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Total synthesis of meayamycin B

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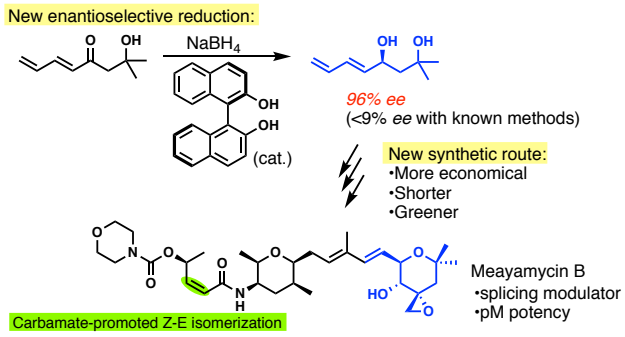
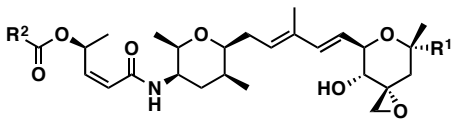


ABSTRACT: Meayamycin B is currently the most potent modulator of the splicing factor 3b subunit 1 and used by dozens of research groups. However, current supply for this natural product analog is limited due to the lengthy synthetic scheme. Here, we report a more concise, more cost effective, and greener synthesis of this compound by developing and employing a novel asymmetric reduction of a prochiral enone to afford an allylic alcohol with high enantioselectivity. In addition to this reaction, this synthesis highlights a scalable Mukaiyama aldol reaction, Nicolaou-type epoxide opening reaction, stereoselective Corey-Chaykovsky type reaction, and a modified Horner-Wadsworth-Emmons Z-selective olefination. We also discuss a Z-E isomerization during the α,β-unsaturated amide formation. The new synthesis of meayamycin B consists of 11 steps in the longest linear sequence and 24 total steps.

Introduction

FR901464 is a natural product first reported in 1996.[1-3] Its structure and biological activity attracted synthetic chemists, culminating in four total syntheses to date.[4-10] A closely related natural product, thailanstatin A, was also syntheized.[11] These synthetic studies afforded spliceostatin A,[12] 1-desoxy FR901464,[5] and meayamycins[9] (Figure 1). Structurally simplified FR901464 analogs, sudemycins, exhibited promising antitumor activity in xenograft models.[13] The efficacy of meayamycins was also examined in mice.[14] FR901464 was found to bind the spliceosome and modulate pre-mRNA splicing.[15] FR901464 and these analogs also perturbed pre-mRNA splicing in live cells.[16, 17] Spliceostatin A and meayamycins have been widely used in the studies on splicing.[18-30] Subsequently, biosynthetic studies of FR901464 and its analogs have become an active area of research.[31-33] Meayamycin B is the most potent splicing modulator to date[34] and is the target in this synthetic study. Our previous synthesis is summarized in Scheme S1 in the Supporting Information.



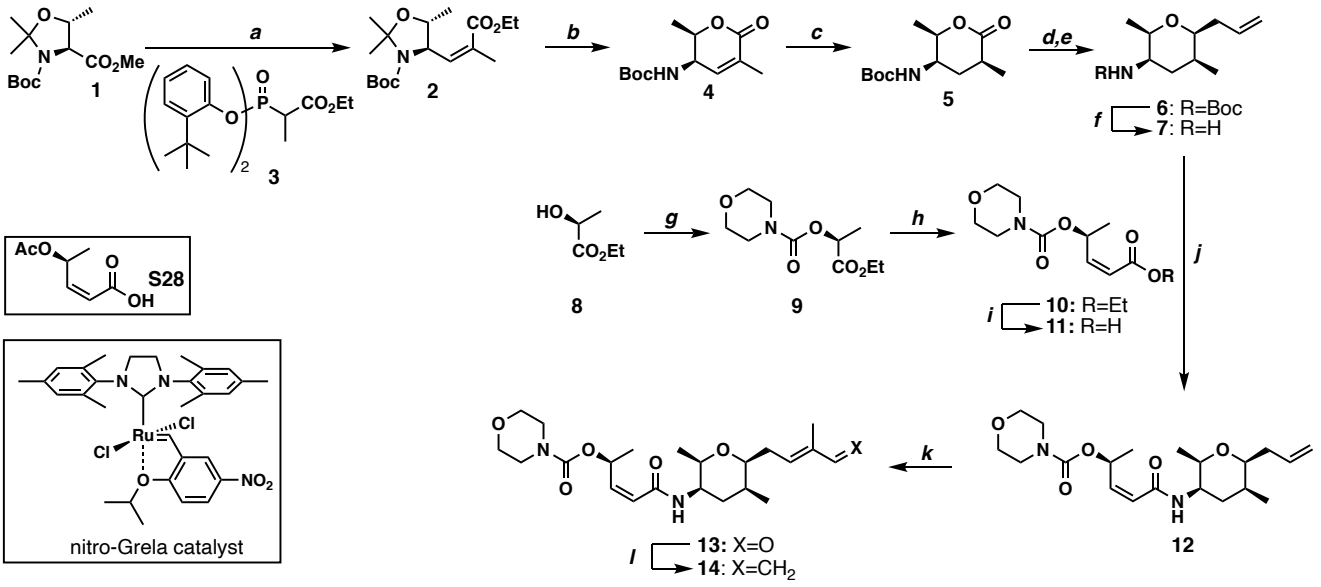
	R^1	R^2
FR901464	OH	CH_3
meayamycin	CH_3	CH_3
meayamycin B	CH_3	
spliceostatin A	OCH_3	CH_3

Figure 1. Structures of FR901464 analogs.

In our previous synthesis of the meayamycin B left-hand fragment **14** (Scheme 1), the unsaturated lactone **4** was prepared in 5 steps from the commercially available L-threonine derivative **1** in 45% overall yield (Scheme S1B in the Supporting Information).[8, 9] This synthesis was undesirable in several aspects; first, the olefination of **1** with $Ph_3P{=}CH_2$ is not atom economical because the carbon installed in this step is lost after the ring-closing metathesis (RCM) step (**S16** to **S17**). Second, although only 1 mol% of a ruthenium precatalyst is required in the RCM step, this is expensive when the synthesis is performed in a multiple-gram scale. Third, the allylic oxidation of **S17** with 6 equivalents of a chromium reagent is not green. To produce meayamycin B for basic and translational studies,[35] a more scalable synthesis was needed.

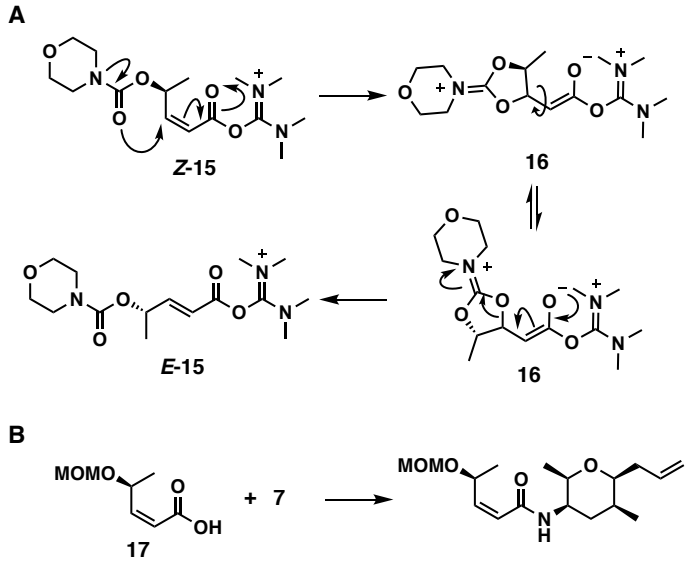
Results and Discussion

We hypothesized that Ando's variant of the Horner-Wadsworth-Emmons (HWE) reaction[36] could be used to install all of the necessary carbon atoms more rapidly with high Z-selectivity. To test this hypothesis, we developed a mole-scale protocol for the preparation of phosphonate **3** (Scheme 1)[37]. Ester **1** was reduced to the aldehyde and subjected to this phosphonate and KO^{t}Bu to form Z-enoate **2** in 80% yield as a single isomer. Subsequently, this enoate underwent acid-catalyzed acetonide deprotection-transesterification to provide the unsaturated lactone **4** in 77% yield in a 9-gram scale. Following our previous route, this lactone was transformed into amine **7** in 4 steps according to our earlier work.[8, 9]



Scheme 1. a) DIBALH (2 equiv), DCM, -78 °C, 4 h, then **3** (1.5 equiv), KO^{t}Bu (1.45 equiv), THF, -78 °C, 45 h, 80%; b) AcOH, 80 °C, 25 h, 77%; c) H_2, PtO_2 (1 mol %), EtOH, 23 °C, quant. (dr = 10:1); d) allyl-MgCl (2.0 equiv), THF, -78 °C, 96%; e) Et_3SiH (10 equiv), BF_3•OEt_2 (4.0 equiv), CF_3CH_2OH (8.0 equiv), DCM, -78 °C; then Boc_2O (0.5 equiv), -78→23 °C, 45% (dr = 10:1); f) TFA/DCM (1:9), 23 °C, used directly; g) 1,1'-carbonyldiimidazole (1.2 equiv), DCM, 23 °C, 1 h, then morpholine (2–5 equiv), 23 °C, 2 h, 97%; h) DIBALH (1.1 equiv), DCM, -78 °C, 3 h; then (o-^{t}BuPhO)$_2$P(=O)CH_2CO_2Et (1.5 equiv), KO^{t}Bu (1.45 equiv), THF, -78 °C, 8 h, 78%; i) NaOH (2.1 equiv), MeOH/H_2O 1:1.1, 0 °C, 2 h, 85%; j) HATU (1 equiv), ^{i}Pr$_2$NEt (3 equiv), **11** (1 equiv), THF or DCM, 0 °C, 30 min, 60%; k) methacrolein (24 equiv), nitro-Grela catalyst (5 mol %), 40 °C, 8 h, 60%; l) Ph_3PCH_3Br (1.5 equiv), KO^{t}Bu (1.49 equiv), THF, 0 °C, 3 h, 69%.

