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Total Synthesis of (−)-Virginiamycin M_2: Application of Crotylsilanes Accessed by Enantioselective Rh(II) or Cu(I) Promoted Carbenoid Si−H Insertion

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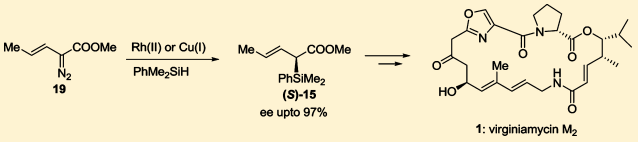
Supporting Information

ABSTRACT: A stereoselective synthesis of the antibiotic (−)-virginiamycin M_2 is detailed. A convergent strategy was utilized that proceeded in 10 steps (longest linear sequence) from enantioenriched silane (*S*)-**15**. This reagent, which was prepared via a Rh(II)- or Cu(I)-catalyzed carbenoid Si−H insertion, was used to introduce the desired olefin geometry and stereocenters of the C1−C5 propionate subunit. A modified Negishi cross-coupling or an efficient alkoxide-directed titanium-mediated alkyne−alkyne reductive coupling strategy was utilized to assemble the trisubstituted (*E*,*E*)-diene. An underutilized late-stage SmI_2-mediated macrocyclization was employed to construct the 23-membered macrocycle scaffold of the natural product.



INTRODUCTION

The virginiamycins belong to a class of antibiotics naturally produced by *Streptomyces* and consist of two principle groups of compounds. Group A virginiamycins are 23-membered macrolides containing an oxazole subunit, such as virginiamycin M_2 (**1**), virginiamycin M_1 (**2**), madumycin II (**3**), and griseoviridin (**4**); group B virginiamycins are cyclic hexadepsipeptides, such as virginiamycin S_4 (**5**) and etamycin (**6**) (Figure 1). They have been used as dietary supplements to accelerate the growth of animals and to prevent and treat bacterial infections. The virginiamycins were found to likely bind synergistically to specific sites on the 23*S* rRNA of the 50*S* ribosome, thus inducing a ribosomal conformational change, interfering with its peptidyl transferase activity.[1] Recently, natural and synthetic derivatives of virginiamycins have exhibited potent antibiotic activity against methicillin-, erythromycin-, and vancomycin-resistant *S. aureus*.[2] These important bioactivities led to an active research area in both academia and industry directed at their further development.[3,4] Efforts toward the semisynthesis of the virginiamycins culminated with the development of Synercid, a mixture of two antibiotics dalfopristin **7** (group A) and quinupristin **8** (group B). This combination of agents was approved in the United States for the treatment of Gram-positive bacterial infections in 1999 (Figure 2).[5]

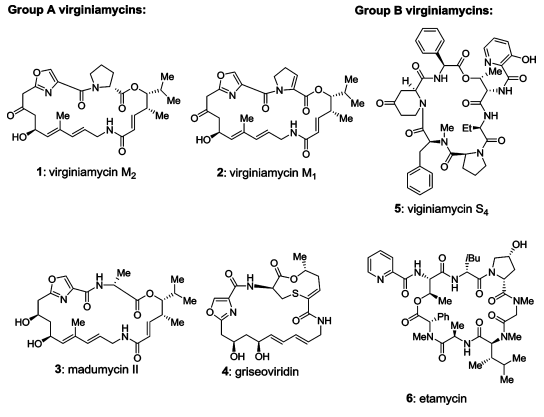


Figure 1. Structures associated with the virginiamycin class of natural products.

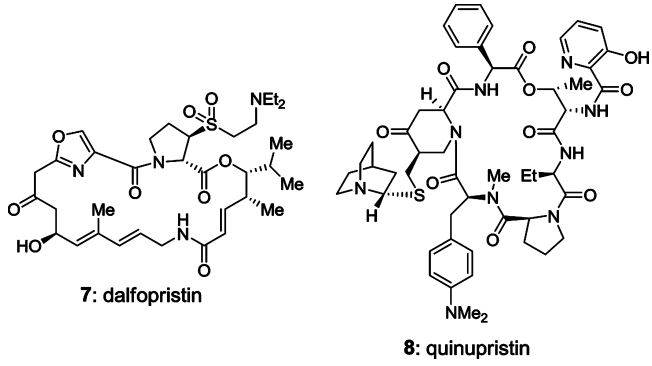


Figure 2. Composition of synercid (dalfopristin/quinupristin = 7:3 w/w).

However, semisynthesis of group A compounds has been limited because of their sensitive functionalities and pH instability.[3] This fact, in addition to its structural complexity,

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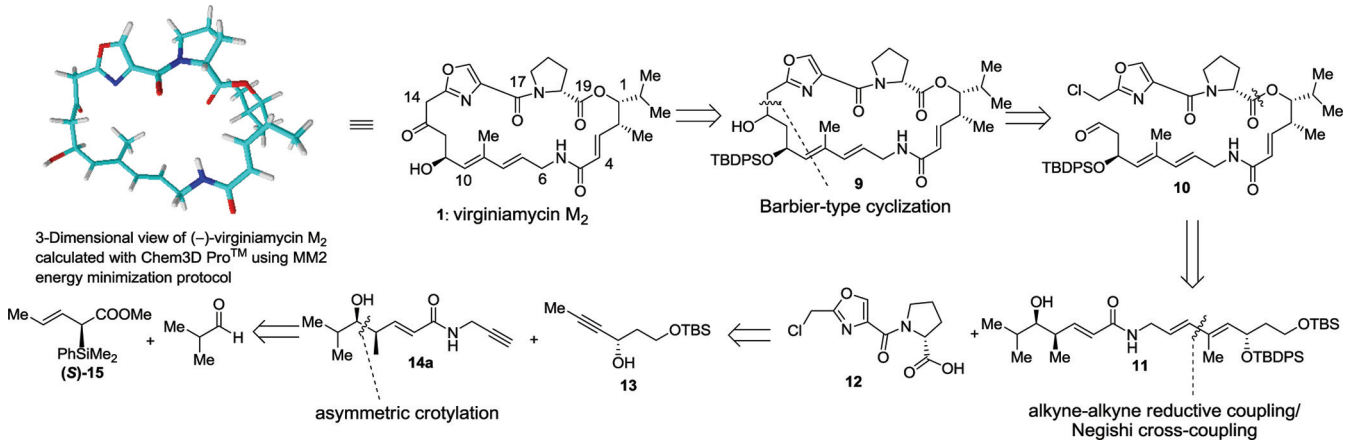
Scheme 1. Retrosynthetic Analysis of Virginiamycin M_2



has spurred many efforts toward their total synthesis including the first total synthesis of a group A natural product virginiamycin M_2 from the Schlessinger group.[4a]

(−)-Virginiamycin M_2 is a typical member of group A class of natural products. Its unique macrolide structure exhibits an unusual array of structural features, including a 23-membered lactone accommodating an 2,4-disubstituted oxazole, an (*E*,*E*)-trisubstituted diene, an α,β-unsaturated lactam, an amino acid residue, a β-hydroxyl ketone subunit, and four stereogenic centers. This material was originally isolated by Todd and co-workers in 1966,[6] and its structure was confirmed by X-ray analysis in 1974.[7] However, because of the pH sensitivity of the β-hydroxyl ketone moiety, the total synthesis of group A compounds had not been achieved until nearly 30 years after their discovery. The important biological properties of virginiamycins and the challenging structure of the group A compounds, together with designing a convergent synthesis enabling structure–activity relationships (SAR) studies, inspired us to develop and excute an efficient synthesis of (−)-virginiamycin M_2. Herein, we provide a detailed account of our efforts that culminated in an enantioselective synthesis of (−)-virginiamycin M_2.[8]

RETROSYNTHETIC ANALYSIS OF (−)-VIRGINIAMYCIN M_2

Our synthetic plans developed for (−)-virginiamycin M_2 were guided by the structural features of the natural product as well as our intention to explore and extend the utility of chiral silane-based bond construction methodology[9] (Scheme 1). As a result of the potential instability of the β-hydroxyl ketone function, we planned to install it at the final stage of the synthesis. As such, virginiamycin M_2 (**1**) may be derived through oxidation and deprotection of the silyl ether **9**. We were encouraged to evaluate the efficiency of a SmI_2-mediated intramolecular Barbier/Reformatsky-type cyclization to construct the 23-membered macrocycle, a strategy that proved to be effective for macrocyclization in our total synthesis of kendomycin.[10] The acyclic framework **10** could be obtained by esterification of the homoallylic alcohol **11** and the *N*-acyloxazolylproline intermediate **12**. To access fragment **11**, metal-mediated cross-coupling strategies were considered to assemble the conjugated (*E*,*E*)-diene, including a modified Negishi cross-coupling[11] and the titanium-mediated reductive alkyne–alkyne cross-coupling[12] between the propargylic alcohol **13** and terminal alkyne **14**. This idea, if successful, would allow for a high degree of flexibility in our synthetic plan and thus access to analogues. Accordingly, the convergent design divided virginiamycin M_2 into three fragments of comparable complexity. The terminal alkyne **14** would be assembled with the aid of our crotylation methodology utilizing the organosilane (*S*)-**15**.[8a] This silane reagent has unique features as it establishes the C1–C2 *syn* configuration while simultaneously creating the C3–C4 (*E*)-unsaturated ester subunit, thereby functioning as a formal vinylogous aldol reagent. The reagent itself will be easily prepared through Rh(II)- or Cu(I)-catalyzed carbenoid Si–H insertion with an α-diazoester **19**.

RESULTS AND DISCUSSION

Preparation of Chiral Silane 15. In a previous investigation concerning the preparation of the homoallylic ether linked to an α,β-unsaturated functional group in the total synthesis of (+)-macbecin I, we took a three-step approach (crotylation/oxidative cleavage/Horner–Wadsworth–Emmons reaction) focusing on the use of crotylsilane reagents of type **16**.[13] In that context, we sought to gain direct access to the homoaldol products **18** utilizing chiral silane reagents of type **15**, as part of our program focused on development of new chiral silane reagents bearing *C*-centered chirality capable of delivering useful levels of asymmetric induction, thereby complementing our previous work in this area (Scheme 2).

This program was initiated by establishing a reproducible asymmetric Si–H metal carbenoid insertion into vinyl diazoesters in order to prepare the chiral silane of type-**15**. A convenient, straightforward pathway to prepare enantioenriched allylsilanes bearing an ester functional group at the chiral center was reported by Davies' group using chiral $Rh_2(DOSP)_4$ catalysts,[14] wherein they reported a problem of instability when attempting to purify **15**. In our hands, however, we did observe that pure silane **15** could be obtained by flash chromatography and stored neat at 4 °C for several months without noticeable decomposition. The use of excess dimethylphenylsilanes was crucial to the success of the carbenoid insertion process with high ee (Table 1, entries 1 and 2). Further experimentation revealed that increasing catalyst loading afforded silane reagents with higher ee up to 97% (entries 3 and 4).

Despite the success with Rh(II) catalysis, a Cu(I)-promoted reaction was evaluated as an economical alternative. Although the idea of Cu(I) catalysis had been used to promote Si–H insertions prior to the application of rhodium catalysis, this area

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Scheme 2. Complementary Crotyl Silane Reagents

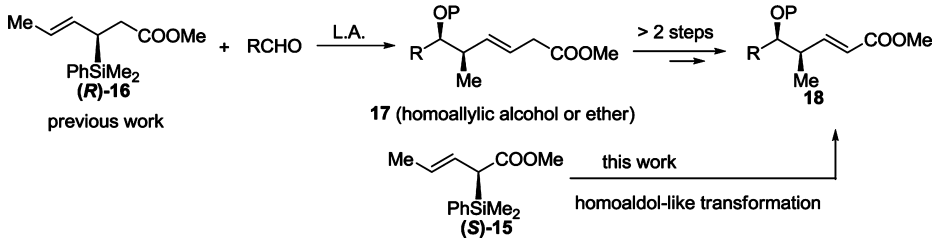
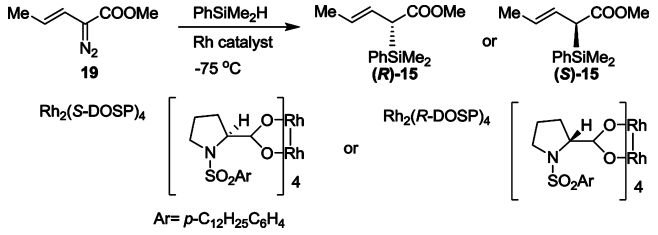
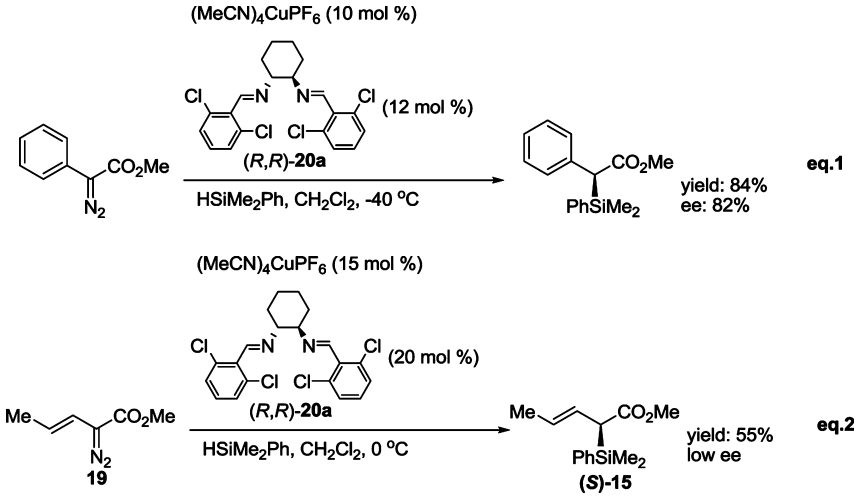


Table 1. Optimization of Rh(II)-Catalyzed Carbenoid Si−H Insertion



entry	catalyst loading (mol %)	equiv of silane	yield[a] (%)	ee[b] (%)
1	1	1.5	65	48
2	1	5	70	88
3	2	5	68	93
4	3	5	72	95−97

[a]Isolated yields were calculated after purification over silica gel. [b]Based on chiral HPLC analysis (ChiralCel OD 1% IPA) of the primary alcohol, which was obtained from an LAH reduction of ester **15**.



of research remained underdeveloped, and few cases of asymmetric variants have been reported.[15] The C_2-symmetric Cu(I) bis-imine complexes, introduced by Jacobsen's group, were affordable and operationally simple to prepare, which allowed for multigram syntheses of ligands that can be custom tailored with respect to their electronic and steric properties.[16] In that context, we previously reported useful levels of selectivity in a Cu(I)-promoted insertion with α-diazophenyl acetates utilizing C_2-symmetric Cu(I) bis-imine complexes (eq 1)[17] and anticipated that we could extend the Cu(I) catalysis to α-diazovinyl acetates (eq 2).

Our evaluation of Cu(I) C_2-symmetric Schiff base complexes did, in fact, demonstrate that these complexes were viable options for promoting carbenoid insertion into Si−H bonds capable of generating crotyl silane **15**. In our initial experiments, we observed that treatment of vinyl diazoester **19** with the chiral Cu(I) complex $(MeCN)_4CuPF_6$·(*R*,*R*)-**20a** in the presence of dimethylphenylsilane at 0 °C, which exhibited good selectivity with α-diazophenyl acetates (eq 1), afforded the chiral allylic silane **15** in moderate yield (55%) but with a negligible level of enantioselectivity (12% ee, eq 2). Efforts to optimize the reaction focused on a solvent,[18] copper source,[19] catalyst loading,[20] and temperature[20] screen with the bis-imine ligand (*R*,*R*)-**20a**. Indeed, a significant dependence of selectivity on solvent, copper catalysts, catalyst loading, and temperature was observed. We observed that 5 mol % of $(CH_3CN)_4CuBF_4$·(*R*,*R*)-**20a** with benzene as the solvent afforded the insertion product (***R***)-**15** with highest selectivity up to 72% ee.[16] Reactions conducted at 0 °C exhibited higher selectivity than those carried out at room temperature, and below that temperature, the reaction rate became extremely slow (taking up to 24 h to reach 20% completion at −20 °C).

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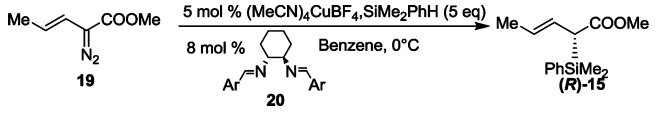
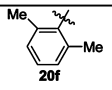
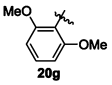
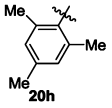
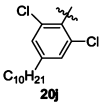
Table 2. 2,6-Disubstituted Ligands in Cu(I)-catalyzed Carbenoid Si−H Insertion



entry	Ar	yield[a] (%)	ee[b] (%)	entry	Ar	yield[a] (%)	ee[b] (%)
1	 **20a**	48	72	6	 **20f**	38	55
2	 **20b**	45	29	7	 **20g**	NR	NA
3	 **20c**	47	46	8	 **20h**	41	46
4	 **20d**	48	70	9	 **20i**	46	68
5	 **20e**	45	64	10	 **20j**	52	78

[a]Isolated yields were calculated after purification over silica gel. [b]Based on chiral HPLC analysis (ChiralCel OD 1% IPA) of the primary alcohol, which was obtained from an LAH reduction of ester **15**.

The carbenoid insertion was also investigated in the absence of bis-imine ligands, which exhibited no obvious ligand acceleration effect since the reaction was completed within 4 h when catalyzed by $(CH_3CN)_4CuBF_4$ without the presence of the bis-imine ligand. Increasing the Cu(I) Schiff base catalyst loading resulted in diminished enantioselectivity (5 mol % catalyst, 72% ee; 15 mol % catalyst, 60% ee; 50 mol % catalyst, 49% ee). Since we observed that the Cu(I) Schiff base complex was not sufficiently soluble in benzene solvent, higher catalyst loading may enhance the background reaction rate, presumably due to the existence of free $(CH_3CN)_4CuBF_4$, which promoted the insertion to afford racemic products, thus resulting in the formation of silane **15** with decreased optical purity.

In efforts to enhance the level of asymmetric induction, a series of aryl-substituted bis-imine ligands were synthesized by condensation of (*R*,*R*)-diaminocyclohexane and selected aromatic aldehydes.[21] The derived ligands were evaluated in the insertion to examine variations of steric and/or electronic properties of the bis-imine complexes. The 2,6-substituents on the aryl ligands were crucial for the Si−H insertion, and reactions became sluggish and almost no selectivity without 2,6-substituents. In a similar manner as the asymmetric aziridination, the 2,6-substituents appeared to minimize the formation of catalytically inactive bimetallic type catalyst (Cu_2L_2), favoring the formation of the active monometallic intermediates (CuL) that went on to afford silane product (***R***)-**15**.[22] A range of 2,6-substituted aryl bis-imine ligands ((*R*,*R*)-**20a** to (*R*,*R*)-**20j**) were screened, and the results are summarized in Table 2. Not surprisingly, variation of the steric or electronic properties of ligands (entries 1 to 8) had a marked effect on the enantioselection of the insertion process. However, none of the ligands that were evaluated showed a significant improvement over the 2,6-dichlorobenzaldehyde derived complex Cu(I)·(*R*,*R*)-**20a**. Altering the electronic property of (*R*,*R*)-**20a** by adding an electronegative chloride atom at the *para* position (entry 9) resulted in slightly eroded selectivity. In an effort to enhance the solubility of the Cu(I) bis-imine complex, a long aliphatic substituent was placed at the *para*-position to achieve ligand (*R*,*R*)-**20j**, which was beneficial to the selectivity (78% ee) while the reactivity was maintained (entry 10). These studies allowed a comparison of chiral Cu(I) vs Rh(II) catalysis, with the $Rh_2(DOSP)_4$ providing slightly higher levels of selectivity for the cases examined in this study.

