JOC The Journal of Organic Chemistry

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Total Synthesis of the Bis-silyl Ether of (+)-15-*epi*-Aetheramide A

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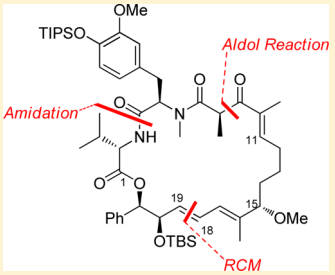
Supporting Information

ABSTRACT: Synthesis of the macrolactone depsipeptide aetheramide A was attempted by three different approaches. The first approach to form the macrolactone involving macrolactonization to form the C1−C21 bond and the second approach using a ring-closing metathesis (RCM) strategy to form the C10−C11 olefinic bond failed. The third approach starting from *R*-mandelic acid, involving the RCM reaction to install the C18−C19 ring junction, was successful in assembling the macrolactone.



INTRODUCTION

Aetheramide A **1** and B **2** (Figure 1) are two novel depsipeptides isolated from the myxobacterial genus *Aetherobacter* by Müller's group.[1] The structures of aetheramides were established with the aid of extensive 1D, 2D NMR quantum mechanical calculations and the α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) esters. Structurally aetheramide A **1** and B **2** are 22- and 21-membered macrolactones containing a polyketide moiety and a dipeptide residue which contain L-valine and an abnormal 3-(4-hydroxy-3-methoxyphenyl)-2-(methylamino) propanoic acid. Aetheramides contain six stereogenic centers in which the absolute configuration of the two stereogenic centers at C8 and C15 was not established. Another interesting observation about aethreamides is that aetheramide A **1** rearranges to aetheramide B **2** with a half-life of 24 h in MeOH. Aetheramides were shown to exhibit potent inhibitory activity against HIV-1, with IC_{50} values of 0.015 μM, and good cytotoxic activity against HCT-116 cells (IC_{50} 0.11 μM). During the course of our investigations concerning the synthesis of aetheramides, Ghosh et al. reported the synthesis of the macrolactone core of **3** aeteheramide A involving an intramolecular lactamization as the key step. For the synthesis of the polyketide unit, they relied on asymmetric dihydroxylation, Wittig olefination, asymmetric allylation, and aldol reactions.[2] However, they faced difficulty in deprotection of the 2-methoxyethoxymethyl (MEM) group in the macrolactone **3** to aetheramide A **1**. At the same time, we reported an expeditious approach for the polyketide unit **4** present in aetheramides starting from a chiral furyl carbinol.[3] Our work was based on the oxidative opening of furan to the corresponding *E*-but-2-ene-1,4-dione and further elaboration using Wittig olefination and Nagao aldol reactions. While this manuscript was under preparation, Gerstmann and Kalesse reported the total synthesis of aethereamide A **1** using an intramolecular lactamization of an acylketene.[4] They have confirmed the stereochemistry at the C15 carbon bearing the methoxy group as *R* by comparison of the ^{1}H NMR data,

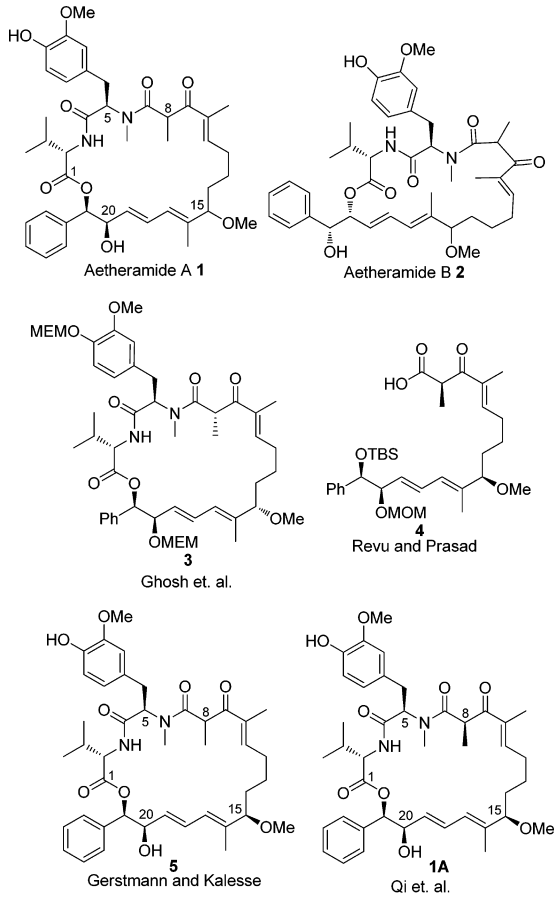


Figure 1. Reported approaches for the synthesis of aetheramide A **1** and B **2**.

Received: October 18, 2016
Published: November 29, 2016

DOI: 10.1021/acs.joc.6b02535
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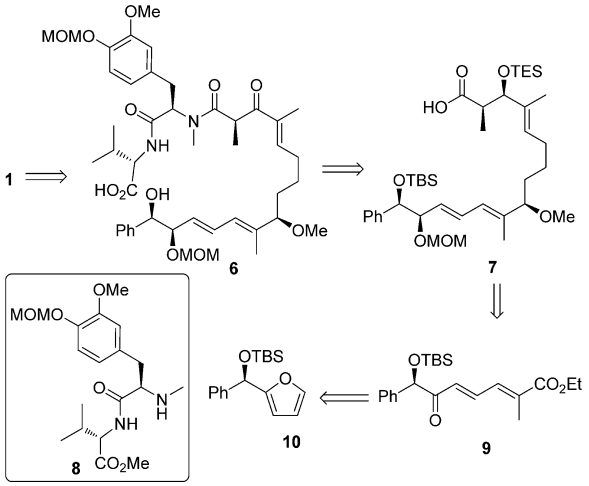
while they were not able to record a conclusive ^{13}C NMR spectrum of the natural product.[5] Very recently, while this manuscript was being submitted, a report by Qi et al. surfaced which described the total synthesis and stereochemical assignment of aetheramides A and B.[6] They affirmed the stereochemistry of the C8 and the C15 centers as *S* and *R*, respectively, and assigned the structure **1A** for aetheramide A. Herein we report in detail our efforts toward the synthesis of aetheramide A **1** involving the macrolactonization strategy and two approaches involving the ring-closing metathesis (RCM) strategy one of which led to the successful synthesis of the bis-silyl ether of aetheramide A.

RESULTS AND DISCUSSION

Macrolactonization Approach. Our initial approach for the synthesis of aetheramide A **1** is outlined in Scheme 1. It

Scheme 1. Retrosynthesis for Synthesis of Aetheramide A 1 Involving the Macrolactonization Strategy



was anticipated to assemble the macrolactone by macrolactonization of the hydroxy acid **6**, the synthesis of which was envisaged by coupling of the polyketide fragment **7** with the dipeptide unit **8**. While synthesis of the dipeptide unit **8** was planned from D-tyrosine and L-valine, synthesis of the polyketide fragment **7** was envisioned by elaboration of the diene ester **9** obtained from the phenyl furyl carbinol **10** involving an oxidative ring opening of the furan moiety to the corresponding keto aldehyde and further elaboration (Scheme 1).

Accordingly, the synthetic sequence commenced with the oxidation of the silyloxy furyl carbinol **10** (prepared from the corresponding known phenyl furyl carbinol) with NBS leading to the keto aldehyde, which on Wittig olefination with the phosphonate $(EtO)_2(O)PCH(CH_3)CO_2Et$ in the presence of LiHMDS as base afforded exclusively the *E*-unsaturated ester **9** in 91% yield. Performing the Witting reaction with the ylide $Ph_3P{=}C(CH_3)$-CO_2Et in refluxing toluene produced the diene ester **9** as a mixture of *E*:*Z* isomers in 78:22 ratio, while the use of NaH as base furnished the product as 84:16 mixture of *E*:*Z* isomers. Reduction of the keto group in **9** with $NaBH_4/CeCl_3$ afforded the alcohol **11** (>95:5 dr) in 87% yield. Conversion of the alcohol in **11** to the MOM ether (93% yield) followed by transformation of the ester to the Weinreb amide **12** was accomplished in 85% yield. Addition of (4-((tetrahydro-2H-pyran-2-yl) oxy) butyl)magnesium bromide to the Weinreb amide **12** gave the ketone **13** in 83% yield. CBS reduction of the keto group present in **13** with $BH_3{\cdot}SMe_2$ using (*S*)-CBS oxazaborolidine[7] as catalyst at −25 °C furnished the alcohol **14** (dr > 99:1) in 82% yield. Conversion of the free alcohol in **14** to the methyl ether (80% yield) followed by selective deprotection of the THP group under mild conditions using pyridinium *p*-toluene sulfonate (PPTS) in MeOH provided the primary alcohol **15** in 84% yield. IBX-mediated oxidation of the alcohol **15** produced the aldehyde, which on Wittig olefination with the ylide $Ph_3P{=}C(CH_3)CO_2Et$ in toluene under reflux conditions afforded the α,β-unsaturated ester **16** in 95% yield in two steps. DIBAL-H reduction of the α,β-unsaturated ester **16** at −78 °C furnished the primary allyl alcohol **17** in 87% yield. The primary alcohol in **17** was oxidized with MnO_2 to yield the aldehyde which was subjected to Nagao aldol reaction[8] with the thiazolidine thione **18** to furnish the aldol adduct **19** in 90% yield in two steps after column chromatography. The secondary alcohol in **19** was protected as its TES ether (92% yield), which on reaction with LiOH and H_2O_2 in THF furnished the acid **7** in 60% yield. Using the same procedure, the diastereomeric alcohol ***dia*-19** as well as the acid ***dia*-7** were prepared from the allylic alcohol **17** using the thiazolidine thione ***ent*-18** derived from D-valine. Alcohol in ***dia*-19** was protected as its TIPS ether ***dia*-19a** and was further converted to the acid ***dia*-7** in 68% yield (Scheme 2).

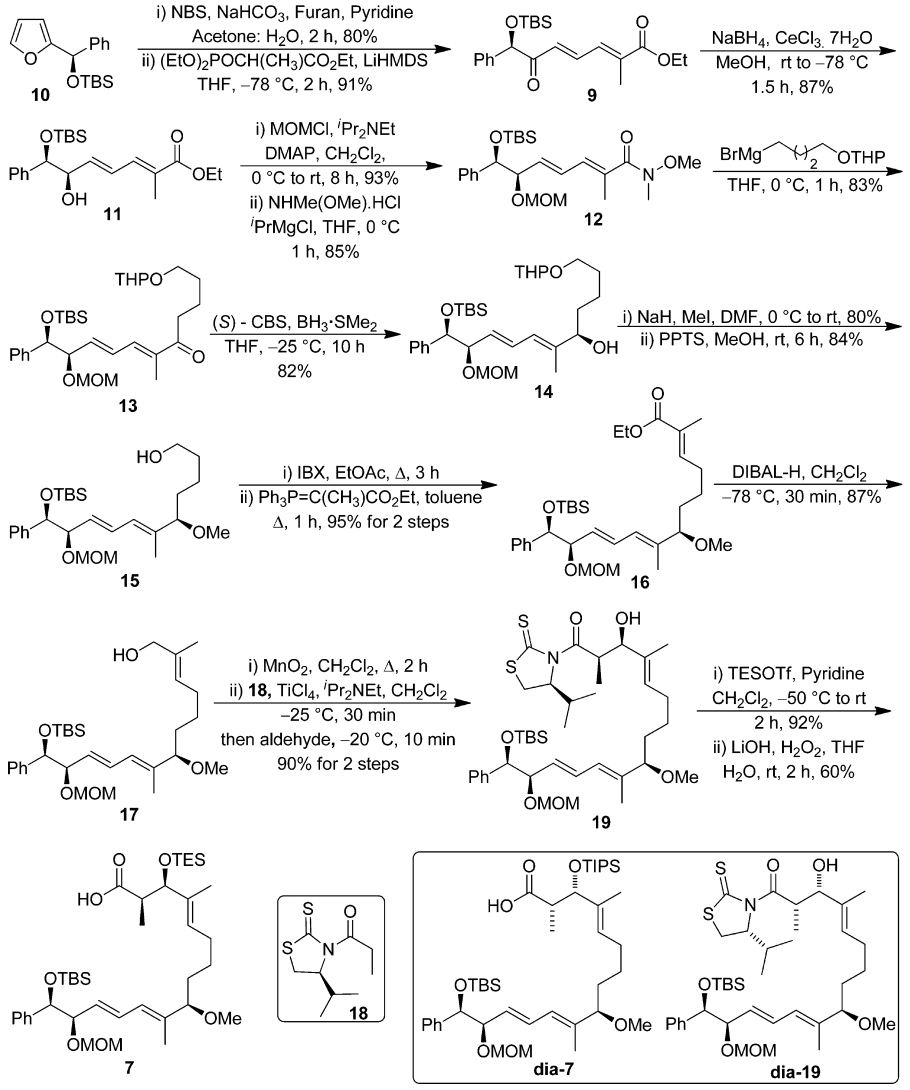
Synthesis of the dipeptide fragment **8** was accomplished as described below. Utilizing a procedure that was described earlier,[9] D-tyrosine was elaborated to the amino ester **20** using Friedel−Crafts acylation, followed by esterification of the carboxylic acid and protection of the free amine as the Cbz carbamate. Protection of the free phenolic hydroxy group in **20** as the MOM ether **21** was accomplished in 82% yield. Baeyer−Villiger oxidation of **21** cleanly furnished the corresponding phenylacetate, which on reaction with K_2CO_3 in MeOH afforded the free phenol **22** in 80% yield in two steps. Conversion of the phenol to the methyl ether (90% yield) with concomitant N-methylation of the carbamate was achieved using NaH/MeI to furnish the N-Me amino ester **22a**, which on reaction with LiOH produced the Cbz protected N-Me amino acid **23** in 93% yield. Coupling of the free acid present in **23** with methyl L-valinate using EDCl, HOBT in Et_3N produced the dipeptide **24** in 80% yield. Removal of the Cbz group using H_2/Pd in MeOH furnished the amino ester **8** in 92% yield (Scheme 3).