In the previous synthesis of fragment **S28** (Scheme 1; also in Scheme S1) en route to FR901464 and meayamycin, an acetyl group was installed on the allylic hydroxy group.[38] However, for the synthesis of meayamycin B, this requires additional two steps to form the carbamate (**S22→14→**meayamycin B). During previous structure-activity relationship studies, a more direct route was developed for various analogs[35] using (*S*)-(-)-ethyl lactate **8** as an inexpensive chiral starting material, but this route had never been used for the synthesis of meayamycin B. Ester **8** was exposed to CDI and morpholine to afford morpholine carbamate **9** in 97% yield, which underwent DIBALH reduction and subsequent HWE reaction with (o-^{t}BuPhO)$_2$P(=O)CH_2CO_2Et[39] to afford Z-enoate **10** in 78% yield. Hydrolysis of **10** with aqueous NaOH afforded acid **11** in 85% yield. With acetate **S28**, amide bond formation with amine **7** using HATU isomerized the *Z*-olefin **S19** to the more stable *E*-isomer in approximately 10% yield.[35] When acid **11** was subjected to the same conditions, this isomerization was more prominent, in a 1:2 ratio favoring the undesired E olefin. We hypothesized that the faster isomerization of the olefin, when starting with acid **11**, might be caused by the greater participation effect of the carbonyl oxygen in the carbamate group of ***Z*-15** (Scheme 2A), allowing for isomerization upon the activation of the carboxylic acid with HATU via intramolecular 1,4-addition (***Z*-15 →16**) followed by rotation and elimination (**16→*E*-15**).



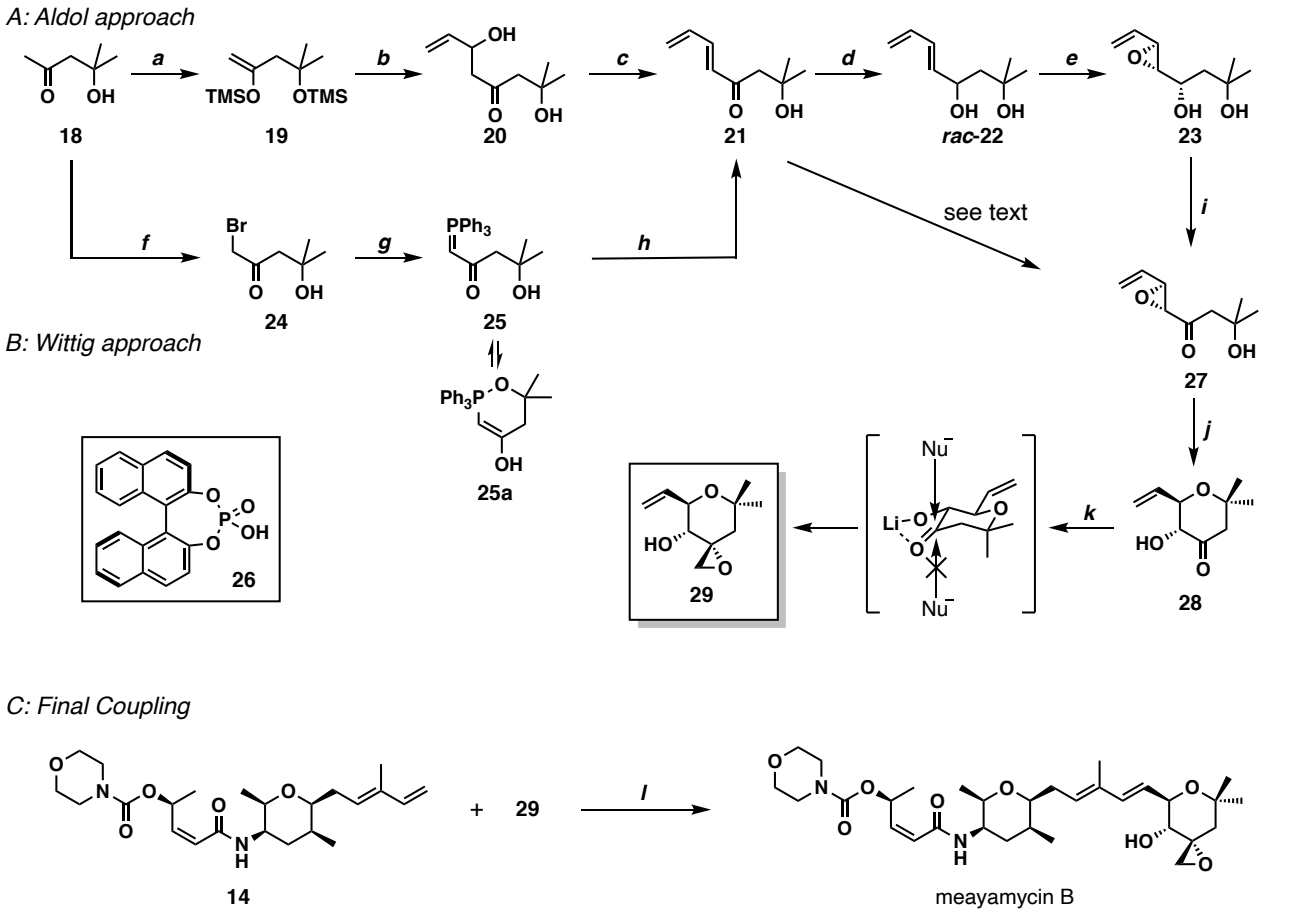
Scheme 2: (A) Proposed mechanism for isomerization. (B) A control experiment with methoxymethyl ether **17**

This hypothesis is supported by preliminary studies with the methoxymethyl ether (MOM) analog **17**, the olefin of which did not isomerize under the same conditions (Scheme 2B; manuscript in preparation). To gain further insights, the coupling reactions were performed between acid **11** and cyclohexylamine in various solvents

and at various temperatures. The olefin isomerization observed during the formation of amide **12** did not occur under these conditions, possibly due to a greater accessibility of the amino group compared to that of amine **7** whose amino group may be in the axial orientation; the higher nucleophilicity may have favorably competed with the intramolecular 1,4-conjugate addition described above. These results support our hypothesis about the origin of *E*/*Z* isomerization during the amide coupling.

These results also led to our next hypothesis that the olefin isomerization might be mitigated if the charged transition state for the conversion of ***Z*-15** to **16** could be destabilized. In effect, the use of less polar solvents such as THF and DCM for the coupling of acid **11** and amine **7** improved the stereochemical integrity of the olefin. Lowering the temperature during addition of the acid to HATU below 0 °C did not affect the isomerization ratio. Using an excess of the amine also suppressed the olefin isomerization, but this was not practical due to the difficult recovery of amine **7**. Nonetheless, this result indicated that the presence of the amine in excess in relation to the in-situ activated carboxylic acid was advantageous. To create such conditions without using amine **7** in excess, acid **11** was added to the amine in a dropwise fashion, competing against and minimizing the olefin isomerization. Several other methods were tested; activation with DCC or mixed anhydrides via chloroformates showed no desired product. Other non-classical methods were also attempted, including use of boric acid derivatives[40] and the Corey-Nicolaou method.[41] All of these methods failed or resulted in inefficient product formation with unidentified side products, which, from ^{1}H-NMR analysis, appear to be 1,4-addition products of the activated complex, prior to amide bond formation. Ultimately, for the optimized conditions to minimize this undesired isomerization, a mixture of acid **11** and ^{i}Pr$_2$NEt was added dropwise to a pre-mixed solution of amine **7** and HATU at 0 °C in THF or DCM to give the desired Z-enamide **12** in 50% yield with negligible isomerization. This amide was then cross-coupled with methacrolein in the presence of nitro-Grela precatalyst to generate aldehyde **13** in 40% yield. Addition of this aldehyde to in-situ prepared $Ph_3P{=}CH_2$ afforded the most advanced left fragment **14** in 83% yield.

We then turned our attention to the right hand fragment **29** and recognized several problems for scaling up our previous scheme (Scheme S1). First, the Zr/Ag-promoted alkynylation, although stereoselective, required stoichiometric amounts of these heavy metals.[42] Second, the use of a selenium reagent was not cost effective.[8, 9] Third, the formation of the tetrahydropyran ring required a stoichiometric quantity of $Hg(OAc)_2$.[9] Importantly, this scheme was lengthy (11 linear steps from propargyl alcohol). To develop a more concise scheme for **29** with less hazardous reagents, we began the preparation of this right fragment with ketone **18** ($3.35/mol, Sigma Aldrich). This ketone was first converted to the TMS ether **19** using TMSCl and NaI in ~90% yield in a 130-gram quantity in sufficient purity to be used without purification for the next step. This material could be purified by distillation for long term storage. The yield suffered when less NaI was used. Although most Lewis acids (e.g., $BF_3{\bullet}OEt_2$) failed to catalyze the Mukaiyama-type aldol condensation between **19** and acrolein, Kobayashi's method[43] afforded 64 grams of alcohol **20** (75% yield). Notably, we were able to reduce the amount of $Yb(OTf)_3{\bullet}6H_2O$ ($12/mmol, Sigma-Aldrich) from 10 mol% as suggested in the original literature[43] to 0.08 mol% without sacrificing the yield. Regioselective β-elimination using Piv_2O and NaOAc gave enone **21** in 77% yield (Route A; cost: $44/mmol of **21**, Sigma Aldrich). Intermediate **21** was also synthesized via a Wittig reaction from ylide **25** in 24% yield (Route B; cost $57/mmol of **21**, Sigma-Aldrich). The low yield was presumably due to the stabilized nature of the ylide **25**, as shown in structure **25a**.[44] Although the Wittig reaction was not efficient, the ylide **25** could be synthesized from inexpensive reagents and required only extractions to purify.



