CDCl_3$) δ 142.1, 142.0, 136.7, 128.45, 128.41, 127.5, 125.89, 125.87, 72.0, 70.3, 40.3, 38.8, 38.5, 32.1, 31.8; HRMS (CI, NH_3) calcd for $C_{21}H_{30}NO_2$ $[M+NH_4]^+$ 328.2277, found 328.2275.

*5.8.4. (1S,2S)-1-Phenylbut-3-ene-1,2-diol (**30**)[48].* $[\alpha]_D^{23}$ +13.6 (*c* 1.17, $CHCl_3$); IR (neat) 3391, 2919, 1710, 1453, 1197, 1125, 995, 928, 762, 700 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 7.34–7.25 (m, 5H), 5.68 (ddd, *J*=17.4, 10.6, 5.6 Hz, 1H), 5.20 (dt, *J*=17.2, 1.5 Hz, 1H), 5.10 (dt, *J*=10.6, 1.5 Hz, 1H), 4.44 (d, *J*=7.1 Hz, 1H), 4.19–4.15 (m, 1H), 2.98 (br s, 2H); ^{13}C (100 MHz, $CDCl_3$) δ 140.4, 136.5, 128.5, 128.3, 127.2, 117.2, 77.8, 77.1; HRMS (ESI) calcd for $C_{10}H_{12}NaO_2$ $[M+Na]^+$ 187.0735, found 187.0730.

*5.8.5. (1R,2R)-1-Phenylbut-3-ene-1,2-diol (ent-**30**).* $[\alpha]_D^{25}$ −4.2 (*c* 0.66, $CHCl_3$); ee 97%; ^1H NMR, ^{13}C NMR and IR and HRMS data were identical to **30**.

*5.8.6. (1S,2E,5R)-1,5-Diphenylpent-2-ene-1,5-diol (**17d**).* $[\alpha]_D^{25}$ +49.6 (*c* 0.23, $CHCl_3$); ee 98%; IR (neat) 3360, 3085, 3061, 3029, 2921, 1667, 1602, 1493, 1452, 1318, 1197, 1028, 1007, 969, 913, 758, 699 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 7.27–7.17 (m, 10H), 5.69–5.66 (m, 2H), 5.08–5.06 (m, 1H), 4.63 (t, *J*=6.6 Hz, 1H), 2.56 (br s, 2H), 2.42–2.39 (m, 2H); ^{13}C (100 MHz, $CDCl_3$) δ 144.1, 143.1, 136.3, 128.7, 128.1, 127.8, 127.7, 126.4, 126.0, 75.1, 73.8, 42.3; HRMS (ESI) calcd for $C_{17}H_{18}O_2Na$ $[M+Na]^+$ 277.1204, found 227.1205.

*5.8.7. (1S,2E,5S)-1,7-Diphenylhept-2-ene-1,5-diol (**17b**).* $[\alpha]_D^{25}$ +2.7 (*c* 1.28, $CHCl_3$); ee 97%; IR (neat) 3360, 3084, 3061, 3026, 2923, 2854, 1602, 1494, 1453, 1319, 1069, 1048, 1030, 969, 748, 698 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 7.33–7.28 (m, 4H), 7.25–7.21 (m, 3H), 7.15–7.12 (m, 3H), 5.74–5.70 (m, 2H), 5.13 (d, *J*=4.8 Hz, 1H), 3.66–3.60 (m, 1H), 2.77–2.70 (m, 1H), 2.66–2.58 (m, 1H), 2.28–2.22 (m, 1H), 2.17–2.09 (m, 1H), 1.75–1.70 (m, 2H); ^{13}C (100 MHz, $CDCl_3$) δ 143.2, 142.2, 136.1, 128.8, 128.63, 128.61, 128.1, 127.9, 126.4, 126.0, 75.2, 70.5, 40.6, 38.8, 32.2; HRMS (ESI) calcd for $C_{19}H_{22}NaO_2$ $[M+Na]^+$ 305.1517, found 305.1515.

*5.8.8. (1R,5R,2E)-1,7-Diphenylhept-2-ene-1,5-diol (ent-**17b**).* $[\alpha]_D^{23}$ −14.1 (*c* 0.70, $CHCl_3$); ^1H NMR, ^{13}C NMR and IR and HRMS data were identical to **17b**.

*5.8.9. (1R,5S,2E)-1,7-Diphenylhept-2-ene-1,5-diol (ent-**10b**).* $[\alpha]_D^{24}$ −16.52 (*c* 0.96, $CHCl_3$); IR (neat) 3351, 3026, 2929, 1493, 1453 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 7.38–7.10 (m, 10H), 5.78–5.68 (m, 2H), 5.12 (d, *J*=4.8 Hz, 1H), 3.68–3.58 (m, 1H), 3.20 (d, *J*=3.2 Hz, 1H), 2.78–2.69 (m, 1H), 2.66–2.56 (m, 1H), 2.48 (d, *J*=4.4 Hz, 1H), 2.28–2.21 (m, 1H), 2.18–2.08 (m, 1H), 1.78–1.69 (m, 2H); ^{13}C (100 MHz, $CDCl_3$) δ 143.0, 141.9, 135.7, 128.4, 128.3, 128.3, 127.52, 127.47, 126.1, 125.7, 74.6, 70.2, 39.9, 38.3, 31.2; HRMS (CI, NH_3) calcd for $C_{19}H_{26}NO_2$ $[M+NH_4]^+$ 300.1964 found 300.1974.

*5.8.10. (3S,7S,4Z)-1,9-Diphenylnon-4-ene-3,7-diol (ent-**19g**).* $[\alpha]_D^{24}$ −38.5 (*c* 1.04, $CHCl_3$); IR (neat) 3351, 3025, 2930, 1602, 1495, 1454, 1030 cm^{-1}; ^1H (500 MHz, $CDCl_3$) δ 7.38–7.28 (m, 4H), 7.22–7.19 (m, 6H), 5.71–5.66 (m, 1H), 5.64–5.58 (m, 1H), 4.42 (ddd (app q), *J*=7.0 Hz, 1H), 3.77–3.71 (dddd (app quintet), *J*=6.5 Hz, 1H), 2.83–2.66 (m, 4H), 2.45–2.38 (dddd, *J*=14.0, 8.5, 4.5, 1.0 Hz, 1H), 2.37 (s, OH broad, 1H), 2.28–2.21 (m, 1H), 2.06 (s, OH broad, 1H), 1.99–1.92 (dddd, *J*=13.5, 9.5, 7.0, 6.5 Hz, 1H), 1.86–1.77 (m, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 142.1, 142.0, 136.1, 128.7, 128.63, 128.61, 128.60, 127.8, 126.1, 126.0, 70.4, 66.8, 38.9, 38.2, 35.1, 32.4, 31.9; HRMS (FAB, Na) calcd for $C_{21}H_{26}O_2$ $[M+Na]^+$ 333.1831, found 333.1817.

*5.8.11. (3S,4S)-6-Phenylhex-1-ene-3,4-diol (**40**)[48].* $[\alpha]_D^{23}$ −18.5 (*c* 0.99, $CHCl_3$); IR (neat) 3386, 2922, 1711, 1496, 1454, 1046, 992, 926, 749, 699 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 7.29–7.15 (m, 5H), 5.83 (ddd, *J*=17.2, 10.8, 6.4 Hz, 1H), 5.33 (dt, *J*=17.2, 1.2 Hz, 1H), 5.23 (dt, *J*=10.8, 1.2 Hz, 1H), 3.94 (tt, *J*=6.0, 1.2 Hz, 1H), 3.49 (ddd, *J*=9.2, 6.0, 3.2 Hz, 1H), 2.88–2.81 (m, 1H), 2.73–2.65 (m, 1H), 1.90 (br s, 2H), 1.88–1.71 (m, 2H); ^{13}C (100 MHz, $CDCl_3$) δ 142.1, 137.7, 128.61, 128.57, 126.0, 117.8, 76.5, 73.8, 34.8, 32.0; HRMS (ESI) calcd for $C_{12}H_{16}NaO_2$ $[M+Na]^+$ 215.1048, found 215.1042.