Coupling of the acid **7** (polyketide fragment) and the dipeptide unit **8** using HATU, $^{i}Pr_2EtN$ in DMF afforded the coupled product **25** in a moderate yield in 68% yield. Deprotection of the TES group in **25** was performed under mild conditions using PPTS in MeOH and CH_2Cl_2 mixture to furnish the compound **26** possessing the free alcohol in 75% yield. Dess−Martin periodinane oxidation[10] of the alcohol in **26** afforded the β-keto amide **27** in excellent yield. Reaction of **27** with LiOH did not furnish the free acid, instead cleavage of the β-keto amide to form the acid **4** was observed in very low yields[11] (Scheme 4).

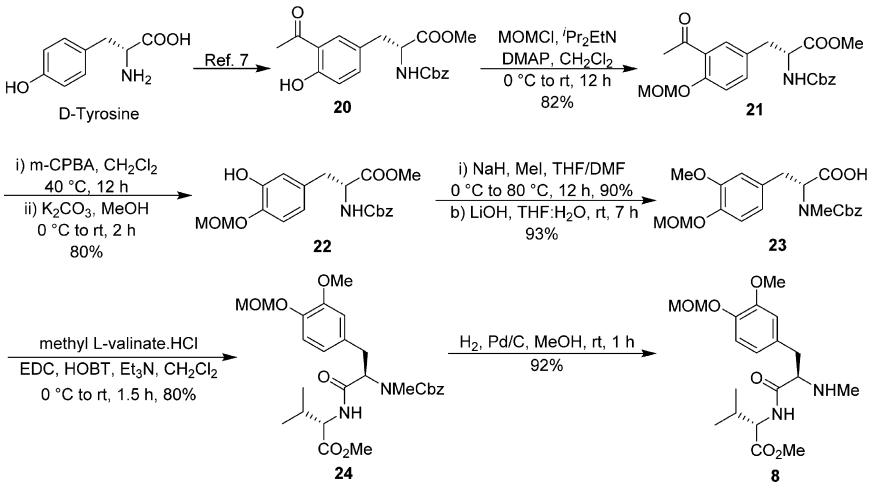
To avoid the unanticipated cleavage of the β-keto amide in **27** instead of the methyl ester hydrolysis in the reaction with LiOH, the β-triisopropyl silyloxy acid ***dia*-7** (prepared in an analogous way to the TBS ether **25**) was coupled with the dipeptide **8** to yield the amide **28** in 68% yield. Reaction of **28** with TBAF afforded the TIPS as well as TBS deprotected compound **29** in 75% yield. Hydrolysis of the ester in **29**

DOI: 10.1021/acs.joc.6b02535
J. Org. Chem. 2017, 82, 438−460

Scheme 2. Synthesis of the Polyketide Chain Present in Aetheramides



Scheme 3. Synthesis of the Dipeptide Unit Present in Aetheramides from D-Tyrosine

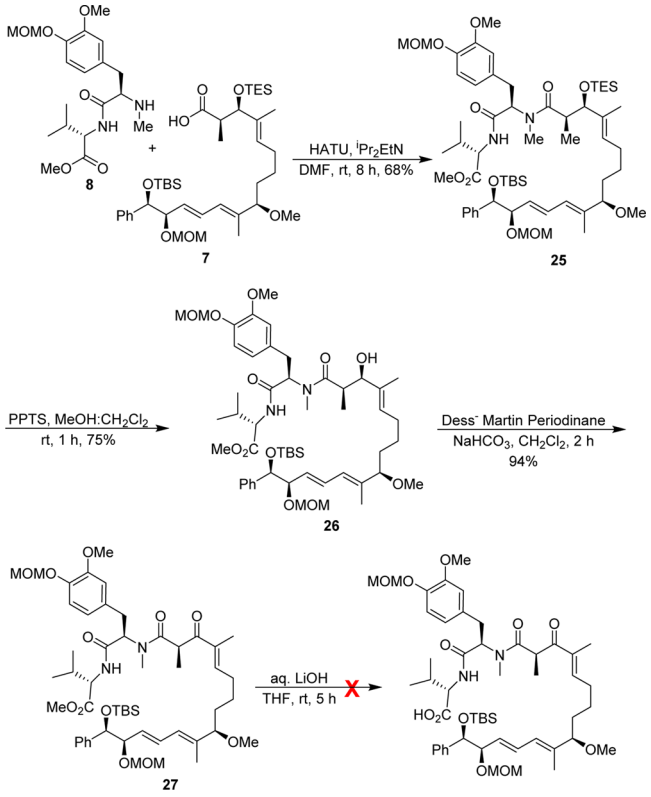


using 1 M aq. LiOH furnished the hydroxy acid **30** in excellent yield. Attempts at macrolactonization of the seco acid **30** to form the macrolactone core of aetheramide using normal esterification as well as Yamaguchi and Shiina macrolactonization methods were futile (Scheme 5).

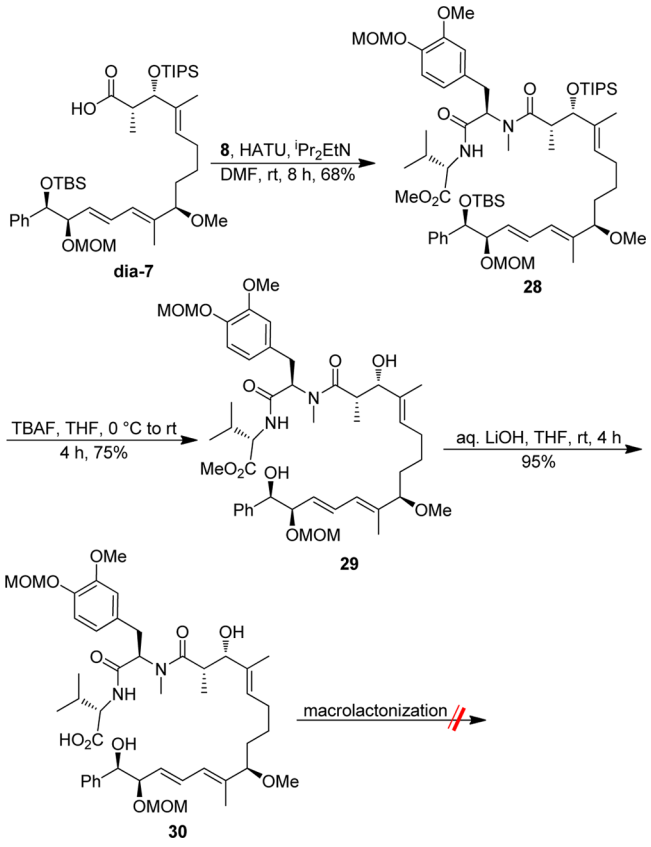
RCM Approach Failing to Produce the Macrolactone. When the macrolactonization of the seco acid **30** failed to

DOI: 10.1021/acs.joc.6b02535
J. Org. Chem. 2017, 82, 438–460

Scheme 4. Attempted Synthesis of the Hydroxy Acid Precursor for Macrolactonization

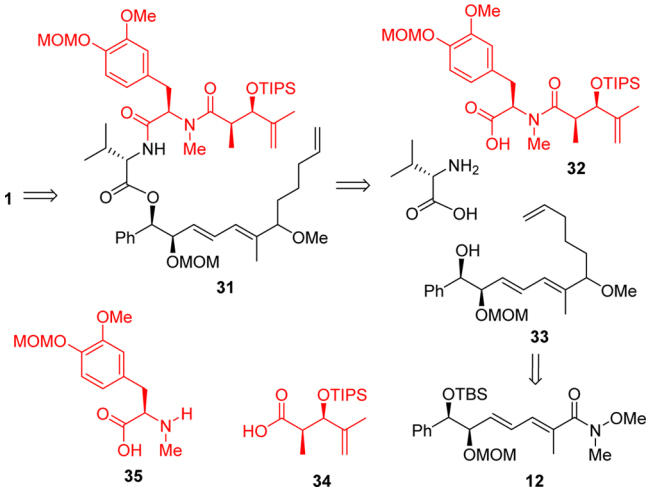


Scheme 5. Attempted Synthesis of the Macrolactone Core of Aetheramide A



produce the required macrolactone, we envisaged the synthesis of aetheramide A **1**, using RCM as the key reaction with the strategic RCM disconnection to form the C10−C11 olefin of the macrolactone. It was anticipated that RCM of the ester **31** should lead to the macrolactone, the synthesis of which was planned by combining the acid fragment derived from functionalized tyrosine **32** and the polyketide chain **33**. Synthesis of **33** was planned by elaboration of the Weinreb amide **12** possessing the orthogonally protected diol functionality. Synthesis of the unsaturated amide **12** was reported by us from furylphenyl carbinol **10**, while synthesis of the functionalized tyrosine fragment **32** was envisaged from the coupling of the *β*-silyloxy acid **34** and the amino acid **35** (Scheme 6).

Scheme 6. Retrosynthesis for Aetheramide A 1 with Key RCM Disconnection

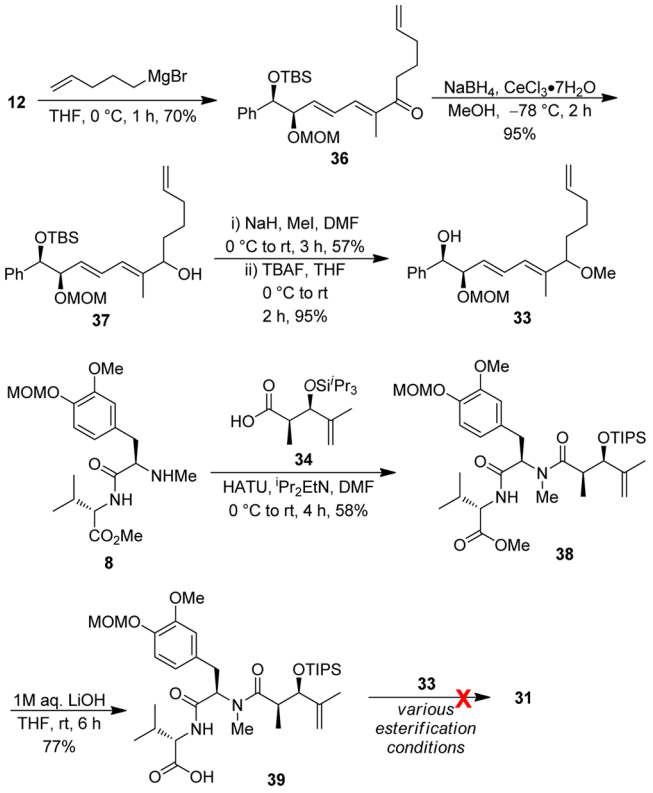


Accordingly, addition of pent-4-en-1-ylmagnesium bromide to the Weinreb amide **12** afforded the ketone **36** in 70% yield. Reduction of the ketone in **36** under Luche reduction conditions using $NaBH_4/CeCl_3{\cdot}7H_2O$ at −78 °C furnished the alcohol **37** in excellent yield as a nonseparable mixture of diastereomers. The alcohol **37** was converted to corresponding methyl ether **37a** in 57% yield, which on treatment with TBAF in THF afforded the required alcohol fragment **33** as a 1:1 mixture of diastereomers (as estimated by ^{1}H NMR) in 95% yield. Coupling of the acid **34**[12] with the free amine in the dipeptide **8** using HATU and ^{i}Pr$_2$EtN afforded the product **38** in 58% yield. Saponification of the methyl ester in **38** using LiOH produced the free acid **39** in 77% yield. However, all our efforts to form the ester **31** from the alcohol and acid fragments **33** and **39** were futile under various conditions with a variety of coupling reagents and were also futile under Yamaguchi esterification and Shiina esterification conditions (Scheme 7).