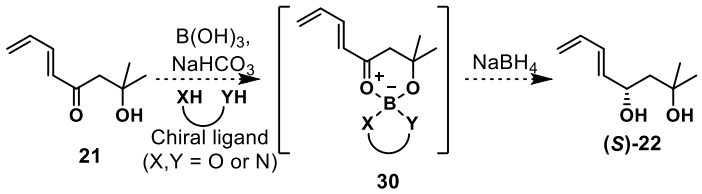
Scheme 3. **A**: a) TMSCl (2.5 equiv), Et_3N (3.0 equiv), NaI (2.3 equiv), MeCN, 23 °C, 4 h, 90%.; b) acrolein (2.0 equiv), $Yb(OTf)_3$•$6H_2O$ (0.08 mol %), toluene/water/EtOH (4:10:1), 23 °C, 3 d, 70%; c) Piv_2O (1.0 equiv), NaOAc (0.3 equiv), DCE, 60 °C, 24 h, 70%; d) $NaBH_4$ (1.5 equiv), MeOH, 0 °C, 1 h, 95%.; e) (+)-diisopropyl tartrate (8.0 mol %), $Ti(O^iPr)_4$ (6.0 mol %), TBHP (1.9 equiv), DCM, -20 °C, 12 h, 38%. **B**: f) Br_2 (1 equiv), MeOH, 0 °C to 23 °C, 3 h, 99%; g) PPh_3 (1.05 equiv), toluene, 23 °C, 7 h; then aqueous NaOH, 64%; h) acrolein (2.0 equiv), DCM, reflux, 24 h, 28%; i) tetrapropylammonium perruthenate (6.0 mol %), 4-methylmorpholine *N*-oxide (3.0 equiv), DCM, 23 °C, 2 h; j) camphorsulfonic acid (1.1 equiv), DCM, 23 °C, 6 h, 70% (2 steps); k) CH_2Br_2 (1.2 equiv), ^{n}BuLi (2.2 equiv), THF, -78→23 °C, 6 h, 73%. **C**: l) nitro-Grela catalyst (2 mol%), DCE, 40 °C, 52 h, 20%.

Our attempts to enantioselectively convert enone **21** to epoxyketone **27** in one step were unsuccessful. For example, La-BINOL-Ph_3As-based[45] enantioselective epoxidation required as much as 30 mol% of (*R*)-BINOL ligand to form the epoxyketone in 30% yield and 70% ee. The cinchona alkaloid-catalyzed asymmetric Darzens condensation[46] did not provide the desired product even after protecting the tertiary hydroxy group as a TMS or THP ether, presumably due to the 1,3-conjugated diene system. Kinetic resolution of racemic epoxy alcohols by an intramolecular epoxide opening catalyzed by [Co^{III}(salen)] complex,[47,48] have been used successfully for the preparation of chiral pyrans by others. However, this method failed to convert racemic epoxide **27** to the enantio-enriched ketone **28**. These failures prompted us to explore a new area of chiral Brønsted acid catalyzed reactions.[49, 50] After preparation and silica gel chromatography purification of (*R*)-BINOL phosphoric acid, epoxide **27** was converted to ketone **28** in 32% yield with an *ee* of >90%. However, this transformation was not reproducible, as different batches of chiral phosphoric acid produced different results. The poor reproducibility may stem from metal impurities.[51] After further investigation, the most promising outcome was 43% *ee* with a mixture of $MgCl_2$

and **26** (1:2) (Scheme 3), though extensive efforts to improve upon this enantioselectivity failed. We also explored enzymatic kinetic resolution of secondary alcohols **28** and **29** using lipases A and B and vinyl acetate, to no avail.[52]

In light of these failed attempts and non-reproducible data, a longer but reproducible and scalable approach was pursued: the reduction of enone **21** and subsequent Sharpless kinetic resolution of alcohol **22** afforded epoxyalcohol **23**[53] in 90% *ee* and 36% yield. This epoxyalcohol was oxidized[54] to form epoxyketone **27** in ~23% yield over 3 steps. This ketone underwent facile anti-Baldwin/Nicolaou-type cyclization under acidic conditions[55] to form cyclic ketone **28** in 77% yield. The ketone was subjected to nucleophilic attack through the putative bidentate chelation model to provide the right fragment **29** in 73% yield as a single diastereomer. This fragment was coupled with the left fragment **14** to afford meayamycin B in 20% yield on the average (Scheme 3C; also see the previous work[38]).

Due to the low yield and difficulty with scaling the Sharpless kinetic resolution of alcohol **22** we turned our attention to the reduction of the prochiral enone **21** to the enantioenriched allylic alcohol (*S*)-**22** (Scheme 4). Despite advances in the field of enantioselective reduction of carbonyls, our efforts to synthesize (*S*)-**22** resulted in unsatisfactory enantioselectivities; for example, the Corey-Bakshi-Shibata reduction[56] produced (*S*)-**22** with 45:55 *er* (56% yield). Neither the Noyori asymmetric reduction[57] nor the Brown asymmetric reduction[58] provided the desired product. These failures prompted us to develop a new enantioselective reduction of **21**. Diastereoselective reduction of chiral β–hydroxyketones have been reported by Shapiro[59] and Evans.[60] On the basis of these works, we asked whether the β-hydroxy functionality of **21** could be exploited to induce enantioselectivity to afford (*S*)-**22**. Recent studies[61] have indicated that under mild basic conditions, boric acid can chelate 1,2-diols. Thus, we hypothesized that under similar reaction conditions, **21** could form a mixed borate ester **30** (Scheme 4) with a chiral bidentate ligand, which would be reduced in a one-pot procedure to obtain the enantioenriched diol (*S*)-**22**.



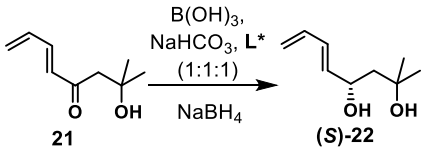
Scheme 4. Hypothesis for enantioselective reduction of prochiral ketone.

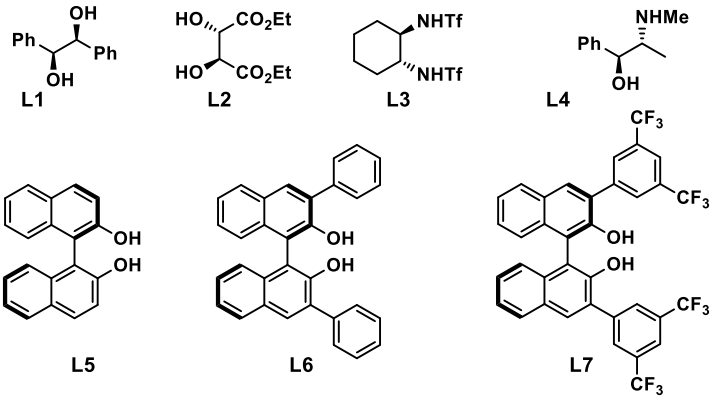
With this admittedly vague hypothesis, several chiral compounds were evaluated as potential ligands (Table 1). While **L1–L4** were discouraging for this transformation (Entries 1–5), the use of axially chiral ligand **L5** with $NaBH_4$ produced (*S*)-**22** in 84% yield with 12:88 *er* (Entry 6). With 50 mol% of the ligand, the *er* was essentially the same (Entry 7). With lower loading of the ligand, the *er* values gradually decreased (Entries 8–11). This trend may be attributed to the competing background racemic reduction of ketone **21** with $NaBH_4$. Although a stoichiometric amount of **L5** was optimal, we did not find this to be a setback because the ligand could be readily recycled with ~90% recovery (see Supporting Information for detail).

Encouraged by the result with the $B(OH)_3$-**L5**-$NaBH_4$ system, we wished to investigate the bulkier BINOL derivatives **L6** and **L7**, which did not induce any appreciable enantioselectivity (Entries 12 and 13). This may be because the added steric bulk hindered the formation of the mixed borate ester with the substrate. Similar axially chiral reducing agents BINAL-H with stoichiometric amounts of the chiral ligand gave good enantioselectivity with ketones in the literature,[62] but this method did not reduce ketone **21** the desired alcohol. The procedure was streamlined by eliminating $B(OH)_3$ from the reaction conditions; simply premixing **L5** and $NaBH_4$ in MeCN for 1 h at 23 °C, followed by reduction at -78 to 4 °C over 12 h led to (*S*)-**22** with 2:98 *er* (Entry 14). Furthermore,

we were able to reduce the amount of (*R*)-BINOL to 20 mol % without sacrificing the *er* (Entry 15). Thus, the optimal ligand was determined to be **L5** for the enantioselective reduction of ketone **21**.

Table 1. Screening of chiral ligands to induce enantioselectivity.





Entry	Ligand (L*)	Amount (equiv)	Yield (%)*	e.r. #
1	–	–	85	50:50
2	**L1**	1	80	50:50
3	**L2**	1	76	45:55
4	**L3**	1	68	50:50
5	**L4**	1	71	50:50
6	**L5**	1	83	12:88
7	**L5**	0.5	84	13:87
8	**L5**	0.2	84	17:83
9	**L5**	0.1	79	20:80
10	**L5**	0.05	81	32:68
11	**L5**	0.025	83	40:60
12	**L6**	0.2	70	55:45
13	**L7**	0.2	73	52:48
14**	**L5**	0.5	58	2:98
15**	**L5**	0.2	79	7:93

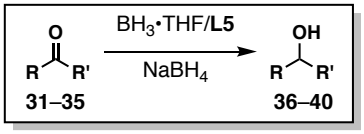
Reaction conditions: (a) $B(OH)_3$, $NaHCO_3$, **L5** (1:1:1), THF, $NaBH_4$, 23 °C, 1 h; then **21** (1 equiv), THF, -78 to 4 °C, 12 h.