Initial Stages of the Virginiamycin M_2 Synthesis: Preparation of the C1−C13 Fragment. The synthesis was initiated by carrying out the preparation of the C1−C8 fragment **14a** featuring an asymmetric crotylation strategy.[8a] Construction of the terminal alkyne **18** began with the asymmetric crotylation between (***S***)-**15** and isobutyraldehyde (Table 3). After reaction optimization, the three-component crotylation promoted by TMSOTf with TMSOBn as the additive (entry 2) proceeded smoothly to afford vinylogous product **18b** in good yield, moderate *syn*/*anti* ratios, and excellent enantioselectivity. However, when TMSOAc was used as the additive, only decomposition of starting materials was observed. In contrast to the three-component process, the two-component crotylation catalyzed by $TiCl_4$ resulted in the vinylogous aldol product **18a** in good yield and excellent diastereo- and enantioselectivity (entry 1). To our surprise, a small amount of α-addition product **18c** could be isolated in 15% yield as a single diastereomer. Importantly, products obtained from this pathway were not observed in the three-component crotylation process, and exclusive α-addition product **18c** was isolated in good yield by simply switching

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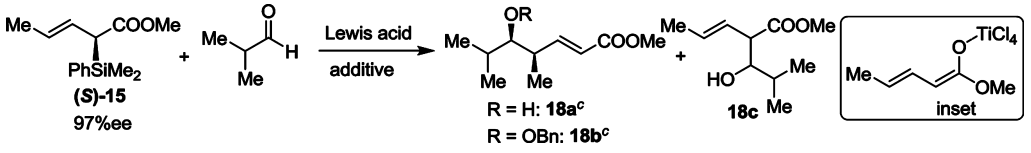
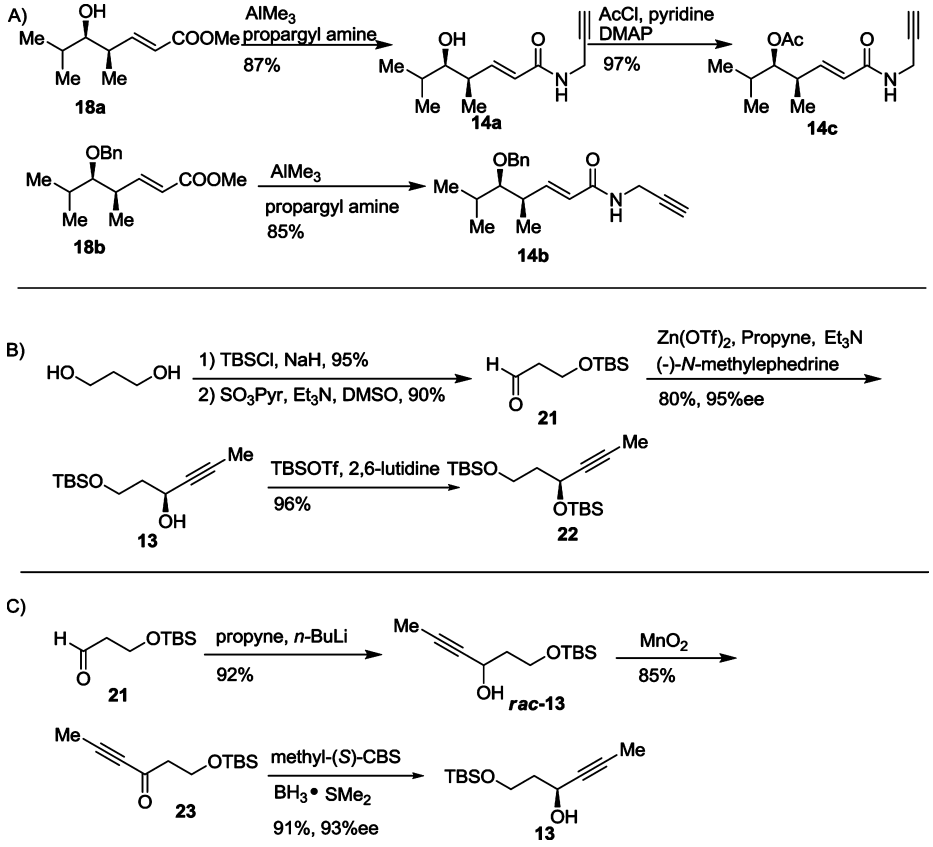
Table 3. Crotylation Using Silane (*S*)-15



entry	Lewis acid	additive	solvent	product	dr[a]	yield[b] (%)
1	$TiCl_4$ (1 equiv)	none	CH_2Cl_2	**18a**	>20:1	63
2	TMSOTf (1 equiv)	TMSOBn (2 equiv)	CH_2Cl_2	**18b**	6.3:1	68
3	$TiCl_4$ (1 equiv)	None	MeCN	**18c**	>20:1	80

[a]Diastereomeric ratio was based on crude ^{1}H NMR analysis of the reaction mixture. [b]Isolated yield. [c]Both products **18a** and **18b** were achieved with 95% ee based on chiral HPLC analysis.

Scheme 3. Preparation of Alkyne Subunits



to the more polar solvent from CH_2Cl_2 to MeCN (entry 3). In that regard, we proposed that the byproduct **18c** was presumably generated through a titanium mediated addition of the dienolate intermediate (inset). Esters **18a** and **18b** were subjected to Weinreb's amidation conditions[23] with propargylamine in the presence of $AlMe_3$ to afford terminal alkyne amides **14a** and **14b** in good yields (Scheme 3A). Notably, a free hydroxyl group in homoaldol product **18a** was compatible in this amidation to achieve product **14a**, which could be acetylated to provide **14c** in excellent yield.

Preparation of the C9−C13 fragment commenced with the monosilylation of 1,3-propandiol, followed by a Parikh−Doering oxidation[24] to afford aldehyde **21** (Scheme 3B). Propargylic ether **13** was accessed via Carreira's protocol[25] in a good yield, with excellent enantioselectivity, which was subsequently protected as its silyl ether **22** using TBSOTf/lutidine. The asymmetric addition proceeded efficiently and without evidence of self-aldol condensation of the starting aldehyde. Meanwhile, in order to develop an operationally simpler method that did not require the use of gaseous propyne at ambient temperature, an alternative pathway was evaluated by employing an enantioselective ketone reduction using Corey's CBS reagent[26] to prepare propargylic alcohol **13** (Scheme 3C). The racemic secondary alcohol ***rac*-13** was introduced by adding aldehyde **21** to the propyne lithium reagent at −78 °C, followed by MnO_2 oxidation to achieve ynone **23**. Asymmetric hydride reduction of **23** using 2-methyl-(*S*)-CBS-oxazaborolidine afforded propargylic alcohol **13** in excellent yield and enantioselectivity (ee = 93%).

Our next challenge was encountered with the assembly to the conjugated diene **11**. While there were several options available for the construction of branched conjugated dienes, a modified Negishi cross-coupling established in our laboratory some time

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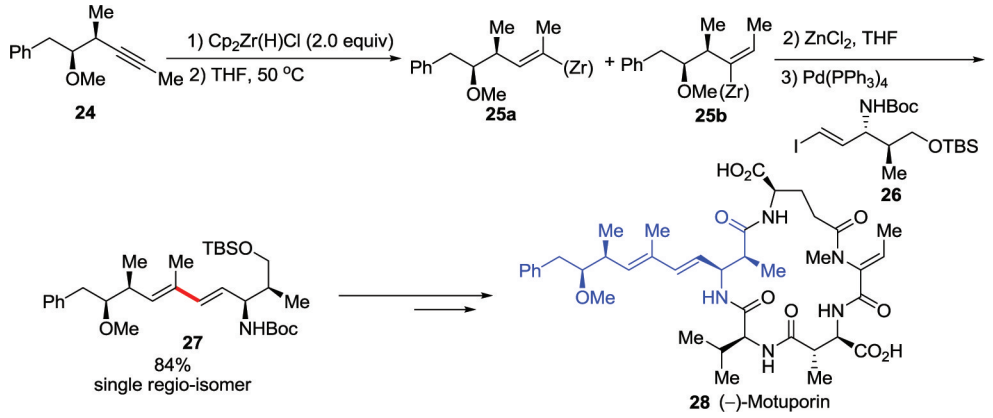
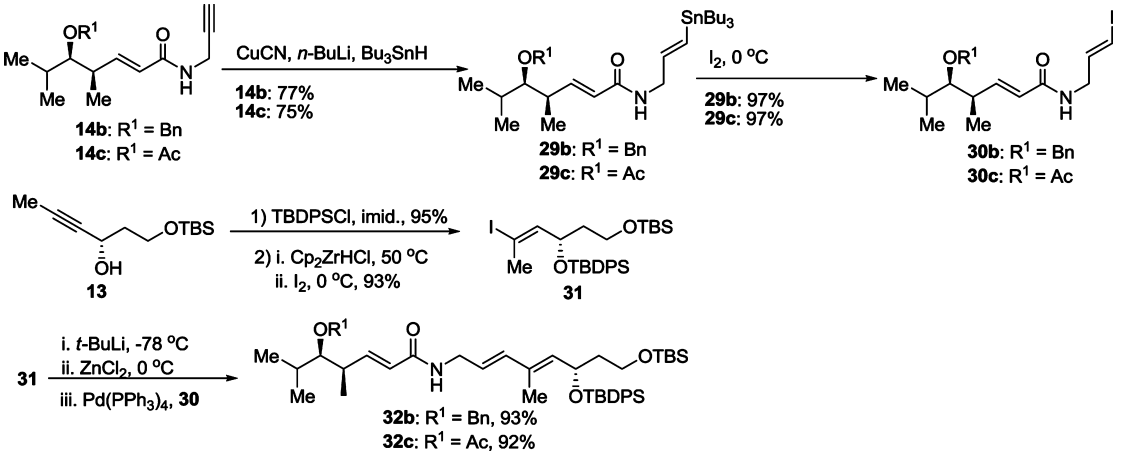
Scheme 4. Previous Synthesis of (−)-Motuporin Using Regioselective Negishi Cross-Coupling



Scheme 5. Assembly of (*E*,*E*)-Diene through Regioselective Negishi Cross-Coupling

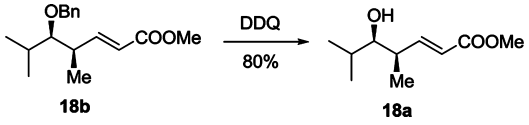


ago to assemble the Adda fragment of (−)-motuporin **28** was selected initially (Scheme 4).[11b,27]

To prepare the *N*-Boc Adda precursor **27**, a modified one-pot Negishi cross-coupling reaction was conducted to afford the product in good yield as a single regioisomer, while other methods such as the hydroboration of internal alkyne **24** with conventional hydroborating reagents (9-BBN, catecholborane) resulted in poor regioselectivity. The use of excess Schwartz's reagent and an elevated temperature were required to achieve the thermodynamic adduct **25a** with good regioselectivity, most likely due to the reversible addition of a second equivalent of Schwartz's reagent to the initially formed alkenyl zirconocene **25b**.[11a,b]

In regard to our synthetic objective, initial experiments were focused on the use of terminal alkyne **14b** (R^1 = Bn), which was converted to vinyl iodide **30b** in a two-step sequence: (i) stannylcupration afforded exclusively the (*E*)-terminal alkenyl stannane **29b**;[4f] (ii) iodination to obtain vinyl iodide **30b** (Scheme 5). In order to gain access to vinyl iodide **31**, the propargylic alcohol **13** was protected as its TBDPS ether. Hydrozirconation of the resulting unsymmetrical acetylene using Schwartz's reagent (Cp_2ZrHCl, 2 equiv, 50 °C), followed by trapping the vinyl zirconium intermediate with iodine, led to the (*E*)-vinyl iodide **31** as a single olefin-isomer, consistent with results of our earlier studies on the *N*-Boc Adda product.[27] With sufficient quantities of vinyl iodides **30b** and **31** now available, the execution of the Negishi cross-coupling followed a protocol of: Li−I exchange, Zn−Li transmetalation, and a Pd(0)-catalyzed coupling afforded the (*E*,*E*)-diene **32b** in high yield. The one-pot Negishi cross-coupling, which would directly convert an internal alkyne to coupled product without generating the intermediate iodide **31**, was also examined in this case. The coupling was initiated with the regioselective hydrozirconation of the silyl ether internal alkyne derivative of **13** with Cp_2ZrHCl (2 equiv, 50 °C) in THF to afford the (*E*)-vinyl zirconate as a single stereoisomer, which was directly transmetalated with anhydrous $ZnCl_2$ to afford the alkenyl zinc intermediate, followed by Pd-catalyzed coupling with vinyl iodide **30b**. However, the yield of product **32b** was disappointingly low (approximately 20%) and was most likely due to the incompatibility of the amide group in the presence of the hydridic reagent.[28]

Using a model substrate **18b**, deprotection of the benzyl group utilizing DDQ cleanly afforded product **18a** (eq 3);



eq. 3

however, we were unable to achieve the cleavage of benzyl group of compound **32b** to cleanly and reproducibly afford secondary alcohol **11** (eq 4).[29]

Since we encountered an unexpected difficulty in the successful removal of the benzyl protecting group in diene **32b** required a change in protecting group strategy, acetate **14c**

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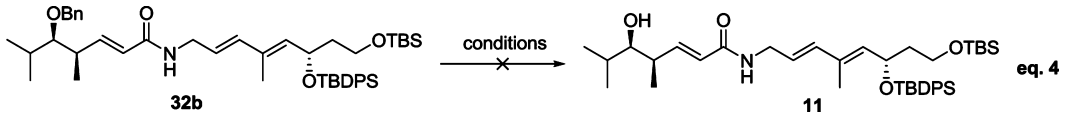
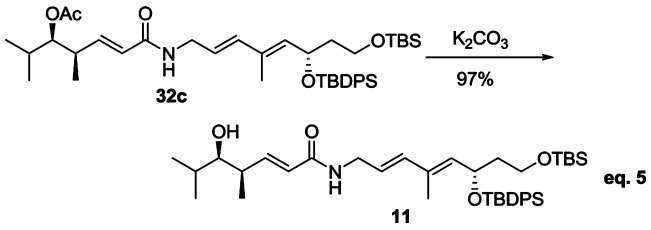


was then applied in a Negishi cross-coupling sequence. After generation of the vinyl iodide **30c** through the same process, a Negishi cross-coupling afforded product **32c** in high yield, which could be cleanly converted to C1−C13 fragment **11** using K_2CO_3 in methanol (eq 5).



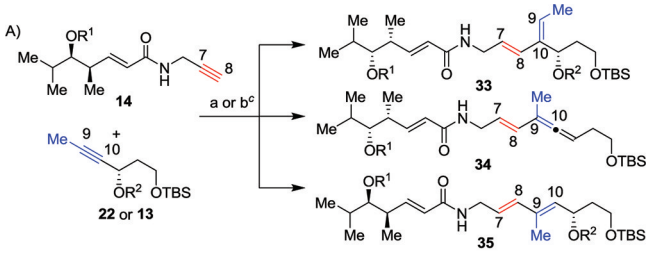
Alternatively, we investigated an alkyne−alkene reductive coupling to assemble C1−C8 and C9−C13 fragments, which enabled a direct comparison with the Negishi cross-coupling strategy (Scheme 6). The titanium alkoxide based coupling reactions of differentially functionalized alkynes were initially introduced by the Sato group[30] and have recently been cleverly extended by Micalizio and co-workers.[12] Although a similar approach utilizing a homopropargylic ether has been reported by Micalizio in the synthesis of callystatin A,[12b] in the present case, the coupling of propargylic silyl ether **22** with terminal alkyne did not afford the desired (*E*,*E*)-diene **35** (Scheme 6A, entries 1 and 2), and only the regioisomer **33** and conjugated allene **34** were isolated and characterized. Since functionalization of the terminal alkyne substrate generally occurred at the terminal carbon of the alkyne,[31] we envisioned that the in situ generated internal alkyne−titanium complex **int-1**[32] may undergo carbometalation with the terminal alkyne presumably through **int-2** and **int-3** to afford **33** and **34**, respectively (Scheme 6B). Notably, instead of forming the (*E*,*E*)-trisubstituted diene after hydrolysis, the corresponding allenic product **34** was isolated and was most likely generated through *β*-elimination of **int-3** as shown in Scheme 6B.[33]

Prior to the start of our coupling experiments, Micalizio had reported an alkoxide-directed reductive cross-coupling.[34] However, at this point, the alkoxide-directed alkyne−alkyne reductive coupling strategy had been underdeveloped in the context of complex natural product synthesis.[35] Further, in order to overcome the influence of the propargylic ether, we planned to evaluate the ability of the free secondary hydroxyl group of propargylic alcohol **13** to direct the reaction. The experiments were initiated by generating the lithium alkoxide using *n*-BuLi, which would then undergo ligand exchange with the titanium reagent[36] to produce lithium isopropoxide, leading to the presumed metallacyclopropene intermediate **int-4** (Scheme 6B).[37] If the structure of the tethered alkoxide **int-4** was to be retained during the C−C bond formation, it would preferentially afford the metallacyclopentadiene intermediate **int-6**, and not **int-5**, since this assembly would encounter significant steric destabilization when forming the bridgehead alkene.[37] Though the coordination of alkoxide with titanium was expected to exhibit considerable ring strain in the bicyclic metallacyclopropene intermediate **int-4**,[37a] diene **35c** was thus obtained in good yield and excellent regioselectivity (Scheme 6A, entry 3) and without detection of byproduct **33c** or **34c**. The free hydroxyl group on the alkyne **14a** was compatible for the reductive coupling as well, since the reaction with alkyne **14a** proceeded in a regioselective manner to afford the desired diol product **35d** (entry 4), which was accompanied by small amounts of allene byproduct **34d**.

In order to validate the assumption that the reaction was indeed alkoxide-directed, we conducted control experiments between internal alkyne **36** and octyne **37** in the absence of an amide group. As shown in Scheme 7, both reactions (**14c** and **36**, *rac*-**13** and **37**) afforded the desired products **35** in good yield and with small amounts of allene byproduct **34** detected spectroscopically. Since allene **34** could be easily separated from the desired product **35**, these control experiments supported a general means of generating (*E*,*E*)-trisubstituted dienes through the alkoxide-directed reductive coupling with propargylic alcohol bearing internal alkyne as substrates.