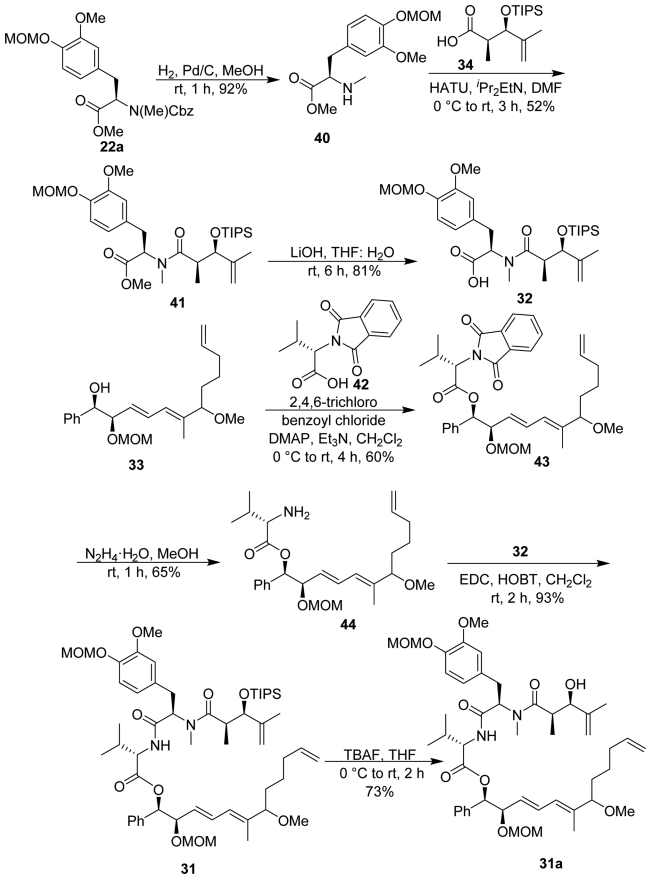
To circumvent this unforeseen difficulty, we detoured from the esterification reaction of the alcohol **33** and acid **39** fragments and envisaged the synthesis of **31** by amide formation between the acid fragment **32** and the valine ester **44** derived from the functionalized phenethanol **33**. Accordingly, tyrosine derived amino ester **40** was coupled to the *β*-silyloxy acid **34** to yield the amide **41**, which on saponification produced the free acid **32** in 81% yield. The amine fragment was synthesized by esterification of *N*-

DOI: 10.1021/acs.joc.6b02535
J. Org. Chem. 2017, 82, 438−460

Scheme 7. Attempted Synthesis of the RCM Precursor 31



Scheme 8. Synthesis of the RCM Precursors 31 and 31a



phthalimide protected L-valine **42** with alcohol **33** under Yamaguchi esterification conditions to yield the ester **43** in 60% yield. Deprotection of pthalimide in **43** using hydrazine hydrate in MeOH afforded the free amine **44** in 65% yield. Gratifyingly, coupling of the amine **44** with the acid **32** using EDCl, HOBT in CH_2Cl_2 formed the amide bond and furnished the RCM precursor **31** in 93% yield. Deprotection of the TIPS group was accomplished using TBAF to yield the free alcohol **31a** in 73% yield (Scheme 8).

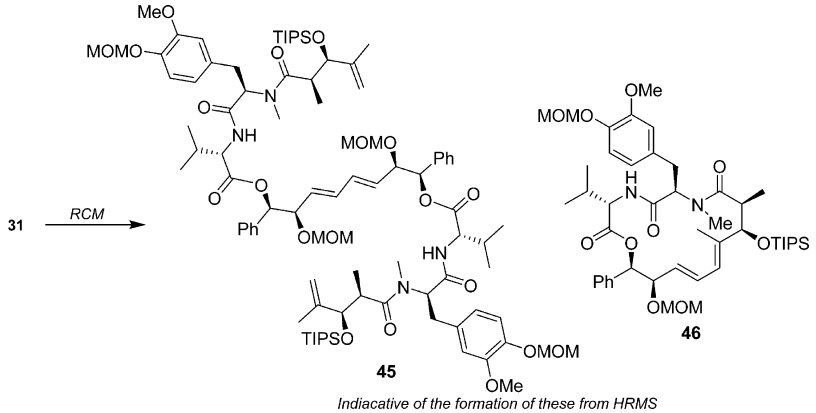
RCM reaction of diene **31** and **31a** was explored under various conditions, however, none of them afforded the desired macrolactone core of aetheramide A. In most cases the starting material was recovered, and no appreciable reaction was observed. However, reaction of **31** in toluene under refluxing conditions resulted in the formation of the dimer **45** and the truncated aetheramide analogue **46**, as evident from the HRMS analysis of the crude reaction mixture (Scheme 9). Reaction of **31a** with Hoveyda−Grubbs' second-generation catalyst furnished a trace amount of the macrolactone, evident from HRMS analysis. However, the yield could not be improved either by increased catalyst loading or by performing the reaction at higher dilution.

Successful RCM Approach for the Formation of 15-*epi*-Aetharamide A. Although RCM reaction of **31** and **31a** failed to produce the required product, formation of the dimer **45** and the truncated analogue **46** have provided the pivotal information that the less substituted alkene in the diene (C_{18}−C_{19} alkene of the aethreamide) was forming the active ruthenium carbene. This positive outcome gave us the impetus to reorganize our approach toward aetheramides. Accordingly, we revised our plan with the anticipation that the macrolactone could be assembled via RCM of an appropriately substituted alkene **47** to form the ring junction at the C_{18}−C_{19} position. Assembly of the tetraene **47** was planned by the coupling of the acid fragment **48** and the amine fragment **49**. Synthesis of the acid fragment **48** was planned by aldol reaction of the aldehyde **50**, the synthesis of which was planned from allyl trityl ether **51**. Synthesis of the amine fragment **49** was envisaged from *R*-mandelic acid **53** (Scheme 10).

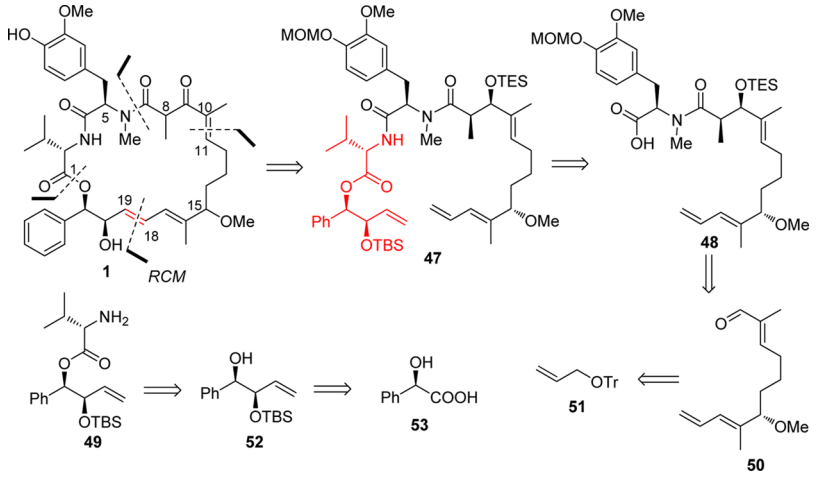
Accordingly synthesis of the acid fragment **48** commenced with the conversion of allyl trityl ether **51** to the *α,β*-unsaturated ester **54** involving oxidative cleavage of the olefin to aldehyde and further Wittig olefination reaction. Formation of the Weinreb amide **55** from the ester **54** was accomplished by reaction of **54** with Weinreb amine and isopropylmagnesium chloride in 70% yield. Addition of (4-((tetrahydro-2H-pyran-2-yl)oxy)butyl)magnesium bromide to the Weinreb amide **55** afforded the ketone **56** in 74% yield, which on CBS reduction afforded the allyl alcohol **57** in 81% yield. Reaction of **57** with NaH and MeI in DMF at 0 °C furnished the methyl ether **58** in 92% yield. Deprotection of the THP as well as the trityl groups in **58** was accomplished by reaction with PPTS in MeOH to afford the diol **59** in 75% yield. Selective oxidation of the allyl alcohol in **59** was accomplished by treating with MnO_2 which on Wittig olefination with $CH_2{=}PPh_3$ afforded the diene **60** in 70% yield. IBX-mediated oxidation of the primary alcohol in **60** followed by Wittig olefination using phosphorane $Ph_3P{=}C(Me)CO_2Et$ furnished the *α,β*-unsaturated ester **61** in 81% in two steps. DIBAL-H reduction of ester in **61** furnished the alcohol **62** in 92% yield. Oxidation of the alcohol **62** to the aldehyde **50** using Dess−Martin periodinane and further Nagao aldol reaction with

DOI: 10.1021/acs.joc.6b02535
J. Org. Chem. 2017, 82, 438−460

Scheme 9. Products Obtained in the RCM Reaction of 31



Scheme 10. Retrosynthesis for Aetheramide A with Strategic C_{18-19} Disconnetction using RCM



titanium enolate derived from thiazolidine thione **18** furnished the required aldol adduct **63** in 85% in two steps. Alcohol in **63** was protected as the corresponding TES ether **64** using TESOTf and pyridine in CH_2Cl_2 in good yield. Thiazolidine thione in **64** was cleaved using LiOH and H_2O_2 to afford the acid **65** in 75% yield. Coupling of the acid **65** with *N*-methyl D-tyrosine ester **40** in the presence of HATU and $^{i}Pr_2EtN$ in DMF afforded the amide **66** in 52% yield. The methyl ester in **66** was hydrolyzed using LiOH to give the acid **48** in 89% yield (Scheme 11).

Synthesis of the amine **49** fragment commenced with the addition of vinylmagnesium bromide to the silyloxy Weinreb amide **67**[13] at 0 °C to furnish the ketone **68** in 82% yield, which on reduction under Luche reduction conditions afforded the allyl alcohol **69** in good yield with 96:4 diastereomeric ratio. Secondary allyl alcohol in **69** was protected as the TBS ether **70**, and the selective deprotection of the TES group was accomplished with PPTS to furnish the benzylic alcohol **52** in 80% yield. Esterification of the benzylic alcohol **52** with N-Fmoc protected L-valine gave the ester **71** in good yield. Deprotection of the Fmoc group by treating with 20% piperidine in DMF afforded the free amine **49** in 93% yield (Scheme 12).

After synthesizing both the acid **48** and the amine **49** fragments, the peptide coupling was achieved using EDCl to furnish the tetraene **47** in 50% yield. RCM reaction of the tetraene **47** using Hoveyda−Grubbs second-generation catalyst in refluxing toluene afforded the vital macrolactone **72** in 45% yield. Though formation of the macrolactone **72** was observed, its purification was cumbersome, and the structure was determined by NMR spectral data. Efforts to deprotect the phenolic MOM groups under acidic conditions resulted in noncharacterizable mixture of products (Scheme 13).

From the above findings and from the difficulties reported by Ghosh et al. in the deprotection of MEM group in their synthesis of aetheramide, it was inferred that the acid-sensitive MOM protecting group for the phenolic hydroxy should be avoided in the synthesis of aetheramide. Hence it was planned to change the phenolic OH protection from MOM ether to the silyl ether. Accordingly methylation of the phenol as well as the carbamate NHCbz in **73** (obtained from tyrosine using the procedure described earlier) using NaH and MeI furnished the O,N-dimethylated product **74** in good yield. Deprotection of the benzyl as well as the Cbz groups in **74** using Pd/C furnished the free amino phenol **75** in 92% yield, which was protected as its TIPS ether **76** in 82% yield. Coupling of **76** with the acid **65** afforded the amide 77 in 60% yield. Hydrolysis of the ester in 77 was accomplished using potassium trimethylsilonate in THF to give the acid **78** in 83% yield. Coupling of the acid **78** with the valine ester **49** afforded **79** in 80% yield. RCM of **79** with Hoveyda−Grubbs' second-generation catalyst afforded the macrolactone, the purification of which turned out to be cumbersome. Hence the product obtained was reacted with PPTS, which selectively deprotected the TES ether to furnish the *β*-

DOI: 10.1021/acs.joc.6b02535
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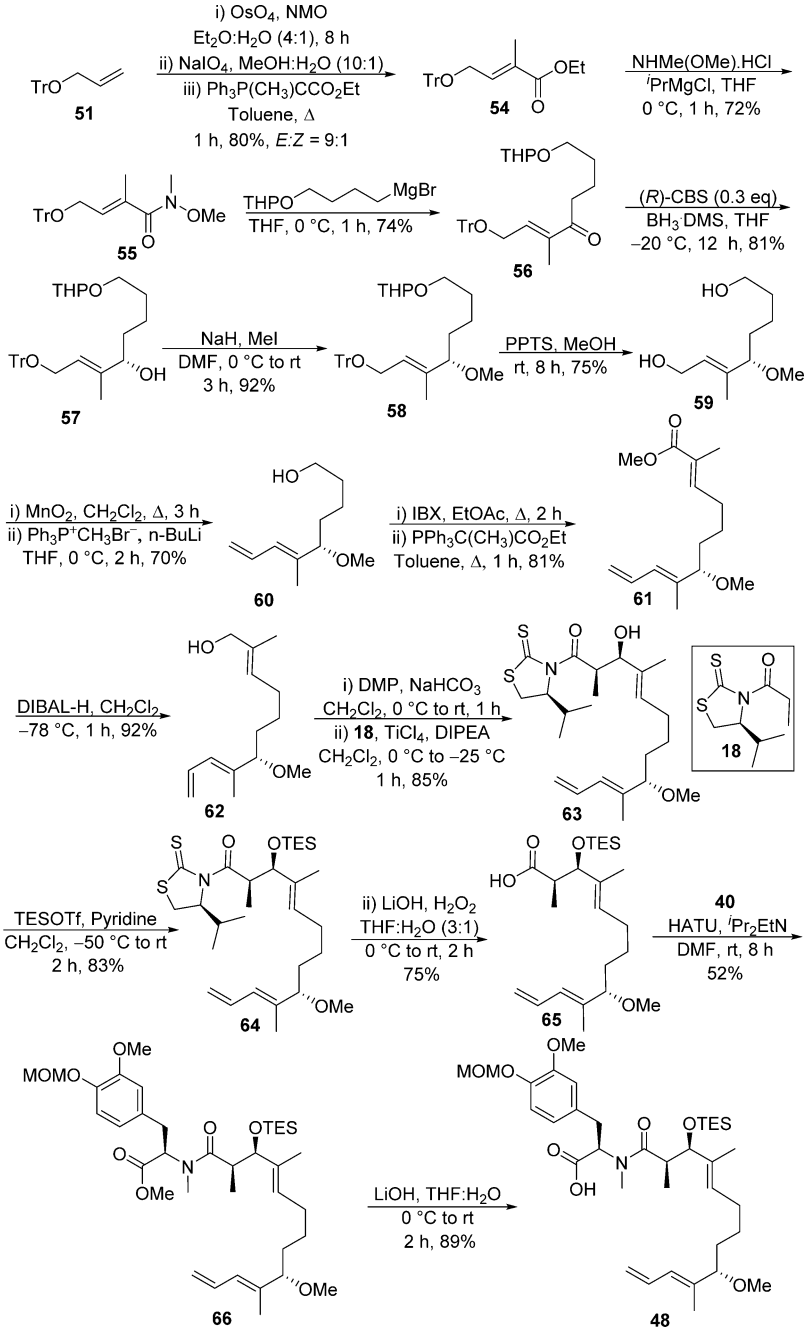
Scheme 11. Synthesis of the Acid Fragment 48



hydroxy amide **80** in 34% yield in two steps. Dess–Martin periodinane oxidation of the alcohol in **80** afforded the *β*-keto amide **81** in 84% yield. The crucial deprotection of the silyl groups in **81** with TBAF was clean and did provide 15-*epi*-aetheramide A **1** as evidenced from HRMS (Scheme 14). However, we were not able to record pure ^{1}H and ^{13}C NMR spectra, and our efforts to purify and isolate by column chromatography were futile.[14]