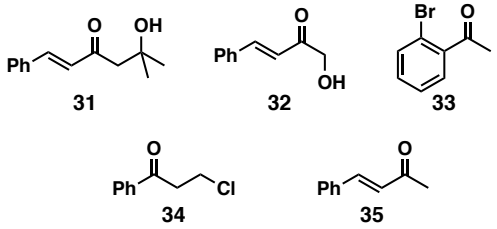
*Isolated yield. #(*R*)-**22**: (*S*)-**22**

** Reaction was performed in MeCN instead of THF without $B(OH)_3$. See Supporting Information for details.

To probe the generality of this enantioselective reduction, we treated prochiral ketone with the premixed solution of **L5** (0.2 equiv) and $NaBH_4$ (0.3 equiv) but the racemate was obtained (Table 2, Entry 1). Thus, we revisited our previous strategy to form the hypothesized intermediate **30** indicated in Scheme 4. Here, we attempted to form this intermediate by using stoichiometric amounts of **L5** and BH_3. With these modified conditions, prochiral ketones **31**–**35** were subjected to the 1:1 BH_3/**L5** mixture in THF for 1 h at 23 °C and the resulting mixture was cooled to -78 °C and exposed to $NaBH_4$ (0.3-0.4 equiv) to obtain alcohol **36**–**40** (Table 2). Lower loading of BH_3 and **L5** resulted in lower enantioselectivities (Entries 2 and 3). Although 1 equiv of **L5** was necessary to achieve high enantioselectivity, **L5** could be recovered by filtration and recrystallization. Though high enantioselectivities could not be obtained with substrates without a hydroxy group (Entries 8-10), α- or β-hydroxyketones resulted in high enantioselectivites (Entries 2, 4, 5). Greater amounts of $NaBH_4$ eroded the enantioselectivity (Entry 6 vs 7), probably due to a background racemic reduction to a greater degree. To render the method catalytic, we tested addition of stoichiometric amount of a sacrificial alcohol (e.g., ^{t}BuOH, ^{i}PrOH), to no avail. To slow the background racemic reduction, we investigated milder reducing agents such as $NaBH_3CN$ and ^{i}PrOH under various conditions, again to no avail. Due to the lower cost of BINOL ($0.17 per mmol, VWR) compared to other commercially available catalytic reducing agents, this stoichiometric method may offer an inexpensive alternative to CBS or Noyori reduction for α- or β-hydroxyketones.

Table 2. Enantioselective reduction of ketones





Entry	Ketone	**L5** (equiv)	$NaBH_4$ (equiv)	Yield (%)*	e.r.
1[b]	**31**	0.2	0.3	77	50:50
2	**31**	1	0.4	69	7:93
3	**31**	0.5	0.4	76	21:79
4	**21**	1	0.4	72[a]	2:98
5	**32**	1	0.4	71	4:96
6	**32**	0.5	0.3	78	12:88
7	**32**	0.5	1.2	88	35:65
8	**33**	1	0.3	45	49:51
9	**34**	1	0.3	49	41:59

10	**35**	1	0.3	40	47:53

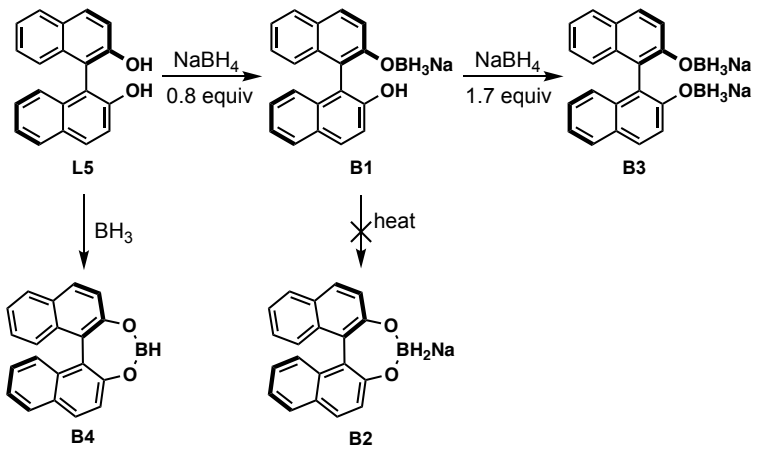
Reaction conditions: (a) BH_3•THF, **L5** (1:1), THF, 1 h; then ketone, THF, $NaBH_4$, -78 to 24 °C, 12 h.

*Yield based on the ^{1}H NMR analyses of crude material.

[a] isolated yield. [b] premixed $NaBH_4$ and **L5** method

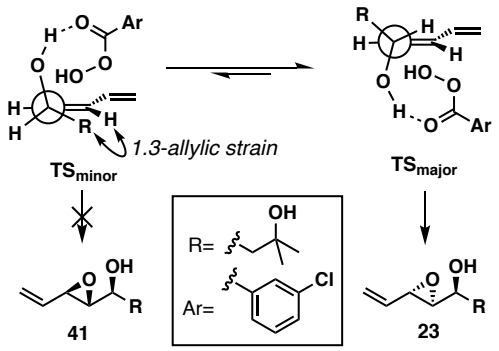
To study the mechanism, we analyzed the premixed solution of **L5** and $NaBH_4$ by ^{1}H and ^{11}B NMR spectroscopy. The ^{1}H NMR spectrum suggested a mixture of symmetric and asymmetric species, likely **B1** (Scheme 5), when a substoichiometric amount of $NaBH_4$ was present (Spectrum 24, Supporting Information). We believe the small amount of the symmetric species is **L5**. Three boron species (δ-20, 5.6, and 9.1 ppm) were observed (Spectrum 25, Supporting Information). Heating the reaction mixture to 130 °C did not lead to cyclization to form **B2** (Spectra 26 and 27, Supporting Information). When additional 1.7 equivalents of $NaBH_4$ was present (i.e., 2.5 equivalents of $NaBH_4$), a single boron species (δ -19 ppm, q, J = 92.8 Hz) was observed in the ^{11}B NMR spectrum besides $NaBH_4$ (Spectrum 28, Supporting Information). Moreover, only a symmetric species was observed by ^{1}H NMR (Spectrum 29, Supporting Information). We propose that **L5** reacted with the substoichiometric amount of $NaBH_4$ to form asymmetric **B1** which then reacts with additional $NaBH_4$ to form **B3** (Scheme 5).

We were unable to obtain ^{1}H NMR spectrum of a mixture of **L5** and BH_3•THF due to its poor stability when exposed to the air to remove THF. Furthermore, ^{13}C NMR spectra were not obtained because the mixure was not stable over prolonged time necessary to obtain ^{13}C NMR. We propose that **B4** may be formed when **L5** and BH_3•THF (1:1) are mixed.



Scheme 5. Observed species generated in THF.

We then carried out the subsequent epoxidation of (*S*)-**22** with mCPBA and found that epoxide **23** was obtained as a single diastereomer in 57% yield. The result may be rationalized by the proposed model by Sharpless, in which the O-C—C=C dihedral angle is estimated to be ~120°.[63] Based on this model, the allylic hydroxy group directs the peracid-mediated oxidation to furnish **23** (Scheme 6). The stereochemical outcome of this epoxidation is consistent with the transition state TS_{major}; the 1,3-allylic strain[64] in transition state TS_{minor} disfavors the formation of the alternative diastereomer **41**. This improved route bypassed the low yielding Sharpless kinetic resolution strategy.



Scheme 6. Rationale for observed diastereoselectivity.

In conclusion, the use of phosphonate **2** shortened the synthetic scheme for **8** by 3 steps, excluding the preparation of this phosphonate. The overall yield from **1** to **5** is higher (63%) than that of the previous scheme (45%). Importantly, the new scheme for the right fragment **29** exploited a new enantioselective reduction of enone **21** to allylic alcohol (*S*)-**22** involving inexpensive and recyclable reagent **L5**. The present synthesis is more concise (current and previous schemes: $204/mmol and $753/mmol for the right fragment **29**, respectively) and requires less hazardous reagents. With this improvement, better access to the left-hand and right-hand fragments allows meayamycin B[35] to be synthesized in 11 steps in the longest linear sequence and 24 total steps. The overall yield of meayamycin B was 0.82% and 0.24% from commercially available starting materials **21** and **1**, respectively.

Experimental Section

General Information and Reagents. All reactions were carried out with freshly distilled solvents under anhydrous conditions, unless otherwise noted. All of the flasks used for carrying out reactions were dried in an oven at 80 °C prior to use. Unless otherwise stated, all reactions that required heating used an oil bath as the heating source with a thermometer submerged in the bath to monitor temperature. Unless specifically stated, the temperature of a water bath during the evaporation of organic solvents using a rotary evaporator was about 35±5 °C. All of the syringes in this study were dried in an oven at 80 °C and stored in a desiccator over Drierite®. Tetrahydrofuran (THF) was distilled over Na metal and benzophenone. Dichloromethane (DCM) was distilled over calcium hydride. Acetonitrile was distilled over calcium hydride and stored over 3Å molecular sieves. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogenous materials, unless otherwise stated. All reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25-mm Merck silica gel plates (60F-254) using UV light (254 nm) for visualization or anisaldehyde in ethanol or 0.2% ninhydrin in ethanol, or 2.4% phosphomolybdic acid/1.4% phosphoric acid/5% sulfuric acid w/v in water as developing agents and heat for visualization. Silica gel (230–400 mesh) was used for flash column chromatography. A rotary evaporator was connected to a water aspirator that produced a vacuum pressure of approximately 60 mmHg when it was connected to the evaporator. NMR spectra were recorded on a Bruker Advance spectrometer at 300 MHz, 400 MHz, 500 MHz, 600 MHz or 700 MHz. The chemical shifts are given in parts per million (ppm) on a delta (δ) scale. The solvent peak was used as a reference value, for ^{1}H NMR: $CHCl_3$ = 7.27 ppm, CH_3OH = 3.31 ppm, DMSO = 2.50 ppm, acetone = 2.05 ppm, for $^{13}C\{^1H\}$ NMR: $CDCl_3$ = 77.00 ppm, CD_3OD = 49.00 ppm, DMSO-d_6 = 49.10 ppm, and acetone-d_6 = 29.40 ppm. The following abbreviations are used to indicate the multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad. High-resolution mass spectra were recorded on a VG 7070 spectrometer or Micromass QTOF instrument. Low-resolution mass spectra [LCMS (ESI)] were recorded on a Shimadzu LCMS-2020. Infrared (IR) spectra were collected on a Mattson Cygnus 100 spectrometer. Samples for acquiring IR spectra were prepared as a thin film on a NaCl plate by dissolving the compound in DCM and then evaporating the DCM.