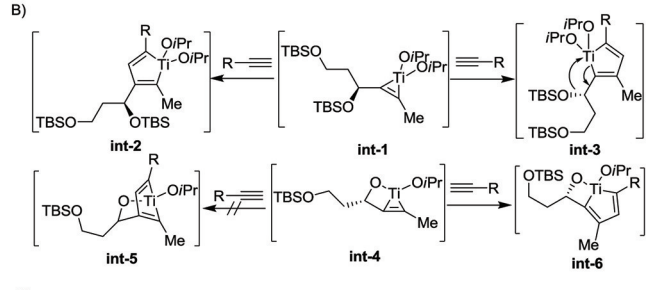
Since the alkoxide-directed alkyne−alkyne reductive coupling product **35d** could be protected to afford diene **11** by making use of the difference in the steric environment of the two secondary hydroxyl groups (Scheme 6C), the reductive

Scheme 6. Alkyne−Alkyne Reductive Coupling with Propargylic Ethers and Alcohols



entry	terminal alkyne **14**	internal alkyne	condition	product (yields)[a] **33**	**34**	**35**
1	**14b**: R^1= Bn	**22**	a	**33a** (45%)	**34a** (19%)	**35a** (0%)
2	**14c**: R^1= Ac	**22**	a	**33b** (49%)	**34b** (39%)	**35b** (0%)
3	**14c**: R^1= Ac	**13**	b	**33c** (0%)	**34c** (0%)	**35c** (71%)
4	**14a**: R^1= H	**13**	b	**33d** (0%)	**34d** (16%)[b]	**35d** (58%)[b]

[a] yields based on pure materials isolated by chromatography over silica gel.
[b] yields based on recovery of starting materials.
[c] condition a: $Ti(O\textit{i}\text{-}Pr)_3Cl$, *c*-$C_5H_9MgCl$, toluene, -78 °C to -30 °C.
condition b: *n*-BuLi, $Ti(O\textit{i}\text{-}Pr)_3Cl$, *c*-$C_5H_9MgCl$, ether, -78 °C to -30 °C.



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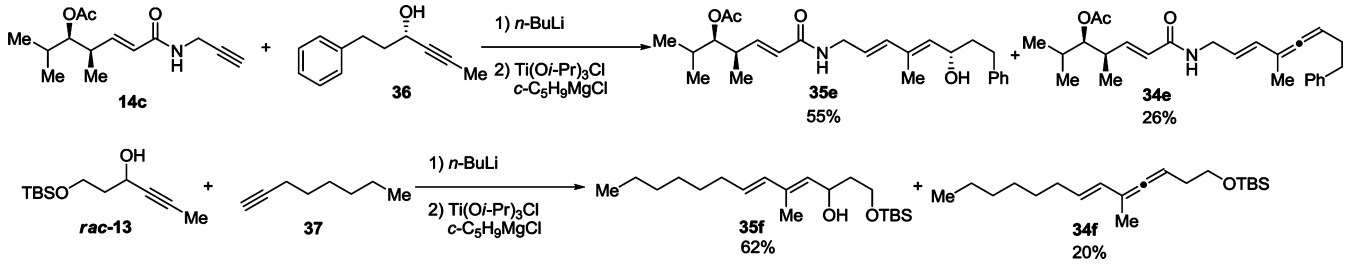
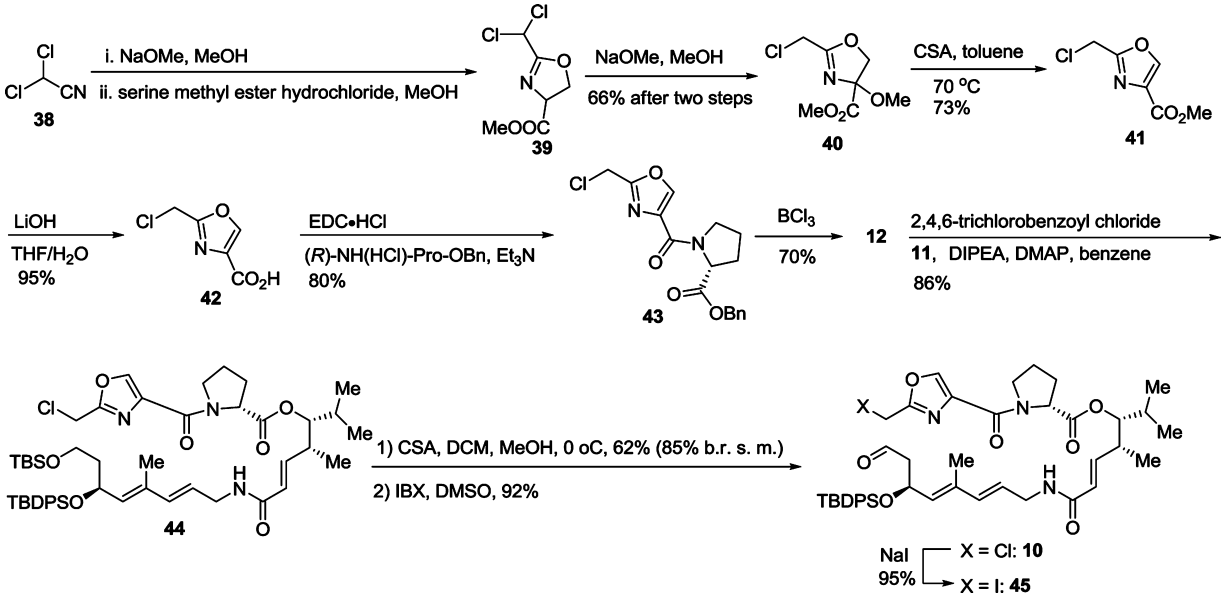
Scheme 7. Control Experiments of Alkoxide-Directed Alkyne−Alkyne Reductive Coupling with Propargylic Alcohol



Scheme 8. Preparation of Acyclic Framework 10



coupling exhibited considerable advantages over the venerable Negishi cross-coupling sequence: (1) it did not require the generation of a preactivated and stereodefined vinyl iodide or vinyl metal species; (2) it was compatible with a free hydroxyl group in the substrate, thus did not require a redundant protection and deprotection. In our synthesis of C1−C13 fragment **11**, the reductive coupling route required a total of seven steps compared to 13-steps using the Negishi cross-coupling strategy, which illustrated its efficiency without requirements of numerous functional group manipulations.

Preparation of C14−C19 Fragment. Synthesis of the C14−C19 subunit (Scheme 8) commenced with the preparation of oxazole ester **41** following Hermitage's protocol.[38] Preparation of oxazoline **39** was achieved by the slow addition of commercial dichloroacetonitrile **38** to a sodium methoxide methanol solution cooled in an ice bath (0 °C) and subsequent condensation with serine methyl ester hydrochloride. Treatment of the dichlorooxazoline **39** with sodium methoxide in methanol, followed by camphorsulfonic acid (CSA) catalyzed elimination of MeOH afforded oxazole **41**. This material was hydrolyzed to the corresponding carboxylic acid **42**, followed by coupling with D-proline benzyl ester hydrochloride to achieve the benzyl protected C14−C19 fragment **43** as a 1:1 mixture of rotamers. A subsequent BCl_3-promoted cleavage of benzyl ester provided the C14−C19 carboxylic acid fragment **12** as a 3:1 mixture of rotamers, whereas Pd/C catalyzed hydrogenation of amide **43** resulted in cleavage of the benzyl ester protecting group as well as the chloro group.

Final Stages of the Virginiamycin M_2 Synthesis. In contrast to the failed attempts to lactonize at the C1 hydroxyl using DCC or HOBT coupling reagents, esterification between **11** and **12** proceeded efficiently using Yamaguchi conditions[39] to yield ester **44** as a 1:1 mixture of rotamers (Scheme 8). The use of CSA proved to be more effective when compared to PPTS and AcOH for the selective monodeprotection of the primary silyl group, which afforded the desired primary alcohol with good yield and within a one hour reaction period. Oxidation of the primary alcohol using IBX in DMSO cleanly afforded aldehyde **10**, which could be further converted to iodide **45** as a mixture of 1:1 rotamers utilizing NaI in acetone. However, by switching to an iodination-oxidation sequence, the IBX reaction of the iodide derivative of **44** resulted in low yield with a significant amount of uncharacterized byproduct.

The functional group array of the advanced intermediates **10** and **45** represented an interesting synthetic challenge in the context of macrolide-forming strategies and an opportunity to evaluate an under-developed Barbier/Reformatsky-type cyclization approach. We were attracted by the potential of the SmI_2-mediated macrocyclizations, which were reported to have considerable merits: (1) the large ionic radius of samarium (approximately 136 pm), and its high oxophilicity, made the samarium atom effectively chelate with the two reacting centers; thus, it was efficient for large-ring macrocyclization; (2) SmI_2-mediated reaction occurred in a homogeneous reaction other than with common heterogeneous variants such as Mg, Zn, and Li, associating with superior reactivity and

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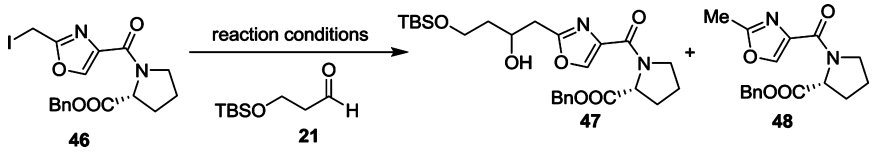
Table 4. Model Study of Barbier/Reformatsky-Type Addition



entry	reagent[a]	T (°C)	time	result[d]
1	SmI_2/THF	rt	15 min	**47** (61%), **48** (25%)[b]
2	SmI_2/Benzene	rt	20 min	**47** (80%), **48** (11%)[b]
3	SmI_2/THF	0	1 h	**47** (55%), **48** (30%)[b]
4	SmI_2/THF	−78	2 h	NR[e]
5	SmI_2−HMPA (1:4)	−78	30 min	NA[f]
6	$Et_2Zn/RhCl(PPh_3)_3$	0	40 min	**47** (20%), **48** (40%)[c]
7	*n*-BuLi	−78	8 h	**47** (48%), **48** (11%)[b]
8	*t*-BuLi	−78	10 h	**47** (20%), **48** (10%)[c]
9	*i*-PrMgCl	−78	30 min	**47** (25%), **48** (40%)[c]

[a]All reactions were conducted at 0.01 M concentration. [b]Isolated product yield. [c]Results based on ^{1}H NMR analysis of crude product. [d]Product **47** was not detected with heterogeneous catalyst systems (activated Zn and In). [e]Only recovering starting material **46**. [f]The amide bond was cleaved.

selectivity; (3) its reducing ability could be easily enhanced by additives.[40] The intramolecular SmI_2-mediated Barbier/Reformatsky reaction has been used to access medium and large carbocycles and lactones,[41] and we have recently applied this strategy in our total synthesis of the natural product kendomycin.[10]

To demonstrate the feasibility of this strategy in the virginiamycin M_2 case, a model study was conducted to form the C11−C19 section of the secondary alcohol **9**. The iodoamide **46**, which was prepared by displacement of the chloride **43** using NaI in acetone, was carried forward to achieve the model product **47**. As shown in Table 4, SmI_2-mediated reductive couplings of **46** with **21** were efficient at room temperature or 0 °C in THF (entries 1 and 3),[42] with the major byproduct as the reduced methyl bearing oxazole **48**. However, no reaction occurred at −78 °C with quantitative recovery of starting materials (entry 4). Attempts at increasing the reducing potential of SmI_2 by using HMPA as an additive[40] led to complete cleavage of the amide bond even at temperatures as low as −78 °C (entry 5). Other metal promoters were investigated in the model coupling experiments and we observed that the homogeneous reagents (Et_2Zn/Wilkinson catalyst,[43] *n*-BuLi, *t*-BuLi, and *i*-PrMgCl, entries 6−9) led to alcohol product **47** in moderate yield with lower efficiency compared to SmI_2. However, the heterogeneous catalysts including activated Zn and In reagents[44] afforded only the reduced byproduct **48**.

With the successful demonstration of the SmI_2-mediated Barbier/Reformatsky coupling with a model system, we turned our efforts to the macrocyclization substrate associated with the virginiamycin M_2 synthesis. There were, however, several challenges ahead with this late stage macrocyclization: (i) acyclic substrates **10** or **45** contained several functional groups which were potentially reactive in an electron-transfer process, including the aromatic amide, the α,β-unsaturated amide, the ester group, and the diene moiety; (ii) to the best of our knowledge, this would be the largest macrocycle (23-membered) formed mediated by SmI_2 to date; (iii) both precursors **10** and **45** contained a mixture of 1:1 rotamers.

Initially, the acyclic aldehyde **45** in THF (0.01 M) was treated with freshly prepared SmI_2 THF solution[10] dropwise until the reaction color turned blue, immediately quenching by carefully bubbling air and adding saturated solution of NH_4Cl (Table 5, entry 1). Not surprisingly, exclusively reduced acyclic aldehyde **49** was obtained, which indicated that the generation of benzylic-like radical intermediate **int-7** may proceed faster than other transformations. In order to further generate the desired samarium species **int-8**, a THF solution of SmI_2 (2 equiv) was employed (entry 2). However, a disappointing yield (approximately 10%) of the desired cyclization product **9** as a mixture of 1:1 diastereomers was obtained, with the major product as the reduced acyclic aldehyde **49** and acyclic alcohol **50**. An even lower yield (<5%) of product **9** was obtained from highly diluted THF solution (0.002 M) (entry 3), which indicated that the initially formed radical **int-7** may abstract a hydrogen atom from the solvent (THF) instead of generating the desired organosamarium species **int-8**. To prevent hydrogen atom abstraction from THF, the Tani group has shown that benzene may be employed as the solvent in SmI_2-promoted intermolecular coupling reactions with aryl and alkynyl radical intermediates.[45] However, this method has not been extensively applied to other SmI_2-promoted reactions, and, to the best of our knowledge, no reports of using benzene to suppress the competitive dehalogenation pathway have been reported in natural product synthesis so far. When the model experiment (Table 4, entry 2) was carried out in benzene in place of THF, the coupling product **47** was obtained in higher yield (80%). Accordingly, the optimized conditions were applied to the macrocyclization, and resulted in the isolation of the desired product **9** in much higher yield as a 1:1 diastereomeric mixture (Table 5, entry 4). The less reactive chloride **10** also participated in the cyclization with similar yield (Table 5, entry 5).

Attempts to oxidize the resulting secondary alcohol **9** using Dess−Martin reagent or standard Swern conditions were unsuccessful as these reactions were complicated by varying amounts of uncharacterized aldehyde byproduct. Ultimately, a modified TFAA−DMSO Swern procedure[46] was used to afford the desired ketone **51** in good yield. Acetylacetone was adapted in the procedure and used as a sacrificial enolizable additive to avoid further enolization and elimination of the β-silyloxy ketone product **51** (Scheme 9). Final deprotection of the C11 TBDPS ether was accomplished by using Schlessinger's protocol[4a] to reveal (−)-virginiamycin M_2 in 70% yield, which was identical in all analytical and spectroscopic aspects

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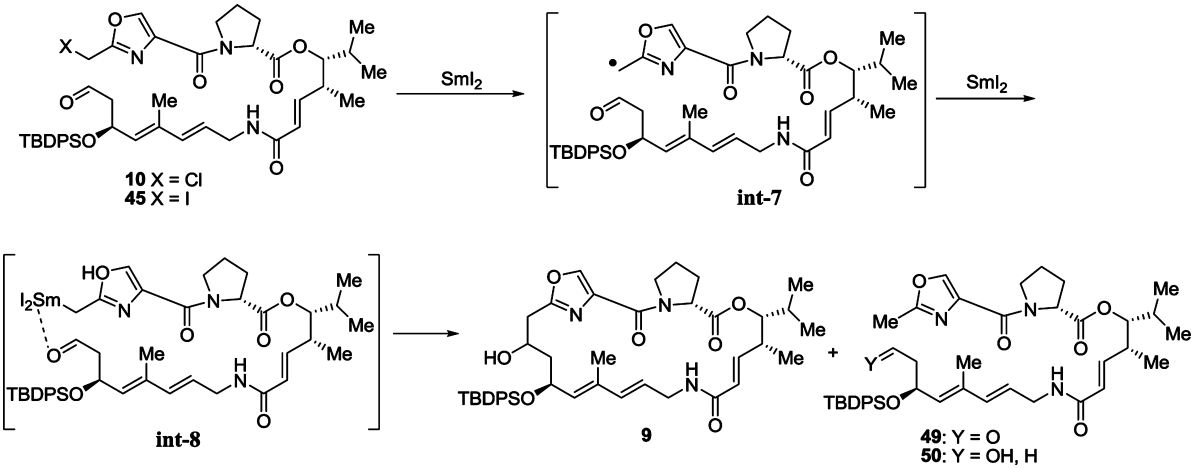
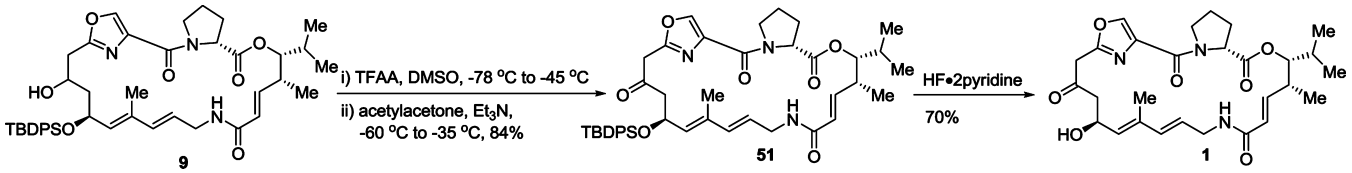
Table 5. SmI_2-Mediated Barbier-Type Macrocyclization To Afford Cyclized Product 9



entry	SM	SmI_2 (equiv)	solvent (conc)	reaction time	ratio of products[a]	yield of 9[b] (%)
1	**45**	1	THF (0.01 M)	2 min	only **49**	0
2	**45**	2	THF (0.01 M)	20 min	**9**/**49**/**50**/dimer = 1:5:2:2	10
3	**45**	4	THF (0.002 M)	8 h	trace **9**, almost **50**	<5
4	**45**	4	benzene (0.002 M)	8 h	**9**/**49**/**50** = 4:0:5	42
5	**10**	4	benzene (0.002 M)	8 h	**9**/**49**/**50** = 4:0:5	40

[a]Product ratios were based on analysis of the crude ^{1}H NMR spectra. [b]Product yields were based on chromatography.

Scheme 9. Completion of the Total Synthesis of Virginiamycin M_2 (1)



(^{1}H and ^{13}C NMR, IR, HRMS, optical rotation) to the published data.[4a]

CONCLUSION

In summary, a highly convergent total synthesis of (−)-virginiamycin M_2 (**1**) was accomplished in 19 steps with the longest linear sequence of 10-steps from silane (*S*)-**15**, or 11-steps from 1,3-propandiol with 6.0% overall yield. On balance, the successful route compared very favorably with the previous synthesis reported by Schlessinger and Uguen.[4] Notable synthetic features included an extension on Rh(II) and Cu(I) promoted carbenoid Si−H insertion to prepare crotylsilane **15** in highly enantioenriched form; the asymmetric crotylation using the resulting crotyl silane to address stereochemical features in the preparation of C1−C5 unsaturated amide subunit; an alkoxide-directed reductive coupling strategy to assemble the (*E*,*E*)-diene, which overcame the reactivity and regioselectivity problems encountered in the undirected coupling; a comparison between Negishi cross-coupling and alkyne−alkyne reductive coupling to prepare the (*E*,*E*)-trisubstituted diene; a SmI_2-promoted macrocyclization in the presence of several potential labile functional groups. The presented modular synthesis should be instructive and amenable for the design and synthesis of analogues of group A pH sensitive virginiamycins, thus enabling further exploration of the promising biological potential of these macrolide antibiotics.