*5.8.12. (1R,3E,5R)-1,7-Diphenylhept-3-ene-1,5-diol (**17c**).* $[\alpha]_D^{25}$ +31.2 (*c* 0.47, $CHCl_3$); ee 97%; IR (neat) 3356, 3061, 3027, 2925, 2858, 1602, 1494, 1453, 1308, 1051, 1029, 970, 748, 699, 546 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 7.32–7.27 (m, 4H), 7.25–7.20 (m, 3H), 7.15–7.12 (m, 3H), 5.64–5.52 (m, 2H), 4.65 (td, *J*=6.6, 3.1 Hz, 1H), 4.02 (q, *J*=6.3 Hz, 1H), 2.66–2.52 (m, 2H), 2.43 (t, *J*=6.3 Hz, 2H), 2.15 (br s, 2H), 1.86–1.68 (m, 2H); ^{13}C (100 MHz, $CDCl_3$) δ 144.1, 142.1, 136.8, 128.67, 128.65, 128.5, 127.92, 127.86, 126.01, 125.99, 73.9, 72.4, 42.3, 38.8, 31.9; HRMS (ESI) calcd for $C_{19}H_{22}O_2Na$ $[M+Na]^+$ 305.1517, found 305.1524.

*5.8.13. (1S,5S,3E)-1,7-Diphenylhept-3-ene-1,5-diol (ent-**17c**).* $[\alpha]_D^{24}$ −21.1 (*c* 0.75 $CHCl_3$); ^1H NMR, ^{13}C NMR and IR, and HRMS data were identical to **17c**.

*5.8.14. (1R,3E,5R)-1-Cyclohexyl-7-phenylhept-3-ene-1,5-diol (**17e**).* $[\alpha]_D^{25}$ +7.5 (*c* 0.59, $CHCl_3$); ee 96%; IR (neat) 3352, 3085, 3062, 3026, 2924, 2852, 1495, 1450, 1311, 1057, 1030, 969, 892, 746, 698 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 7.28–7.23 (m, 2H), 7.18–7.13 (m, 3H), 5.65 (ddd, *J*=15.4, 7.3, 6.1 Hz, 1H), 5.58 (dd, *J*=15.4, 6.6 Hz, 1H), 4.08 (q, *J*=6.3 Hz, 1H), 3.38–3.33 (m, 1H), 2.74–2.60 (m, 2H), 2.30–2.24 (m, 1H), 2.13–2.05 (m, 1H), 1.93 (br s, 1H), 1.91–1.72 (m, 5H), 1.66–1.63 (m, 2H), 1.37–1.28 (m 1H), 1.27–094 (m, 5H); ^{13}C (100 MHz, $CDCl_3$) δ 142.1, 136.3, 128.8, 128.65, 128.57, 126.0, 75.4, 72.4, 43.4, 38.9, 37.4, 32.0, 29.3, 28.3, 26.7, 26.5, 26.3; HRMS (ESI) calcd for $C_{19}H_{28}O_2Na$ $[M+Na]^+$ 311.1987, found 311.1990.

*5.8.15. (1E,3R,5E,7R)-1,9-Diphenylnona-1,5-diene-3,7-diol (**17f**).* $[\alpha]_D^{25}$ +12.6 (*c* 0.45, $CHCl_3$); ee 95%; IR (neat) 3350, 3060, 3026, 2923, 2857, 1494, 1452, 1316, 1100, 1030, 967, 747, 694 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 7.34–7.32 (m, 2H), 7.29–7.18 (m, 5H), 7.16–7.12 (m, 3H), 6.55 (d, *J*=15.7 Hz, 1H), 6.19 (dd, *J*=15.9, 6.6 Hz, 1H), 5.67 (dt, *J*=15.4, 6.6 Hz, 1H), 5.60 (dd, *J*=15.7, 6.1 Hz, 1H), 4.32–4.27 (m, 1H), 4.07 (q, *J*=6.6 Hz, 1H), 2.70–2.58 (m, 2H), 2.41–2.28 (m, 2H), 2.10 (br s, 2H), 1.90–1.73 (m, 2H); ^{13}C (100 MHz, $CDCl_3$) δ 142.1,

136.9, 136.7, 131.8, 130.7, 128.8, 128.63, 128.55, 127.9, 127.5, 126.7, 126.0, 72.4, 72.2, 40.6, 38.8, 31.9; HRMS (ESI) calcd for $C_{21}H_{24}O_2Na$ $[M+Na]^+$ 331.1674, found 331.1679.

*5.8.16. (1E,3S,5E,7S)-1,9-Diphenylnona-1,5-diene-3,7-diol (ent-**17f**).* $[\alpha]_D^{25}$ −14.0 (*c* 0.59, $CHCl_3$); ee 95%; ^1H NMR, ^{13}C NMR and IR and HRMS data were identical to **17f**.

*5.8.17. (1R,2E,5R)-6-(Benzyloxy)-1-cyclohexylhex-2-ene-1,5-diol (**17h**).* $[\alpha]_D^{25}$ −14.0 (*c* 0.59, $CHCl_3$); ee 96%; IR (neat) 3399, 2923, 2852, 1451, 1097, 1027, 1001, 971, 735, 697 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 7.33–7.23 (m, 5H), 5.56 (dt, *J*=15.4, 6.6 Hz, 1H), 5.49 (dd, *J*=15.4, 6.3 Hz, 1H), 4.50 (s, 2H), 3.84–3.78 (m, 1H), 3.72 (t, *J*=6.6 Hz, 1H), 3.43 (dd, *J*=9.3, 3.3 Hz, 1H), 3.31 (dd, *J*=9.3, 7.3 Hz, 1H), 2.41 (br s, 1H), 2.20–2.14 (m, 2H), 1.82–1.78 (m, 1H), 1.72–1.58 (m, 4H), 1.36–1.27 (m, 1H), 1.24–1.05 (m, 3H), 0.96–0.83 (m, 2H); ^{13}C (100 MHz, $CDCl_3$) δ 138.1, 135.2, 128.6, 128.1, 128.0, 127.9, 77.6, 74.2, 73.6, 70.1, 43.7, 36.6, 29.0, 28.9, 26.7, 26.32, 26.25; HRMS (ESI) calcd for $C_{19}H_{28}O_3Na$ $[M+Na]^+$ 327.1936, found 327.1942.

*5.8.18. (2S,3E,6S)-1-{[tert-Butyl(dimethyl)silyl]oxy}-8-phenyloct-3-ene-2,6-diol (**17i**).* $[\alpha]_D^{25}$ −14.0 (*c* 0.59, $CHCl_3$); ee 96%; IR (neat) 3383, 3027, 2951, 2928, 2857, 1471, 1462, 1455, 1361, 1254, 1111, 1052, 1006, 971, 837, 778, 747, 699 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 7.26–7.22 (m, 2H), 7.17–7.12 (m, 3H), 5.77–5.69 (m, 1H), 5.50 (ddd, *J*=15.4, 6.1, 1.3 Hz, 1H), 4.13–4.09 (m, 1H), 3.65–3.60 (m, 1H), 3.59 (dd, *J*=10.1, 3.8 Hz, 1H), 3.41 (dd, *J*=10.1, 7.8 Hz, 1H), 2.77 (dt, *J*=13.9, 7.6 Hz, 1H), 2.64 (dt, *J*=13.9, 8.1 Hz, 1H), 2.28–2.22 (m, 1H), 2.14 (dt, *J*=14.1, 7.8 Hz, 1H), 1.77–1.72 (m, 2H), 0.87 (s, 9H), 0.04 (s, 6H); ^{13}C (100 MHz, $CDCl_3$) δ 142.3, 132.3, 129.3, 128.64, 128.57, 126.0, 72.8, 70.2, 67.3, 40.9, 38.7, 32.2, 26.1, 18.5, −5.13, −5.16; HRMS (ESI) calcd for $C_{20}H_{34}O_3NaSi$ $[M+Na]^+$ 373.2175, found 373.2184.