In conclusion, a systematic investigation for the target oriented total synthesis of macrolactone natural product aetheramide A by three different approaches is presented. The first approach involved macrolactonization; however, it did not form the macrolactone, while the second approach involved the RCM for the C_{10}–C_{11} bond formation which afforded a truncated analogue. The successful approach for the macrolactone was accomplished with formation of the strategic C_{18}–C_{19} bond by RCM. Synthesis of the precursor for the successful RCM reaction was achieved using chiral pool mandelic acid to install the chiral centers at the C20, C21 positions, while CBS reduction and Nagao aldol reactions were utilized to install the chiral centers at the C15 and C8 positions, respectively.

■ EXPERIMENTAL SECTION

General Procedures. Column chromatography was performed on silica gel, Acme grade 100–200 mesh. TLC plates were visualized either with UV, in an iodine chamber, or with phosphomolybdic acid spray. All reagents were purchased from commercial sources and used without additional purification. THF was freshly distilled over Na-benzophenone ketyl. Melting points were uncorrected. ^{1}H NMR

DOI: 10.1021/acs.joc.6b02535
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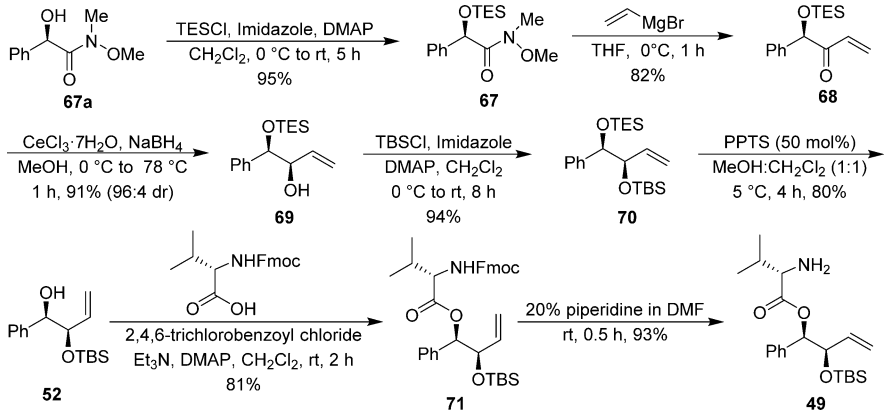
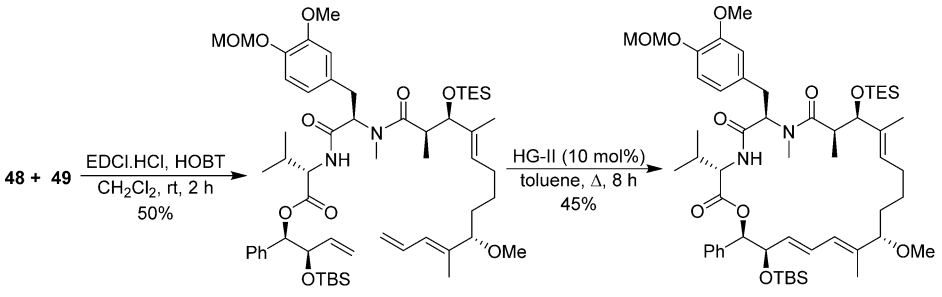
Scheme 12. Synthesis of the Amine Fragment 49

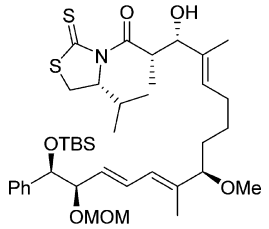


Scheme 13. Formation of the Macrolactone Core of Aetheramide 72



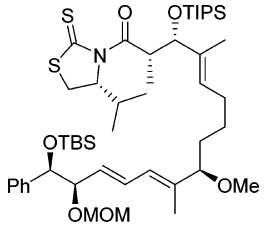
attempted deprotection of MOM and TBS groups under acidic conditions led to non-characterizable mixture of products

and ^{13}C NMR spectra were recorded on a 400 MHz machine in $CDCl_3$ as solvent with TMS as reference. HRMS was obtained using a Q-TOF spectrometer using electrospray ionization (ESI).



*Preparation of (2S,3S,4E,9R,10E,12E,14R,15R)-15-((tert-Butyldimethylsilyl)oxy)-3-hydroxy-1-((R)-4-isopropyl-2-thioxothiazolidin-3-yl)-9-methoxy-14-(methoxymethoxy)-2,4,10-trimethyl-15-phenylpentadeca-4,10,12-trien-1-one (**dia-19**).* To a stirred solution of the alcohol **17** (0.14 g, 0.27 mmol) in CH_2Cl_2 was added MnO_2 (0.241 g, 2.7 mmol) at room temperature, and the resulting suspension was refluxed for 2 h. The reaction mixture was filtered through a Celite pad and concentrated to afford the crude aldehyde, which was used as such in the next step without further purification.

To a stirred solution of thiazolidine thione ***ent*-18** (0.114 g, 0.54 mmol) in freshly distilled CH_2Cl_2 (15 mL) was added $TiCl_4$ (0.06 mL, 0.54 mmol) dropwise at −25 °C under inert atmosphere and was stirred for 5 min. Diisopropylethylamine (0.14 mL, 0.81 mmol) was introduced into the reaction mixture, and the resulting dark brown reaction mixture was stirred for 30 min at −25 °C. The solution of crude aldehyde (obtained above) in CH_2Cl_2 (4 mL) was added dropwise at −25 °C and stirred at the same temperature. After completion of the reaction (15 min), it was quenched by addition of saturated NH_4Cl solution (10 mL). The reaction mixture was extracted with EtOAc (2 × 10 mL). The organic layer was washed with brine and then dried over anhyd. Na_2SO_4. It was concentrated in vacuo to provide the crude residue which was purified by silica gel column chromatography using petroleum ether:EtOAc (5:1) as eluent to afford the pure alcohol ***dia*-19** (0.17 g, 92% for 2 steps) as a yellow oil. $[\alpha]_D$: −147.1 (*c* 1.06, $CHCl_3$); IR (Neat): ν_{max} 3355, 2931, 2887, 1604, 1466 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35−7.20 (m, 5H), 6.35 (dd, *J* = 15.2, 10.8 Hz, 1H), 5.87 (d, *J* = 10.8 Hz, 1H), 5.54 (t, *J* = 6.8 Hz, 1H), 5.40 (dd, *J* = 15.4, 7.2 Hz, 1H), 5.24−5.18 (m, 1H), 5.00 (dd, *J* = 7.0, 3.6 Hz, 1H), 4.39, 4.06 (ABq, *J* = 6.4 Hz, 1H), 4.58 (d, *J* = 6.8 Hz, 1H), 4.47 (s, 1H), 4.21(t, *J* = 6.2 Hz, 1H), 3.55−3.45 (m, 1H), 3.41 (t, *J* = 6.4 Hz, 1H), 3.15 (s, 3H), 3.13 (s, 3H), 3.01 (d, *J* = 11.6 Hz, 1H), 2.86 (bs, 1H), 2.40−2.28 (m, 1H), 2.10−1.92 (m, 2H), 1.59 (bs, 3H), 1.58 (bs, 3H), 1.47−1.32 (m, 2H), 1.10−1.00 (m, 8H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.87 (s, 9H), 0.04 (s, 3H), −0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.9, 178.0, 141.5, 137.4, 133.5, 129.9, 128.8, 127.5 (2 × C), 127.1 (3 × C), 126.9, 126.1, 94.5, 87.0, 80.7, 77.8, 74.8, 71.8, 55.8, 55.2, 40.7, 33.2, 30.7, 29.6, 27.4, 25.73 (3 × C), 25.67, 19.0, 18.2, 17.4, 13.5, 11.0, 10.6, −4.9, −5.0; HRMS: *m*/*z* calcd for $C_{39}H_{63}NO_6S_2Si$ + Na 756.3764; found 756.3763.



*Preparation of (2S,3S,4E,9S,10E,12E,14R,15R)-15-((tert-Butyldimethylsilyl)oxy)-1-((R)-4-isopropyl-2-thioxothiazolidin-3-yl)-9-methoxy-14-(methoxymethoxy)-2,4,10-trimethyl-15-phenyl-3-((triisopropylsilyl)oxy)pentadeca-4,10,12-trien-1-one (**dia-19a**).* To a solution of ***dia*-19** (0.17 g, 0.24 mmol) and pyridine (0.04 mL, 0.48 mmol) in CH_2Cl_2 (2 mL) was added TIPSOTf (0.064 mL, 0.36 mmol) at −50 °C. The mixture was allowed to warm up to room

DOI: 10.1021/acs.joc.6b02535
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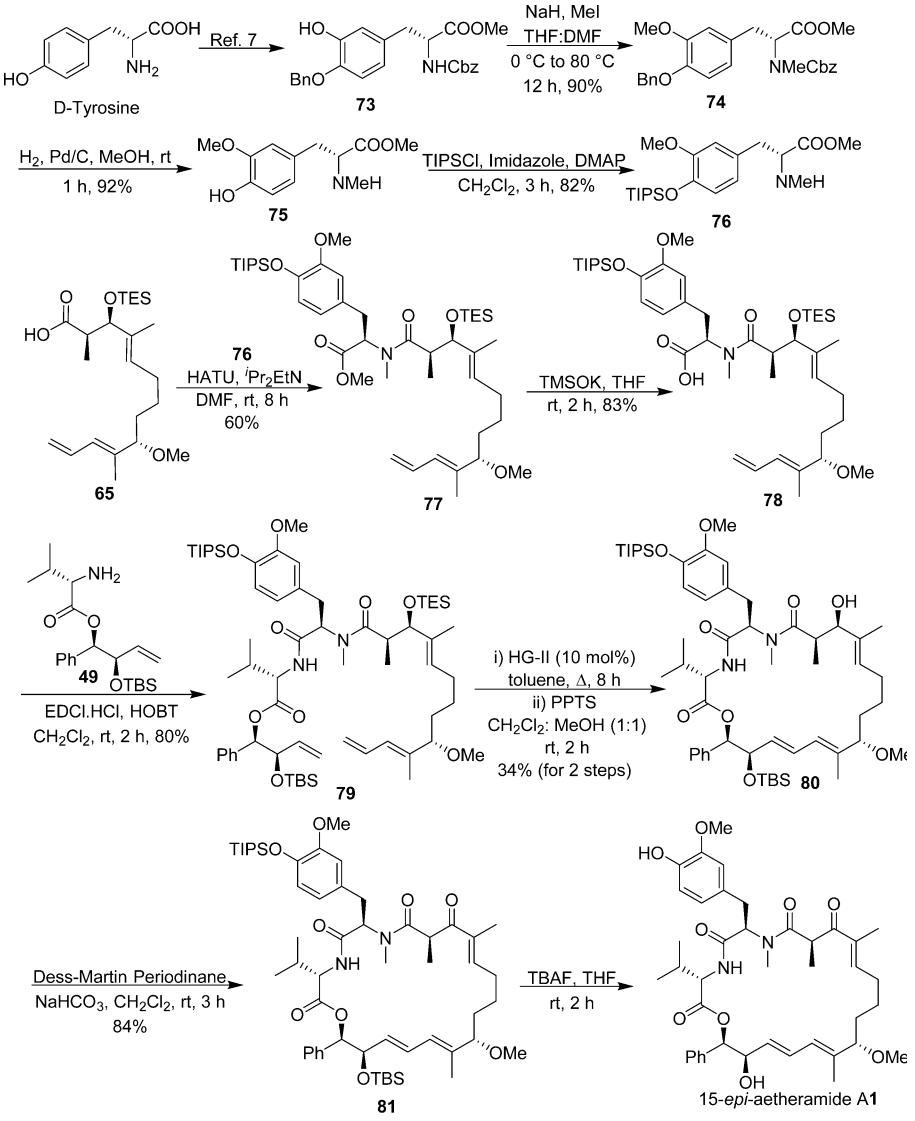
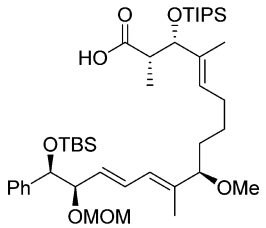
Scheme 14. Total Synthesis of 15-*epi*-Aetheramide A 1