EXPERIMENTAL SECTION

General Information. All reactions were carried out in oven- or flame-dried glassware under argon atmosphere. Triethylamine and pyridine were distilled before use. *N*,*N*-Dimethylformamide and dimethyl sulfoxide were distilled over calcium hydride and stored over 4 Å molecular sieves. *n*-Butyllithium was purchased and standardized by titration with menthol/2,2′-dipyridyl. All other reagents were used as supplied. Dichloromethane, toluene, diethyl ether, benzene, tetrahydrofuran, and acetonitrile were obtained from a dry solvent system (alumina) and used without further drying. Unless otherwise noted, reactions were magnetically stirred and monitored by thin layer chromatography with 0.20 mm silica gel 60 Å plates. Flash chromatography was performed on 32−63 μm 60 Å silica gel. Yields referred to chromatographically and spectroscopically pure compounds, unless otherwise noted. ^{1}H and ^{13}C NMR spectra were taken in $CDCl_3$ at 300, 400, or 500 MHz (as indicated), respectively. Chemical shifts are reported in parts per million relative to $CDCl_3$ (^{1}H, δ 7.24; ^{13}C, δ 77.0). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sept = septuplet, m = multiplet, br = broad), coupling constant, integration. For spectra which contain mixtures of amide rotamers, the signals that can be assigned as specific to a particular rotamer are designated with an asterisk for the major and a double asterisk for the minor; signals that have contributions from both rotamers are not denoted with a special character. Diastereomeric ratios were determined by ^{1}H NMR analysis of crude mixtures, operating at signal/noise ratio of 200:1. Infrared spectra were recorded as thin films on NaCl pleates. Optical rotations were recorded on a digital polarimeter at 589 nm and reported as follows: $[\alpha]^{20}_D$ (concentration in g/100 mL solvent and solvent). High resolution

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mass-spectra were obtained by electrospray ionization in positive-ion mode (M + H or M + Na) as indicated.

General Procedure for Preparation of Diimine Ligands 20. (*R*,*R*)-1,2-Diammonium cyclohexane mono-(+)-tartrate salt[47] (2.97 g, 11.2 mmol, 1 equiv) was added to a 200 mL round-bottom flask equipped with a stir bar, followed by addition of K_2CO_3 (3.12 g, 22.5 mmol, 2 equiv) and distilled water (15 mL). The mixture was stirred for 30 min, and EtOH (60 mL) was added. Then a solution of aldehyde (22.5 mmol, 2 equiv) in EtOH (25 mL) was added dropwise. The flask was equipped with a reflux condenser, and the resulting mixture was refluxed for 2 h before being diluted by water (20 mL). The resulting mixture was cooled in an ice bath for 1 h. The product was collected by vacuum filtration and washed with EtOH (2 × 10 mL). The crude solid was redissolved in CH_2Cl_2 (50 mL) and washed with water (2 × 30 mL). After drying over $MgSO_4$, the solvent was removed under reduced pressure to afford product **20** in 80−95% yield.

(1*R*,2*R*,N^1*E*,N^2*E*)-N^1,N^2-Bis(2,6-dichlorobenzylidene)-cyclohexane-1,2-diamine ((*R*,*R*)-20a): $[\alpha]^{20}_D$ +18.3 (*c* = 1.6, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 2H), 7.26 (d, *J* = 2.0 Hz, 2H), 7.13 (m, 4H), 3.58 (m, 2H), 1.87 (m, 6H), 1.49 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.6, 134.8, 132.9, 129.9, 128.6, 74.9, 32.9, 24.2 ppm; IR (thin film) ν_{max} 2930, 2859, 1646, 1430, 772 cm^{-1}; HRMS (CI/NH_3) *m*/*z* calcd for $C_{20}H_{19}Cl_4N_2$ [M + H]$^+$ 427.0302, found 427.0313.

(1*R*,2*R*,N^1*E*,N^2*E*)-N^1,N^2-Bis(2,6-difluorobenzylidene)-cyclohexane-1,2-diamine ((*R*,*R*)-20b): $[\alpha]^{20}_D$ +80.5 (*c* = 1.4, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (s, 2H), 7.24 (m, 2H), 6.83 (m, 4H), 3.46 (m, 2H), 1.89 (m, 6H), 1.50 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2, 159.8, 151.6, 130.9, 114.1, 111.8, 111.5, 75.3, 32.5, 24.2 ppm; IR (thin film) ν_{max} 3319, 3267, 1621, 1463, 1220, 1055 cm^{-1}; HRMS (CI/NH_3) *m*/*z* calcd for $C_{20}H_{19}F_4N_2$ [M + H]$^+$ 363.1484, found 363.1473.

(1*R*,2*R*,N^1*E*,N^2*E*)-N^1,N^2-Bis(2-chloro-6-fluorobenzylidene)-cyclohexane-1,2-diamine ((*R*,*R*)-20c): $[\alpha]^{20}_D$ +44.0 (*c* = 1.7, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (s, 2H), 7.16 (m, 4H), 6.93 (m, 2H), 3.49 (m, 2H), 1.87 (m, 6H), 1.49 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.8, 159.4, 154.4, 135.1, 130.6, 130.5, 125.4, 123.4, 123.3, 115.0, 114.7, 75.1, 32.6, 24.2 ppm; IR (thin film) ν_{max} 2929, 2859, 1645, 1568, 1448, 1245, 899 cm^{-1}; HRMS (CI/NH_3) *m*/*z* calcd for $C_{20}H_{19}Cl_2F_2N_2$ [M + H]$^+$ 395.0893, found 395.0894.

(1*R*,2*R*,N^1*E*,N^2*E*)-N^1,N^2-Bis(2-bromo-6-chlorobenzylidene)-cyclohexane-1,2-diamine ((*R*,*R*)-20d): $[\alpha]^{20}_D$ +24.1 (*c* = 4.3, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (s, 2H), 7.44 (d, *J* = 7.8 Hz, 2H), 7.28 (d, *J* = 7.2 Hz, 2H), 7.05 (t, *J* = 8.1 Hz, 2H), 3.60 (m, 2H), 1.88 (m, 6H), 1.49 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 134.6, 134.3, 131.7, 130.2, 129.2, 123.9, 74.7, 32.8, 24.2 ppm; IR (thin film) ν_{max} 2929, 2854, 1652, 1550, 1426, 782 cm^{-1}; HRMS (CI/NH_3) *m*/*z* calcd for $C_{20}H_{19}Br_2Cl_2N_2$ [M + H]$^+$ 514.9292, found 514.9275.

(1*R*,2*R*,N^1*E*,N^2*E*)-N^1,N^2-Bis(2,6-dibromobenzylidene)-cyclohexane-1,2-diamine ((*R*,*R*)-20e): $[\alpha]^{20}_D$ +31.2 (*c* = 4.4, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (s, 2H), 7.48 (d, *J* = 8.1 Hz, 4H), 6.97 (t, *J* = 7.8 Hz, 2H), 3.62 (m, 2H), 1.86 (m, 6H), 1.49 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 135.6, 132.4, 130.5, 123.6, 74.5, 32.8, 24.2 ppm; IR (thin film) ν_{max} 3319, 3060, 2923, 2848, 1652, 1419, 1223, 1056 cm^{-1}; HRMS(CI/NH_3) *m*/*z* calcd for $C_{20}H_{19}N_2Br_4$ [M + H]$^+$ 602.8282, found 602.8286.

(1*R*,2*R*,N^1*E*,N^2*E*)-N^1,N^2-Bis(2,6-dimethylbenzylidene)-cyclohexane-1,2-diamine ((*R*,*R*)-20f): $[\alpha]^{20}_D$ −30.0 (*c* = 0.6, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (s, 2H), 7.06 (m, 2H), 6.94 (m, 4H), 3.45 (m, 2H), 2.26 (s, 12H), 1.85 (m, 6H), 1.50 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.4, 137.2, 134.1, 128.4, 128.3, 75.5, 33.5, 24.5, 20.5 ppm; IR (thin film) ν_{max} 2921, 2852, 1646, 1463, 1371, 769 cm^{-1}; HRMS (CI/NH_3) *m*/*z* calcd for $C_{24}H_{31}N_2$ [M + H]$^+$ 347.2487, found 347.2474.

(1*R*,2*R*,N^1*E*,N^2*E*)-N^1,N^2-Bis(2,4,6-trimethylbenzylidene)-cyclohexane-1,2-diamine ((*R*,*R*)-20h): $[\alpha]^{20}_D$ −48.9 (*c* = 3.0, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (s, 2H), 6.79 (s, 4H), 3.45 (m, 2H), 2.28 (s, 12H), 2.25 (s, 6H), 1.86 (m, 6H), 1.53 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1, 138.1, 137.3, 131.2, 129.1, 75.6, 33.5, 24.5, 21.0, 20.6 ppm; IR (thin film) ν_{max} 2923, 2854, 1646, 1436, 846 cm^{-1}; HRMS (CI/NH_3) *m*/*z* calcd for $C_{26}H_{35}N_2$ [M + H]$^+$ 375.2800, found 375.2789.

(1*R*,2*R*,N^1*E*,N^2*E*)-N^1,N^2-Bis(2,4,6-trichlorobenzylidene)-cyclohexane-1,2-diamine ((*R*,*R*)-20i): $[\alpha]^{20}_D$ +16.6 (*c* = 2.2, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (s, 2H), 7.24 (s, 4H), 3.52 (m, 2H), 1.81 (m, 6H), 1.45 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 135.3, 134.9, 131.2, 128.6, 75.0, 32.7, 24.1 ppm; IR (thin film) ν_{max} 3319, 3263, 2923, 1652, 1224, 1057 cm^{-1}; HRMS(CI/NH_3) *m*/*z* calcd for $C_{20}H_{17}Cl_6N_2$ [M + H]$^+$ 494.9523, found 494.9535.

(1*R*,2*R*,N^1*E*,N^2*E*)-N^1,N^2-Bis(2,6-dichloro-4-decylbenzylidene)-cyclohexane-1,2-diamine ((*R*,*R*)-20j): $[\alpha]^{20}_D$ +29.2 (*c* = 0.7, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 2H), 7.06 (s, 4H), 3.54 (m, 2H), 2.50 (t, *J* = 12.5 Hz, 4H), 1.85 (m, 6H), 1.53 (m, 6H), 1.23 (m, 28H), 0.87 (t, *J* = 10.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.6, 145.7, 134.5, 130.1, 128.6, 74.9, 35.1, 32.9, 31.9, 30.7, 29.6, 29.5, 29.4, 29.3, 29.0, 24.3, 22.7, 14.1 ppm; IR (thin film) ν_{max} 2926, 2855, 1647, 1465 cm^{-1}; HRMS (CI/NH_3) *m*/*z* calcd for $C_{40}H_{59}Cl_4N_2$ [M + H]$^+$ 707.3432, found 707.3414.

(*R*,*E*)- and (*S*,*E*)-Methyl 2-(Dimethyl(phenyl)silyl)pent-3-enoate ((*R*)-15 and (*S*)-15) Using Rh(II) Catalysts. To a stirred solution of Rh_2(*S*-DOSP)$_4$ (190 mg, 0.1 mmol, 0.02 equiv) in pentane (5 mL, molecular sieves dried overnight before using) was added dimethylphenylsilane (3.88 mL, 25 mmol, 5 equiv). The mixture was cooled to −78 °C, and the diazo ester **19** (700 mg, 5 mmol, 1 equiv) in pentane (5 mL) was added dropwise over a period of 10 min. The mixture was stirred at −75 °C for 24 h and concentrated in vacuo. Chromatography on silica gel (hexane, hexane/ethyl acetate 98:2) afforded (*R*)-**15** (843 mg, 68% yield) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (m, 2H), 7.34 (m, 3H), 5.56 (dd, *J* = 15.6, 10.0 Hz, 1H), 5.19 (dt, *J* = 15.6, 6.8 Hz, 1H), 3.49 (s, 3H), 3.00 (d, *J* = 10.0 Hz, 1H), 1.62 (d, *J* = 6.8 Hz, 3H), 0.35 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 135.7, 133.9, 129.4, 127.6, 124.9,124.7, 51.0, 43.2, 17.9, −4.6, −4.6 ppm; $[\alpha]^{20}_D$ +37.5 (*c* = 2.2, CH_2Cl_2); IR (thin film) ν_{max} 3071, 2951, 1717, 1428, 1250, 1149, 698 cm^{-1}; HRMS (CI/NH_3) *m*/*z* calcd for $C_{14}H_{20}O_2NaSi$ [M + Na]$^+$ 271.1130, found 271.1162. Using the racemic versions of **15**, the baseline separation by HPLC could not be achieved. To obtain an accurate ee analysis of the insertion product, (*R*)-**15** was reduced to the primary alcohol using LAH in diethyl ether. HPLC analysis was now straightforward using ChiralCel OD, 1% IPA/hexane, 1 mL/min, t_R 15.5 min, t_S 11.6 min, and exhibited 93% ee. Catalyst Rh_2(*R*-DOSP)$_4$ afforded product (*S*)-**15** with the same yield and ee. (*S*)-**15**: $[\alpha]^{20}_D$ −22.3 (*c* = 0.7, CH_2Cl_2).

(*R*,*E*)- and (*S*,*E*)-Methyl 2-(Dimethyl(phenyl)silyl)pent-3-enoate ((*R*)-15 and (*S*)-15) Using Cu(I) Catalysts. To a round-bottom flask charged with a stir bar were added $(CH_3CN)_4Cu(BF_4)$ (157 mg, 0.5 mmol, 0.05 equiv) and the bis-imine ligand (*R*,*R*)-**20j** (534 mg, 0.7 mmol, 0.07 equiv). The mixture was dissolved in benzene (25 mL), and the resulting homogeneous yellow solution was allowed to stir at room temperature for 30 min. To this solution was added via syringe neat dimethylphenylsilane (7.76 mL, 50 mmol, 5 equiv), which was then cooled to 0 °C. To the cooled reaction mixture was slowly added a solution of diazo ester (1.4 g, 10 mmol, 1 equiv) in benzene (25 mL) over 1 h by syringe pump. The solution was allowed to stir at 0 °C for another 12 h before being flushed through a thin pad of silica gel to remove the remaining catalyst. The resulting solution was then concentrated under vacuum. The crude product was purified by silica chromatography, hexane eluant recovered dimethylphenylsilane, using 1% ethyl acetate/hexanes as the eluant afforded (*R*)-**15** as a yellow oil (1.3 g, 5.21 mmol, 52% yield). To obtain an accurate ee analysis of the insertion product, (*R*)-**15** was reduced to the primary alcohol by LAH in diethyl ether. HPLC analysis using ChiralCel OD, 1% IPA/hexane, 1 mL/min, t_R 15.5 min, t_S 11.6 min exhibited 78% ee.

(4*R*,5*R*,*E*)-Methyl 5-Hydroxy-4,6-dimethylhept-2-enoate (18a). To a round-bottom flask equipped with a stir bar were added isobutyraldehyde (720 mg, 10 mmol, 4 equiv) and silane (*S*)-**15** (620 mg, 2.5 mmol, 1 equiv). The flask was capped with a septum. Anhydrous CH_2Cl_2 (5 mL) was added to the flask under argon

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protection, and the solution was cooled to −78 °C. Neat $TiCl_4$ (544 uL, 5 mmol, 2 equiv) was added dropwise, and the resulting mixture was stirred at −20 °C for 72 h. The reaction was then diluted with CH_2Cl_2 (20 mL), quenched with saturated sodium bicarbonate (20 mL), and warmed to room temperature. The mixture was extracted with ether (3 × 10 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification over silica gel (10% EtOAc/hexane) afforded product **18a** (292 mg, 63%) as a colorless oil and as a single diastereomer: $[\alpha]^{20}_D$ +33.3 (c = 2.9, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) 6.91 (dd, J = 16.0, 8.0 Hz, 1H), 5.85 (d, J = 16.0 Hz, 1H), 3.71 (s, 3H), 3.25 (t, J = 5.5 Hz, 1H), 2.49 (m, 1H), 1.70 (m, 1H), 1.36 (br, 1H), 1.07 (d, J = 7.0 Hz, 3H), 0.91 (d, J = 7.0 Hz, 3H), 0.90 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 167.0, 152.0, 120.7, 79.2, 51.5, 40.0, 30.9, 19.7, 16.5, 14.0 ppm; IR (thin film) ν_{max} 3457, 2963, 1724, 1437, 1279, 1049, 863 cm^{-1}; HRMS(CI/NH_3) m/z calcd for $C_{10}H_{19}O_3$ $[M + H]^+$ 187.1334, found 187.1328. HPLC analysis using ChiralCel OD, 1% IPA/hexane, 1 mL/min, t_R 11.9 min, t_S 24.0 min exhibited 95% ee.

(4*R*,5*R*,*E*)-Methyl 5-(Benzyloxy)-4,6-dimethylhept-2-enoate (18b). To a round-bottom flask equipped with a stir bar were added isobutyraldehyde (360 mg, 5 mmol, 2 equiv), silane (*S*)-**15** (620 mg, 2.5 mmol, 1 equiv), and TMSOBn (900 mg, 5 mmol, 2 equiv). The flask was capped with a septum. Anhydrous CH_2Cl_2 (5 mL) was added to the flask under argon protection. The solution was cooled to −78 °C. TMSOTf (450 uL, 2.5 mmol, 1 equiv) was added dropwise, and resulting mixture was stirred at −60 °C for 72 h. Then the reaction was diluted with CH_2Cl_2 (20 mL), quenched with saturated sodium bicarbonate (20 mL), and warmed to room temperature. The mixture was extracted with ether (3 × 10 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification over silica gel (2% EtOAc/hexane) afforded product **18b** (469 mg, 68%) as a colorless oil and as a 6.3:1 mixture of diastereomers: $[\alpha]^{20}_D$ +9.4 (c = 0.4, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 5H), 6.98 (dd, J = 15.6, 8.0 Hz, 1H), 5.83 (d, J = 15.6 Hz, 1H), 4.53 (s, 2H), 3.71 (s, 3H), 3.07 (t, J = 5.6 Hz, 1H), 2.62 (m, 1H), 1.80 (m, 1H), 1.10 (d, J = 6.8 Hz, 3H), 0.93 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 152.6, 138.6, 128.3, 127.6, 127.5, 120.1, 87.8, 75.2, 51.5, 39.8, 31.3, 20.3, 17.5, 14.7 ppm; IR (thin film) ν_{max}2963, 1723, 1656, 1275, 1176, 1066 cm^{-1}; HRMS (CI/NH_3) m/z calcd for $C_{17}H_{24}O_3Na$ $[M + Na]^+$ 299.1623, found 299.1671. Ee analysis of product **18b** was determined on the alcohol derivative after deprotection of the benzyl group, which exhibited 95% ee (ChiralCel OD, 1% IPA/hexane, 1 mL/min, t_R 11.9 min, t_S 24.0 min).