3-(tert-butyl) 4-methyl (4S,5R)-2,2,5-trimethyloxazolidine-3,4-dicarboxylate (1)

Refer to the paper[9] for synthesis and spectroscopic data.

tert-butyl (4R,5R)-4-((Z)-3-ethoxy-2-methyl-3-oxoprop-1-en-1-yl)-2,2,5-trimethyloxazolidine-3-carboxylate (2)

DIBALH (1.0 M in hexanes, 87.0 mL) was added to a stirred solution of **1** (22.10 g, 49.10 mmol) in DCM (100 mL) at -78 °C dropwise via a syringe under a nitrogen atmosphere over 1 h. After the addition, the mixture was stirred at the same temperature for 3 h (Flask A). A stirred solution of **3** (12.30 g, 49.60 mmol) in THF (Flask B) at 0 °C was treated with KO^{t}Bu (5.06 g, 45.1 mmol) under a nitrogen atmosphere. After 20 min at the same temperature, the mixture was transferred to the solution of Garner's aldehyde (Flask A) at -78 °C by cannula. The resulting mixture was slowly warmed to 25 °C and stirred at this temperature for 45 h. The reaction mixture was quenched with aqueous potassium sodium tartrate (1M, 200 mL) at room temperature. The mixture was stirred for 30 min at room temperature and extracted with EtOAc (3 × 250 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered through a cotton plug, and concentrated *in vacuo*. The residue was purified by flash chromatography (2→8% EtOAc in hexanes) on silica gel (400 mL) to afford the ester **2** (11.80 g, 80% yield) as a colorless oil. *Data for ester **2**:* R_f = 0.48 (20% EtOAc in hexanes); $[\alpha]_D^{24}$ +47.6 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} = 3421, 2980, 2933, 1786 (C=O), 1701 (C=O), 1454, 1378, 1306, 1255, 1221, 1177, 1133, 1087, 1027 cm^{-1}; ^{1}H NMR (400 MHz, 348K, C_6D_6): δ = 5.67 (d, 1H, *J* = 6.6 Hz), 5.08 (app t, 1H, *J* = 7.8 Hz), 3.99 (q, 2H, *J* = 7.2 Hz), 3.83 (qd, 1H, *J* = 7.8, 6.6 Hz), 1.86 (s, 3H), 1.75 (s, 3H), 1.63 (s, 3H), 1.40 (s, 9H), 1.40–1.38 (m, 3H), 0.97 (t, 3H, *J* = 7.2 Hz) ppm; ^{13}C{^{1}H} NMR (100 MHz, 348K, C_6D_6): δ = 167.5, 152.7, 143.2, 95.1, 79.6, 76.4, 62.7, 60.9, 29.0, 27.5, 26.5, 21.2, 19.2, 14.8 ppm; HRMS (ESI-TOF) *m/z*: [(M-Boc+H)+H]$^+$ Calcd for $C_{12}H_{22}NO_3$ 228.1600; found 228.1603.

tert-butyl ((2R,3R)-2,5-dimethyl-6-oxo-3,6-dihydro-2H-pyran-3-yl)carbamate (4)

A solution of ester **2** (8.80 g, 26.9 mmol) in AcOH (125 mL) was heated to 80 ºC under air atmosphere. The mixture was stirred at the same temperature for 25 h. The solvent was removed in vacuo, and the residue was purified by flash chromatography (5→40% EtOAc in hexanes) on silica gel (300 mL) to afford the unsaturated lactone **4** (5.00 g, 77% yield) as a white solid. Spectroscopic data for unsaturated-lactone **4** matched that in the previous literature.[8]

tert-butyl ((2R,3R,5S)-2,5-dimethyl-6-oxotetrahydro-2H-pyran-3-yl)carbamate (5*)*

Refer to the paper[8] for synthesis and spectroscopic data.

tert-butyl ((2R,3R,5S)-6-allyl-6-hydroxy-2,5-dimethyltetrahydro-2H-pyran-3-yl)carbamate (S18)

Refer to the paper[8] for synthesis and spectroscopic data.

tert-butyl ((2R,3R,5S,6S)-6-allyl-2,5-dimethyltetrahydro-2H-pyran-3-yl)carbamate (6)

Refer to the paper[8] for synthesis and spectroscopic data.

(2R,3R,5S,6S)-6-allyl-2,5-dimethyltetrahydro-2H-pyran-3-amine (7)

Refer to the paper[8] for synthesis and spectroscopic data.

(S)-1-ethoxy-1-oxopropan-2-yl morpholine-4-carboxylate (9)

Refer to the paper for synthesis and spectroscopic data.[38]

(S,Z)-5-ethoxy-5-oxopent-3-en-2-yl morpholine-4-carboxylate (10)

Refer to the paper for synthesis and spectroscopic data.[38]

(S,Z)-4-((morpholine-4-carbonyl)oxy)pent-2-enoic acid (11)

Refer to the paper for synthesis and spectroscopic data.[38]

(S,Z)-5-(((2R,3R,5S,6S)-6-allyl-2,5-dimethyltetrahydro-2H-pyran-3-yl)amino)-5-oxopent-3-en-2-yl morpholine-4-carboxylate (12)

An oven-dried, 50-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a rubber septum and a nitrogen inlet was charged with amine **7** (2.22 mmol), CH_2Cl_2 (5 mL), and *O*-(7-azabenzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate (844 mg, 2.22 mmol), followed by *N, N′*- diisopropylethylamine (1.15 mL, 6.66 mmol) via a syringe. The resulting mixture was stirred at 23 °C for 5 min and then a solution of carboxylic acid **11** (2.22 mol) in CH_2Cl_2 (2 mL) was added dropwise. The resulting pale-yellow solution was stirred 23 °C for 20 h. Saturated aqueous ammonium chloride (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered through a cotton plug, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (30→55% EtOAc in hexanes) on silica gel (70 mL) to afford the amide **12** (421 mg, 50% yield) as a colorless oil. *Data for amide **12**:* R_f = 0.48 (80% EtOAc in hexanes); $[\alpha]_D^{17}$ -24.8 (*c* 1.0, MeOH); IR (film): 3419, 3072, 2931, 1687 (C=O), 1658 (C=O), 1523, 1437, 1373, 1332, 1278, 1246, 1116 cm^{-1}; ^1H NMR (400 MHz, 293 K, $CDCl_3$) δ 6.19–6.09 (m, 1H), 5.92 (dd, 1H, *J* = 11.6, 7.8 Hz), 5.84–5.74 (m, 1H), 5.69 (dd, 1H, *J* = 11.6, 1.2 Hz), 5.11 (dd, 1H, *J* = 17.2, 1.6 Hz), 5.05 (dd, 1H, *J* = 10.2, 0.8 Hz), 3.98–3.92 (m, 1H), 3.69–3.64 (m, 5H), 3.53 (dt, 1H, *J* = 7.1, 2.7 Hz), 3.46 (t, 4H, *J* = 5.1 Hz), 2.37–2.30 (m, 1H), 2.16–2.09 (m, 1H), 1.96–1.94 (m, 2H), 1.79–1.75 (m, 1H), 1.41 (d, 3H, *J* = 6.5 Hz), 1.15 (d, 3H, *J* = 6.5 Hz), 1.02 (d, 3H, *J* = 7.3 Hz) ;$^{13}C\{^1H\}$ NMR (100 MHz, 293 K, $CDCl_3$) δ 165.0, 155.0, 144.5, 134.9, 122.3, 116.9, 80.8, 77.4, 76.1, 70.3, 66.7, 47.1, 37.5, 36.0, 29.0, 20.3, 18.0, 15.1; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{20}H_{32}N_2O_5Na$ 403.2209; Found 403.2220.