temperature and was stirred at room temperature for 2 h. After the reaction was complete (TLC), it was washed with saturated aq. $NaHCO_3$ solution (5 mL) and was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (5 mL) and dried over anhyd. Na_2SO_4, and the solvent was evaporated off to give crude residue which was purified by silica gel column chromatography using petroleum ether:EtOAc (10:1) as eluent to afford desired product ***dia*-19a** (0.15 g, 75%) as yellow oil. $[\alpha]_D$: −110.9 (*c* 1.28, $CHCl_3$); IR (Neat): ν_{max} 2931, 2862, 1694, 1602, 1462 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.37−7.17 (m, 5H), 6.35 (dd, *J* = 15.2, 11.0 Hz, 1H), 5.87 (d, *J* = 11.0 Hz, 1H), 5.40 (dd, *J* = 15.4, 7.2 Hz, 1H), 5.33 (t, *J* = 6.4 Hz, 1H), 5.21(dd, *J* = 7.6, 6.0 Hz, 1H), 5.17−5.07 (m, 1H), 4.70 (d, *J* = 5.2 Hz, 1H), 4.66 (d, *J* = 6.8 Hz, 1H), 4.58 (d, *J* = 6.8 Hz, 1H), 4.48 (d, *J* = 9.2 Hz, 1H), 4.21 (t, *J* = 6.0 Hz, 1H), 3.45−3.33 (m, 2H), 3.15 (s, 3H), 3.13 (s, 3H), 2.89 (d, *J* = 11.6 Hz, 1H), 2.14 (dq, *J* = 13.0, 6.4 Hz, 1H), 1.97 (td, *J* = 14.8, 7.6 Hz, 1H), 1.87−1.75 (m, 1H), 1.61 (s, 3H), 1.58 (s, 3H), 1.48−1.29 (m, 2H), 1.26 (d, *J* = 6.8 Hz, 3H), 1.30−1.15 (m, 2H), 1.10−1.00 (m, 21H), 0.98 (d, *J* = 6.8, 3H), 0.90 (s, 9H), 0.89−0.84 (m, 3H), 0.05 (s, 3H), −0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.3, 176.0, 141.6, 137.6, 135.8, 129.9, 128.8 (2 × C), 127.6 (2 × C), 127.1 (3 × C), 126.8, 94.5, 87.1, 80.8, 80.4, 77.8, 71.3, 55.8, 55.2, 43.1, 33.6, 30.8, 28.5, 27.6, 25.8 (3 × C), 25.4, 19.0, 18.3, 18.2 (3 × C), 18.1 (3 × C), 17.0, 15.5, 12.6 (3 × C), 11.7, 11.0, −4.8, −4.9; HRMS: *m*/*z* calcd for $C_{48}H_{83}NO_6S_2Si_2$ + Na 912.5098; found 912.5096.



*Preparation of (2S,3S,4E,9S,10E,12E,14R,15R)-15-((tert-Butyldimethylsilyl)oxy)-9-methoxy-14-(methoxymethoxy)-2,4,10-trimethyl-15-phenyl-3-((triisopropylsilyl)oxy)pentadeca-4,10,12-trienoic acidd (**dia-7**).* To a stirred solution of thione ***dia*-19a** (0.150 g, 0.21 mmol) in THF (3 mL) were added LiOH (0.63 mL of 1.0 M aq. solution, 0.63 mmol) followed by H_2O_2 (1.0 mL of 30% w/v solution in water). The reaction mixture was stirred for 2 h at room temperature and was acidified to pH = 7 carefully with 2 N HCl. The reaction mixture was extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine (5 mL), dried over anhyd. Na_2SO_4, and concentrated. The crude residue thus obtained was purified by silica gel column chromatography using EtOAc as eluent to afford ***dia*-7** (0.106 g, 68%) as a colorless oil. $[\alpha]_D$: −28.4 (*c* 1.9, $CHCl_3$); IR (Neat): ν_{max} 3400, 2919, 1710, 1655, 1086 cm^{-1};

DOI: 10.1021/acs.joc.6b02535
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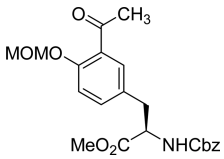
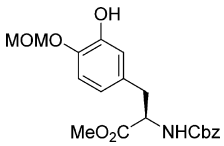
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40−7.20 (m, 5H), 6.34 (dd, J = 15.2, 11.0 Hz, 1H), 5.87 (d, J = 11.0 Hz, 1H), 5.41 (dd, J = 15.2, 7.2 Hz, 1H), 5.33 (t, J = 7.2 Hz, 1H), 4.70, 4.66 (ABq, J = 6.8 Hz, 2H), 4.58 (d, J = 6.8 Hz, 1H), 4.31 (d, J = 6.8 Hz, 1H), 4.27−4.16 (m, 1H), 3.41 (t, J = 6.4 Hz, 1H), 3.15 (s, 3H), 3.14 (s, 3H), 2.74−2.61 (m, 1H), 2.08−1.95 (m, 2H), 1.59 (s, 3H), 1.58 (s, 3H), 1.50−1.20 (m, 4H), 1.15−1.00 (m, 24H), 0.87 (s, 9H), 0.04 (s, 3H), −0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.5 (Cq), 141.6 (Cq), 137.3 (Cq), 134.3 (Cq), 130.1 (CH), 129.5 (CH), 128.8 (CH), 127.6 (2 × CH), 127.2 (3 × CH), 127.0 (CH), 94.5 (CH_2), 87.2 (CH), 81.0 (CH), 80.8 (CH), 77.8 (CH), 55.8 (CH_3), 55.2 (CH_3), 44.2 (CH), 33.0 (CH_2), 27.2 (CH_2), 25.8 (3 × CH_3), 25.4 (CH_2), 18.3 (Cq), 18.0 (3 × CH_3), 17.9 (3 × CH_3), 13.0 (CH_3), 12.3 (3 × CH), 11.3 (CH_3), 11.0 (CH_3), −4.8 (CH_3), −4.9 (CH_3); HRMS: m/z calcd for $C_{42}H_{74}O_7Si_2$ + Na 769.4871; found 769.4873.

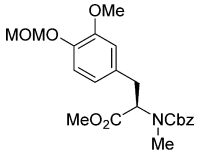


*Preparation of Methyl (R)-3-(3-Acetyl-4-(methoxymethoxy)-phenyl)-2-(((benzyloxy)carbonyl)amino) Propanoate (**21**).* To a precooled (0 °C) solution of **20**[9] (4.17 g, 11.25 mmol) in dichloromethane (20 mL) were added DMAP (0.274 g, 2.25 mmol) and ^{i}Pr$_2$NEt (11.7 mL, 67.48 mmol) dropwise followed by MOMCl (2.60 mL, 33.74 mmol). The reaction mixture was slowly allowed to warm to room temperature and stirred at room temperature for 6 h. After completion of the reaction (TLC), it was poured into water (30 mL) and extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with brine (5 mL) and dried over Na_2SO_4. Evaporation of solvent gave the crude residue which was purified by silica gel column chromatography using petroleum ether:EtOAc (3:1) as an eluent to furnish **21** (3.71 g, 82%) as a colorless oil. $[\alpha]_D^{24}$: −45.0 (c 0.5, $CHCl_3$); IR (Neat): ν_{max} 3341, 2953, 1725, 1608, 1494 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, J = 2.4 Hz, 1H), 7.40−7.26 (m, 5H), 7.17 (dd, J = 8.4, 2.4 Hz, 1H), 7.08 (d, J = 8.4 Hz, 1H), 5.41 (d, J = 7.2 Hz, 1H), 5.24 (s, 2H), 5.08 (s, 2H), 4.62 (dd, J = 13.6, 6.0 Hz, 1H), 3.73 (s, 3H), 3.49 (s, 3H), 3.11 (dd, J = 14.0, 5.4 Hz, 1H), 3.03 (dd, J = 14.0, 6.2 Hz, 1H), 2.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.3, 171.7, 155.6, 136.1, 134.3, 130.9, 129.0, 128.7, 128.5 (3 × C), 128.2, 128.0 (2 × C), 115.0, 94.4, 67.0, 56.4, 54.7, 52.4, 37.1, 31.8; HRMS: m/z calcd for $C_{22}H_{25}NO_7$ + Na 438.1529; found 438.1526.

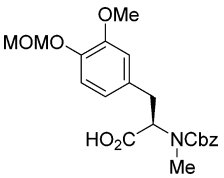


*Preparation of Methyl (R)-2-(((Benzyloxy)carbonyl)amino)-3-(3-hydroxy-4-(methoxymethoxy) phenyl) Propanoate (**22**).* A solution of **21** (0.91 g, 2.26 mmol) in 10 mL of dry CH_2Cl_2 was treated with mCPBA (57−85%, 1.20 g) and warmed at 40 °C overnight. The solution was diluted with ether and washed with saturated sodium thiosulfate (15 mL), sat. sodium bicarbonate (15 mL), and brine (20 mL), dried over anhyd. Na_2SO_4, and concentrated in vacuo to afford a crude residue.

To a stirred solution of the crude residue (obtained above) in MeOH (10 mL) was added potassium carbonate (0.468 g, 3.39 mmol) at room temperature. The stirring was continued until completion (TLC) of the reaction. Then MeOH was evaporated in vacuo to give crude, which was washed with water (10 mL), followed by brine (5 mL), and was extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, concentrated, and purified by silica gel column chromatography using petroleum ether:EtOAc (3:1) as eluent to furnish **22** (0.70 g, 80%) as a colorless oil. $[\alpha]_D^{24}$: −47.4 (c 2.1, $CHCl_3$); IR (Neat): ν_{max} 3368, 2955, 1744, 1512, 1221 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43−7.24 (m, 5H), 6.95 (d, J = 8.2 Hz, 1H), 6.70 (d, J = 2.0 Hz, 1H), 6.53 (dd, J = 8.2, 2.0 Hz, 1H), 6.21 (bs, 1H), 5.38 (d, J = 7.4 Hz, 1H), 5.12 (s, 2H), 5.08 (s, 2H), 4.61 (dd, J = 13.8, 5.8 Hz, 1H), 3.70 (s, 3H), 3.47 (s, 3H), 3.08−2.93 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 156.6, 146.3, 143.6, 136.1, 130.5, 128.3 (3 × C), 128.0, 127.9, 120.8, 116.2, 115.6, 95.8, 66.8, 56.2, 54.7, 52.2, 37.3; HRMS: m/z calcd for $C_{20}H_{23}NO_7$ + Na 412.1372; found 412.1374.



*Preparation of Methyl (R)-2-(((benzyloxy)carbonyl) (methyl)-amino)-3-(3-methoxy-4-(methoxymethoxy) phenyl) Propanoate (**22a**).* To a precooled solution of alcohol **22** (1.863 g, 4.62 mmol) in THF:DMF (15 mL:1.5 mL) was added NaH (0.407 g of 60% dispersed in mineral oil, 10.17 mmol) portion wise at 0 °C and stirred at the same temperature for 0.5 h. Then methyl iodide (1.5 mL, 23.11 mmol) was introduced into the reaction mixture at 0 °C and slowly warmed to room temperature, raised to 80 °C, and the stirring was continued for an additional 8 h. After completion of the reaction (TLC), it was cooled to room temperature and was cautiously quenched by addition of sat. NH_4Cl solution (20 mL). The reaction mixture was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine (20 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude residue which was purified by silica gel column chromatography using petroleum ether:EtOAc (5:1) as eluent to furnish **22a** (1.74 g, 90%) as a colorless oil as a mixture of rotamers. $[\alpha]_D^{24}$: + 11.6 (c 1.25, $CHCl_3$); IR (Neat): ν_{max} 2948, 1742, 1697, 1512, 1450 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37−7.15 (m, 5H$_{maj+min}$), 7.07−6.98 (m, 1H$_{maj+min}$), 6.80−6.68 (m, 0.7H$_{maj}$), 6.67−6.56 (m, 1H$_{maj+min}$, 0.3H_{min}), 5.19 (s, 2H$_{maj+min}$), 5.15−4.95 (m, 2H$_{maj+min}$), 4.78 (dd, J = 10.4, 4.4 Hz, 0.3H_{min}), 4.35−4.05 (m, 0.7H$_{maj}$), 3.79 (s, 2H$_{maj}$), 3.74 (s, 1H_{min}), 3.73 (s, 2H$_{maj}$), 3.68 (s, 1H_{min}), 3.50 (s, 3H$_{maj+min}$), 3.35−3.20 (m, 0.7H$_{maj}$), 3.10−2.90 (m, 0.3H_{min}, 1H$_{maj+min}$), 2.88 (s, 1H_{min}), 2.81 (s, 2H$_{maj}$); ^{13}C NMR (100 MHz, CDCl3): δ 173.8 (maj), 171.4(min), 156.5 (maj+min), 149.5 (maj +min), 145.1 (maj+min), 136.5 (maj), 136.2 (min), 131.1 (maj +min), 128.3 (3 × C maj+min), 127.7 (min+min), 127.4 (maj+min), 120.9 (min+maj), 116.2 (maj+min), 112.2 (min), 112.0 (maj), 95.4 (maj+min), 67.3 (min), 67.1 (maj), 60.6 (min), 59.8 (maj), 56.0 (maj+min), 55.6 (maj+min), 52.2 (maj+min), 34.7 (min), 34.3 (maj), 32.0 (min), 31.5 (maj); HRMS: m/z calcd for $C_{22}H_{27}NO_7$ + Na 440.1788; found 440.1784.