(*E*)-Methyl 2-(1-Hydroxy-2-methylpropyl)pent-3-enoate (18c). To a round-bottom flask equipped with a stirbar were added freshly distilled isobutyraldehyde (72 mg, 1 mmol, 4 equiv) and silane (*S*)-**15** (62 mg, 0.25 mmol, 1 equiv). The flask was capped with a rubber septum. Anhydrous MeCN (0.5 mL) was added to the flask under argon protection, and the solution was cooled to −30 °C. Next, neat $TiCl_4$ (27.2 uL, 0.25 mmol, 1 equiv, freshly distilled colorless liquid) was added dropwise, and the resulting mixture was stirred at −20 °C for 24 h. Then the reaction was diluted with MeCN (2 mL) and quenched with saturated sodium bicarbonate (2 mL). After warming to room temperature, the mixture was extracted with ether (3 × 1 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification over silica gel (10% EtOAc/hexane) afforded the α-addition product **18c** (37 mg, 80% yield) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.66 (dq, J = 15.5, 6.5 Hz, 1H), 5.56 (dd, J = 15.5, 9.0 Hz, 1H), 3.69 (s, 3H), 3.54 (t, J = 6.0 Hz, 1H), 3.15 (m, 1H), 2.57 (br, 1H), 1.71 (d, J = 6.0 Hz, 3H), 1.65 (m, 1H), 0.95 (d, J = 6.5 Hz, 3H), 0.87 (d, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 131.4, 124.3, 76.3, 52.3, 52.0, 30.7, 19.1, 18.1, 17.7 ppm; IR (thin film) ν_{max} 3469, 2961, 1720, 1436, 1144, 969 cm^{-1}; HRMS (CI/NH_3) m/z calcd for $C_{10}H_{19}O_3$ $[M + H]^+$ 187.1334, found 187.1342.

(4*R*,5*R*,*E*)-5-Hydroxy-4,6-dimethyl-*N*-(prop-2-ynyl)hept-2-enamide (14a). A solution of 2 M trimethylaluminum in CH_2Cl_2 (6 mL, 12 mmol, 4 equiv) was added dropwise, over 30 min, to a stirred solution of propargylamine (830 uL, 12 mmol, 4 equiv) in dry CH_2Cl_2 (20 mL) at 0 °C, under an atmosphere of argon. The mixture was stirred at rt for 30 min, and the hydroxyl ester **18a** (558 mg, 3 mmol, 1 equiv) in CH_2Cl_2 (5 mL) was added in one portion. The mixture was heated under reflux for 5 h and then cooled to 0 °C before carefully quenching with H_2O (20 mL). The mixture was extracted with CH_2Cl_2 (3 × 20 mL), dried by $MgSO_4$, and concentrated. The residue was purified by flash chromatography (silica gel, 50% EtOAc/hexane) to afford product **14a** (545 mg, 87% yield) as a white solid: $[\alpha]^{20}_D$ +33.5 (c = 0.8, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.82 (dd, J = 15.5, 8.0 Hz, 1H), 5.79 (d, J = 15.5 Hz, 1H), 5.61 (br, 1H), 4.10 (dd, J = 5.5, 2.5 Hz, 2H), 3.24 (m, 1H), 2.47 (m, 1H), 2.23 (t, J = 2.5 Hz, 1H), 1.84 (m, 1H), 1.40 (d, J = 5.0 Hz, 1H), 1.07 (d, J = 6.5 Hz, 3H), 0.90 (d, J = 7.0 Hz, 3H), 0.89 (d, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 148.4, 122.6, 79.5, 79.1, 71.6, 39.6, 30.8, 29.2, 19.7, 16.9, 13.7 ppm; IR (thin film) ν_{max} 3302, 2963, 1669, 1635, 1540, 1032, 987 cm^{-1}; HRMS (CI/NH_3) m/z calcd for $C_{12}H_{20}NO_2$ $[M + H]^+$ 210.1494, found 210.1502.

(3*R*,4*R*,*E*)-2,4-Dimethyl-7-oxo-7-(prop-2-ynylamino)hept-5-en-3-yl Acetate (14c). Acetyl chloride (44 uL, 0.612 mmol, 1.6 equiv) was added dropwise to a stirred solution of hydroxyamide **14a** (80 mg, 0.383 mmol, 1 equiv) and pyridine (50 μL, 0.612 mmol, 1.6 equiv) in dry CH_2Cl_2 (3 mL) at 0 °C. DMAP (3 mg, catalytic) was added in one portion, and the mixture was stirred overnight while warming to rt. The reaction then was diluted with saturated NH_4Cl solution (2 mL), extracted with CH_2Cl_2 (2 × 3 mL), washed with brine (2 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified using flash chromatography (silica gel, 30% EtOAc/hexane) to afford the acetate product **14c** (93 mg, 97% yield) as a white solid: $[\alpha]^{20}_D$ +16.4 (c = 1.1, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.70 (dd, J = 15.5, 8.0 Hz, 1H), 5.84 (br, 1H), 5.80 (d, J = 15.5 Hz, 1H), 4.73 (dd, J = 7.5, 5.0 Hz, 1H), 4.08 (m, 2H), 2.59 (m, 1H), 2.21 (t, J = 2.5 Hz, 1H), 2.04 (s, 3H), 1.83 (m, 1H), 0.99 (d, J = 7.0 Hz, 3H), 0.85 (d, J = 4.5 Hz, 3H), 0.83 (d, J = 4.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 165.2, 146.3, 123.0, 79.7, 79.4, 71.6, 38.4, 29.7, 29.2, 20.8, 19.6, 16.4, 15.1 ppm; IR (thin film) ν_{max} 3287, 2969, 1734, 1671, 1542, 1242, 1022 cm^{-1}; HRMS (CI/NH_3) m/z calcd for $C_{14}H_{21}NO_3Na$ $[M + Na]^+$ 274.1419, found 274.1409.

(*S*)-1-(*tert*-Butyldimethylsilyloxy)hex-4-yn-3-ol (13) Generated from Carreira's Protocol. $Zn(OTf)_2$ (726 mg, 2 mmol, 2 equiv) and (−)-*N*-methylephedrine (376 mg, 2.1 mmol, 2.1 equiv) were added to a flame-dried round-bottom flask, which was purged with argon (three times) and then sealed with a rubber septum. Toluene (7 mL) and freshly distilled Et_3N (212 mg, 2.1 mmol, 2.1 equiv) were added at ambient temperature and the mixture was stirred vigorously for 2 h (a turbid milky mixture). Then 0.3 mL of propyne was transferred to the reaction mixture from a cold trap (−78 °C) via cannula. The reaction was stirred under a propyne atmosphere (propyne-filled balloon). After 5 min, aldehyde **21**[48] (188 mg, 1 mmol, 1 equiv) in toluene (1 mL) was added over 5 h by the syringe pump and further stirred for another 12 h. The reaction was diluted with NH_4Cl saturated solution (10 mL), extracted with Et_2O (3 × 15 mL), washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography on silica gel (5−10% EtOAc/hexane) provided **13** (181 mg, 80% yield, 95% ee) as a colorless oil: $[\alpha]^{20}_D$ −10.0 (c = 2.9, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.54 (m, 1H), 3.98 (m, 1H), 3.79 (m, 1H), 3.31 (d, J = 5.6 Hz, 1H), 1.91 (m, 1H), 1.82 (s, 3H), 1.81 (m, 1H), 0.87 (s, 9H), 0.05 (d, J = 2.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 80.8, 79.8, 62.0, 61.2, 38.9, 25.8, 18.1, 3.5, −5.6 ppm; IR (thin film) ν_{max} 3395, 2955, 2928, 2857, 1514, 1256, 1102, 514 cm^{-1}; HRMS (CI/NH_3) m/z calcd for $C_{12}H_{24}O_2NaSi$ $[M + Na]^+$ 251.1443, found 251.1435. Chiral HPLC: since compound **13** was not UV active, and it cannot be detected by HPLC. To check the product's % ee, **13** was converted to the benzoate derivative.

(*S*)-1-(*tert*-Butyldimethylsilyloxy)hex-4-yn-3-yl Benzoate. Alcohol **13** (22.8 mg, 0.1 mmol, 1 equiv) was dissolved in dry CH_2Cl_2 (0.5 mL, 0.2 M) and treated with BzCl (35 mg, 0.25 mmol, 2.5 equiv), pyridine (79 mg, 1.0 mmol, 10 equiv), and a catalytic amount DMAP (~1 mg). The mixture was stirred overnight under argon atmosphere and then poured into aqueous saturated NH_4Cl (2 mL) and extracted

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with Et_2O (2 × 2 mL). The combined organic phase was dried by $MgSO_4$, filtered, and concentrated. The residue was purified by chromatography (1% EtOAc/hexane) to afford the product (30 mg, 93% yield) as a colorless oil: $[\alpha]^{20}_D$ −23.2 (c = 4.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (m, 2H), 7.54 (m, 1H), 7.42 (m, 2H), 5.67 (m, 1H), 3.79 (m, 1H), 2.13 (m, 1H), 2.05 (m, 1H), 1.83 (d, J = 2 Hz, 3H), 0.86 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 132.9, 130.1, 129.7, 128.3, 81.9, 76.7, 62.3, 58.9, 38.2, 25.8, 18.2, 3.6, −5.5 ppm; IR (thin film) ν_{max} 3330, 2892, 2811, 1773, 1511, 723 cm^{-1}; HRMS (CI/NH_3) m/z calcd for $C_{19}H_{28}O_3NaSi$ $[M + Na]^+$ 355.1705, found 355.1722; HPLC (WhelkO, 1% IPA/hexane, 1 mL/min, t_S 6.2 min, t_R 7.0 min) showed 95% ee.

(*S*)-4,6-Bis(*tert*-butyldimethylsilyloxy)hex-2-yne (22). Alcohol **13** (114 mg, 0.5 mmol, 1 equiv) and 2,6-lutidine (173 μL, 1.5 mmol, 3 equiv) were dissolved in CH_2Cl_2 (2 mL). TBSOTf (172 μL, 0.75 mmol, 1.5 equiv) was carefully added at −78 °C by syringe. Then the cooling bath was removed, and the reaction was stirred for an additional 4 h at rt. The reaction was quenched by aqueous saturated NH_4Cl (2 mL) and extracted with Et_2O (2 × 5 mL). The combined organic phase was dried by $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by chromatography (1% EtOAc/hexane) to afford the product **22** (164 mg, 96% yield) as a colorless oil: $[\alpha]^{20}_D$ −21.1 (c = 6.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.49 (m, 1H), 3.69 (m, 2H), 1.82 (m, 2H), 1.80 (d, J = 2 Hz, 3H), 0.88 (s, 9H), 0.86 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H), 0.02 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 80.9, 80.0, 60.0, 59.2, 42.0, 25.9, 18.3, 3.5, −4.5, −5.1, −5.3, −5.4 ppm; IR (thin film) ν_{max} 2929, 2857, 1472, 1254, 1096, 835, 775 cm^{-1}; HRMS (CI/NH_3) m/z calcd for $C_{18}H_{38}O_2NaSi_2$ $[M + Na]^+$ 365.2308, found 365.2324.

1-(*tert*-Butyldimethylsilyloxy)hex-4-yn-3-ol (*rac*-13). *n*-BuLi (5.8 mL, 13 mmol, 1.3 equiv, 2.5 M in hexanes) and THF (10 mL) were added to a flame-dried round-bottom flask and cooled to −78 °C. Then propyne (1.5 mL) was transferred to the reaction mixture from a cold trap (−78 °C) via cannula. The reaction was stirred at −78 °C for 30 min and then warmed to 0 °C. After 20 min, the mixture was recooled to −78 °C. Aldehyde **21** (1.88 g, 10 mmol, 1 equiv) in THF (5 mL) was added over 5 min by the syringe and then warmed to 0 °C to further stir for another 4 h. The reaction was diluted with saturated NH_4Cl solution (10 mL), extracted with Et_2O (3 × 15 mL), washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography on silica gel (10% EtOAc/hexane) provided ***rac*-13** (2.09 g, 92% yield) as a colorless oil.

1-(*tert*-Butyldimethylsilyloxy)hex-4-yn-3-one (23). To a solution of ***rac*-13** (2.28 g, 10 mmol, 1 equiv) in CH_2Cl_2 (50 mL) was added MnO_2 (13 g, 150 mmol, 15 equiv, activated at 150 °C for 12 h) at rt. After being stirred for 8 h, the mixture was filtered through Celite. The filtrate was concentrated under reduced pressure and purified over silica gel with EtOAc/hexanes (5/95) to afford product ketone **23** as a colorless oil (1.92 g, 85% yield): ^{1}H NMR (400 MHz, $CDCl_3$) 3.94 (t, J = 6.4 Hz, 2H), 2.70 (t, J = 6.0 Hz, 2H), 1.99 (s, 3H), 0.85 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.1, 90.0, 80.1, 58.3, 48.2, 25.6, 18.0, 3.9, −5.6 ppm; IR (thin film) ν_{max} 3482, 2956, 2930, 2857, 2216, 1676, 1255, 1003, 836 cm^{-1}; HRMS (CI/NH_3) m/z calcd for $C_{12}H_{23}O_2Si$ $[M + H]^+$ 227.1467, found 227.1497.

(*S*)-1-(*tert*-Butyldimethylsilyloxy)hex-4-yn-3-ol (13) Generated from CBS Asymmetric Reduction. Ketone **23** (1.8 g, 8 mmol) was dissovled in THF (40 mL, 0.2 M) and cooled to −30 °C. To this solution was added 2-methyl (*S*)-CBS oxazaborolidine (1.0 M in toluene, 16 mL, 16 mmol, 2 equiv), and borane−dimethyl sulfide (2.0 M in THF, 20 mL, 40 mmol, 5 equiv) was added dropwise over 5 min. After the resulting reaction mixture was stirred for 1 h at −30 °C, the reaction was quenched by addition of ethanol (10 mL), warmed to room temperature, and diluted with water (40 mL) and diethyl ether (40 mL). The organic layer was dried over $MgSO_4$, concentrated under reduced pressure, and purified by flash column chromatography (SiO_2, 10/90 EtOAc/hexanes) to afford enantioenriched **13** as a colorless oil (1.66 g, 91% yield, 93% ee).

(3*R*,4*R*,*E*)-2,4-Dimethyl-7-oxo-7-((*E*)-3-(tributylstannyl)-allylamino)hept-5-en-3-yl Acetate (29c). CuCN (356 mg, 4 mmol, 2 equiv) was suspended in anhydrous THF (20 mL) under argon protection. The mixture was cooled to −78 °C, a 2.5 M solution *n*-BuLi in hexanes (3.2 mL, 8 mmol, 4 equiv) was added dropwise over 5 min, and the reaction was then stirred at −78 °C for 15 min. Bu_3SnH (2.13 mL, 8 mmol, 4 equiv) was added dropwise over 5 min. The reaction turned yellow, and gas was generated. The mixture was further stirred 15 min at −78 °C. A solution of the alkyne **14c** (502 mg, 2 mmol, 1 equiv) in anhydrous THF (5 mL) was added dropwise, and the mixture was stirred for another 3 h at −78 °C before being quenched with 10% NH_3/NH_4Cl solution (20 mL). The mixture was allowed to warm to rt, and the solids were filtered off. The filtrate was extracted with EtOAc (3 × 15 mL), the extracts were washed with brine, dried over $MgSO_4$, and concentrated, and the residue was purified by flash chromatography (silica gel, 15% EtOAc/hexane) to afford the vinyl stannane **29c** (815 mg, 75%) as a colorless oil: $[\alpha]^{20}_D$ +2.2 (c = 1.5, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.69 (dd, J = 15.4,8.2 Hz, 1H), 6.12 (dt, J = 19.0, 1.3 Hz, 1H), 5.95 (dt, J = 19.0, 5.3 Hz, 1H), 5.80 (dd, J = 15.4, 0.8 Hz, 1H), 5.49 (br, 1 H), 4.75 (dd, J = 7.4, 5.0 Hz, 1H), 3.97 (m, 2 H), 2.60 (m, 1 H), 2.05 (s, 3H), 1.86 (m, 1 H), 1.52 (q, J = 7.4 Hz, 6H), 1.28 (sept, J = 7.4 Hz, 6H), 1.03 (d, J = 7.4 Hz, 3H), 0.88 (m,21 H); ^{13}C NMR (75 MHz, $CDCl_3$)170.6, 165.2, 144.8, 143.3, 129.8, 123.8, 79.6, 44.7, 38.2, 29.6, 28.8, 27.0, 20.6, 19.5, 16.1, 15.2, 13.5, 9.2 ppm; IR (thin film) ν_{max} 3275, 2959, 2927, 2872, 1743, 1630, 1238, 986 cm^{-1}; HRMS(CI/NH_3) m/z calcd for $C_{26}H_{50}NO_3Sn$ $[M + H]^+$ 544.2812, found 544.2805.

(3*R*,4*R*,*E*)-7-((*E*)-3-Iodoallylamino)-2,4-dimethyl-7-oxohept-5-en-3-yl Acetate (30c). To a cooled (0 °C), stirred solution of vinylstannane **29c** (543 mg, 1 mmol, 1 equiv) in CH_2Cl_2 (33 mL) was added iodine (381 mg, 1.5 mmol, 1.5 equiv). After being stirred for 20 min at 0 °C, the reaction was quenched with saturated $Na_2S_2O_3$ solution until the reaction mixture turned colorless. The organic layer was separated, and the water layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (15% EtOAc/hexane) to afford vinyl iodide **30c** (367 mg, 97%) as a slightly yellow thick oil: $[\alpha]^{20}_D$ +8.9 (c = 3.6, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) 6.65 (dd, J = 15.0, 8.0 Hz, 1H), 6.49 (dt, J = 14.5, 6.0 Hz, 1H), 6.24 (dt, J = 14.5, 1.5 Hz, 1H), 6.19 (br, 1H), 5.80 (dd, J = 15.5, 1.0 Hz, 1H), 4.70 (dd, J = 7.5, 5.0 Hz, 1H), 3.82 (m, 2 H), 2.56 (m, 1 H), 2.01 (s, 3H), 1.81 (m, 1 H), 0.98 (d, J = 7.0 Hz, 3H), 0.82 (d, J = 6.5 Hz, 3H), 0.81 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 170.9, 165.5, 145.8, 141.4, 123.3, 79.7, 78.4, 43.5, 38.3, 29.7, 20.8, 19.6, 16.4, 15.1 ppm; IR (thin film) ν_{max} 3280, 2967, 1739, 1669, 1632, 1240, 1020 cm^{-1}; HRMS (CI/NH_3) m/z calcd for $C_{14}H_{23}INO_3$ $[M + H]^+$ 380.0723, found 380.0718.

(*S*,*E*)-1-(*tert*-Butyl(1-(*tert*-butyldimethylsilyloxy)-5-iodohex-4-en-3-yloxy)(phenyl)silyl)benzene (31). To a suspension of Schwartz's reagent (516 mg, 2 mmol, 2 equiv) in dry THF (3 mL) was added a solution of the TBDPS ether (466 mg, 1 mmol, 1 equiv) in dry THF (3 mL) at ambient temperature under an argon atmosphere. The mixture was warmed to 50 °C and stirred for 1.5 h in the dark. The mixture was cooled to 0 °C, and a solution of iodine (280 mg, 2.2 mmol, 2.2 equiv) in dry THF (5 mL) was added to the mixture. The mixture was further stirred at 0 °C for 10 min and was quenched by saturate $Na_2S_2O_3$ water solution (15 mL) at rt. The organic layer was separated, and the water layer was extracted by diethyl ether (2 × 15 mL). The combined organic extracts were washed with brine and dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (1% EtOAc/hexane) to afford iodide **31** (551 mg, 93%) as a single regioisomer: $[\alpha]^{20}_D$ −52.3 (c = 0.6, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.64 (m, 4H), 7.37 (m, 6H), 6.08 (dq, J = 9.2, 1.2 Hz, 1H), 4.49 (dt, J = 9.2, 6.4 Hz, 1H), 3.59 (m, 2H), 1.84 (m, 1H), 1.78 (d, J = 1.6 Hz, 3H), 1.60 (m, 1H), 1.03 (s, 9H), 0.80 (s, 9H), −0.04 (s, 3H), −0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 143.7, 135.9, 135.8, 133.8, 129.6, 129.5, 127.6, 127.5, 96.4, 68.3, 65.8, 59.0, 40.7, 27.8, 27.0,

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25.9, 19.3, 18.1, −5.4 ppm; IR (thin film) ν_{max}3071, 2929, 1471, 1256, 1111, 835, 701 cm^{-1}; HRMS (CI/NH_3) *m*/*z* calcd for $C_{28}H_{43}IO_2NaSi_2$ [M + Na]$^+$ 617.1744, found 617.1760.