(S,Z)-5-(((2R,3R,5S,6S)-2,5-dimethyl-6-((E)-3-methyl-4-oxobut-2-en-1-yl)tetrahydro-2H-pyran-3-yl)amino)-5-oxopent-3-en-2-yl morpholine-4-carboxylate (13)

A 10-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a nitrogen inlet and a rubber septum was charged with amide **12** (270 mg, 0.95 mmol), methacrolein (1.20 mL, 14.0 mmol) and nitro-Grela Grubbs catalyst (6.3 mg, 9.4 μmol). The resulting mixture was stirred at 45 °C for 22 h, and additional nitro-Grela Grubbs catalyst (6.3 mg, 9.4 μmol) was added. The stirring was continued for 13 h and the mixture was concentrated *in vacuo*. The residue was purified by flash chromatography (30→80% EtOAc in hexanes) on silica gel (15 mL) to afford the aldehyde **13** (185 mg, 60%) as a colorless oil. *Data for aldehyde **13**:* R_f = 0.27 (80% EtOAc in hexanes); $[\alpha]_D$ ^{17} -9.9 (*c* 1.0, DCM); IR (film): ν_{max} = 3354, 2969, 2925, 2857, 2717, 1687 (br, unresolved, C=O), 1518, 1426, 1301, 1276, 1242, 1118, 1071, 1023 cm^{-1}; ^1H NMR (400 MHz, 293 K, $CDCl_3$) δ 9.41 (s, 1H), 6.56 (app t, *J* = 6.8 Hz, 1H), 6.38 (d, *J* = 8.8 Hz, 1H), 6.14 (dq, *J* =13.6, 6.8 Hz, 1H), 5.94 (dd, *J* = 11.6, 8.0 Hz, 1H), 5.74 (d, *J* = 11.6 Hz, 1H), 3.95–3.92 (m, 1H), 3.70–3.64 (m, 6H, 11,15-H), 3.47–3.34 (m, 4H), 2.60–2.52 (m, 1H) 2.43–2.36 (m, 1H), 1.81–1.77 (m, 1H), 1.75 (s, 3H), 1.63–1.56 (m, 2H), 1.41 (d, *J* = 6.5 Hz,

3H), 1.16 (d, J = 6.5 Hz, 3H), 1.07 (d, J = 7.5 Hz, 3H) ;$^{13}C\{^1H\}$ NMR (100 MHz, 293 K, $CDCl_3$) δ 195.0, 165.1, 154.9, 150.5, 143.9, 140.6, 122.4, 79.7, 76.1, 70.1, 66.6, 46.8, 35.8, 32.8, 31.6, 20.2, 17.7, 15.1, 9.5; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd. for $C_{22}H_{35}N_2O_6$ 423.2495; Found 423.2484.

(S,Z)-5-(((2R,3R,5S,6S)-2,5-dimethyl-6-((E)-3-methylpenta-2,4-dien-1-yl)tetrahydro-2H-pyran-3-yl)amino)-5-oxopent-3-en-2-yl morpholine-4-carboxylate (14)

An oven-dried, 50-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a rubber septum and a nitrogen inlet was charged with methyltriphenylphosphonium bromide (803 mg, 2.25 mmol) and THF (8.0 mL). The solution was cooled in an ice-water bath, and a solution of KO^{t}Bu in THF (1M, 1.90 mL, 1.90 mmol) was added via a syringe. The mixture was stirred for 10 min at the same temperature. A solution of aldehyde **13** (183 mg, 0.57 mmol) in THF (7.0 mL) was added to the mixture via cannula, and the stirring was continued for 30 min. After 30 min H_2O (5.0 mL) was added and the mixture was concentrated *in vacuo*. After removal of THF, the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered through a cotton plug, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (10→50% EtOAc in hexanes) on silica gel (20 mL) to afford the diene **14** (124 mg, 69% yield) as a colorless oil. Spectroscopic data for diene **14** matched that in the previous literature.[38]

2,2,4,4,8,8-hexamethyl-6-methylene-3,7-dioxa-2,8-disilanonane (19)

A 2-L round-bottomed flask equipped with a Teflon-coated magnetic stir bar containing ketone **18** (25.2 mL, 203.50 mmol) was purged with argon. Et_3N (85.0 mL, 612 mmol) and TMSCl (65.0 mL, 510 mmol) were added to the flask at 23 °C and the mixture was stirred at the same temperature for 30 min. A solution of NaI (66.801 g, 448 mmol; dried overnight under high vacuum in a 140 °C sand bath) in dry MeCN (500 mL; dried over 4Å molecular sieves overnight) was added to the reaction mixture over 1 h at the same temperature. The mixture was stirred for an additional 3.5 h, then diluted with ice-cold H_2O (1.5 L). The mixture was extracted with EtOAc (3 × 250 mL). The combined organic layers were dried over Na_2SO_4, filtered through a cotton plug, and concentrated *in vacuo*. The resulting crude residue of enol ether **19** (53.002 g, quantitative yield) was >90% pure by ^1H NMR spectroscopic analysis and used after the crude material was passed through a plug of neutral aluminum with 90 % EtOAc in hexanes before the next step. *Data for enol ether **19**:* IR (film): ν_{max} = 2961, 1620, 1321, 1251, 1042 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 293 K): δ 4.07 (*br* s, 1H), 4.05 (br s, 1H), 2.19 (s, 2H), 1.26 (s, 6H), 0.19 (s, 9H), 0.10 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 293 K): δ 157.1, 92.9, 73.9, 51.9, 30.1, 2.8, 0.17; HRMS of **19** was not obtainable.

2,6-dihydroxy-2-methyloct-7-en-4-one (20)

Toluene (13.4 mL) and acrolein (5.0 mL, 75 mmol) were added to a 250-mL round-bottomed flask equipped with a Teflon-coated magnetic stir bar containing **19** (13.030 g, 50.00 mmol). The flask was cooled on an ice-water bath (0 °C external temperature), then a solution of $Yb(OTf)_3•6H_2O$ (25.0 mg, 40.3 μmol) in H_2O/EtOH (1:10 v/v, 36.6 mL) was added. The mixture was stirred at room temperature for 3 d and then concentrated *in vacuo*. The crude residue was purified by flash chromatography (10→60% EtOAc in hexanes) on silica gel (1.5 L) to afford hydroxy ketone **20** as a colorless oil (6.031 g, 70% yield). *Data for hydroxy ketone **20**:* R_f = 0.18 (40% EtOAc in hexanes); IR (film): ν_{max} = 3410 (br O-H), 2974, 2932, 1701 (C=O), 1378, 1144 cm^{-1}; ^1H NMR (400 MHz, 1% CD_3OD in $CDCl_3$, 293 K): δ 5.91 (ddd, J = 16.4, 10.4, 5.6 Hz, 1H), 5.33 (dt, J = 17.2, 2.4 Hz, 1H), 5.17 (dt, J = 10.4, 2.0 Hz, 1H), 4.62-4.57 (m, 1H), 2.67–2.66 (m, 4H), 1.27 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 293 K):

δ 212.3, 139.2, 115.2, 69.9, 68.6, 54.4, 50.7, 29.3; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd. for $C_9H_{17}O_3$ 173.1178; Found 173.1184.

1-bromo-4-hydroxy-4-methylpentan-2-one (24)

Ketone **18** (10.01 g, 86.10 mmol) in MeOH (60.0 mL) was added to a 250-mL round-bottomed flask equipped with a Teflon-coated magnetic stir bar, and the stirred solution was cooled to 0 °C. To the mixture was added Br_2 (4.40 mL, 86.10 mmol) dropwise using a syringe, and the resultant mixture was slowly warmed to 23 °C over 3 h. The mixture was poured into H_2O (200 mL) and extracted with DCM (50 mL × 4). The combined organic layers were dried over Na_2SO_4, filtered through a cotton plug, and concentrated *in vacuo* to afford bromoketone **24** as a pale-yellow oil (16.601 g, 99% yield). *Data for bromo ketone **24**:* R_f = 0.57 (60% EtOAc in hexanes); IR (film): ν_{max} = 3433 (br O-H), 2975, 2249, 1715 (C=O), 1465, 1382, 1173, 1057, 978, 911, 733 cm^{-1}; ^1H NMR (400 MHz, 1% CD_3OD in $CDCl_3$, 293 K): δ 3.91 (s, 2H), 2.83 (s, 2H), 1.28 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 293 K): δ 203.0, 70.0, 50.9, 35.4, 29.4; HRMS (ESI-TOF) *m/z*: $[M\text{-}OH+H]^+$ Calcd. for $C_6H_{12}BrO$ 179.0066; Found 178.9959.

4-hydroxy-4-methyl-1-(triphenyl-l5-phosphaneylidene)pentan-2-one (25)

A 250-mL round-bottomed flask equipped with a Teflon-coated magnetic stir bar was treated with bromoketone **24** (10.02 g, 51.31 mmol), benzene (80.0 mL), PPh_3 (14.22 g, 53.86 mmol), and the resulting solution was stirred at 23 °C for 7 h. The mixture was poured into H_2O (1 L) and extracted with DCM (100 mL × 3). The aqueous layer was treated with 4 M NaOH (15.0 mL, 60.0 mmol) and extracted with DCM (100 mL × 4). The combined organic layers were dried over Na_2SO_4, filtered through a cotton plug, and concentrated *in vacuo* to afford crude ylide **25**. This ylide was washed with hexanes (100 mL × 3) until TLC analysis showed absence of PPh_3 to obtain ylide **25** as a yellowish white solid (12.302 g, 64% yield). *Data for ylide **25**:* R_f = 0.24 (40% EtOAc in hexanes); IR (film): ν_{max} = 3266 (br O-H), 3057, 2967, 1675 (C=O), 1528, 1437, 1404, 1282, 1106, 998 cm^{-1}; ^1H NMR (300 MHz, 1% CD_3OD in $CDCl_3$, 293 K): δ 7.67–7.43 (m, 15H), 3.80–3.71 (d, *J* = 25.6 Hz, 1H), 2.43 (s, 2H), 1.24 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 293 K): δ 192.8, 133.1 (d, *J* = 10.0 Hz), 132.4 (d, *J* = 2.5 Hz), 129.0 (d, *J* = 11.3 Hz), 126.1 (d, *J* = 90.0 Hz), 70.2, 55.1 (d, *J* = 103.8 Hz), 50.3 (d, 13.8), 29.7; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd. for $C_{24}H_{26}O_2P$ 377.1665; Found 377.1675. m.p.: 184.5–185.2 °C.

(E)-2-hydroxy-2-methylocta-5,7-dien-4-one (21)

(Method A): To a 250-mL round-bottomed flask equipped with a Teflon-coated magnetic stir bar and a reflux condenser was added ylide **25** (12.320 g, 32.75 mmol), DCM (105 mL) at 23 °C, to which acrolein (4.3 mL, 64 mmol) was added dropwise. The mixture was refluxed at 40 °C for 24 h, and then concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (10→50% EtOAc in hexanes) on silica gel (200 mL) to afford enone **21** as a pale-yellow oil (1.41 g, 28% yield).