*Preparation of (R)-2-(((Benzyloxy)carbonyl)(methyl)amino)-3-(3-methoxy-4-(methoxymethoxy) phenyl) Propanoic Acid (**23**).* To a stirred solution of **22a** (1.404 g, 3.26 mmol) in THF (16 mL) was added 2 M aq. solution of LiOH (8.14 mL, 16.29 mmol), and the solution was stirred at room temperature for 4 h. Progress of the reaction was monitored by TLC and after completion of the reaction, and it was diluted with water (5 mL), neutralized with dil. HCl (pH = 4) and extracted with EtOAc (2 × 10 mL). The combined organic layer was washed with brine (5 mL) and dried (anhyd. Na_2SO_4). The solvent was removed under reduced pressure and silica gel column chromatography of the resulting crude residue using EtOAc as eluent afforded **23** (1.22 g, 93%) as a colorless oil as a mixture of rotamers. $[\alpha]_D$: +13.2 (c 2.5, $CHCl_3$); IR (Neat): ν_{max} 3377, 2835, 1802, 1705, 1514 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (bs, 1H$_{maj+min}$), 7.40−7.15 (m, 5H$_{maj+min}$), 7.04 (d, J = 8.0 Hz, 1H$_{maj+min}$), 6.83−6.56 (m, 2H$_{maj+min}$), 5.20 (s, 2H$_{maj+min}$), 5.17−5.02 (m, 2H$_{maj+min}$), 5.04−4.94 (m, 0.7H$_{maj}$), 4.87−4.77 (m, 0.3H_{min}),

DOI: 10.1021/acs.joc.6b02535
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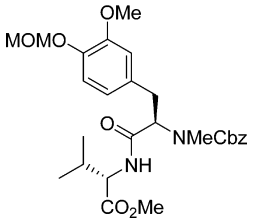
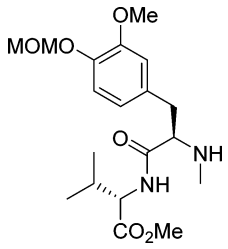
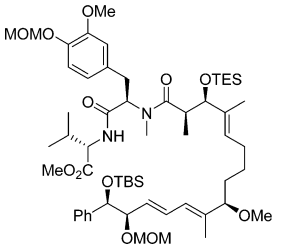
3.77 (s, 2H$_{maj}$), 3.72 (s, 1H_{min}), 3.50 (s, 3H$_{maj+min}$), 3.44−3.22 (m, 0.7H$_{maj}$), 3.20−3.10 (m, 0.3H_{min}), 3.10−2.95 (m, 1H$_{maj+min}$), 2.88 (s, 1H_{min}), 2.81 (s, 2H$_{maj}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.6 (maj), 175.5 (min), 156.8 (maj), 155.8 (min), 149.6 (maj+min), 145.5 (min), 145.1 (maj), 136.3 (maj), 136.0 (min), 131.0 (maj), 129.7 (min), 128.5 (maj+min), 128.4 (maj+min), 128.2 (maj), 128.0 (min), 127.9 (maj), 127.8 (min), 127.5 (maj+min), 121.5 (min), 120.9 (maj), 116.2 (maj+min), 112.7 (maj), 112.0 (min), 95.4 (min), 95.3 (maj), 67.6 (min), 67.4 (maj), 60.5 (maj), 60.3 (min), 56.1 (maj), 55.7 (maj), 34.6 (maj), 34.1 (CHmin), 32.0 (maj+min), 21.0 (min), 20.7 (maj); HRMS: m/z calcd for $C_{21}H_{25}NO_7$ + Na 426.1529; found 426.1529.



*Preparation of Methyl ((R)-2-(((Benzyloxy)carbonyl) (methyl)-amino)-3-(3-methoxy-4-(methoxymethoxy) phenyl) propanoyl)-L-valinate (**24**).* To a stirred solution of acid **23** (1.175 g, 2.91 mmol) in CH_2Cl_2 (15 mL) were added EDCl·HCl (1.673 g, 8.73 mmol), HOBT (1.10 g, 8.15 mmol), and Et_3N (0.81 mL, 5.83) in sequence at room temperature, it was cooled to 0 °C, and methyl L-valinate (0.974 g, 5.83 mmol) was introduced into the reaction mixture at the same temperature. Then it was slowly warmed to room temperature and stirred. After completion of the reaction (TLC), it was washed with water and extracted with ethyl acetate (3 × 25 mL). The combined organic layers were washed with brine (5 mL) and dried over anhyd. Na_2SO_4. The solvent was removed in vacuo, and silica gel column chromatography of the resulting crude residue using petroleum ether:EtOAc (2:1) as eluent afforded **24** (1.21 g, 80%) as a colorless oil as a mixture of rotamers $[\alpha]_D$: +65.6 (c 0.8, $CHCl_3$); IR (Neat): ν_{max} 3382, 2927, 2370, 1741, 1265 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45−7.15 (m, 5H$_{rot1+rot2}$), 7.03 (d, J = 8.0 Hz, 1H$_{rot1+rot2}$), 6.80−6.55 (m, 3H$_{rot1+rot2}$), 5.25−4.90 (m, 3H$_{rot1+rot2}$), 5.19 (s, 1H$_{rot1}$), 5.14 (s, 1H$_{rot2}$), 4.47 (bd, J = 4.8 Hz, 1H$_{rot1+rot2}$), 3.81 (s, 1.5H$_{rot1+rot2}$), 3.80 (s, 1.5H$_{rot1+rot2}$), 3.69 (s, 1.5H$_{rot1+rot2}$), 3.50 (s, 1.5H$_{rot1+rot2}$), 3.75−3.60 (m, 1H$_{rot1+rot2}$), 3.50 (s, 2H$_{rot1+rot2}$), 3.40−3.25 (m, 1H$_{rot1+rot2}$), 3.00−2.80 (m, 1H$_{rot1+rot2}$), 2.87 (s, 3H$_{rot1+rot2}$), 2.12 (td, J = 12.4, 6.0 Hz, 1H$_{rot1+rot2}$), 0.86 (d, J = 6.8 Hz, 3H$_{rot1+rot2}$), 0.81 (d, J = 6.8 Hz, 3H$_{rot1+rot2}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9 (rot1+rot2), 171.0 (rot1+rot2), 155.8 (rot1+rot2), 149.5 (rot1+rot2), 145.2 (rot1+rot2), 135.9 (rot1+rot2), 130.4 (rot1+rot2), 128.3 (2 × C rot1+rot2), 127.9 (rot1+rot2), 127.7 (rot1+rot2), 127.3 (rot1+rot2), 121.2 (rot1+rot2), 116.2 (rot1+rot2), 112.4 (rot1+rot2), 95.0 (rot1+rot2), 77.3 (rot1+rot2), 66.7 (rot1+rot2), 57.0 (rot1+rot2), 55.8 (rot1+rot2), 55.5 (rot1+rot2), 51.9 (rot1+rot2), 38.1 (rot1+rot2), 30.8 (rot1+rot2), 18.7 (rot1+rot2), 18.5 (rot1+rot2), 17.5 (rot1+rot2); HRMS: m/z calcd for $C_{27}H_{36}N_2O_8$ + Na 539.2369; found 539.2364.

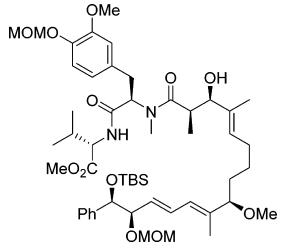


*Preparation of Methyl ((R)-3-(3-Methoxy-4-(methoxymethoxy)-phenyl)-2-(methylamino) propanoyl)-L-valinate (**8**).* To a solution of **24** (1.136 g, 2.06 mmol) in MeOH (20 mL) was added 10% palladium on activated charcoal (0.114 g) under argon atmosphere. The reaction mixture was stirred for 1 h under hydrogen atmosphere. After completion of the reaction (TLC), it was filtered through a short pad of Celite, and the Celite pad was washed with EtOAc (20 mL). Evaporation of solvent followed by silica gel column chromatography of the resulting crude residue using EtOAc as eluent yielded **8** (0.722 g, 92%) as a colorless oil. $[\alpha]_D$: +52.0 (c 0.39, $CHCl_3$); IR (Neat): ν_{max} 3382, 2923, 1659, 1512, 1463 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 9.2 Hz, 1H), 6.98 (d, J = 8.0 Hz, 1H), 6.70 (s, 1H), 6.64 (d, J = 8.0 Hz, 1H), 5.11 (s, 2H), 4.45 (dd, J = 9.2, 4.8 Hz, 1H), 3.77 (s, 3H), 3.67 (s, 3H), 3.42 (s, 3H), 3.13 (dd, J = 9.8, 4.0 Hz, 1H), 3.05 (dd, J = 13.8, 3.8 Hz, 1H), 2.55 (dd, J = 13.8, 10.0 Hz, 1H), 2.23 (s, 3H), 2.12 (td, J = 13.0, 6.4 Hz, 1H), 1.49 (bs, 1H), 0.87 (d, J = 6.8 Hz, 3H), 0.82 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4, 172.0, 149.7, 145.1, 131.6, 120.9, 116.3, 112.1, 96.2, 66.1, 56.3, 55.9, 55.6, 51.8, 38.7, 35.4, 30.8, 18.9, 17.5; HRMS: m/z calcd for $C_{19}H_{30}N_2O_6$+H 383.2182; found 383.2184.



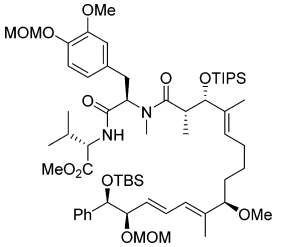
*Preparation of Methyl ((R)-2-((2R,3R,4E,9S,10E,12E,14R,15R)-15-((tert-Butyldimethylsilyl)oxy)-9-methoxy-14-(methoxymethoxy)-N,2,4,10-tetramethyl-15-phenyl-3-((triethylsilyl)oxy) Pentadeca-4,10,12-trienamido)-3-(3-methoxy-4-(methoxymethoxy) phenyl) propanoyl)-L-valinate (**25**).* To a stirred solution of the acid **7** (0.072 g, 0.10 mmol) in DMF (1 mL) was added HATU (0.057 g, 0.15 mmol) at rt, and after stirring was continued for 5 min, ^{i}Pr$_2$EtN (0.04 mL, 0.3 mmol) was introduced into the reaction flask and stirred for 15 min at rt. Then amine **8** (0.059 g, 0.15 mmol) in DMF (2 mL) was added to the reaction and stirred. After the reaction was complete (as indicated by TLC), the contents were poured into ice cold water and extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (10 mL) and dried over anhyd. Na_2SO_4. The crude residue obtained after removal of solvent in vacuo was purified by silica gel column chromatography using petroleum ether:EtOAc (4:1) as eluent to afford the required product **25** (0.065 g, 68%) as a colorless oil. $[\alpha]_D$: −1.5 (c 0.20, $CHCl_3$); IR (neat): ν_{max} 2955, 2935, 1746, 1651, 1512 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40−7.20 (m, 5H), 7.01 (d, J = 8.0 Hz, 1H), 6.76 (s, 1H), 6.69 (d, J = 8.0 Hz, 1H), 6.50−6.25 (m, 2H), 5.86 (d, J = 10.8 Hz, 1H), 5.61−5.47 (m, 1H), 5.41 (d, J = 7.2 Hz, 1H), 5.40−5.30 (m, 1H), 5.17 (dd, J = 11.8, 6.4 Hz, 2H), 4.70 (d, J = 4.8 Hz, 1H), 4.65 (d, J = 6.4 Hz, 1H), 4.58 (d, J = 6.4 Hz, 1H), 4.50−4.42 (m, 1H), 4.31−4.17 (m, 1H), 4.12 (d, J = 9.0 Hz, 1H), 3.85 (s, 3H), 3.70 (s, 3H), 3.47 (s, 3H), 3.38 (t, J = 6.0 Hz, 1H), 3.30 (dd, J = 14.6, 6.2 Hz, 1H), 3.15 (s, 3H), 3.10 (s, 3H), 2.86 (s, 3H), 2.95−2.70 (m, 2H), 2.15−1.92 (m, 2H), 1.85−1.75 (m, 1H), 1.58 (s, 3H), 1.55 (s, 3H), 1.45−1.40 (m, 4H), 1.00−0.80 (m, 21H), 0.81 (d, J = 6.8 Hz, 3H), 0.76 (d, J = 6.8 Hz, 3H), 0.54 (q, J = 7.6 Hz, 6H), 0.04 (s, 3H), −0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.2, 171.9, 170.3, 149.5, 144.9, 141.5, 137.5, 135.2, 131.1, 129.9, 128.9, 128.4, 127.6 (2 × C), 127.1 (3 × C), 126.9, 121.3, 116.2, 112.4, 95.4, 94.4, 87.0, 80.7, 80.1, 77.8, 57.1, 56.4, 55.9, 55.8 (2 × C), 55.2, 51.9, 41.4, 33.8, 33.4, 31.2, 30.9, 27.5, 25.7 (3 × C), 25.4, 18.9, 18.2, 17.8, 15.0, 11.2, 10.9, 6.8 (3 × CH), 4.7 (3 × CH), −4.8, −5.0; HRMS: m/z for $C_{58}H_{96}N_2O_{12}Si_2$ + Na calcd: 1091.6400; found: 1091.6401.