*5.8.19. (1R,5S,3E)-1,7-Diphenylhept-3-ene-1,5-diol (ent-**10c**).* $[\alpha]_D^{24}$ +28.4 (*c* 1.08, $CHCl_3$); IR (neat) 3360, 3027, 2925, 1949, 1878, 1807, 1669, 1603, 1495, 1454 cm^{-1}; ^1H (500 MHz, $CDCl_3$) δ 7.38–7.17 (m, 10H), 5.72–5.66 (m, 1H), 5.62 (dd, *J*=15.5, 6.5 Hz, 1H), 4.67 (td, *J*=6.6, 3.1 Hz, 1H), 4.04–3.96 (m, 1H), 2.74–2.62 (m, 2H), 2.54–2.52 (m, 2H), 2.01 (d, OH, *J*=3.5 Hz, 1H), 1.92–1.76 (m, 2H), 1.54 (d, OH, *J*=4.0 Hz, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 144.0, 142.1, 136.6, 128.6, 128.5, 127.8, 127.5, 126.01, 125.97, 73.8, 72.1, 42.1, 38.7, 31.9; HRMS (CI, NH_3) calcd for $C_{19}H_{26}NO_2$ $[M+NH_4]^+$ 300.1964 found 300.1951.

5.9. Synthesis of aldehyde 4

*5.9.1. (E)-5-(4-Methoxybenzyloxy)-pent-2-en-1-al (**55**).* To a solution of alkene **54**[40] (3.12 g, 16.2 mmol) in CH_2Cl_2 (70 mL) under argon, were successively added acrolein (freshly distilled, 3.25 mL, 48.7 mmol) and Hoveyda–Grubbs second-generation catalyst[39] (weighed in a glove box, 254 mg, 0.40 mmol) as a solution in CH_2Cl_2 (3 mL). The reaction mixture was stirred overnight at room temperature, then directly concentrated in vacuo. The residue was purified by flash chromatography (8/2: hexanes/EtOAc) to give **55** (3.04 g, 85%) as a brown oil; IR (neat) 2999, 2934, 2907, 2855, 1614, 1586, 1514, 1464, 1442, 1361, 1302, 1247, 1209, 1173, 1097, 1036, 972, 821 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 9.51 (d, *J*=7.8 Hz, 1H), 7.26 (d, *J*=8.7 Hz, 2H), 6.89 (d, *J*=8.7 Hz, 2H), 6.87 (dt, *J*=16.1, 6.0 Hz, 1H), 6.17 (ddt, *J*=15.7, 7.8, 1.4 Hz, 1H), 4.46 (s, 2H), 3.81 (s, 3H), 3.61 (t, *J*=6.2 Hz, 2H), 2.62 (tdd, *J*=6.4, 6.4, 1.5 Hz, 2H); ^{13}C (100 MHz, $CDCl_3$) δ 194.1, 159.5, 155.4, 134.3, 130.2, 129.5, 114.1, 73.0, 67.8, 55.5, 33.3; HRMS (ESI) calcd for $C_{13}H_{16}O_3$ $[M+Na]^+$ 243.0997, found 243.0995.

*5.9.2. (S,E)-8-(4-Methoxybenzyloxy)-octa-1,5-dien-4-ol (**56**).* (−)-Ipc_2BOMe (5.68 g, 17.9 mmol) was weighed in a glove box. Et_2O (72 mL) was added and the suspension was cooled to 0 °C. Allylmagnesium bromide (1 M in Et_2O, 16.6 mL, 16.6 mmol) was added dropwise. The mixture was stirred for 1 h, then was cooled to −78 °C and a solution of aldehyde **55** (3.04 g, 13.8 mmol) in Et_2O (17.5 mL) was added via cannula. The mixture was stirred for 3 h, then MeOH (1.8 mL), followed by NaOH (3 N, 17.4 mL, 52.3 mmol) and H_2O_2 (30% in H_2O, 17.3 mL, 169 mmol) were added. The solution was warmed to 23 °C and stirred overnight. The mixture was cooled at 0 °C and neutralize with HCl (3 N). The aqueous phase was extracted with Et_2O. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the crude by flash chromatography (gradient elution 85/15 to 70/30: hexanes/ethyl acetate) provided **56** (2.99 g, 83%) as a colorless oil: ee 96%; $[\alpha]_D^{22}$ −10.5 (*c* 0.89, $CHCl_3$); IR (neat) 3419 (br), 2933, 2907, 2858, 1613, 1514, 1464, 1448, 1361, 1302, 1248, 1174, 1094, 1035, 972, 916, 821 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 7.28–7.24 (m, 2H), 6.90–6.86 (m, 2H), 5.80 (ddt, *J*=17.3, 9.9, 7.1 Hz, 1H), 5.70 (dt, *J*=15.5, 6.6 Hz, 1H), 5.57 (dd, *J*=15.5, 6.5 Hz), 5.16–5.14 (m, 1H), 5.11 (br s, 1H), 4.44 (s, 2H), 4.17–4.10 (m, 1H), 3.81 (s, 3H), 3.48 (t, *J*=6.8 Hz, 2H), 2.35 (dt, *J*=6.8, 6.7 Hz, 2H), 2.31–2.23 (m, 2H), 1.70 (m, OH); ^{13}C (100 MHz, $CDCl_3$) δ 159.4, 134.50, 134.1, 130.7, 129.5, 128.5, 118.3, 113.9, 72.7, 71.8, 69.6, 55.5, 42.1, 32.8; HRMS (ESI) calcd for $C_{16}H_{22}O_3$ $[M+Na]^+$ 285.1467, found 285.1468.

*5.9.3. (S)-1-((2S,3S)-3-(2-(4-Methoxy-benzyloxy)-ethyl)oxiran-2-yl)-but-3-en-1-ol (**57**).* To a solution L-(+)-DET (freshly distilled, 1.19 mL, 6.86 mmol, dried over MS 4 Å for 1.5 h) in CH_2Cl_2 (11.2 mL) was added $Ti(OiPr)_4$ (freshly distilled, 1.75 mL, 5.72 mmol) at −40 °C, resulting in a slightly yellow solution. This mixture was stirred for 40 min, then a solution of alcohol **56** (3.0 g, 11.4 mmol, dried over MS 4 Å for 2 h) in CH_2Cl_2 (9 mL) was added via cannula. The mixture was stirred for 45 min at −20 °C, then a cold solution of TBHP (5.5 M in decane, 2.08 mL, 11.4 mmol, dried over MS 4 Å for 2 h) in CH_2Cl_2 (9 mL) was added via cannula. The solution was stirred at −20 °C for 7 h, then stored in a −20 °C freezer for 20 h. The mixture was allowed to warm to 0 °C, then NaOH (1 M, sat with NaCl, 17.6 mL) and H_2O (11 mL) were added. This mixture was stirred for 2 h at room temperature. It was then filtered through a plug of Celite, which was rinsed with CH_2Cl_2. The combined filtrates were washed with brine. The aqueous phase was extracted with CH_2Cl_2, the combined organic extracts dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the crude product by flash chromatography (gradient elution 85/15 to 70/30: hexanes/ethyl acetate) afforded **57** (2.20 g, 69%) as a clear oil: 99% de; $[\alpha]_D^{22}$ −5.5 (*c* 1.02, $CHCl_3$); IR (neat) 3437 (br), 2933, 2912, 2862, 1745, 1642, 1613, 1586, 1514, 1465, 1442, 1363, 1302, 1249, 1175, 1096, 1035, 917, 821 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 7.27–7.25 (m, 2H), 6.86–6.90 (m, 2H), 5.86 (ddt, *J*=17.1, 10.1, 7.1 Hz, 1H), 5.17–5.14 (m, 1H), 5.13–5.11 (m, 1H), 4.50–4.43 (m, 2H), 3.81 (br s, 4H), 3.58 (t, *J*=6.3 Hz, 2H), 3.14 (td, *J*=9.1, 2.2 Hz, 1H), 2.84 (dd, *J*=3.0, 3.0 Hz, 1H), 2.42–2.25 (m, 2H), 2.08 (br s, 1H), 1.91–1.76 (m, 2H); ^{13}C (100 MHz, $CDCl_3$) δ 159.4, 133.9, 130.4, 129.5, 118.3, 114.0, 73.0, 68.4, 66.8, 60.5, 55.5, 53.4, 38.3, 32.3; HRMS (ESI) calcd for $C_{16}H_{22}O_4$ $[M+Na]^+$ 301.1416, found 301.1415.