(Method B): A 1-L round-bottomed flask equipped with a Teflon-coated magnetic stir bar was treated with hydroxy ketone **20** (24.292 g, 141.07 mmol), DCE (40 mL), Ac_2O (13.35 mL, 141.1 mmol) and NaOAc (3.472 g, 42.33 mmol). The mixture was stirred in a 60 °C oil bath for 24 h. The mixture was cooled to 23 °C, then diluted with EtOAc (250 mL) and saturated aqueous sodium bicarbonate (200 mL). The organic layer was separated, dried over Na_2SO_4, filtered through a cotton plug, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (10→50% EtOAc in hexanes) on silica gel (1 L) to afford enone **21** as a pale-yellow oil (15.238 g, 70% yield).

(Method C): A 25-mL round-bottomed flask equipped with a Teflon-coated magnetic stir bar was treated with hydroxy ketone **20** (110 mg, 0.60 mmol), DCE (1.0 mL), Piv_2O (0.14 mL, 0.70 mmol) and NaOAc (25.1 mg, 0.30 mmol). The mixture was stirred in a 60 °C oil bath for 24 h. The mixture was cooled to 23 °C, then diluted with DCM (5.0 mL) and saturated aqueous sodium bicarbonate (5.0 mL). The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (10→50% EtOAc in hexanes) on silica gel (10 mL) to afford enone **21** as a pale-yellow oil (77.1 mg, 83% yield). *Data for enone **21***: R_f = 0.33 (40% EtOAc in hexanes); IR (film): ν_{max} = 3437 (br O-H), 2973, 1678 (C=O), 1204, 1110 cm^{-1}; ^1H NMR (400 MHz, 1% CD_3OD in $CDCl_3$, 293 K): δ 7.18 (dd, *J* = 15.6 Hz, 10.8 Hz, 1H), 6.51 (dt, *J* = 17.2 10.8 Hz, 1H), 6.18 (d, *J* = 15.6 Hz, 1H), 5.72 (d, *J* = 17.2 Hz, 1H), 5.60 (d, *J* = 10.0 Hz, 1H), 2.75 (s, 2H), 1.27 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 293 K): δ 202.0, 143.7, 135.1, 131.1, 127.5, 69.9, 50.7, 29.6; HRMS (ESI-TOF) *m/z*: $[M-CH_3]^+$ Calcd. for $C_9H_{14}O_2$ 139.0759; Found 139.0756.

(E)-2-methylocta-5,7-diene-2,4-diol (22)

A 250-mL round-bottomed flask equipped with a Teflon-coated magnetic stir bar was treated with enone **21** (2.40 g, 15.4 mmol) and MeOH (60 mL). The mixture was cooled to 0 °C and $NaBH_4$ (1.16 g, 30.8 mmol) was added over 15 min. The mixture was stirred at the same temperature for 30 min, then diluted with saturated aqueous NH_4Cl (50 mL). MeOH was removed *in vacuo*, then the resulting mixture was extracted with Et_2O (3 × 40 mL). The organic layer was washed with aqueous NH_3 (5 mL x 2), brine (10 mL), dried over Na_2SO_4, filtered through a cotton plug, and concentrated *in vacuo*. Allylic alcohol **22** was used directly in the next step (2.30 g, 95% yield). *Data for allylic alcohol **22**:* R_f = 0.30 (40% EtOAc in hexanes); IR (film): ν_{max} = 3369, 3088, 3040, 2973, 2935, 1654, 1605, 1467, 1380, 1326, 1253, 1153, 1058, 1004, 952, 908, 857, 768 cm^{-1}; ^1H NMR (400 MHz, 1% CD_3OD in $CDCl_3$, 293 K): δ 6.36-6.20 (m, 2H), 5.72 (dd, *J* = 14.8, 6.4 Hz, 1H), 5.21 (dd, *J* = 16.4, 2.0 Hz, 1H), 4.93 (dd, *J* = 10.0, 2.0 Hz, 1H), 4.57-4.52 (m, 1H), 1.78 (dd, *J* = 14.8, 10.8, 1H), 1.58 (dd, *J* = 14.8, 2.4, 1H), 1.33 (s, 3H), 1.26 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 293 K): δ 136.5, 136.3, 130.5, 117.6, 71.6, 70.2, 47.8, 31.8, 27.7. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd. for $C_9H_{17}O_2$ 157.1223; Found 157.1229.

Enantioselective reduction of (E)-2-hydroxy-2-methylocta-5,7-dien-4-one (21)

(Method A): A clean and dry 10-mL round-bottomed flask was treated with $NaHCO_3$, H_3BO_3 and Ligand (**L***) (1:1:1) and stirred in 10:1 MeOH/water mixture (2 mL) at 23 °C. After 1 h, the mixture was concentrated *in vacuo* and water was removed by adding MeOH (4 mL × 3) and concentrating under reduced pressure to obtain a white solid, to which was added enone **21** (31 mg, 0.2 mmol) in 1 mL THF and stirred at 23 °C. After 1 h, the solution was cooled to -78 °C and $NaBH_4$ (2.3 mg, 0.06 mmol, 0.3 equiv) was added. The mixture was slowly warmed to 23 °C over 12 h and was quenched with saturated aqueous NH_4Cl (1.0 mL), and THF was removed *in vacuo*. The resulting mixture was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with brine, conc. NH_3 and dried over Na_2SO_4, filtered through a cotton plug, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (5→30% EtOAc in hexanes) on silica gel (10 mL) to afford (*S*)-**22** as a clear oil. A solution of (*S*)-**22** was prepared in 5% ^{i}PrOH in hexanes (1mg/mL). The enantiomeric ratio was determined by chiral HPLC with (S,S)-Whelk-O 1 column [eluent: 5:95 ^{i}PrOH/hexanes; 1.0 mL/min flow rate, detection: 231 nm; t_R 7.7min, t_R 8.2 min. The results are summarized in Table 1.

(Method B): A clean and dry 10-mL round-bottomed flask was treated with (*R*)-1,1'-binaphthol (**L5**) (0.04 mmol, 20 mol%) and stirred with $NaBH_4$ (0.5 equiv) in MeCN (2 mL) at 23 °C. After 1 h, the mixture was concentrated *in vacuo* to obtain a white solid, which was resuspended in dry THF (1 mL) and cooled to -78 °C. This mixture was treated with enone **21** (31 mg, 0.2 mmol) in THF (0.5 mL), and the resulting mixture was slowly warmed to 0 °C over 16 h. The mixture was quenched with saturated aqueous NH_4Cl (1.0 mL), and THF was removed *in*

vacuo. The resulting mixture was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with conc. NH_3 (2 mL) to remove any $B(OH)_3$, dried over Na_2SO_4, filtered through a cotton plug, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (5→30% EtOAc in hexanes) on silica gel (10 mL) to afford allylic alcohol (*S*)-**22** as a clear oil. A solution of (*S*)-**22** was prepared in 5% ^{i}PrOH in hexanes (1mg/mL). The enantiomeric ratio was determined by chiral HPLC with (S,S)-Whelk-O 1 column [eluent: 5:95 ^{i}PrOH/hexanes; 1.0 mL/min flow rate, detection: 231 nm; $\mathbf{t}_R$ 7.7min, $\mathbf{t}_R$ 8.2 min. The results are summarized in Table 1.

(Method C): A 500-mL round-bottomed flask was treated with (*R*)-1,1'-binaphthol (**L5**) (18.9 g, 66 mmol, 1.0 equiv) and dry THF (120 mL) and cooled to 0 °C. 1 M BH_3•THF in THF (66.0 mL, 1 equiv) was added to the resulting solution dropwise over 20 min, and the mixture was stirred for 1 h at the same temperature. Enone **21** (66 mmol) in THF (120 mL) was added dropwise over 45 min at 0 °C. After an additional 1 h, the mixture was cooled to -78 °C and treated with $NaBH_4$ (832 mg, 0.3 equiv) in 4 portions over 2 h and allowed to warm to 23 °C over 12 h. The reaction mixture was then quenched with sat. NH_4Cl (100 mL) at 0 °C and stirred for 30 min. The mixture was concentrated *in vacuo* to remove THF, followed by vacuum filtration to remove a precipitated white solid. The obtained white precipitate was recrystallized from hot hexanes to recover (*R*)-1,1'-binaphthol (**L5**) (12.1 g, 42 mmol, 63% recovery). The aqueous layer was extracted with Et_2O (2 × 100 mL). The combined organic layers were washed with conc. NH_3 (20 mL) to remove any $B(OH)_3$, dried over Na_2SO_4, filtered through a cotton plug, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (5→30% EtOAc in hexanes) on silica gel (400 mL) to afford alcohol (*S*)-**22** (7.30 g, 71%) as clear oil. A solution of the product was prepared in 5% ^{i}PrOH in hexanes (1mg/mL). The enantiomeric ratio was determined by chiral HPLC with (S,S)-Whelk-O 1 column [For compound (*S*)-**22**: eluent: 5:95 ^{i}PrOH/hexanes; 1.0 mL/min flow rate, detection: 231 nm; $\mathbf{t}_R$ 7.7min, $\mathbf{t}_R$ 8.2 min.

Data for allylic alcohol **(*S*)-22** $[\alpha]_D^{21}$ -3.5 (*c* 1.0, DCM).