DOI: 10.1021/acs.joc.6b02535
J. Org. Chem. 2017, 82, 438−460

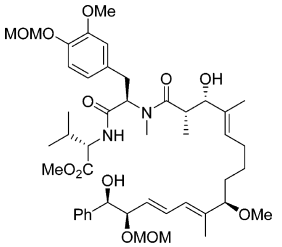


*Preparation of Methyl ((R)-2-((2R,3R,4E,9S,10E,12E,14R,15R)-15-((tert-Butyldimethylsilyl)oxy)-3-hydroxy-9-methoxy-14-(methoxymethoxy)-N,2,4,10-tetramethyl-15-phenylpentadeca-4,10,12-trienamido)-3-(3-methoxy-4-(methoxymethoxy) phenyl)propanoyl)-L-valinate (**26**).* To a stirred solution of the amide **25** (0.065 g, 0.08 mmol) in CH_2Cl_2:MeOH (1 mL, 1:1) was added PPTS (0.020 g, 0.08 mmol) at room temperature and stirred for 1 h. After completion of the reaction (TLC), it was stirred with solid $NaHCO_3$ (0.05 g) for 5 min. It was then filtered through a short pad of Celite, and the Celite pad was washed with CH_2Cl_2 (20 mL). The solvent was evaporated off, and the crude residue thus obtained was purified by silica gel column chromatography using petroleum ether:EtOAc (3:2) as eluent to afford **26** (0.043 g, 75%) as a colorless oil. $[\alpha]_D$: +17.8 (c 0.95, $CHCl_3$); IR (neat): ν_{max} 3412, 2933, 2859, 1747, 1658 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36−7.26 (m, 5H), 7.23 (d, J = 7.0 Hz, 1H), 7.03 (d, J = 8.0 Hz, 1H), 6.76 (s, 1H), 6.72 (d, J = 8.0 Hz, 1H), 6.67 (d, J = 8.8 Hz, 1H), 6.35 (dd, J = 15.2, 11.2 Hz, 1H), 5.87 (d, J = 10.8 Hz, 1H), 5.57 (t, J = 7.4 Hz, 1H), 5.51 (t, J = 8.2 Hz, 1H), 5.40 (dd, J = 15.2, 7.2 Hz, 1H), 5.19, 5.17 (ABq, J = 6.4 Hz, 2H), 4.70 (d, J = 7.2 Hz, 1H), 4.66 (d, J = 6.8 Hz, 1H), 4.58 (d, J = 6.8 Hz, 1H), 4.43 (dd, J = 8.8, 4.6 Hz, 1H), 4.28 (bs, 1H), 4.21 (t, J = 6.0 Hz, 1H), 3.85 (s, 3H), 3.70 (s, 3H), 3.49 (s, 3H), 3.40 (dd, J = 11.0, 5.2 Hz, 1H), 3.28 (dd, J = 14.6, 7.2 Hz, 1H), 3.14 (s, 3H), 3.13 (s, 3H), 2.95 (s, 3H), 2.78 (dd, J = 12.2, 6.4 Hz, 1H), 2.15 (td, J = 13.6, 6.8 Hz, 1H), 2.09−1.92 (m, 2H), 1.58 (s, 3H), 1.54 (s, 3H), 1.50−1.15 (m, 4H), 0.98−0.76 (m, 9H), 0.87 (s, 9H), 0.04 (s, 3H), −0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.2, 172.1, 170.2, 149.6, 145.1, 141.6, 137.5, 132.5, 130.8, 129.9, 128.8, 127.6 (2 × C), 127.1 (3 × C), 127.0, 125.9, 121.0, 116.4, 112.1, 95.5, 94.4, 87.1, 80.7, 77.8, 74.1, 57.2, 56.3, 56.0, 55.82, 55.79, 55.2, 52.1, 37.5, 33.3, 33.0, 31.2, 30.4, 29.6, 27.5, 25.7 (3 × CH), 19.0, 18.2, 17.5, 13.9, 10.9, 9.3, −4.8, −5.0; HRMS: m/z for $C_{52}H_{82}N_2O_{12}Si$ + Na calcd: 977.5535; found: 977.5538.

*Preparation of Methyl ((R)-2-((2R,4E,9S,10E,12E,14R,15R)-15-((tert-Butyldimethylsilyl)oxy)-9-methoxy-14-(methoxymethoxy)-N,2,4,10-tetramethyl-3-oxo-15-phenylpentadeca-4,10,12-trienamido)-3-(3-methoxy-4-(methoxymethoxy) phenyl) propanoyl)-L-valinate (**27**).* To a stirred solution of the alcohol **26** (0.032 g, 0.03 mmol) 15 in dry CH_2Cl_2 (2 mL) were added $NaHCO_3$ (6 mg, 0.07 mmol) and Dess−Martin periodinane (0.021 g, 0.05 mmol) at 0 °C under nitrogen atmosphere. The reaction mixture was warmed to room temperature and stirred for 2 h. After completion of the reaction (TLC), it was washed with saturated aqueous solutions of $NaHCO_3$ (3 mL) and $Na_2S_2O_3$ (3 mL) and diluted with EtOAc (5 mL). The aqueous phase was extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over anhyd. Na_2SO_4, and concentrated to give crude residue which was purified by silica gel column chromatography to afford β-keto amide **27** (0.03 g, 94%) as a colorless oil. $[\alpha]_D$: +13.1 (c 1.55, $CHCl_3$); IR (neat): ν_{max} 2932, 2858, 1750, 1659, 1461 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38−7.20 (m, 6H), 7.06 (d, J = 8.2 Hz, 1H), 7.01 (d, J = 8.2 Hz, 1H), 6.81 (s, 1H), 6.69 (d, J = 8.2 Hz, 1H), 6.64 (t, J = 7.2 Hz, 1H), 6.34 (dd, J = 15.6, 10.8 Hz, 1H), 5.92−5.80 (m, 2H), 5.41 (dd, J = 15.2, 7.2 Hz, 1H), 5.18 (s, 2H), 4.70 (d, J = 5.2 Hz, 1H), 4.66 (d, J = 6.4 Hz, 1H), 4.58 (d, J = 6.4 Hz, 1H), 4.48−4.38 (m, 1H), 4.25−4.12 (m, 2H), 3.84 (s, 3H), 3.70 (s, 3H), 3.51 (s, 3H), 3.45−3.38 (m, 1H), 3.16 (s, 3H), 3.13 (s, 3H), 2.84 (dd, J = 15.6, 11.2 Hz, 1H), 2.63 (s, 3H), 2.35−2.20 (m, 3H), 1.77 (s, 3H), 1.65−1.50 (m, 2H), 1.58 (s, 3H), 1.45−1.30 (m, 2H), 1.28 (d, J = 7.2 Hz, 3H), 1.02 (d, J = 6.8 Hz, 3H), 0.99 (d, J = 7.2 Hz, 3H), 0.87 (s, 9H), 0.04 (s, 3H), −0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.2, 172.4, 171.8, 170.6, 149.6, 144.8, 144.4, 141.5, 137.0, 135.7, 131.7, 130.3, 128.7, 127.6 (2 × C), 127.2, 127.1 (3 × C), 120.8, 116.4, 111.9, 95.6, 94.5, 86.7, 80.7, 77.7, 58.0, 56.1, 56.0, 55.9, 55.8, 55.2, 51.8, 45.2, 33.4, 33.0, 30.3, 30.2, 29.2, 25.7 (3 × C), 24.9, 19.1, 18.2, 18.1, 15.5, 11.4, 11.0, −4.8, −5.0; HRMS: m/z for $C_{52}H_{80}N_2O_{12}Si$ + Na calcd: 975.5378; found: 975.5375.



*Preparation of Methyl ((R)-2-((2R,3R,4E,9S,10E,12E,14R,15R)-15-((tert-Butyldimethylsilyl)oxy)-9-methoxy-14-(methoxymethoxy)-N,2,4,10-tetramethyl-15-phenyl-3-((triisopropylsilyl) oxy) pentadeca-4,10,12-trienamido)-3-(3-methoxy-4-(methoxymethoxy) phenyl)propanoyl)-L-valinate (**28**).* Compound **28** was prepared from the acid ***dia*-7** (0.05 g, 0.065 mmol) and amine **8** (0.037 g, 0.097 mmol) in 68% yield (0.049 g) as a colorless oil, following the same procedure described for the synthesis of **25**. $[\alpha]_D$: +50.0 (c 0.10, $CHCl_3$); IR (neat): ν_{max} 2923, 2866, 1751, 1682, 1455 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35−7.20 (m, 5H), 7.22 (d, J = 6.8 Hz, 1H), 7.02 (d, J = 8.2 Hz, 1H), 6.82−6.73 (m, 2H), 6.67 (d, J = 8.0 Hz, 1H), 6.34 (dd, J = 15.0, 10.8 Hz, 1H), 5.86 (d, J = 10.8 Hz, 1H), 5.39 (dd, J = 15.4, 7.2 Hz, 1H), 5.32 (t, J = 7.6 Hz, 2H), 5.17 (s, 2H), 4.69 (d, J = 5.4 Hz, 1H), 4.66 (d, J = 6.6 Hz, 1H), 4.59 (d, J = 6.8 Hz, 1H), 4.38−4.25 (m, 2H), 4.21 (t, J = 6.2 Hz, 1H), 3.83 (s, 3H), 3.68 (s, 3H), 3.48 (s, 3H), 3.37 (t, J = 6.4 Hz, 1H), 3.26 (dd, J = 14.2, 8.4 Hz, 1H), 3.16 (s, 3H), 3.09 (s, 3H), 2.94 (s, 3H), 2.69 (dd, J = 14.2, 7.2 Hz, 1H), 2.10 (dt, J = 13.2, 6.6 Hz, 1H), 1.98−1.85 (m, 1H), 1.85−1.70 (m, 3H), 1.57 (s, 3H), 1.36 (s, 3H), 1.45−1.30 (m, 2H), 1.27 (d, J = 6.8 Hz, 3H), 1.10−0.98 (m, 21H), 0.87 (s, 9H), 0.90−0.80 (m, 3H), 0.82 (d, J = 6.8 Hz, 3H), 0.04 (s, 3H), −0.10 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 176.9, 171.9, 170.6, 149.6, 145.0, 141.6, 137.6, 135.2, 131.6, 129.9, 128.9, 128.5, 127.6 (2 × C), 127.2 (3 × C), 126.8, 120.9, 116.6, 112.8, 95.5, 94.5, 87.0, 80.9, 80.8, 77.8, 57.3, 56.3, 56.0, 55.84, 55.78, 55.2, 51.9, 42.6, 33.5, 33.1, 30.9, 30.2 (C), 27.5 (C), 25.8 (3 × C), 25.6, 19.0, 18.3, 18.2 (3 × C), 18.1 (3 × C), 17.5, 15.0, 12.6, 11.2, 11.0, −4.8, −4.9; HRMS: m/z for $C_{61}H_{102}N_2O_{12}Si_2$ + Na calcd: 1133.6869; found: 1133.6875.