(4*R*,5*R*,*E*)-5-(Benzyloxy)-*N*-((*S*,2*E*,4*E*)-8-(*tert*-butyldimethylsilyloxy)-6-(*tert*-butyldiphenylsilyloxy)-4-methylocta-2,4-dienyl)-4,6-dimethylhept-2-enamide (32b) Generated through Negishi Cross-Coupling. A solution of **31** (594 mg, 1.0 mmol, 1.5 equiv) in dry diethyl ether (2 mL) was treated with *t*-BuLi (1.18 mL, 1.7 M in pentane, 2 mmol, 3.0 equiv) at −78 °C for 30 min and then with a solution of $ZnCl_2$ (1.0 mL, 1 M THF solution, 1.0 mmol, 1.5 equiv) at −78 °C for another 20 min. The reaction mixture was transferred to 0 °C, treated with a solution of **30b** (286 mg, 0.67 mmol, 1 equiv) and $Pd(PPh_3)_4$ (77 mg, 0.067 mmol, 0.1 equiv) in THF (3 mL), and stirred overnight with warming to rt. The reaction was quenched with saturated NH_4Cl solution (3 mL), extracted with CH_2Cl_2 (3 × 5 mL), washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. This crude product was purified by flash chromatography (silica gel, 20% EtOAc/hexane) to afford product **32b** (478 mg, 93%) as a colorless oil: $[\alpha]^{20}_D$ −38.3 (*c* = 0.8, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) 7.63 (m, 4H), 7.35 (m, 11H), 6.87 (dd, *J* = 15.2, 8.0 Hz, 1H), 5.99 (d, *J* = 15.6 Hz, 1H), 5.76 (d, *J* = 15.2 Hz, 1H), 5.43 (dt, *J* = 15.6, 6.4 Hz, 1H), 5.37 (d, *J* = 8.8 Hz, 1H), 5.36 (br, 1H), 4.67 (m, 1H), 4.55 (s, 2H), 3.92 (m, 2 H), 3.62 (m, 1H), 3.50 (m, 1H), 3.08 (m, 1H), 2.59 (m, 1H), 1.84 (m, 2H), 1.59 (m, 1H), 1.23 (s, 3H), 1.11 (d, *J* = 6.8 Hz, 3H), 1.02 (s, 9H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.81 (s, 9H), −0.05 (s, 3H), −0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$)165.5, 147.9, 138.8, 136.9, 135.9, 135.8, 135.8, 135.3, 134.4, 134.2, 132.3, 129.4, 129.3, 128.3, 127.6, 127.4, 127.3, 123.6, 122.6, 87.9, 75.2, 67.6, 59.3, 41.5, 41.4, 39.7, 31.2, 27.0, 25.8, 20.3, 19.3, 18.1, 17.4, 15.1, 12.4, −5.4 ppm; IR (thin film) υ_{max} 3293, 2955, 2940, 1730, 1629, 1211, 1101, 867 cm^{-1}; HRMS (CI/NH_3) *m*/*z* calcd for $C_{47}H_{69}NO_4Si_2Na$ [M + Na]$^+$ 790.4663, found 790.4634.

(3*R*,4*R*,*E*)-7-((*S*,2*E*,4*E*)-8-(*tert*-Butyldimethylsilyloxy)-6-(*tert*-butyldiphenylsilyloxy)-4-methylocta-2,4-dienylamino)-2,4-dimethyl-7-oxohept-5-en-3-yl Acetate (32c) Generated through Negishi Cross-Coupling. A solution of **31** (891 mg, 1.5 mmol, 1.5 equiv) in dry diethyl ether (3 mL) was treated with *t*-BuLi (1.77 mL, 1.7 M in pentane, 3 mmol, 3.0 equiv) at −78 °C for 30 min and then with a solution of $ZnCl_2$ (1.5 mL, 1 M THF solution, 1.5 mmol, 1.5 equiv) at −78 °C for another 20 min. The reaction mixture was transferred to 0 °C, treated with a solution of **30c** (380 mg, 1 mmol, 1 equiv) and $Pd(PPh_3)_4$ (115 mg, 0.1 mmol, 0.1 equiv) in THF (5 mL), and stirred overnight with warming to rt. The reaction was quenched with aqueous NH_4Cl (5 mL), extracted with CH_2Cl_2 (3 × 10 mL), washed with brine, dried over $MgSO_4$, filtered, and concentrated. This crude product was purified by flash chromatography (silica gel, 20% EtOAc/hexane) to afford product **32c** (662 mg, 92%) as a colorless oil: $[\alpha]^{20}_D$ −40.2 (*c* = 0.4, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) 7.61 (m, 4H), 7.32 (m, 6H), 6.68 (dd, *J* = 15.2, 8.0 Hz, 1H), 5.98 (d, *J* = 15.6 Hz, 1H), 5.78 (d, *J* = 15.6 Hz, 1H), 5.53 (br, 1H), 5.43 (dt, *J* = 15.6, 6.4 Hz, 1H), 5.37 (d, *J* = 8.8 Hz, 1H), 4.75 (m, 1H), 4.66 (m, 1H), 3.92 (m, 2 H), 3.69 (m, 1H), 3.49 (m, 1H), 2.59 (m, 1H), 2.05 (s, 3H), 1.85 (m, 2H), 1.58 (m, 1H), 1.22 (s, 3H), 1.01 (s, 9H), 1.00 (d, *J* = 5.2 Hz, 3H), 0.86 (m, 6H), 0.80 (s, 9H), −0.05 (s, 3H), −0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$)170.9, 165.3, 145.3, 136.8, 135.8, 135.8, 135.3, 134.4, 134.1, 132.3, 129.4, 129.3, 127.4, 127.2, 123.7, 123.5, 79.7, 67.6, 59.3, 41.5, 41.4, 38.3, 29.7, 26.9, 25.8, 20.8, 19.7, 19.3, 18.1, 16.3, 15.3, 12.4, −5.5 ppm; IR (thin film) ν_{max} 3277, 2958, 2931, 1742, 1629, 1239, 1105, 702 cm^{-1}; HRMS (CI/NH_3) *m*/*z* calcd for $C_{42}H_{65}NO_5Si_2Na$ [M + Na]$^+$ 742.4299, found 742.4293.

(3*R*,4*R*,*E*)-7-((*S*,2*E*,4*Z*)-5,7-Bis(*tert*-butyldimethylsilyloxy)-4-ethylidenehept-2-enylamino)-2,4-dimethyl-7-oxohept-5-en-3-yl Acetate (33b) and (3*R*,4*R*,*E*)-7-((*E*)-8-(*tert*-Butyldimethylsilyloxy)-4-methylocta-2,4,5-trienylamino)-2,4-dimethyl-7-oxohept-5-en-3-yl Acetate (34b) Generated through Alkyne−alkyne Reductive Coupling. To a −78 °C solution of alkyne **22** (68 mg, 0.2 mmol, 2 equiv) in toluene (2 mL) were added sequentially $ClTi(OiPr)_3$ (1.0 M in hexanes, 0.2 mL, 0.2 mmol, 2 equiv) and *c*-C_5H_9MgCl (2.0 M in Et_2O, 0.2 mL, 0.4 mmol, 4 equiv) dropwise. The resulting yellow solution turned brown while warming slowly to −30 °C over 1.5 h. The reaction mixture was stirred at −30 °C for another 1 h and then cooled to −78 °C at which point terminal alkyne **14c** (25 mg, 0.1 mmol, 1 equiv) in toluene (0.5 mL) was added slowly to the reaction by syringe. After being warmed slowly to −30 °C over 1.5 h, the reaction mixture was further stirred at −30 °C for an additional 1 h. The reaction was quenched with saturated NH_4Cl solution (3 mL). The mixture was warmed to rt before extracting with EtOAc (3 × 5 mL). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated. Purification over silica gel (20% EtOAc/hexane) afforded diene **33b** (29 mg, 49% yield) as a colorless oil and allene **34b** (18 mg, 39% yield) as a colorless oil (single diastereomer, the absolute configuration was not determined). **33b**: $[\alpha]^{20}_D$ −16.2 (*c* = 2.1, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 6.65 (dd, *J* = 15.0, 8.0 Hz, 1H), 6.02 (d, *J* = 16.0 Hz, 1H), 5.90 (dt, *J* = 15.5, 6.0 Hz, 1H), 5.75 (dd, *J* = 15.5, 1.0 Hz, 1H), 5.52 (q, *J* = 7.0 Hz, 1H), 5.39 (br, 1H), 4.84 (m, 1H), 4.74 (m, 1H), 3.96 (m, 1H), 3.86 (m, 1H), 3.64 (m, 1H), 3.54 (m, 1H), 2.57 (m, 1H), 2.04 (s, 3H), 1.86 (m, 2H), 1.70 (d, *J* = 7.0 Hz, 3H), 1.58 (m, 1H), 1.00 (d, *J* = 7.0 Hz, 3H), 0.86 (m, 24H), 0.02 (s, 6H), 0.01 (s, 3H), −0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 170.8, 165.2, 145.2, 140.5, 132.9, 125.0, 124.1, 123.9, 79.7, 66.1, 59.4, 42.1, 39.9, 38.4, 29.7, 25.9, 25.8, 20.8, 19.7, 18.2, 18.1, 16.2, 15.5, 13.6, −4.9, −5.2, −5.3, −5.4 ppm; IR (thin film) υ_{max} 3278, 2957, 2930, 2857, 1743, 1240, 1090, 836, 776 cm^{-1}; HRMS (CI/NH_3) *m*/*z* calcd for $C_{32}H_{61}NO_5Si_2Na$ [M + Na]$^+$ 618.3986, found 618.3967. **34b**: $[\alpha]^{20}_D$ +23.1 (*c* = 1.7, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 6.68 (dd, *J* = 15.5, 8.5 Hz, 1H), 6.11 (d, *J* = 15.5 Hz, 1H), 5.78 (dd, *J* = 15.5, 1.0 Hz, 1H), 5.50 (m, 2H), 5.19 (s, 1H), 4.74 (m, 1H), 3.97 (br, 2H), 3.64 (t, *J* = 6.5 Hz, 2H), 2.58 (m, 1H), 2.19 (m, 2H), 2.05 (s, 3H), 1.84 (m, 1H), 1.75 (s, 3H), 1.00 (d, *J* = 6.5 Hz, 3H), 0.86 (m, 15H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 207.5, 170.9, 165.3, 145.4, 132.0, 123.7, 123.4, 99.1, 87.3, 79.8, 62.8, 41.5, 38.4, 32.6, 29.7, 25.9, 20.8, 19.7, 18.3, 16.4, 15.6, 15.3, −5.3 ppm; IR (thin film) ν_{max} 3289, 2959, 2930, 2857, 1959, 1741, 1670, 1240, 1100, 836 cm^{-1}.

(3*R*,4*R*,*E*)-7-((*S*,2*E*,4*E*)-8-(*tert*-Butyldimethylsilyloxy)-6-hydroxy-4-methylocta-2,4-dienylamino)-2,4-dimethyl-7-oxohept-5-en-3-yl Acetate (35c) through Alkoxide-Directed Alkyne−alkyne Reductive Coupling. To a −78 °C solution of alkyne **13** (68 mg, 0.3 mmol, 3 equiv) in Et_2O (3 mL) were added sequentially *n*-BuLi (2.5 M in hexanes, 112 *μ*L, 0.28 mmol, 2.8 equiv), $ClTi(OiPr)_3$ (1.0 M in hexanes, 280 *μ*L, 0.28 mmol, 2.8 equiv), and *c*-C_5H_9MgCl (2.0 M in Et_2O, 280 *μ*L, 0.56 mmol, 5.6 equiv) dropwise. The resulting yellow solution turned brown while warming slowly to −30 °C over 1.5 h. The reaction mixture was stirred at −30 °C for an additional 1 h and then cooled to −78 °C at which point terminal alkyne **14c** (25 mg, 0.1 mmol, 1 equiv) in Et_2O (0.5 mL) was added slowly by syringe to the reaction flask. After being warmed slowly to −30 °C over 1.5 h, the mixture was further stirred at −30 °C for another 10 h. The reaction was quenched with saturated NH_4Cl solution (2 mL). The mixture was warmed to rt before extracting with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification over silica gel (30% EtOAc/hexane) afforded product **35c** (34 mg, 71% yield) as a colorless oil and as a single regioisomer: $[\alpha]^{20}_D$ +15.8 (*c* = 0.6, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 6.68 (dd, *J* = 15.5, 8.0 Hz, 1H), 6.16 (d, *J* = 15.5 Hz, 1H), 5.78 (dd, *J* = 15.5, 1.5 Hz, 1H), 5.64 (dt, *J* = 15.5, 6.5 Hz, 1H), 5.54 (br, 1H), 5.48 (d, *J* = 8.5 Hz, 1H), 4.74 (m, 1H), 4.68 (m, 1H), 3.96 (m, 2H), 3.86 (m, 1H), 3.77 (m, 1H), 3.13 (br, 1H), 2.58 (m, 1H), 2.05 (s, 3H), 1.83 (m, 2H), 1.75 (s, 3H), 1.63 (m, 1H), 1.00 (d, *J* = 7.0 Hz, 3H), 0.87 (s, 9H), 0.85 (m, 6H), −0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 171.0, 165.4, 145.5, 136.7, 134.6, 133.7, 124.3, 123.6, 79.7, 68.3, 61.9, 41.5, 38.7, 38.4, 29.7, 25.8, 20.9, 19.7, 18.1, 16.3, 15.3, 12.8, −5.5; IR (thin film) υ_{max} 3293, 2959, 1741, 1669, 1631, 1540, 1240, 1096, 836 cm^{-1}; HRMS (CI/NH_3) *m*/*z* calcd for $C_{26}H_{47}NO_5SiNa$ [M + Na]$^+$ 504.3121, found 504.3124.

(4*R*,5*R*,*E*)-*N*-((*S*,2*E*,4*E*)-8-(*tert*-Butyldimethylsilyloxy)-6-hydroxy-4-methylocta-2,4-dienyl)-5-hydroxy-4,6-dimethylhept-2-enamide (35d) through Alkoxide-Directed Alkyne−alkyne Reductive Coupling. To a solution of alkyne **13** (136 mg, 0.6 mmol,

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3 equiv) in Et_2O (2 mL) at −78 °C were added sequentially *n*-BuLi (2.5 M in hexanes, 224 μL, 0.56 mmol, 2.8 equiv), $ClTi(O\text{-}i\text{-}Pr)_3$ (1.0 M in hexanes, 560 μL, 0.56 mmol, 2.8 equiv), and *c*-C_5H_9MgCl (2.0 M in Et_2O, 560 μL, 1.12 mmol, 5.6 equiv) dropwise. The resulting yellow solution turned brown while warming slowly to −30 °C over 1.5 h. The reaction mixture was stirred at −30 °C for an additional 1 h and then cooled to −78 °C at which point terminal alkyne **14a** (42 mg, 0.2 mmol, 1 equiv) in Et_2O (1 mL) was added slowly to the reaction by syringe. After being warmed slowly to −30 °C over 1.5 h, the mixturew was further stirred at −30 °C for another 24 h. The reaction was quenched with saturated NH_4Cl solution (3 mL). The mixture was warmed to rt before extracting with EtOAc (3 × 5 mL). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification over silica gel (50% EtOAc/hexane) afforded product **35d** (42 mg, 48% yield) as a colorless oil with recovered starting material **14a** (8 mg): $[\alpha]^{20}_D$ +16.2 (*c* = 2.4, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 6.78 (dd, *J* = 15.6, 8.0 Hz, 1H), 6.17 (d, *J* = 15.6 Hz, 1H), 5.81 (d, *J* = 15.2 Hz, 1H), 5.64 (dt, *J* = 14.8, 6.0 Hz, 1H), 5.64 (br, 1H), 5.47 (d, *J* = 8.4 Hz, 1H), 4.68 (m, 1H), 3.98 (m, 2H), 3.85 (m, 1H), 3.76 (m, 1H), 3.23 (t, *J* = 5.2 Hz, 1H), 3.21 (br, 1H), 2.47 (m, 1H), 1.75 (s, 3H), 1.59−1.80 (m, 3H), 1.06 (d, *J* = 6.5 Hz, 3H), 0.88 (m, 6H), 0.89 (s, 9H), −0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 147.5, 136.7, 134.7, 133.7, 124.4, 123.2, 79.2, 68.2, 61.8, 41.5, 39.6, 38.8, 30.8, 25.8, 19.7, 18.1, 16.7, 14.0, 12.8; IR (thin film) ν_{max} 3294, 2957, 2929, 2858, 1668, 1628, 1547, 1255, 1096, 836 cm^{-1}; HRMS (CI/NH_3) *m*/*z* calcd for $C_{24}H_{45}NO_4NaSi$ $[M + Na]^+$ 462.3016, found 462.3001.

(3*R*,4*R*,*E*)-7-((*S*,2*E*,4*E*)-6-Hydroxy-4-methyl-8-phenylocta-2,4-dienylamino)-2,4-dimethyl-7-oxohept-5-en-3-yl Acetate (35e) through Alkoxide-Directed Alkyne−alkyne Reductive Coupling. To a −78 °C solution of alkyne **36** (53 mg, 0.3 mmol, 3 equiv) in Et_2O (3 mL) were added sequentially *n*-BuLi (2.5 M in hexanes, 112 μL, 0.28 mmol, 2.8 equiv), $ClTi(O\text{-}i\text{-}Pr)_3$ (1.0 M in hexanes, 280 μL, 0.28 mmol, 2.8 equiv), and *c*-C_5H_9MgCl (2.0 M in Et_2O, 280 μL, 0.56 mmol, 5.6 equiv) dropwise. The resulting yellow solution turned brown while warming slowly to −30 °C over 1.5 h. The reaction mixture was stirred at −30 °C for an additional 1 h and then cooled to −78 °C at which point terminal alkyne **14c** (25 mg, 0.1 mmol, 1 equiv) in Et_2O (0.5 mL) was added slowly by syringe to the reaction flask. After warming slowly to −30 °C over 1.5 h, the mixture was further stirred at −30 °C for another 12 h. The reaction was quenched with saturated NH_4Cl solution (2 mL). The mixture was warmed to rt before extracting with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification over silica gel (40% EtOAc/hexane) afforded allene **34e** (11 mg, 26% yield) and (70% EtOAc/hexane) the desired product **35e** (23 mg, 55% yield) as a colorless oil: $[\alpha]^{20}_D$ −1.0 (*c* = 1.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 2H), 7.16 (m, 3H), 6.69 (dd, *J* = 15.2, 8.0 Hz, 1H), 6.18 (d, *J* = 15.6 Hz, 1H), 5.80 (d, *J* = 15.2 Hz, 1H), 5.70 (m, 2H), 5.47 (d, *J* = 8.4 Hz, 1H), 4.76 (dd, *J* = 7.2, 5.2 Hz, 1H), 4.47 (q, *J* = 8.0 Hz, 1H), 3.99 (t, *J* = 6.0 Hz, 2H), 2.64 (m, 3H), 2.06 (s, 3H), 1.85 (m, 2H), 1.79 (m, 1H), 1.73 (s, 3H), 1.01 (d, *J* = 6.4 Hz, 3H), 0.86 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 165.5, 145.5, 141.7, 136.4, 134.6, 134.5, 128.3, 125.8, 124.8, 123.6, 79.8, 67.8, 41.4, 38.9, 38.3, 31.6, 29.7, 20.8, 19.7, 16.4, 15.2, 12.9 ppm; IR (thin film) υ_{max} 3286, 2967, 2936, 1739, 1240, 1121, 700 cm^{-1}; HRMS (CI/NH_3) *m*/*z* calcd for $C_{26}H_{37}NO_4Na$ $[M + Na]^+$ 450.2620, found 450.2617.