*5.9.4. (3S,5S)-1-(4-Methoxy-benzyloxy)-oct-7-ene-3,5-diol (**58**).* To a solution of epoxide **57** (2.2 g, 7.90 mmol) in THF (39.5 mL) was added MeOH (0.16 mL) and Red-Al® (3.3 M in toluene, 6.0 mL, 19.8 mmol) at 0 °C (gas evolution!) over a period of 10 min. After being warmed to 23 °C over 2 h, the solution was stirred for 16 h. NaOH (3 N, 23.7 mL) was added at 0 °C followed by water. The aqueous phase was extracted with Et_2O and the combined organic phases washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the crude by flash chromatography (1/2: hexanes/ethyl acetate) afforded **58** (2.06 g,

93%) as colorless oil: $[\alpha]_D^{24}$ +16.8 (*c* 1.06, $CHCl_3$); IR (neat) 3402, 2937, 1613, 1514, 1303, 1249, 1175, 1090, 1035, 821 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 7.25–7.23 (m, 2H), 6.90–6.86 (m, 2H), 5.83 (ddt, *J*=17.1, 10.2, 7.1 Hz, 1H), 5.15–5.11 (m, 1H), 5.11–5.09 (m, 1H), 4.46 (s, 2H), 4.19–4.13 (m, 1H), 4.02–3.95 (m, 1H), 3.81 (s, 3H), 3.73 (q, *J*=4.8 Hz, 1H), 3.67 (td, *J*=9.2, 3.8 Hz, 1H), 3.51 (d, *J*=2.6 Hz, OH), 2.84 (d, *J*=3.9 Hz, OH), 2.26 (ddt, *J*=6.7, 6.7, 1.2 Hz, 2H), 1.94–1.86 (m, 1H), 1.71–1.61 (m, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 159.5, 135.1, 130.0, 129.6, 117.9, 114.1, 73.3, 69.8, 69.4, 68.3, 55.5, 42.3, 42.3, 36.4; HRMS (ESI) calcd for $C_{16}H_{24}O_4$ $[M+Na]^+$ 303.1572, found 303.1566.

*5.9.5. (3S,5S)-3,5-Bis-(tert-Butyldimethylsilanyloxy)-1-(4-methoxybenzyloxy)-oct-7-ene (**59**).* To a solution of diol **58** (2.06 g, 7.35 mmol) in DMF (14.7 mL) were added imidazole (2.02 g, 29.4 mmol) and TBSCl (4.31 g, 27.2 mmol). The mixture was stirred overnight and then poured into water (100 mL) and diluted with Et_2O. The aqueous phase was extracted with Et_2O and the combined organic phases were washed several times with water, then with brine. The combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the crude product by flash chromatography (95/5: hexanes/ethyl acetate) afforded the **59** (3.2 g, 86%) as pale yellow oil: $[\alpha]_D^{24}$ +3.4 (*c* 1.23, $CHCl_3$); IR (neat)=2945, 2929, 2895, 2857, 1614, 1514, 1472, 1463, 1361, 1250, 1099, 1041, 1004, 836, 807, 884 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 7.27–7.24 (m, 2H), 6.89–6.85 (m, 2H), 5.81 (m_c, 1H), 5.06–5.02 (m, 2H), AB signal (δ_A=4.40, δ_B=4.42, J_{AB}=11.5 Hz), 3.87 (m_c, 1H), 3.80–3.76 (m, 4H), 3.50 (t, *J*=6.8 Hz, 2H), 2.28–2.14 (m, 2H), 1.83–1.53 (m, 4H), 0.87 (s, 9H), 0.86 (s, 9H), 0.05 (s, 9H), 0.03 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 159.3, 135.2, 130.9, 129.4, 117.1, 113.9, 72.9, 69.8, 67.7, 67.0, 55.5, 45.6, 42.4, 37.9, 26.1, 18.32, 18.28, −3.86, −3.91, −4.0, −4.1; HRMS (ESI) calcd for $C_{28}H_{52}O_4Si_2$ $[M+Na]^+$ 531.3302, found 531.3305.

*5.9.6. (3S,5S)-3,5-Bis-(tert-butyldimethylsilanyloxy)-7-(4-methoxybenzyloxy)-heptane-1-al (**4**).* To a solution of alkene **59** (1.75 g, 3.44 mmol) in dioxane (26 mL) and water (8.6 mL) were added 2,6-lutidine (freshly distilled, 0.865 mL, 7.43 mmol), OsO_4 (2.5 wt% in 2-methyl-2-propanol, 0.862 mL, 0.07 mmol), and $NaIO_4$ (2.95 g, 13.7 mmol). This mixture was stirred for 5 h, then the brown suspension was diluted with water and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2, the combined organic phases washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the crude product by flash chromatography (95/5: hexanes/ethyl acetate) afforded **4** (1.57 g, 89%) as yellow oil: $[\alpha]_D^{24}$ −4.9 (*c* 1.23, $CHCl_3$); IR (neat) 2954, 2930, 2857, 1727, 1514, 1472, 1464, 1250, 1102, 1040, 1005, 837, 809, 776 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 9.78 (t, *J*=2.5 Hz, 1H), 7.26–7.23 (m, 2H), 6.89–6.85 (m, 2H), AB signal (δ_A=4.39, δ_B=4.42, J_{AB}=11.5 Hz), 4.24 (dddd, app. tt, *J*=6.0 Hz, 1H), 3.87 (dddd, app. tt, *J*=6.1 Hz, 1H), 3.81 (s, 3H), 3.49 (t, *J*=6.6 Hz, 2H), 2.57 (ddd, *J*=15.4, 4.5, 2.1 Hz, 1H), 2.49 (ddd, *J*=15.4, 6.5, 3.0 Hz, 1H), 1.84–1.64 (m, 4H), 0.87 (s, 9H), 0.86 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H), 0.054 (s, 3H), 0.047 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 202.3, 159.3, 130.7, 129.5, 113.9, 72.9, 67.5, 66.6, 66.5, 55.5, 51.5, 46.3, 38.0, 26.1, 25.9, 18.2, 18.1, −4.0, −4.1, −4.2; HRMS (ESI) calcd for $C_{27}H_{50}O_5Si_2$ $[M+Na]^+$ 533.3095, found 533.3099.