(E)-5-hydroxy-5-methyl-1-phenylhex-1-en-3-one (31)

A 50-mL round-bottomed flask equipped with a Teflon-coated magnetic stir bar and a reflux condenser was treated with ylide **25** (376 mg, 1 mmol) and DCM (5 mL) at 23 °C, to which PhCHO (2 mmol) was added dropwise. The mixture was refluxed at 40 °C for 4 h, and then concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (10→50% EtOAc in hexanes) on silica gel (200 mL) to afford enone **31** as pale-yellow oil (151 mg, 74% yield). *Data for enone* **31**: R_f = 0.56 (40% EtOAc in hexanes); IR (film): ν_{max} = 3459 (br O-H), 3030, 2970, 1675 (C=O), 1501, 1200, 1130 cm^{-1}; ^{1}H NMR (400 MHz, 1% CD_3OD in $CDCl_3$, 293 K): δ 7.60 (d, *J* = 16.2 Hz, 1H), 7.57–7.55 (m, 2H), 7.42–7.40 (m, 3H), 6.76 (d, *J* = 16.2 Hz, 1H), 2.86 (s, 2H), 1.32 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 293 K): δ 201.7, 143.8, 134.3, 130.9, 129.2, 128.6, 127.0, 70.1, 51.0, 29.6. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd. for $C_{13}H_{17}O_2$ 205.1150; Found 205.1158.

(E)-2-methyl-6-phenylhex-5-ene-2,4-diol (36)

A 10-mL round-bottomed flask was treated with (*R*)-1,1'-binaphthol (**L5**) (28 mg, 01 mmol, 1.0 equiv) and dry THF (0.3 mL) and cooled to 0 °C. 1 M BH_3•THF in THF (0.1 mL, 1 equiv) was added to the resulting solution dropwise, and the mixture was stirred for 1 h at the same temperature. Enone **31** (0.1 mmol) in THF (0.2 mL) was added dropwise at 0 °C. After an additional 1 h, the mixture was cooled to -78 °C and treated with $NaBH_4$ (2 mg, 0.3 equiv) and allowed to warm to 23 °C over 12 h. The reaction mixture was then quenched with sat. NH_4Cl (1 mL) at 0 °C and stirred for 30 min. The mixture was concentrated *in vacuo* to remove THF, followed by vacuum filtration to remove a precipitated white solid. The aqueous layer was extracted with Et_2O (2 × 5 mL). The

combined organic layers were washed with conc. NH_3 (0.5 mL) to remove any $B(OH)_3$, dried over Na_2SO_4, filtered through a cotton plug, and concentrated *in vacuo*. The crude residue was purified by prep TLC (5→30% EtOAc in hexanes) to afford alcohol (*S*)-**36** (14.7 mg, 86 % *ee*, 67 %) as clear oil.. *Data for allylic alcohol* **36**: R_f = 0.40 (40% EtOAc in hexanes); IR (film): ν_{max} = 3369, 3088, 3030, 2973, 2935, 1654, 1503, 1464, 1390, 1329, 1244, 1153, 1058, 1004, 957 cm^{-1}; ^1H NMR (400 MHz, 1% CD_3OD in $CDCl_3$, 293 K): δ 7.38 (d, *J* = 7.2 Hz, 1H), 7.33 (app t, *J* = 7.2, Hz, 2H), 7.23 (d, *J* = 7.2 Hz, 2H), 6.63 (d, *J* = 16.0 Hz, 1H), 6.25 (dd, *J* = 16.0, 6.4 Hz, 1H), 4.72 (d, *J* = 8.0 Hz, 1H), 3.37 (br. s, 1H), 2.85 (br. s, 1H) 1.88 (dd, *J* = 14.4, 10.8 Hz, 1H), 1.68 (dd, *J* = 14.4, 2.4 Hz, 2H), 1.39 (s, 3H), 1.30 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 293 K): δ 136.8, 132.3, 129.9, 128.7, 127.8, 126.6, 71.8, 70.9, 48.2, 32.1, 27.9. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd. for $C_{13}H_{19}O_2$ 207.1307; Found 207.1301.

(S)-3-methyl-1-((2S,3S)-3-vinyloxiran-2-yl)butane-1,3-diol (23)

(Method A): A 250-mL round-bottomed flask equipped with a Teflon-coated magnetic stir bar containing enantioenriched **22** (2.30 g, 14.7 mmol) was purged with argon. DCM (60 mL) and 4Å molecular sieves (3.10 g) were added to the flask. The mixture was cooled to -20 °C (external temperature), then $Ti(O^iPr)_4$ (0.38 g, 1.34 mmol), (+)-diisopropyl tartrate (0.50 g, 2.10 mmol) and ^{t}BuOOH solution in isooctane (1.4 mL, 8.0 mmol) were added sequentially at the same temperature. The mixture was stirred at the same temperature for 13 h, then diluted with 1 M NaOH (50 mL), Celite ® (3.0 g), Na_2SO_4 (3.0 g), NaCl (3.0 g). The mixture was stirred for 40 min, then filtered through a pad of Celite® and Florisil mixture. The filtrate was concentrated *in vacuo*, and the resulting crude residue was purified by flash chromatography (10→70% EtOAc in hexanes with 1% NEt_3) on silica gel (200 mL) to afford unreacted allylic alcohol **22** and epoxy alcohol **23** as clear oils (1.38 g, ca. 55%) with impurities of titanium and tartrate. The recovered **22** was resubjected to the same conditions to afford **23** (1.80g, ca. 71% after 2 cycles) as a clear oil with minor impurities. The impure epoxy alcohol **23** was used in the next step without further purification. The *% ee* was not determined at this stage due to the presence of impurities. *Data for epoxy alcohol **23**:* R_f = 0.35 (60% EtOAc in hexanes); The compound was not characterized due to impurities.

(Method B): A 25-mL round-bottomed flask equipped with a Teflon-coated magnetic stir bar containing enantioenriched **22** (43 mg, 0.28 mmol) was dissolved in DCM (2 mL) and was cooled to 0 °C (external temperature). To the stirred solution was added $NaHCO_3$ (46 mg, 0.55 mmol) and mCPBA (52 mg, 0.30 mmol) sequentially and stirred at the same temperature for 1 h, then stirred at 23 °C for 1 h. The reaction was then quenched with saturated $Na_2S_2O_3$ solution and extracted with DCM (10 mL × 3) and the combined organic layers were dried over Na_2SO_4, filtered through a cotton plug, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (5→50% EtOAc in hexanes) on silica gel (15 mL) to afford epoxy alcohol **23** as a clear oil (27 mg, 57% yield).*Data for epoxy alcohol* **23**: $[\alpha]_D^{21}$ -2.8 (*c* 0.9, DCM).

(5R,6R)-5-hydroxy-2,2-dimethyl-6-vinyltetrahydro-4H-pyran-4-one (28)

A 250-mL round-bottomed flask equipped with a Teflon-coated magnetic stir bar containing **23** (911 mg) was treated with DCM (200 mL), 4Å molecular sieves (3.30 g), TPAP (101 mg, 0.29 mmol), and NMO (2.50 g, 18.4 mmol) at 23 °C. The mixture was stirred at the same temperature for 40 min, then filtered through a plug of silica. The filtrate was concentrated to approximately 200 mL of DCM remaining in the flask. To the flask was added CSA (860 mg, 3.70 mmol) at 23 °C. The mixture was stirred at the same temperature for 19 h, then Et_3N (1 mL) was added. The mixture was concentrated *in vacuo*, and the crude residue was purified by flash chromatography (10→30% EtOAc in hexanes) on silica gel (50 mL) to afford ketone **28** as a clear oil (650 mg, 92% *ee*, 70% yield, over 2 steps). *Data for ketone **28**:* R_f = 0.35 (30% EtOAc in hexanes); $[\alpha]_D^{20}$ +28.1 (*c* 1.0, DCM); IR (film): ν_{max} = 3474 (br, O-H), 2975, 2934, 1723 (C=O), 1374, 1240, 1107, 1080 cm^{-1}; ^1H NMR (400 MHz, 1% CD_3OD in $CDCl_3$, 293 K): δ 6.04 (ddd, *J* = 16.8, 10.4, 5.2 Hz, 1H), 5.47 (app. d, *J* = 16.8 Hz, 1H), 5.33 (app. d, *J* = 10.4

Hz, 1H), 3.95-5.20 (m, 2H), 2.66 (d, *J* = 13.2 Hz, 1H), 2.50 (d, *J* = 13.2 Hz, 1H), 1.43 (s, 3H), 1.20 (s, 3H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$, 293 K): δ 207.4, 135.5, 118.0, 77.9, 76.7, 76.4, 51.5, 30.8, 23.6; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd. for $C_9H_{15}O_3$ 171.1021; Found 171.1006.

(3R,4R,5R)-7,7-dimethyl-5-vinyl-1,6-dioxaspiro[2.5]octan-4-ol (29)

A 25-mL round-bottomed flask equipped with a Teflon-coated magnetic stir bar containing ketone **28** (200 mg, 1.18 mmol) was purged with N_2. To the flask was added THF (12.0 mL) and CH_2Br_2 (246 mg, 1.42 mmol). The flask was cooled to -78 °C, then ^{n}BuLi (1.60 mL, 2.60 mmol) was added. The mixture was stirred for 7 h, while warming the cooling bath to 20 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl (15.0 mL), and THF was removed *in vacuo*. The resulting mixture was extracted with Et_2O (3 × 15 mL). The combined organic layers were dried over Na_2SO_4, filtered through a cotton plug, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (5→30% EtOAc in hexanes) on silica gel (40 mL) to afford epoxide **29** as a white solid (157 mg, 73% yield). *Data for epoxide* **29** $[\alpha]_D^{20}$ +68.3 (*c* 1.2, DCM). Spectroscopic data for epoxide **29** matches that in the previous literature.[9]

Supporting Information

A scheme of the previous synthetic route, copies of HPLC chromatograms, ^{1}H, ^{11}B, and ^{13}C NMR spectra.

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Notes

The authors declare no competing financial interest.

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