(4*E*,6*E*)-1-(*tert*-Butyldimethylsilyloxy)-5-methyltrideca-4,6-dien-3-ol (35f) through Alkoxide-Directed Alkyne−alkyne Reductive Coupling. To a −78 °C solution of alkyne ***rac*-13** (68 mg, 0.3 mmol, 3 equiv) in Et_2O (3 mL) were added sequentially *n*-BuLi (2.5 M in hexanes, 112 μL, 0.28 mmol, 2.8 equiv), $ClTi(OiPr)_3$ (1.0 M in hexanes, 280 μL, 0.28 mmol, 2.8 equiv), and *c*-C_5H_9MgCl (2.0 M in Et_2O, 280 μL, 0.56 mmol, 5.6 equiv) dropwise. The resulting yellow solution turned brown while warming slowly to −30 °C over 1.5 h. The reaction mixture was stirred at −30 °C for an additional 1 h then cooled to −78 °C at which point 1-octyne **37** (11 mg, 0.1 mmol, 1 equiv) in Et_2O (0.5 mL) was added slowly by syringe to the reaction flask. After warming slowly to −30 °C over 1.5 h, the mixture was further stirred at −30 °C for another 12 h. The reaction was quenched with saturated NH_4Cl solution (2 mL). The mixture was warmed to rt before extracting with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification over silica gel (2% EtOAc/hexane) afforded allene **34f** (6 mg, 20% yield) and (20% EtOAc/hexane) the desired product **35f** (21 mg, 62% yield) as a colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 6.02 (d, *J* = 15.5 Hz, 1H), 5.64 (dt, *J* = 15.5, 7.0 Hz, 1H), 5.37 (d, *J* = 8.5 Hz, 1H), 4.68 (m, 1H), 3.84 (m, 1H), 3.77 (m, 1H), 2.91 (br, 1H), 2.06 (q, *J* = 6.5 Hz, 2H), 1.78 (m, 1H), 1.76 (s, 3H), 1.64 (m, 1H), 1.33 (m, 2H), 1.23 (m, 6H), 0.89 (m, 12H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.9, 134.2, 131.9, 130.1, 68.0, 61.7, 39.1, 32.8, 31.7, 29.5, 28.9, 25.9, 22.6, 18.1, 14.1, 12.9, −5.5, −5.5 ppm; IR (thin film) ν_{max} 3396, 2955, 2928, 2858, 1471, 1255, 1096, 836 cm^{-1}; HRMS (CI/NH_3) *m*/*z* calcd for $C_{20}H_{39}OSi$ $[M + H - H_2O]^+$ 323.2770, found 323.2782.

(4*R*,5*R*,*E*)-*N*-((*S*,2*E*,4*E*)-8-(*tert*-Butyldimethylsilyloxy)-6-(*tert*-butyldiphenylsilyloxy)-4-methylocta-2,4-dienyl)-5-hydroxy-4,6-dimethylhept-2-enamide (11). Diol **35d** (137 mg, 0.3 mmol, 1 equiv) and TBDPSCl (83 mg, 0.3 mmol, 1 equiv) were dissolved in dry CH_2Cl_2 (3 mL, 0.1 M) and cooled to 0 °C. Imidazole (62 mg, 0.9 mmol, 3 equiv) was added to the solution, and this mixture was further stirred at 0 °C for another 3 h under an argon atmosphere. The mixture was poured into saturated NH_4Cl solution (2 mL) and extracted with CH_2Cl_2 (2 × 5 mL). The combined organic phases were dried by $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, 40% EtOAc/hexane) to afford the product **11** (186 mg, 92% yield) as a white glassy type solid: $[\alpha]^{20}_D$ −30.0 (*c* = 0.4, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (m, 4H), 7.32 (m, 6H), 6.80 (dd, *J* = 15.2, 7.6 Hz, 1H), 5.98 (d, *J* = 16.0 Hz, 1H), 5.78 (d, *J* = 15.6 Hz, 1H), 5.43 (dt, *J* = 15.6, 6.4 Hz, 1H), 5.38 (m, 2H), 4.66 (m, 1H), 3.92 (m, 2 H), 3.60 (m, 1H), 3.49 (m, 1H), 3.26 (m, 1H), 2.48 (m, 1H), 1.83 (m, 1H), 1.72 (m, 1H), 1.58 (m, 1H), 1.22 (d, *J* = 15.6 Hz, 4.8 Hz, 3H), 1.08 (d, *J* = 6.8 Hz, 3H), 1.01 (s, 9H), 0.89 (m, 6H), 0.80 (s, 9H), −0.05 (s, 3H), −0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 147.6, 136.8, 135.8, 135.8, 135.3, 134.4, 134.1, 132.3, 129.4, 129.3, 127.4, 127.2, 123.6, 123.2, 79.1, 67.6, 59.3, 41.5, 41.4, 39.6, 30.8, 26.9, 25.8, 19.7, 19.3, 18.1, 16.8, 13.8, 12.4, −5.5 ppm; IR (thin film) ν_{max} 3294, 2957, 2930, 2857, 1668, 1629, 1256, 1106, 702 cm^{-1}; HRMS (CI/NH_3) *m*/*z* calcd for $C_{40}H_{63}NO_4Si_2Na$ $[M + Na]^+$ 700.4193, found 700.4176.

2-(Chloromethyl)oxazole-4-carboxylic Acid (42). Oxazole ester **41** (1.75 g, 10 mmol, 1 equiv) was dissolved in THF (70 mL) and H_2O (18 mL) cosolvent. LiOH (360 mg, 15 mmol, 1.5 equiv) was added to this mixture at rt in one portion and stirred for another 12 h. CH_2Cl_2 (100 mL) and water (100 mL) were added to this mixture, and the aqueous phase was adjusted to pH 4 using a $KHSO_4$ (1 M) solution. The organic phase was separated, and the aqueous phase was extracted with EtOAc (3 × 80 mL). The combined organic phases were dried over Na_2SO_4, filtered, and evaporated under reduced pressure to afford product **42** (1.53 mg, 95% yield) as a white solid, which was pure enough for further use: ^1H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 4.66 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 160.4, 146.1, 133.2, 35.1 ppm; IR (thin film) ν_{max} 3137, 1682, 1589, 1442, 1305, 1114, 988, 880 cm^{-1}; HRMS (CI/NH_3) *m*/*z* calcd for $C_5H_5ClNO_3$ $[M + H]^+$ 161.9958, found 161.9950.

(*R*)-Benzyl 1-(2-(Chloromethyl)oxazole-4-carbonyl)-pyrrolidine-2-carboxylate (43). The oxazole acid **42** (730 mg, 4.54 mmol, 1 equiv) was dissolved in CH_2Cl_2 (60 mL), and EDC·HCl (870 mg, 4.54 mmol, 1 equiv) was added to the solution. After the solution was stirred for 30 min, NH(HCl)-Pro-OBn (1.2 g, 5.0 mmol, 1.1 equiv) and TEA (0.63 mL, 45.4 mmol, 1 equiv) were added, and the mixture was stirred for another 12 h. CH_2Cl_2 (50 mL) and water (50 mL) were added, and the aqueous phase was adjusted to pH 4 using a $KHSO_4$ (1 M) solution. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phase was dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (20% to 30% EtOAc/hexane) to

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afford product **43** (1.26 g, 80% yield) as a mixture of 1:1 rotamers: $[\alpha]^{20}_{D}$ +35.6 (c = 0.8, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23** (s, 1H), 8.18* (s, 1H), 7.32 (m, 5H), 5.29* (dd, J = 8.8, 3.2 Hz, 1H), 5.17 (m, 2H), 4.67** (dd, J = 8.8, 4.0 Hz, 1H), 4.60** (s, 2H), 4.24* (q, J = 12.8 Hz, 2H), 4.07** (m, 2H), 3.81* (m, 1H), 3.70* (m, 1H), 2.07 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 171.8, 159.8, 158.3, 158.0, 144.8, 144.7, 137.6, 137.5, 135.7, 135.6, 128.5, 128.4, 128.4, 128.2, 128.1, 128.0, 66.8, 60.5*, 59.9**, 48.8**, 47.6*, 35.6**, 35.3*, 31.6*, 28.5**, 25.2**, 21.9* ppm; IR (thin film) υ_{max} 3471, 3033, 2957, 2882, 1744, 1627, 1427, 1173, 751 cm^{-1}; HRMS (CI/NH_3) m/z calcd for $C_{17}H_{17}ClN_2O_4Na$ [M + Na]$^+$ 371.0775, found 371.0781.

(*R*)-1-(2-(Chloromethyl)oxazole-4-carbonyl)pyrrolidine-2-carboxylic Acid (12). Oxazole benzyl ester **43** (696 mg, 2 mmol, 1 equiv) was dissolved in dry CH_2Cl_2 (60 mL) and cooled to −20 °C. BCl_3 (6 mL, 1 M solution in hexane, 6 mmol, 3 equiv) was added dropwise to the reaction. It was further stirred for 3 h while the temperature was allowed to warm to 0 °C. Then EtOAc (50 mL) and saturated aqueous $NaHCO_3$ solution (50 mL) were added, and the aqueous phase was acidified to pH 2 by adding $KHSO_4$ (1 M) solution. The phase was separated, and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated. The residue was purified by column chromatography on silica gel (5% MeOH/CH_2Cl_2) to afford the acid product **12** (360 mg, 70% yield) as a mixture of 3:1 rotamers: $[\alpha]^{20}_{D}$ +128.0 (c = 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30* (s, 1H), 8.27** (s, 1H), 5.28** (dd, J = 4.8, 4.0 Hz, 1H), 4.72* (d, J = 5.2 Hz, 1H), 4.58* (s, 2H), 4.55** (s, 2H), 4.09* (m, 2H), 3.73** (m, 2H), 1.92−2.37 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7**, 173.3*, 161.6*, 159.9**, 158.7*, 158.2**, 145.7*, 145.0**, 137.3**, 136.8*, 60.8*, 60.2**, 49.5*, 47.6**, 35.5**, 35.4*, 31.4**, 27.4*, 25.3*, 21.8** ppm; IR (thin film) ν_{max} 3128, 2967, 1733, 1586, 1448, 1180, 1116, 748 cm^{-1}; HRMS (CI/NH_3) m/z calcd for $C_{10}H_{11}ClN_2O_4Na$ [M + Na]$^+$ 281.0305, found 281.0310.

(*R*)-((3*R*,4*R*,*E*)-7-((*S*,2*E*,4*E*)-8-(*tert*-Butyldimethylsilyloxy)-6-(*tert*-butyldiphenylsilyloxy)-4-methylocta-2,4-dienylamino)-2,4-dimethyl-7-oxohept-5-en-3-yl) 1-(2-(Chloromethyl)-oxazole-4-carbonyl)pyrrolidine-2-carboxylate (44). 2,4,6-Trichlorobenzoyl chloride (35 μL, 0.225 mmol, 2.25 equiv) was added under argon to a suspension of oxazole acid **12** (39 mg, 0.15 mmol, 1.5 equiv) in benzene (0.5 mL), followed by DIPEA (39 μL, 0.225 mmol, 2.25 equiv), and the reaction turned into a clear solution. A solution of TBDPS ether **11** (66 mg, 0.1 mmol, 1 equiv) in benzene (0.5 mL) was added to the resulting solution, after which DMAP (27 mg, 0.225 mmol, 2.25 equiv) was added in one portion. The mixture was stirred overnight, diluted with EtOAc (2 mL), and washed with water (2 mL). The water phase was extracted by EtOAc (3 × 5 mL). The combined organic phase were dried over $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography on silica gel (35% EtOAc/hexane) to afford product **44** (79 mg, 86% yield) as a mixture of 1:1 rotamers: $[\alpha]^{20}_{D}$ +6.4 (c = 0.8, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24** (s, 1H), 8.17* (s, 1H), 7.60 (m, 4H), 7.32 (m, 6H), 6.57 (m, 1H), 5.99 (m, 1H), 5.79* (d, J = 15.6 Hz, 1H), 5.72** (d, J = 15.2 Hz, 1H), 5.54** (m, 1H), 5.47 (m, 2H), 5.37 (d, J = 9.2 Hz, 1H), 4.77 (m, 1H), 4.67* (m, 1H), 4.65 (m, 1H), 4.57* (s, 2H), 4.51** (s, 2H), 4.09 (m, 1H), 3.93 (m, 2H), 3.72 (m, 1H), 3.52 (m, 2H), 2.57 (m, 1H), 2.28 (m, 1H), 2.04 (m, 1H), 1.91 (m, 3H), 1.60 (m, 2H), 1.22 (s, 3H), 1.01 (s, 9H), 0.99 (m, 3H), 0.94 (m, 6H), 0.80 (s, 9H), −0.06 (s, 3H), −0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 171.2, 165.8, 165.1, 159.7, 158.3, 145.3, 145.0, 144.8, 144.7, 137.7, 137.5, 137.0, 136.7, 135.9, 135.9, 135.5, 135.3, 134.4, 134.4, 134.2, 134.2, 132.4, 132.3, 129.4, 129.3, 127.4, 127.3, 124.3, 123.9, 123.8, 123.5, 81.2, 80.8, 67.7, 60.4, 60.3, 59.4, 59.4, 48.8, 47.2, 41.5, 41.4, 38.3, 37.7, 35.5, 35.5, 31.6, 30.0, 29.9, 28.8, 27.0, 25.9, 25.3, 21.5, 19.7, 19.4, 19.3, 18.1, 17.5, 17.1, 14.7, 14.2, 12.4, 12.4, −5.4 ppm; IR (thin film) ν_{max} 3750, 3300, 2931, 2857, 1742, 1671, 1634, 1427, 1110, 702 cm^{-1}; HRMS (CI/NH_3) m/z calcd for $C_{50}H_{72}ClN_3O_7NaSi_2$ [M + Na]$^+$ 940.4495, found 940.4487.

(*R*)-((3*R*,4*R*,*E*)-7-((*S*,2*E*,4*E*)-6-(*tert*-Butyldiphenylsilyloxy)-8-hydroxy-4-methylocta-2,4-dienylamino)-2,4-dimethyl-7-oxohept-5-en-3-yl) 1-(2-(Chloromethyl)oxazole-4-carbonyl)pyrrolidine-2-carboxylate. To a solution of **44** (44 mg, 0.048 mmol, 1 equiv) in a mixture of CH_2Cl_2 (0.5 mL) and MeOH (0.5 mL) at 0 °C was added CSA (2.5 mg, 0.01 mmol, 0.2 equiv) in one portion. Stirring was maintained at 0 °C for an additional 1 h prior to quenching with saturated $NaHCO_3$ solution (1 mL). The separated aqueous layer was extracted with EtOAc (3 × 3 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (50% EtOAc/hexane) to afford the alcohol product (38 mg, 62% yield) as a mixture of 1:1 rotamers, with recovering starting material **44** (25 mg): $[\alpha]^{20}_{D}$ −32.2 (c = 1.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19** (s, 1H), 8.11* (s, 1H), 7.56 (m, 4H), 7.33 (m, 6H), 6.53 (m, 1H), 6.01* (m, 1H), 5.96 (m, 1H), 5.72* (d, J = 16.0 Hz, 1H), 5.66** (d, J = 15.6 Hz, 1H), 5.50** (m, 1H), 5.45 (m, 2H), 5.39** (m, 1H), 4.71 (m, 1H), 4.64 (m, 1H), 4.60** (m, 1H), 4.53* (s, 2H), 4.46** (s, 2H), 4.03 (m, 1H), 3.95 (m, 1H), 3.83 (m, 1H), 3.68 (m, 2H), 3.55 (m, 1H), 2.52 (m, 1H), 2.20 (m, 1H), 2.17* (m, 1H), 2.02** (m, 1H), 1.79−2.01 (m, 3H),1.70 (m, 2H), 1.48 (s, 3H), 1.19 (s, 9H), 0.99 (s, 9H), 0.82−0.93 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0**, 171.7*, 166.0*, 165.2**, 159.8, 158.4**, 158.3*, 145.3**, 145.1*, 144.8*, 144.7**, 137.7**, 137.5*, 136.5**, 136.2*, 135.9**, 135.8*, 134.6**, 134.3*, 133.7*, 133.7**, 132.6*, 132.4**, 129.7*, 129.6**, 127.6*, 127.4**, 124.5*, 124.3**, 124.0*, 123.8**, 81.2**, 80.9*, 69.2*, 69.2**, 60.4**, 60.3*, 59.8*, 59.7**, 48.8**, 47.2*, 41.5, 40.0, 38.2**, 37.7*, 35.5**, 35.4*, 31.6**, 30.0**, 29.9*, 28.8*, 27.0, 25.3*, 21.4**, 19.6, 19.4, 19.2, 17.6*, 17.3**, 14.2**, 14.0*, 12.4 ppm; IR (thin film) υ_{max} 3305, 2977, 2325, 1756, 1683, 702 cm^{-1}; HRMS (CI/NH_3) m/z calcd for $C_{44}H_{58}ClN_3O_7NaSi$ [M + Na]$^+$ 826.3630, found 826.3613.