5.10. Synthesis of aldehyde 3

*5.10.1. (R)-7-Azido-4-[(tert-butyldimethylsilanyloxy)]-1-hepten (**52**).* (−)-Ipc_2BOMe (6.64 g, 21.0 mmol) was weighed in a glove box. Et_2O (84 mL) was added and the suspension was cooled to 0 °C. Allylmagnesium bromide (1 M in Et_2O, 19.3 mL, 19.3 mmol) was added dropwise. The mixture was stirred for 1 h, then was cooled to −78 °C and a solution of known aldehyde **49**[34] (3.04 g, 13.8 mmol) in Et_2O (22.0 mL) was added via cannula. The mixture was stirred for 3 h at −78 °C, then MeOH (2.1 mL), followed by NaOH (3 N, 22.0 mL, 66.3 mmol) and H_2O_2 (30% in H_2O, 22.0 mL, 215 mmol) were added. The solution was warmed to 23 °C and stirred overnight. The mixture was cooled at 0 °C and neutralize with HCl (3 N). The aqueous phase extracted with Et_2O. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and carefully concentrated under reduced pressure (removal of solvent at 250 Torr/0 °C owing to the volatility of the product). The azidoalcohol **50** was obtained as a ca. 1:2 mixture with isopinocampheol **51** as a viscous oil. To this mixture of **50** and isopinocampheol **51** in DMF (10 mL) were added TBSCl (11.3 g, 71.4 mmol) and imidazole (5.27 g, 77.4 mmol). After being stirred overnight, the mixture was poured into water (100 mL) and Et_2O. The aqueous phase was extracted with Et_2O and the combined organic phases were washed several times with water, then with brine. The combined extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the crude product by flash chromatography (95/5: hexanes/ethyl acetate) afforded **52** (3.4 g, 73% over two steps) as a clear oil: ee 91%; $[\alpha]_D^{26}$ +13.1 (*c* 1.09, $CHCl_3$); IR (neat) 2955, 2931, 2858, 2093, 1472, 1464, 1361, 1256, 1092, 1041, 1005, 939, 914, 837, 809, 775 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 5.84–5.74 (m, 1H), 5.08–5.06 (m, 1H), 5.03 (br s, 1H), 3.73 (dddd, app. tt, *J*=5.7 Hz, 1H), 3.27 (t, *J*=6.9 Hz, 2H), 2.22 (dd, app. t, *J*=6.0 Hz, 2H), 1.74–1.43 (m, 4H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 134.8, 117.1, 71.3, 51.7, 41.9, 33.6, 25.9, 24.7, 18.1, −4.4, −4.6; HRMS (ESI) calcd for $C_{13}H_{27}N_3OSi$ $[M+Na]^+$ 292.1821, found 292.1830.

*5.10.2. tert-Butyl ((4R)-4-{[tert-butyl(dimethyl)silyl]oxy}hept-6-en-1-yl)carbamate (**53**).* To a room temperature solution of alkene **52** (1.0 g, 3.49 mmol) in wet Et_2O (9 mL) was added tributylphosphine (1.07 mL, 4.19 mmol). The mixture was stirred for 1.5 h at ambient temperature and then cooled to −50 °C. Di-*tert*-butyl dicarbonate (923 mg, 4.19 mmol) as a solution in Et_2O (2.6 mL) was slowly added and the resulting mixture was stirred for 2 h. The reaction was quenched with a solution of saturated $NaHCO_3$ (11.6 mL), and allowed to warm to room temperature and stirred overnight. The aqueous phase was separated and extracted with Et_2O. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the crude product by flash chromatography (gradient elution 98/2 to 80/20: hexanes/ethyl acetate) afforded **53** (845 mg, 70%) as clear oil: $[\alpha]_D^{27}$ +10.6 (*c* 0.5, $CHCl_3$); IR (neat) 3349, 2929, 2857, 1693 (broad), 1513, 1365, 1251, 1172, 1117, 1002, 912, 835, 773 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 5.84–5.71 (m, 1H), 5.06–5.02 (m, 1H), 5.01 (br s, 1H), 4.54 (br s, 1H), 3.71 (app quint, *J*=5.7 Hz, 1H), 3.17–3.02 (m, 2H), 2.23–2.18 (m, 2H), 1.43 (s, 9H), 1.60–1.39 (m, 4H), 0.88 (s, 9H), 0.044 (s, 3H), 0.037 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 156.2, 135.3, 117.1, 79.2, 71.7, 42.1, 40.9, 34.0, 28.6, 27.6, 26.1, 18.3, −4.2, −4.3; HRMS (ESI) calcd for $C_{18}H_{37}NO_3Si$ $[M+Na]^+$ 366.2440, found 366.2449.

*5.10.3. tert-Butyl ((4R,6E)-4-{[tert-butyl(dimethyl)silyl]oxy}-8-oxooct-6-en-1-yl)carbamate (**3**).* To a solution of alkene **53** (273 mg, 0.79 mmol) in CH_2Cl_2 (2.4 mL) under argon were successively added acrolein (freshly distilled, 0.159 mL, 2.38 mmol) and Hoveyda–Grubbs second-generation catalyst[39] (weighed in a glove box, 12 mg, 0.020 mmol) as a solution in CH_2Cl_2 (1 mL). The reaction was stirred overnight at room temperature, then concentrated in vacuo and directly purified by flash chromatography (8/2: hexanes/EtOAc). This afforded aldehyde **3** (276 mg, 94%) as a clear oil, which solidified when stored in the freezer: $[\alpha]_D^{27}$ +10.0 (*c* 0.69, $CHCl_3$); IR (neat) 3360, 2930, 2858, 1693 (broad), 1520, 1365, 1252, 1172, 836, 775 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 9.51 (d, *J*=8.0 Hz, 1H), 6.86 (dt, *J*=15.6, 7.4 Hz, 1H), 6.13 (ddt, *J*=15.6, 7.9, 1.3 Hz, 1H), 4.52 (br s, 1H), 3.87 (app quint, *J*=5.6 Hz, 1H), 3.19–3.03 (m, 2H),

2.56–2.41 (m, 2H), 1.56–4.46 (m, 4H), 1.44 (s, 9H), 0.88 (s, 9H), 0.06 (s, 3H), 0.035 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 194.0, 156.2, 155.1, 135.1, 79.4, 70.8, 40.6, 34.5, 28.6, 26.0, 25.9, 18.3, −4.25, −4.27; HRMS (ESI) calcd for $C_{19}H_{37}NO_4Si$ $[M+Na]^+$ 394.2390, found 394.2391.