(*R*)-((3*R*,4*R*,*E*)-7-((*S*,2*E*,4*E*)-6-(*tert*-Butyldiphenylsilyloxy)-4-methyl-8-oxoocta-2,4-dienylamino)-2,4-dimethyl-7-oxohept-5-en-3-yl) 1-(2-(Chloromethyl)oxazole-4-carbonyl)pyrrolidine-2-carboxylate (10). IBX (29.5 mg, 0.1 mmol, 2 equiv) was added to the alcohol (42 mg, 0.05 mmol, 1 equiv) in DMSO (1 mL) at rt. After stirring 6 h, the reaction was quenched by addition of CH_2Cl_2 (2 mL) and water (1 mL). Saturated aqueous $NaHCO_3$ (1 mL) was then added, and the mixture was further stirred for 10 min. Then the layers were separated and the aqueous layer was extracted with EtOAc (3 × 3 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography on silica gel (40% EtOAc/hexane) to afford the aldehyde product **10** (38 mg, 92% yield) as a mixture of 1:1 rotamers: $[\alpha]^{20}_{D}$ −12.0 (c = 0.4, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (m, 1H), 8.23** (s, 1H), 8.15* (s, 1H), 7.59 (m, 4H), 7.37 (m, 6H), 6.57 (m, 1H), 6.18* (t, J = 5.6 Hz, 1H), 6.00* (d, J = 15.6 Hz, 1H), 5.99** (d, J = 15.6 Hz, 1H), 5.77* (d, J = 15.6 Hz, 1H), 5.72** (d, J = 15.2 Hz, 1H), 5.61** (t, J = 6.0 Hz, 1H), 5.52 (m, 1H), 5.47 (d, J = 9.2 Hz, 1H), 5.43* (m, 1H), 4.92 (m, 1H), 4.75 (m, 1H), 4.63** (m, 1H), 4.57* (s, 2H), 4.51** (s, 2H), 4.08 (m, 2H), 3.92 (m, 1H), 3.72 (m, 1H), 2.48−2.62 (m, 3H), 2.17−2.29 (m, 2H), 1.72−2.12 (m, 5H), 1.25 (s, 3H), 0.99 (s, 9H), 0.84−0.95 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.0, 171.8, 171.5, 165.7, 165.1, 164.9, 159.7, 158.3, 158.2, 144.9, 144.8, 144.5, 144.3, 137.5, 137.2, 135.6, 135.4, 135.3, 133.3, 133.1, 133.0, 132.7, 132.6, 132.5, 129.7, 129.5, 127.5, 127.3, 125.3, 125.2, 125.0, 124.2, 123.7, 81.0, 80.9, 80.6, 66.2, 60.2, 60.1, 51.5, 48.6, 47.0, 47.0, 41.5, 41.1, 38.0, 37.6, 37.5, 35.4, 35.3, 31.4, 29.8, 29.7, 29.1, 28.6, 26.9, 25.1, 24.7, 21.2, 19.4, 19.3, 19.2, 19.0, 17.3, 17.2, 16.9, 14.8, 14.1, 14.0, 12.4 ppm; IR (thin film) ν_{max} 3299, 3071, 2964, 2932, 2857, 1741, 1630, 1428, 1113, 704 cm^{-1}; HRMS (CI/NH_3) m/z calcd for $C_{44}H_{56}ClN_3O_7NaSi$ [M + Na]$^+$ 824.3474, found 824.3456.

(*R*)-((3*R*,4*R*,*E*)-7-((*S*,2*E*,4*E*)-6-(*tert*-Butyldiphenylsilyloxy)-4-methyl-8-oxoocta-2,4-dienylamino)-2,4-dimethyl-7-oxohept-5-en-3-yl) 1-(2-(Iodomethyl)oxazole-4-carbonyl)pyrrolidine-2-carboxylate (45). Chloroaldehyde **10** (90.5 mg, 0.045 mmol, 1 equiv) and NaI (8 mg, 0.054 mmol, 1.2 equiv) were dissolved in acetone (1.5 mL) at ambient temperature. After being stirred 6 h in the absence of light, the solution was diluted with EtOAc (2 mL) and water (4 mL). After careful evaporation of acetone, additional EtOAc (2 mL) was added. The organic phase was separated, and the aqueous phase was extracted with EtOAc (3 × 3 mL). The combined organic extracts were washed with saturated aqueous $Na_2S_2O_3$ solution

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(4 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (40% EtOAc/hexane) to afford product **45** (38 mg, 95% yield) as a mixture of 1:1 rotamers: $[\alpha]^{20}_D$ −16.0 (c = 1.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (m, 1H), 8.21** (s, 1H), 8.12* (s, 1H), 7.61 (m, 4H), 7.37 (m, 6H), 6.58 (m, 1H), 6.13* (t, J = 5.6 Hz, 1H), 6.01* (d, J = 16.0 Hz, 1H), 5.99** (d, J = 16.0 Hz, 1H), 5.77* (d, J = 15.6 Hz, 1H), 5.71** (d, J = 15.6 Hz, 1H), 5.55** (t, J = 6.0 Hz, 1H), 5.50 (m, 2H), 5.48** (m, 1H), 4.92 (m, 1H), 4.75 (m, 1H), 4.64* (m, 1H), 4.34* (s, 2H), 4.28** (s, 2H), 4.06 (m, 2H), 3.66−3.98 (m, 2H), 2.46−2.61 (m, 3H), 2.15−2.29 (m, 2H), 1.80−2.06 (m, 4H), 1.26 (s, 3H), 1.15 (m,1H), 1.00 (s, 9H), 0.88−0.98 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.2, 172.1, 171.7, 166.0, 165.2, 159.9, 159.8, 144.7, 144.5, 144.1, 138.0, 137.8, 136.1, 135.8, 135.8, 133.5, 133.3, 133.2, 133.1, 129.8, 129.7, 127.7, 127.5, 125.4, 81.2, 80.8, 66.5, 60.5, 60.4, 60.3, 51.7, 48.8, 47.2, 41.4, 38.3, 37.7, 33.9, 31.6, 30.0, 28.8, 26.9, 25.3, 24.9, 21.5, 19.8, 19.4, 19.2, 17.7, 13.9, 12.6 ppm; IR (thin film) ν_{max} 3308, 2962, 1734, 1635, 1427, 1111, 702 cm^{-1}; HRMS (CI/NH_3) m/z calcd for $C_{44}H_{56}IN_3O_7NaSi$ $[M + Na]^+$ 916.2830, found 916.2800.

(2*R*)-Benzyl 1-(2-(4-(*tert*-Butyldimethylsilyloxy)-2-hydroxybutyl)oxazole-4-carbonyl)pyrrolidine-2-carboxylate (47) and (*R*)-Benzyl 1-(2-Methyloxazole-4-carbonyl)-pyrrolidine-2-carboxylate (48). Iodide **46** (44 mg, 0.1 mmol, 1 equiv) and aldehyde **21** (19 mg, 0.1 mmol, 1 equiv) were placed into a flame-dried round-bottom flask. Dry benzene (10 mL, 0.01 M) was then added into the flask. Freshly prepared SmI_2 THF solution (0.15 M solution, 2.6 mL, 0.4 mmol, 4 equiv) was introduced by the syringe within 5 min to the stirred solution. After being stirred for another 20 min at rt, the reaction was quenched by bubbling in air, followed by the addition of saturated NH_4Cl aqueous solution (10 mL), and stirring for another 15 min. The biphasic mixture was separated, and the aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 20−40% EtOAc/hexane) to afford alcohol **47** (40 mg, 80% yield) as 1:1 diastereomers and the reduced byproduct **48** (3.5 mg, 11% yield). **47**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14* (s, 1H), 8.11** (s, 1H), 7.29 (m, 5H), 5.33* (m, 1H), 5.12 (m, 2H), 4.66** (m, 1H), 4.28* (m, 1H), 4.20** (m, 1H), 4.09 (m, 1H), 3.77 (m, 3H), 2.94 (m, 1H), 2.74 (m, 1H), 2.26 (m, 1H), 2.17 (m, 1H), 1.97 (m, 1H), 1.86 (m, 1H), 1.74 (m, 1H), 1.65 (m, 1H), 0.86 (m, 9H), 0.04 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 171.9, 161.9*, 161.9**, 160.3*, 160.3**, 143.4*, 143.3**, 136.8*, 136.8**, 135.7*, 135.5**, 128.5, 128.1, 68.7*, 68.1**, 66.8*, 66.7**, 61.5*, 61.4**, 60.7*, 60.5**, 48.7*, 47.5**, 38.1*, 37.9**, 35.7*, 35.7**, 31.7**, 28.5*, 25.8, 25.2*, 21.8**, 18.1, −5.5, −5.5 ppm; IR (thin film) ν_{max} 3428, 2954, 2856, 1747, 1617, 1436, 1170, 1093, 836 cm^{-1}; HRMS (CI/NH_3) m/z calcd for $C_{26}H_{38}N_2O_6SiNa$ $[M + Na]^+$ 525.2397, found 525.2379. **48**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09** (s, 1H), 8.06* (s, 1H), 7.30 (m, 5H), 5.32* (dd, J = 8.8, 3.2 Hz, 1H), 5.16 (m, 2H), 4.66** (dd, J = 9.2, 4.4 Hz, 1H), 4.07 (m,1H), 3.80* (m, 1H), 3.70** (m, 1H), 2.45** (s, 3H), 2.21 (m, 1H), 2.20* (s, 3H), 1.82−2.06 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 171.9, 160.7**, 160.6*, 160.6*, 160.4**, 143.3*, 143.2**, 136.9*, 136.8**, 135.8**, 135.7*, 128.5, 128.2, 66.9, 59.7*, 59.8**, 48.7*, 47.4**, 31.6**, 28.5*, 25.8*, 21.8**, 13.7*, 13.6** ppm; IR (thin film) ν_{max} 3447, 2956, 1745, 1628, 1588, 1426, 1174, 1112, 751 cm^{-1}; HRMS (CI/NH_3) m/z calcd for $C_{17}H_{18}N_2O_4Na$ $[M + Na]^+$ 337.1164, found 337.1166.

13-Hydroxy-11-*O*-(*tert*-butyldiphenylsilyl)virginiamycin M_2 (9). Newly made SmI_2 in THF solution was prepared as follows: $C_2H_4I_2$ (freshly purified white crystal, 564 mg, 2 mmol) and Sm^0 powder (330 mg, 2.2 mmol) was placed in a flame-dried round-bottom flask and purged with argon three times. Degassed, dry THF (10 mL) was added, and this mixture was stirred in the dark for 8 h to afford approximate 0.15 M SmI_2 THF solution (titrated with 0.05 M iodine THF solution before using.) Chloride **10** (40 mg, 0.05 mmol, 1 equiv) was placed into a flame-dried round-bottom flask and purged with argon three times. Degassed dry benzene (25 mL, 0.002 M) was then added into the flask. Freshly prepared SmI_2 THF solution (0.15 M solution, 1.33 mL, 0.2 mmol, 4 equiv) was introduced by the syringe pump within 4 h to the stirred solution. After stirring for another 4 h at rt, the reaction was quenched by bubbling in air, followed by the addition of saturated NH_4Cl aqueous solution (20 mL), stirring for 15 min. The biphasic mixture was separated, and the aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 40% EtOAc/hexane) to afford **9** (15 mg, 40% yield) as 1:1 diastereomers. **(13*S*)-13-Hydroxy-11-*O*-(*tert*-butyldiphenylsilyl)-virginiamycin M_2 (13*S*)-9:** $[\alpha]^{20}_D$ −31.5 (c = 0.7, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.63 (m, 4H), 7.33 (m, 6H), 6.38 (dd, J = 16.0, 3.0 Hz, 1H), 6.01 (d, J = 15.0 Hz, 1H), 5.93 (m, 1H), 5.75 (d, J = 9.5 Hz, 1H), 5.71 (d, J = 16.0 Hz, 1H), 5.47 (m, 1H), 4.84 (m, 1H), 4.60−4.67 (m, 2H), 4.54 (m, 1H), 4.47 (m, 1H), 3.62−3.67 (m, 2H), 3.22 (m, 1H), 3.08 (d, J = 17.5 Hz, 1H), 2.80 (dd, J = 17.0, 10 Hz, 1H), 2.73 (m, 1H), 2.20 (d, J = 13.0 Hz, 1H), 1.93−2.08 (m, 3H), 1.45−1.75 (m, 3H), 1.07 (s, 9H), 1.00−1.04 (m, 9H), 0.95 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 167.1, 161.1, 160.3, 144.3, 143.3, 136.9, 136.6, 135.9, 135.8, 132.9, 132.6, 132.4, 132.3, 130.0, 130.0, 127.8, 127.5, 124.8, 123.8, 81.4, 70.9, 66.8, 59.2, 48.0, 42.7, 41.6, 36.8, 35.0, 29.3, 28.1, 26.9, 25.6, 19.9, 19.1, 18.5, 11.8, 9.0 ppm; IR (thin film) ν_{max} 3312, 3070, 2960, 2928, 2856, 1742, 1670, 1624, 1428, 1183, 1111, 703 cm^{-1}; HRMS (CI/NH_3) m/z calcd for $C_{44}H_{57}N_3O_7NaSi$ $[M + Na]^+$ 790.3863, found 790.3853. **(13*R*)-13-Hydroxy-11-*O*-(*tert*-butyldiphenylsilyl) virginiamycin M_2 (13*R*)-9:** $[\alpha]_D^{20}$ −41.0 (c = 0.6, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.63 (m, 4H), 7.35 (m, 6H), 6.44 (dd, J = 16.5, 4.0 Hz, 1H), 6.02 (d, J = 15.5 Hz, 1H), 5.86 (d, J = 6.5 Hz, 1H), 5.75 (dd, J = 16.5, 2.0 Hz, 1H), 5.45 (m, 1H), 5.39 (d, J = 9.5 Hz, 1H), 4.72−4.80 (m, 3H), 4.50 (m, 1H), 4.13 (m, 1H), 3.94 (m, 1H), 3.78 (m, 1H), 3.30 (m, 1H), 2.71−2.82 (m, 3H), 2.60 (br, 1H), 1.82−2.08 (m, 5H), 1.61−1.71 (m, 2H), 1.05 (s, 3H), 1.03 (s, 9H), 0.87−0.95 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 166.4, 162.3, 160.2, 144.7, 143.8, 143.4, 136.9, 135.9, 135.8, 134.8, 134.0, 133.8, 133.1, 129.7, 129.6, 127.6, 127.4, 124.4, 123.8, 81.1, 68.8, 67.3, 59.2, 48.5, 43.5, 41.5, 36.6, 35.6, 29.3, 28.1, 26.9, 24.8, 19.8, 19.2, 18.6, 12.6, 10.1 ppm; IR (thin film) ν_{max} 3312, 3070, 2960, 2928, 2856, 1742, 1670, 1624, 1428, 1183, 1111, 703 cm^{-1}; HRMS (CI/NH_3) m/z calcd for $C_{44}H_{57}N_3O_7NaSi$ $[M + Na]^+$ 790.3863, found 790.3853.

11-*O*-(*tert*-Butyldiphenylsilyl)virginiamycin M_2 (51). In a flame-dried round-bottom flask, TFAA (14.0 μL, 0.1 mmol, 5 equiv) in CH_2Cl_2 (1 mL) was cooled to −78 °C. DMSO (14.2 μL, 0.2 mmol, 10 equiv) was added, and the solution was stirred at −78 °C for 20 min. Alcohol **9** (15 mg, 0.02 mmol, 1 equiv) in CH_2Cl_2 (0.5 mL) was added into the solution by the syringe. The reaction was warmed to −45 °C gradually in 30 min. Then the reaction was cooled to −60 °C. Acetylacetone (10 μL) and Et_3N (50 μL, 0.36 mmol, 18 equiv) was added, and the reaction was stirred at −60 °C for 30 min and warmed to −35 °C gradually. The reaction was quenched by adding water (1 mL) and warmed to rt. Saturated aqueous NH_4Cl solution was carefully added to adjust the aqueous phase to neutral. The biphasic mixture was separated, and the aqueous phase was extracted with EtOAc (3 × 3 mL). The combined organic phase were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by preparative thin layer chromatography in the dark, using 80% EtOAc/hexane as developing solvent. The product band was eluted with EtOAc (5 × 1 mL), and the EtOAc was evaporated to obtain product **51** (12 mg, 84% yield) as a glassy solid: $[\alpha]^{20}_D$ −22.0 (c = 0.7, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.59 (m, 4H), 7.36 (m, 6H), 6.77 (d, J = 6.0 Hz, 1H), 6.41 (dd, J = 16.5, 5.5 Hz, 1H), 5.94 (d, J = 15.5 Hz, 1H), 5.78 (dd, J = 16.0, 1.5 Hz, 1H), 5.51 (m, 1H), 5.21 (d, J = 9.0 Hz, 1H), 4.90 (m, 1H), 4.74 (dd, J = 15.0, 2.5 Hz, 1H), 4.69 (dd, J = 9.0, 4.0 Hz, 1H), 4.49 (m, 1H), 3.92 (m, 1H), 3.81 (d, J = 15.0 Hz, 1H), 3.69 (m, 1H), 3.58 (d, J = 15.0 Hz, 1H), 3.34 (m, 1H), 2.97 (dd, J = 15.0, 9.0 Hz, 1H), 2.68−2.74 (m, 2H), 2.25 (m, 1H), 1.92 (m, 4H), 1.20 (d, J = 1.0 Hz, 3H), 1.03 (s, 9H), 0.99 (d, J = 7.0 Hz, 3H), 0.95 (d, J = 6.5 Hz, 1H); ^{13}C NMR (75 MHz,$CDCl_3$) δ 199.5, 171.6, 166.8, 160.8, 156.4,

143.7, 143.6, 137.6, 136.7, 135.8, 135.7, 133.7, 133.6, 133.4, 133.0, 129.7, 129.6, 127.6, 127.5, 124.9, 124.7, 81.3, 66.6, 59.8, 50.2, 48.5, 44.0, 40.8, 36.6, 29.7, 28.4, 26.8, 25.0, 19.7, 19.1, 18.8, 12.3, 11.1 ppm; IR (thin film) ν_{max} 3308, 3070, 2962, 2930, 2856, 1733, 1672, 1628, 1428, 1183, 1111, 703 cm^{-1}; HRMS (CI/NH_3) m/z calcd for $C_{44}H_{55}N_3O_7NaSi$ $[M + Na]^+$ 788.3707, found 788.3694.

(−)-Virginiamycin M_2 (1). To ketone **51** (12 mg, 0.016 mmol, 1 equiv) in CH_2Cl_2 (0.2 mL) at rt was added HF·2pyridine (3.5 N in CH_2Cl_2, 90 μL, 20 equiv). The resulting mixture was stirred at rt for more than 36 h (monitored by TLC). The reaction mixture was diluted with CH_2Cl_2 (2 mL), cooled to 0 °C, and then quenched carefully with 5% aqueous $NaHCO_3$ solution (1 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 2 mL). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by preparative thin layer chromatography, using EtOAc as developing solvent. The product band was removed with EtOAc (5 × 1 mL), and the EtOAc was evaporated to obtain the natural product (**1**) (6 mg, 70% yield) as a white glassy solid: $[\alpha]^{20}_D$ −35.0 (c = 0.4, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (s, 1H), 6.46 (dd, J = 16.5, 5.0 Hz, 1H), 6.31 (br, 1H), 6.10 (d, J = 15.0 Hz, 1H), 5.76 (dd, J = 16.5, 2.0 Hz, 1H), 5.66 (m, 1H), 5.39 (d, J = 9.0 Hz, 1H), 4.89 (m, 1H), 4.72 (dd, J = 10.0, 2.0 Hz, 1H), 4.67 (dd, J = 9.0, 3.5 Hz, 1H), 4.43 (m, 1H), 3.97 (m, 1H), 3.81 (s, 2H), 3.71 (m, 1H), 3.38 (m, 1H), 3.03 (dd, J = 17.0, 6.0 Hz, 1H), 2.87 (dd, J = 17.0, 5.5 Hz, 1H), 2.72 (m, 1H), 2.43 (br, 1H), 2.16 (m, 1H), 1.87−1.95 (m, 3H), 1.83 (m, 1H), 1.70 (s, 3H), 1.02 (d, J = 7.0 Hz, 3H), 0.97 (d, J = 6.0 Hz, 3H), 0.93 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.4, 171.7, 166.8, 160.2, 156.8, 144.4, 144.1, 137.1, 136.9, 134.4, 132.5, 125.4, 124.2, 81.5, 65.3, 59.7, 48.8, 48.4, 43.2, 41.0, 36.7, 29.5, 38.4, 25.1, 19.8, 18.7, 12.7, 10.2 ppm; IR (thin film) ν_{max} 3329, 2924, 1736, 1670, 1621, 1441, 1183, 1110, 986 cm^{-1}; HRMS (CI/NH_3) m/z calcd for $C_{28}H_{37}N_3O_7Na$ $[M + Na]^+$ 550.2529, found 550.2515.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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