*5.10.4. tert-Butyl {(4R,6E,8S,10E,12S,14S,16S)-4,14,16-tris{[tert-butyl(dimethyl)silyl]oxy}-8,12-dihydroxy-18-[(4-methoxybenzyl)-oxy]octadeca-6,10-dien-1-yl}carbamate (**60**).* To a 0 °C solution of borohydride **26*R*** (81.0 mg, 0.250 mmol, 1 equiv, considering a 90% yield for the conversion of borohydride **26*R*** to borane **25*R*** based on titration[3]) in toluene (0.5 mL) was added TMSCl (32.0 μL, 0.250 mmol, 1 equiv). The reaction mixture was stirred for 10 min, then was cooled to −78 °C and a solution of allene **45** (0.114 g, 0.325 mmol, 1.3 equiv) in toluene (1 mL)/CH_2Cl_2 (0.1 mL) was added dropwise. The viscous mixture was stirred at −30 °C for 1 h. The resulting clear reaction mixture was then cooled to −78 °C and a solution of **4** (0.213 mmol, 0.85 equiv) in CH_2Cl_2 (0.25 mL) was added. 4 hours later, a solution of **3** (0.300 mmol, 1.2 equiv) in CH_2Cl_2 (0.25 mL) followed by $BF_3\cdot OEt_2$ (47.0 μL, 0.375 mmol, 1.5 equiv) were added and the reaction mixture was stirred for an additional 4 h. A pH 7 buffer solution (KH_2PO_4/NaOH) (1 mL) followed by THF (1.5 mL) and MeOH (0.5 mL) were then added and the mixture was stirred at 20 °C for 24 h. The biphasic mixture was poured into a saturated aqueous NH_4Cl solution, and the crude product was extracted with ethyl acetate (3×). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, hexanes/ethyl acetate, gradient elution: 7:3 to 6:4 to 1:1) to afford **60** (163 mg, 83%) as a colorless oil: $[\alpha]_D^{25}$ −4.7 (*c* 0.64, $CHCl_3$); IR (neat) 3375, 2953, 2929, 2896, 2856, 1694, 1514, 1472, 1463, 1389, 1365, 1250, 1172, 1098, 1041, 1005, 971, 836, 809, 774 cm^{-1}; ^{1}H (400 MHz, $CDCl_3$) δ 7.24 (d, *J*=8.6 Hz, 2H), 6.87 (d, *J*=8.6 Hz, 2H), 5.70–5.47 (m, 4H), 4.63 (br s, 1H), 4.41 (m, overlap, 1H), 4.40 (dd, *J*=12.0, 11.6 Hz, 2H), 4.10 (app q, *J*=6.2 Hz, 1H), 4.06–3.99 (m, 1H), 3.82 (m, overlap, 1H), 3.79 (s, 3H), 3.74–3.66 (m, 1H), 3.50 (t, *J*=6.8 Hz, 2H), 3.15–3.02 (m, 2H), 2.34–2.13 (m, 4H), 1.89–1.63 (m, 6H), 1.43 (s, 9H), 1.62–1.35 (m, 7H), 0.88 (s, 18H), 0.86 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H), 0.041 (s, 3H), 0.035 (s, 6H); ^{13}C (100 MHz, $CDCl_3$) δ 159.3, 156.2, 136.8, 134.9, 130.8, 129.5, 128.1, 126.2, 114.0, 79.23, 72.9, 72.1, 71.8, 69.4, 69.3, 67.7, 66.8, 55.5, 45.0, 42.8, 40.8, 40.6, 40.4, 37.5, 33.9, 28.7, 26.3, 26.1, 26.0, 18.3, 18.2, 18.1, −3.9, −4.1, −4.1, −4.3, −4.4; HRMS (ESI) calcd for $C_{49}H_{93}NO_9NaSi_3$ $[M+Na]^+$ 946.6056, found 946.6063.

The absolute stereochemistry of the two hydroxyl groups in **60** was assigned by using the Mosher ester method.

*5.10.5. tert-Butyl {(4R,6E,8S,10E,12S,14R,16S)-4,8,12,14,16-pentakis{[tert-butyl(dimethyl)silyl]oxy}-18-[(4-methoxybenzyl)oxy]octadeca-6,10-dien-1-yl}carbamate (**2**).* To a solution of alcohol **60** (20 mg, 0.022 mmol) in CH_2Cl_2 (0.25 mL) was added imidazole (12 mg, 0.18 mmol) and TBSCl (20 mg, 0.13 mmol). The mixture was stirred overnight, then concentrated in vacuo. The crude product was directly purified by flash chromatography (gradient elution 99/1 to 90/10: hexanes/ethyl acetate) to give **2** (24 mg, 94%) as clear oil: $[\alpha]_D^{27}$ −3.5 (*c* 0.45, $CHCl_3$); IR (neat) 2953, 2928, 2887, 2856, 1718, 1513, 1471, 1462, 1248, 1171, 1064, 1040, 1004, 971, 832, 807, 771 cm^{-1}; ^{1}H (400 MHz, $CDCl_3$) δ 7.24 (d, *J*=8.8 Hz, 2H), 6.86 (d, *J*=8.8 Hz, 2H), 5.59–5.37 (m, 4H), 4.53 (br s, 1H), 4.41 (dd, *J*=11.6, 11.6 Hz, 2H), 4.21–4.14 (m, 1H), 4.07 (app q, *J*=6.1 Hz, 1H), 3.91–3.78 (m, 2H), 3.80 (s, 3H), 3.73–3.64 (m, 1H), 3.50 (t, *J*=6.8 Hz, 2H), 3.16–3.01 (m, 2H), 2.27–2.12 (m, 4H), 1.89–1.79 (m, 1H), 1.43 (s, 9H), 1.72–1.36 (m, 9H), 0.88 (s, 18H), 0.872 (s, 9H), 0.869 (s, 9H), 0.86 (s, 9H), 0.06 (s, 3H), 0.05–0.03 (m, 21H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 159.2, 156.1, 136.4, 135.8, 131.1, 129.4, 126.8, 126.4, 113.9, 79.2, 73.6, 72.7, 71.9, 71.3, 67.5, 67.4, 66.9, 55.5, 47.4, 46.9, 41.7, 40.9, 40.3, 37.5, 33.7, 28.7, 26.23, 26.19, 26.14, 26.11, 18.5, 18.4, 18.30, 18.25, −3.2, −3.3, −3.5, −3.9, −4.06, −4.13, −4.2, −4.38, −4.45; HRMS (ESI) calcd for $C_{61}H_{121}NO_9Si_5$ $[M+Na]^+$ 1174.7785, found 1174.7780.

*5.10.6. tert-Butyl {(4R,6E,8R,10E,12R,14S,16S)-4,14,16-tris{[tert-butyl(dimethyl)silyl]oxy}-8,12-dihydroxy-18-[(4-methoxy-benzyl)oxy]octadeca-6,10-dien-1-yl}carbamate (**61**).* To a 0 °C solution of borohydride **25S** (81.0 mg, 0.250 mmol, 1 equiv, considering a 90% yield for the conversion of borohydride **26S** to borane **25S** based on titration[8d]) in toluene (0.5 mL) was added TMSCl (32 μL, 0.250 mmol, 1 equiv). The reaction mixture was stirred for 10 min, then was cooled to −78 °C and a solution of allene **45** (0.114 g, 0.325 mmol, 1.3 equiv) in toluene (1 mL)/CH_2Cl_2 (0.1 mL) was added dropwise. The viscous mixture was stirred at −30 °C for 1 h. The resulting clear reaction mixture was then cooled to −78 °C and a solution of **4** (0.213 mmol, 0.85 equiv) in CH_2Cl_2 (0.25 mL) was added. After 4 h, a solution of **3** (0.300 mmol, 1.2 equiv) in CH_2Cl_2 (0.25 mL) followed by $BF_3\cdot OEt_2$ (47 μL, 0.375 mmol, 1.5 equiv) were added and the reaction mixture was stirred for an additional 4 h. A pH 7 buffer solution (KH_2PO_4/NaOH) (1 mL) followed by THF (1.5 mL) and MeOH (0.5 mL) were then added. The resulting mixture was stirred at 20 °C for 24 h. The biphasic mixture was poured into saturated aqueous NH_4Cl solution, and the crude product was extracted with ethyl acetate (3×). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, hexanes/ethyl acetate, gradient elution: 7:3 to 6:4 to 1:1) to afford **61** (153 mg, 78%) as a colorless oil: $[\alpha]_D^{25}$ −7.8 (*c* 0.50, $CHCl_3$); IR (neat) 3374, 2953, 2929, 2895, 2856, 1695, 1514, 1472, 1462, 1365, 1250, 1172, 1098, 1040, 1005, 971, 835, 808, 774 cm^{-1}; ^{1}H (400 MHz, $CDCl_3$) δ 7.24 (d, *J*=8.6 Hz, 2H), 6.86 (d, *J*=8.6 Hz, 2H), 5.70–5.47 (m, 4H), 4.67 (br s, 1H), 4.40 (dd, *J*=12.0, 11.6 Hz, 2H), 4.26–4.17 (m, 1H), 4.08 (app q, *J*=6.3 Hz, 1H), 3.92–3.85 (m, 1H), 3.85–3.78 (m, 1H), 3.79 (s, 3H), 3.74–3.66 (m, 1H), 3.48 (t, *J*=6.8 Hz, 2H), 3.15–3.02 (m, 2H), 2.31–2.14 (m, 4H), 2.10–1.90 (br s, 1H), 1.83–1.57 (m, 6H), 1.57–1.36 (m, 6H), 1.43 (s, 9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.85 (s, 9H), 0.084 (s, 3H), 0.079 (s, 3H), 0.044 (s, 3H), 0.035 (s, 3H), 0.030 (s, 6H); ^{13}C (100 MHz, $CDCl_3$) δ 159.3, 156.2, 136.3, 134.9, 130.7, 129.5, 127.9, 126.6, 113.9, 79.2, 72.9, 71.8, 71.7, 71.3, 70.7, 67.5, 66.8, 55.4, 47.0, 44.6, 40.8, 40.6, 40.4, 37.6, 33.9, 28.6, 26.08, 26.06, 26.04, 25.9, 18.3, 18.2, 18.1, −3.6, −4.0, −4.2, −4.3, −4.4; HRMS (ESI) calcd for $C_{49}H_{93}NO_9NaSi_3$ $[M+Na]^+$ 946.6056, found 946.6060.

The absolute stereochemistry of the two hydroxyl groups in **61** was assigned by using the Mosher ester method.

*5.10.7. tert-Butyl {(4R,6E,8R,10E,12R,14R,16S)-4,8,12,14,16-pentakis{[tert-butyl(dimethyl)silyl]oxy}-18-[(4-methoxy-benzyl)oxy]octadeca-6,10-dien-1-yl}carbamate (**62**).* To a solution of alcohol **61** (20 mg, 0.022 mmol) in CH_2Cl_2 (0.25 mL) were added imidazole (12 mg, 0.176 mmol) and TBSCl (20 mg, 0.126 mmol). The mixture was stirred overnight and then concentrated in vacuo. The crude product was directly purified by flash chromatography (gradient elution 99/1 to 90/10: hexanes/ethyl acetate) to give **62** (23 mg, 90%) as clear oil: $[\alpha]_D^{27}$ −5.3 (*c* 1.47, $CHCl_3$); IR (neat) 2953, 2928, 2886, 2856, 1709, 1513, 1471, 1462, 1363, 1248, 1171, 1078, 1039, 1004, 832, 807, 772, 733 cm^{-1}; ^{1}H (400 MHz, $CDCl_3$) δ 7.24 (d, *J*=8.8 Hz, 2H), 6.86 (d, *J*=8.8 Hz, 2H), 5.59–5.37 (m, 4H), 4.54 (br s, 1H), 4.41 (dd, *J*=11.6, 11.6 Hz, 2H), 4.21 (app q, *J*=6.7 Hz, 1H), 4.07 (app q, *J*=5.9 Hz, 1H), 3.89–3.81 (m, 1H), 3.80 (s, 3H), 3.78–3.71 (m, 1H), 3.71–3.64 (m, 1H), 3.48 (t, *J*=6.8 Hz, 2H), 3.16–3.01 (m, 2H), 2.27–2.12 (m, 4H), 1.85–1.73 (m, 1H), 1.72–1.36 (m, 9H), 1.43 (s, 9H), 0.89–0.88 (m, 27H), 0.87 (s, 9H), 0.86 (s, 9H), 0.045 (s, 9H), 0.04 (s, 9H), 0.03 (s, 6H), 0.02 (s, 6H); ^{13}C (100 MHz, $CDCl_3$) δ 159.3, 156.1, 135.6, 135.5, 131.0, 129.4, 127.0, 126.4, 113.9, 79.2, 73.4, 72.8, 71.9, 71.1, 67.7, 67.6, 66.9, 55.5, 47.1, 46.8, 41.8, 41.0, 40.5, 37.8, 33.9, 28.7, 26.21, 26.16, 26.1, 25.9, 18.5, 18.4, 18.31, 18.27, −3.5, 3.7, −3.8, −3.9,

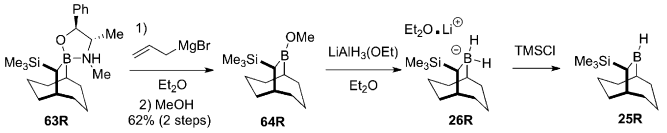
−4.06, −4.14, −4.2, −4.3, −4.4, −4.5; HRMS (ESI) calcd for $C_{61}H_{121}NO_9Si_5$ $[M+Na]^+$ 1174.7785, found 1174.7793.

Acknowledgements

We thank the National Institutes of Health (GM038436) for support of this research, and the German Academic Exchange Service (DAAD) for a postdoctoral fellowship to A.S.

References and notes

1. Examples of natural products containing (*E*)-1,5-*syn*-diol units: (a) Amphidinol 3: Murata, M.; Matsuoka, S.; Matsumori, N.; Paul, G. K.; Tachibana, K. *J. Am. Chem. Soc.* **1999**, *121*, 870; (b) Tetrafibricin: Kobayashi, Y.; Czechtizky, W.; Kishi, Y. *Org. Lett.* **2003**, *5*, 93; (c) Marinomycins A–C: Kwon, H. C.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *J. Am. Chem. Soc.* **2006**, *128*, 1622; (d) Aigialomycin F: Isaka, M.; Yangchum, A.; Intamas, S.; Kocharin, K.; Gareth Jones, E. B.; Kongsaeree, P.; Prabpai, S. *Tetrahedron* **2009**, *65*, 4396; (e) Marinisporolides: Kwon, H. C.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *J. Org. Chem.* **2009**, *74*, 675.
2. (a) BouzBouz, S.; Cossy, J. *Org. Lett.* **2004**, *6*, 3469.
3. (a) BouzBouz, S.; Cossy, J. *Org. Lett.* **2001**, *3*, 1451; (b) BouzBouz, S.; Simmons, R.; Cossy, J. *Org. Lett.* **2004**, *6*, 3465.
4. Schmidt, D. R.; O'Malley, S. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 1190.
5. Nicolaou, K. C.; Nold, A. L.; Milburn, R. R.; Schindler, C. S.; Cole, K. P.; Yamaguchi, J. *J. Am. Chem. Soc.* **2007**, *129*, 1760.
6. Friestad, G. K.; Sreenilayam, G. *Org. Lett.* **2010**, *12*, 5016.
7. Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* **2008**, *41*, 40.
8. (a) Brown, H. C.; Narla, G. *J. Org. Chem.* **1995**, *60*, 4686; (b) Barrett, A. G. M.; Braddock, C. D.; de Koning, P. D.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **2000**, *65*, 375; (c) Flamme, E. M.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 13644; (d) Kister, J.; DeBaillie, A. C.; Lira, R.; Roush, W. R. *J. Am. Chem. Soc.* **2009**, *131*, 14174; (e) Cheng, M.; Handa, M.; Roush, W. *J. Am. Chem. Soc.* **2009**, *131*, 14602; (f) Morgan, J. B.; Morken, J. P. *Org. Lett.* **2003**, *5*, 2573; (g) Pelz, N. F.; Woodward, A. R.; Burks, H. E.; Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 16328; (h) Woodward, A. R.; Burks, H. E.; Chan, L. M.; Morken, J. P. *Org. Lett.* **2005**, *7*, 5505; (i) Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 74; (j) Gonzalez, A. Z.; Roman, J. G.; Alicea, E.; Canales, E.; Soderquist, J. A. *J. Am. Chem. Soc.* **2009**, *131*, 1269.
9. (a) Flamme, E. M.; Roush, W. R. *Org. Lett.* **2005**, *7*, 1411; (b) Owen, R. M.; Roush, W. R. *Org. Lett.* **2005**, *7*, 3941; (c) Hicks, J. D.; Flamme, E. M.; Roush, W. R. *Org. Lett.* **2005**, *7*, 5509; (d) Lira, R.; Roush, W. R. *Org. Lett.* **2007**, *9*, 4315.
10. Kamiyama, T.; Umino, T.; Fujisaki, N.; Fujimori, K.; Satoh, T.; Yamashita, Y.; Ohshima, S.; Watanabe, J.; Yokose, K. *J. Antibiot.* **1993**, *46*, 1039.
11. (a) Satoh, T.; Yamashita, Y.; Kamiyama, T.; Watanabe, J.; Steiner, B.; Hadvary, P.; Arisawa, M. *Thromb. Res.* **1993**, *72*, 389; (b) Satoh, T.; Yamashita, Y.; Kamiyama, T.; Arisawa, M. *Thromb. Res.* **1993**, *72*, 401; (c) Satoh, T.; Kouns, W. C.; Yamashita, Y.; Maiyama, T.; Steiner, B. *Biochem. J.* **1994**, *301*, 785; (d) Satoh, T.; Kouns, W. C.; Yamashita, Y.; Kamiyama, T.; Steiner, B. *Biochem. Biophys. Res. Commun.* **1994**, *204*, 325.
12. Lira, R.; Roush, W. R. *Org. Lett.* **2007**, *9*, 533.
13. (a) Gudipati, V.; Bajpai, R.; Curran, D. P. *Collect. Czech. Chem. Commun.* **2009**, *74*, 771; (b) Zhang, K.; Gudipati, V.; Curran, D. P. *Synlett* **2010**, 667; (c) Gudipati, V.; Curran, D. P. *Tetrahedron Lett.* **2011**, *52*, 2254; (d) After our mansuscript was submitted for publication, Krisch's synthesis of the C(21)–C(40) frragment of tetrafibricin was published: Kumpulainen, E. T. T.; Kang, B.; Krische, M. J. *Org. Lett.* **2011**, *13*, 2484.
14. Kister, J.; Nuhant, P.; Lira, R.; Sorg, S.; Roush, W. R. *Org. Lett.* **2011**, *13*, 1868.
15. Brown, H. C.; Singaram, B. *J. Org. Chem.* **1984**, *49*, 945.
16. (a) Mikhailov, B. M. *Organomet. Chem. Rev., Sect. A* **1972**, *8*, 1; (b) Kramer, G. W.; Brown, H. C. *J. Organomet. Chem.* **1977**, *132*, 9.
17. (a) Beletskaya, I.; Pelter, A. *Tetrahedron* **1997**, *53*, 4957; (b) Burgess, K.; Ohlmeyer, M. J. *Chem. Rev.* **1991**, *91*, 1179.
18. Burgos, C. H.; Canales, E.; Matos, K.; Soderquist, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 8044.
19. (a) Munoz-Hernandez, L.; Soderquist, J. A. *Org. Lett.* **2009**, *11*, 2571; (b) Ess, D. H.; Kister, J.; Chen, M.; Roush, W. R. *Org. Lett.* **2009**, *11*, 5538.
20. (a) Soderquist, J. A.; Matos, K.; Burgos, C. H.; Lai, C.; Vaquer, J.; Medina, J. R.; Huang, S. D. *ACS Symp. Ser.* **2001**, *783*, 176; (b) Gonzalez, A. Z.; Roman, J. G.; Gonzalez, E.; Martinez, J.; Medina, J. R.; Matos, K.; Soderquist, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 9218 and references cited therein.
21. Nonracemic borane **25R** [10-TMS-9/BBD-H] is easily prepared from pseudoephedrine complex **63R** by using Soderquist's procedure[20] Both enantiomers of **63R** are commercially available but also are easily prepared in two steps from racemic B-OMe/9-BBN **64**.[20b] We found, however, that generation of **25R** from the mono-diethyl etherate borohydride **26R** is best performed in the presence of allene, owing to the instability of **25R**.[8d]



22. Chen, M.; Roush, W. R. *Org. Lett.* **2010**, *12*, 2706.
23. (a) Carosi, L.; Lachance, H.; Hall, D. G. *Tetrahedron Lett.* **2005**, *46*, 8981; (b) Carosi, L.; Hall, D. G. *Angew. Chem., Int. Ed.* **2007**, *46*, 5913; (c) Peng, F.; Hall, D. G. *J. Am. Chem. Soc.* **2007**, *129*, 3070; (d) Peng, F.; Hall, D. G. *Tetrahedron Lett.* **2007**, *48*, 3305; (e) Carosi, L.; Hall, D. G. *Can. J. Chem.* **2009**, *87*, 650.
24. Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.
25. (a) Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, *25*, 265; (b) Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, *25*, 1879; (c) Keck, G. E.; Abbott, D. E. *Tetrahedron Lett.* **1984**, *25*, 1883; (d) Keck, G. E.; Savin, K. A.; Cressman, E. N. K.; Abbott, D. E. *J. Org. Chem.* **1994**, *59*, 7889; (e) Marshall, J. A. *Chem. Rev.* **1996**, *96*, 31 and articles cited therein.
26. Prevost, C.; Gaudemar, M.; Honigberg, J. C. R. *Acad. Sci. (Paris)* **1950**, *230*, 1186.
27. Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467.
28. (a) Aspinall, H. C.; Browning, A. F.; Greeves, N.; Ravenscroft, P. *Tetrahedron Lett.* **1994**, *35*, 4639; (b) Aspinall, H. C.; Greeves, N.; McIver, E. G. *Tetrahedron Lett.* **1998**, *39*, 9283.
29. Yanagisawa, A.; Nakashima, H.; Ishiba, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 4723.
30. Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780.
31. (a) Denmark, S. E.; Weber, E. J.; Wilson, T. M.; Willson, T. M. *Tetrahedron* **1989**, *45*, 1053; (b) Keck, G. E.; Dougherty, S. M.; Savin, K. A. *J. Am. Chem. Soc.* **1995**, *117*, 6210.
32. Batey, R. A.; Thadani, A. N.; Smil, D. V. *Tetrahedron Lett.* **1999**, *40*, 4289.
33. BF3·OEt2 proved to be the most efficient Lewis acid in a previous study: Batey, R. A.; Thadani, A. N.; Smil, D. V.; Lough, A. J. *Synthesis* **2000**, 990.
34. Hudlicky, T.; Frazier, J. O.; Seoane, G.; Tiedje, M.; Seoane, A.; Kwart, L. D.; Beal, C. *J. Am. Chem. Soc.* **1986**, *108*, 3755.
35. (a) Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432; (b) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1989**, *54*, 1570; (c) Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401.
36. (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512; (b) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.
37. Afonso, C. A. M. *Tetrahedron Lett.* **1995**, *36*, 8857.
38. Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 58.
39. Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791.
40. Six, Y. *Eur. J. Org. Chem.* **2003**, 1157.
41. Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
42. Page, P. C. B.; Rayner, C. M.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2403.
43. Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511.
44. Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004**, *6*, 3217.
45. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
46. (a) Batey, R. A.; Quach, T. D. *Tetrahedron Lett.* **2001**, *42*, 9099; (b) Thadani, A. N.; Batey, R. A. *Org. Lett.* **2002**, *4*, 3827.
47. Bagutski, V.; Ros, A.; Aggarwal, V. K. *Tetrahedron* **2009**, *65*, 9956.
48. Lombardo, M.; Morganti, S.; Trombini, C. *J. Org. Chem.* **2003**, *68*, 997.