*Preparation of Methyl ((R)-2-((2R,3R,4E,9S,10E,12E,14R,15R)-3,15-Dihydroxy-9-methoxy-14-(methoxymethoxy)-N,2,4,10-tetramethyl-15-phenylpentadeca-4,10,12-trienamido)-3-(3-methoxy-4-(methoxymethoxy)phenyl)propanoyl)-L-valinate (**29**).* To a precooled solution (0 °C) of **28** (0.04 g, 0.036 mmol) in dry THF (1 mL) was added TBAF (0.07 mL of 1.0 M solution in THF, 0.072 mmol) dropwise under nitrogen atmosphere. The resulting solution was gradually warmed to room temperature and was stirred at the same temperature for 4 h. After completion of reaction (as indicated by TLC), the reaction mixture was diluted with brine (5 mL) and extracted with EtOAc (2 × 5 mL). The combined organic layers were dried over anhyd. Na_2SO_4, and the crude residue obtained after evaporation of solvent was purified by silica gel column chromatography using petroleum ether:EtOAc (1:3) as eluent to afford **29** (0.024 g, 75%) as a colorless oil. $[\alpha]_D$: +54.7 (c 1.2, $CHCl_3$); IR (neat): ν_{max} 3412, 2919, 2851, 1744, 1608 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.42−7.23 (m, 5H), 7.04 (d, J = 8.2

DOI: 10.1021/acs.joc.6b02535
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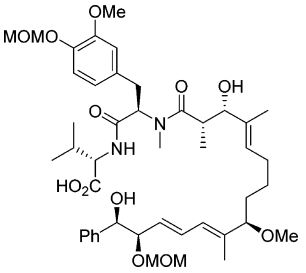
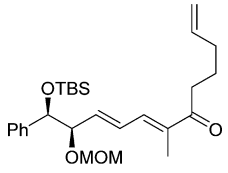
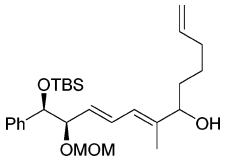
Hz, 1H), 6.78 (s, 1H), 6.73 (d, J = 8.2 Hz, 1H), 6.58 (d, J = 8.4 Hz, 1H), 6.30 (dd, J = 15.4, 11.0 Hz, 1H), 5.88 (d, J = 10.8 Hz, 1H), 5.54 (t, J = 7.2 Hz, 1H), 5.47 (dd, J = 13.8, 8.6 Hz, 1H), 5.18 (s, 2H), 4.75 (d, J = 6.8 Hz, 1H), 4.64 (d, J = 6.4 Hz, 1H), 4.58 (d, J = 6.6 Hz, 1H), 4.39 (dd, J = 8.4, 4.7 Hz, 1H), 4.25 (bs, 1H), 4.22 (t, J = 7.2 Hz, 1H), 4.04 (bs, 1H), 3.84 (s, 3H), 3.70 (s, 3H), 3.48 (s, 3H), 3.42−3.37 (m, 1H), 3.34−3.27 (m, 1H), 3.26 (s, 3H), 3.18 (bs, 1H), 3.12 (s, 3H), 2.93 (s, 3H), 2.98−2.90 (m, 2H), 2.72−2.65 (m, 1H), 2.20−2.10 (m, 1H), 2.05−1.96 (m, 2H), 1.56 (s, 3H), 1.45 (s, 3H), 1.50−1.35 (m, 2H), 1.30−1.20 (m, 2H), 1.07 (d, J = 6.8 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H), 0.83 (d, J = 6.8 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 179.1, 171.9, 170.1, 149.7, 145.1, 140.2, 138.7, 132., 131.1, 130.1, 128.5, 128.0 (2 × C), 127.7, 127.0, 126.4, 126.2, 121.0, 116.5, 112.4, 95.5, 94.2, 87.0, 81.5, 76.7, 75.0, 57.2, 56.4, 56.1, 56.0, 55.8, 55.6, 52.0, 37.7, 33.3, 32.8, 31.1, 30.3, 27.5, 25.7, 19.0, 17.4, 13.6, 11.1, 9.6; HRMS: m/z for $C_{46}H_{68}N_2O_{12}$ + Na calcd: 863.4670; found: 863.4673.



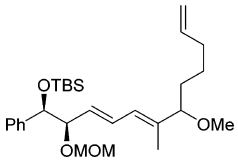
*Preparation of ((R)-2-((2R,3R,4E,9S,10E,12E,14R,15R)-3,15-Dihydroxy-9-methoxy-14-(methoxymethoxy)-N,2,4,10-tetramethyl-15-phenylpentadeca-4,10,12-trienamido)-3-(3-methoxy-4-(methoxymethoxy) phenyl)propanoyl)-L-valine (**30**).* To a stirred solution of **29** (0.024 g, 0.028 mmol) in THF (1.0 mL) was added 1 M aq. solution of LiOH (0.08 mL, 0.08 mmol) at rt, and the solution was stirred at the same temperature for 4 h. After progress of the reaction was monitored by TLC and after completion of reaction, it was diluted with water (5 mL) and extracted with Et_2O (2 × 5 mL) to remove organic impurities. The aqueous layer was neutralized with dil.HCl (pH = 4) and extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (5 mL) and dried (anhyd. Na_2SO_4). Solvent was removed under reduced pressure to afforded **30** (0.022 g, 95%) as colorless oil. $[\alpha]_D$: +56.7 (c 0.6, $CHCl_3$); IR (neat): ν_{max} 3400, 2919, 1710, 1739, 1655 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42−7.28 (m, 5H), 7.04 (d, J = 8.2 Hz, 1H), 6.79 (s, 1H), 6.73 (d, J = 8.0 Hz, 1H), 6.66 (d, J = 8.0 Hz, 1H), 6.33 (dd, J = 15.2, 11.0 Hz, 1H), 5.88 (d, J = 11.2 Hz, 1H), 5.60−5.40 (m, 3H), 5.18 (s, 2H), 4.73 (d, J = 6.6 Hz, 1H), 4.66 (d, J = 6.0 Hz, 1H), 4.57 (d, J = 6.6 Hz, 1H), 4.45−4.38 (m, 1H), 4.29−4.18 (m, 1H), 4.05 (bs, 1H), 3.84 (s, 3H), 3.49 (s, 3H), 3.42 (t, J = 4.8 Hz, 1H), 3.23 (s, 3H), 3.30−3.20 (m, 1H), 3.13 (s, 3H), 2.93 (s, 3H), 2.98−2.88 (m, 1H), 2.70−2.62 (m, 1H), 2.25−2.10 (m, 1H), 2.08−1.92 (m, 2H), 1.57 (s, 3H), 1.45 (s, 3H), 1.35−1.20 (m, 4H), 1.03 (d, J = 6.8 Hz, 3H), 0.95−0.74 (m, 6H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 179.1, 174.1, 170.2, 149.8, 145.2, 140.1, 138.9, 135.8, 131.1, 130.0, 128.5, 128.1 (2 × C), 127.8, 127.0 (2 × C), 126.3, 125.5, 121.1, 116.7, 112.5, 95.6, 94.2, 87.1, 81.4, 76.7, 74.9, 57.1, 56.6, 56.1, 56.0, 55.9, 55.6, 37.8, 34.2, 33.3, 30.3, 29.7, 27.4, 25.8, 22.7, 19.1, 17.3, 14.1, 13.7; HRMS: m/z for $C_{45}H_{66}N_2O_{12}$ + Na calcd: 849.4513; found: 849.4511.



*Preparation of (7E,9E,11R,12R)-12-((tert-Butyldimethylsilyl)oxy)-11-(methoxymethoxy)-7-methyl-12-phenyldodeca-1,7,9-trien-6-one (**36**).* To a solution of the Weinreb amide **12** (1.60 g, 4.23 mmol) in dry THF (10 mL) was added a freshly prepared solution of pent-4-en-1-ylmagnesium bromide (7.94 mL of 0.80 M solution in THF, 6.34 mmol) at 0 °C. Progress of the reaction was monitored by TLC, and after the reaction was complete (~1 h), it was cautiously quenched by addition of sat. NH_4Cl solution (15 mL), and the organic layer was extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with brine (30 mL) and dried (anhyd. Na_2SO_4). Evaporation of solvent followed by silica gel column chromatography of the resultant crude residue with petroleum ether:EtOAc (10:1) as eluent yielded **36** (1.36 g, 70%) as a colorless oil. $[\alpha]_D$: −55.3 (c 0.53, $CHCl_3$); IR (Neat): ν_{max} 2400, 1730, 1374, 1213, 748 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38−7.18 (m, 5H), 6.89 (d, J = 11.2 Hz, 1H), 6.50 (dd, J = 11.2, 5.2 Hz, 1H), 5.86−4.71 (m, 2H), 5.07−4.92 (m, 2H), 4.71 (d, J = 5.6 Hz, 1H), 4.66 (s, 2H), 4.31 (d, J = 6.0 Hz, 1H), 3.24 (s, 3H), 2.64 (t, J = 7.4 Hz, 2H), 2.06 (q, J = 7.0 Hz, 2H), 1.81 (s, 3H), 1.78−1.66 (m, 2H), 0.87 (s, 9H), 0.05 (s, 3H), −0.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.8, 140.9, 138.14, 138.11, 136.8, 136.1, 128.5, 127.7 (2 × C), 127.4, 127.7 (2 × C), 115.0, 95.1, 80.6, 77.5, 55.4, 36.4, 33.1, 25.7 (3 × C), 23.8, 18.2, 11.6, −4.9, −5.0; HRMS: m/z calcd for $C_{27}H_{42}O_4Si$ + Na 481.2750; found 481.2746.



*Preparation of (7E,9E,11R,12R)-12-((tert-Butyldimethylsilyl)oxy)-11-(methoxymethoxy)-7-methyl-12-phenyldodeca-1,7,9-trien-6-ol (**37**).* To a stirred solution of the ketone **36** (0.17 g, 0.37 mmol) in methanol (3 mL) was added $CeCl_3{\cdot}7H_2O$ (0.28 g, 0.74 mmol) at room temperature and stirred at the same temperature for 0.5 h. The reaction mixture was cooled to −78 °C, $NaBH_4$ (0.021 g, 0.55 mmol) was added, and the reaction mixture was stirred at −20 °C for 1 h. After completion of the reaction (TLC), it was cautiously quenched by addition of water (1 mL). After evaporation of MeOH in vacuo, the crude residue was washed with water and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (30 mL) and dried over anhyd. Na_2SO_4. Silica gel column chromatography of the crude residue obtained after evaporation of the solvent, with petroleum ether:EtOAc (10:1) as an eluent, gave desired alcohol **37** (0.16 g, 95%) as a colorless oil. $[\alpha]_D$: −54.7 (c 0.70, $CHCl_3$); IR (Neat): ν_{max} 3344, 2361, 1029, 665 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38−7.16 (m, 5H), 6.32 (dd, J = 15.2, 11.0 Hz, 1H), 5.92 (d, J = 11.0 Hz, 1H), 5.79 (ddt, J = 13.6, 10.2, 6.8 Hz, 1H), 5.39 (dd, J = 15.2, 7.2 Hz, 1H), 5.05−4.90 (m, 2H), 4.69 (d, J = 5.4 Hz, 1H), 4.66 (d, J = 6.8 Hz, 1H), 4.58 (d, J = 6.8 Hz, 1H), 4.20 (t, J = 6.4 Hz, 1H), 4.00 (t, J = 6.4 Hz, 1H), 3.16 (s, 3H), 2.06 (q, J = 7.0 Hz, 2H), 1.66 (s, 3H), 1.59−1.48 (m, 2H), 1.47−1.36 (m, 1H), 1.36−1.24 (m, 1H), 0.87 (s, 9H), 0.04 (s, 3H), −0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.5, 140.0, 138.6, 130.0, 129.0, 127.6 (2 × C), 127.2 (3 × C), 124.6, 114.6, 94.4, 80.0, 77.8, 77.2, 55.2, 34.2, 33.5, 25.8 (3 × C), 24.9, 18.2, 11.9, −4.8, −4.9; HRMS: m/z calcd for $C_{27}H_{44}O_4Si$ + Na 483.2907; found 483.2906.



*Preparation of (5R,6R)-5-((1E,3E)-5-Methoxy-4-methyldeca-1,3,9-trien-1-yl)-8,8,9,9-tetramethyl-6-phenyl-2,4,7-trioxa-8-siladecane (**37a**).* To a precooled solution of alcohol **37** (0.14 g, 0.30 mmol) in dry DMF (5 mL) was added NaH (0.024 g of 60% dispersed in mineral oil, 0.6 mmol) portion wise at 0 °C, and the solution was stirred at same temperature for 1 h. Then methyl iodide (0.16 mL, 1.5 mmol) was introduced into the reaction mixture at 0 °C and slowly warmed to room temperature and stirred for an additional 4 h. After completion of the reaction (TLC), this was cautiously quenched by addition of saturated NH_4Cl solution (10

DOI: 10.1021/acs.joc.6b02535
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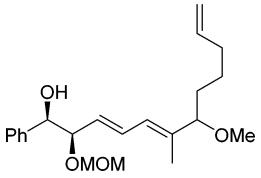
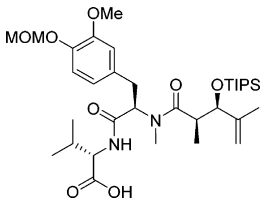
mL). The reaction mixture was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (5 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude residue which was purified by silica gel column chromatography using petroleum ether:EtOAc (5:1) as eluent to furnish **37a** (0.082 g, 57%) as a colorless oil. $[\alpha]_D$: −72.3 (*c* 0.54, $CHCl_3$); IR (Neat): ν_{max} 2928, 2855, 2349, 1745, 1459 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.40−7.18 (m, 5H), 6.35 (dd, *J* = 15.2, 11.0 Hz, 1H), 5.88 (d, *J* = 11.0 Hz, 1H), 5.85−5.71 (m, 1H), 5.41 (dd, *J* = 15.2, 7.2 Hz, 1H), 5.06−4.90 (m, 2H), 4.70 (d, *J* = 5.2 Hz, 1H), 4.67 (d, *J* = 6.6 Hz, 1H), 4.58 (d, *J* = 6.8 Hz, 1H), 4.25−4.15 (m, 1H), 3.42 (t, *J* = 6.2 Hz, 1H), 3.15 (s, 3H), 3.14 (s, 3H), 2.04 (dd, *J* = 13.6, 6.8 Hz, 2H), 1.59 (s, 3H), 1.52−1.28 (m, 4H), 0.87 (s, 9H), 0.04 (s, 3H), −0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.6, 138.7, 137.5, 130.0, 128.8, 127.6 (2 × C), 127.1 (3 × C), 126.9, 114.5, 94.5, 87.0, 80.8, 77.8, 55.9, 55.2, 33.6, 33.0, 25.8 (3 × C), 25.1, 18.3, 11.0, −4.8, −4.9; HRMS: *m*/*z* calcd for $C_{28}H_{46}O_4Si$ + Na 497.3063; found 497.3063.

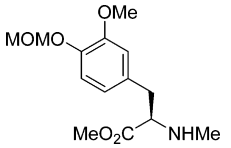


*Preparation of (1R,2R,3E,5E)-7-Methoxy-2-(methoxymethoxy)-6-methyl-1-phenyldodeca-3,5,11-trien-1-ol (**33**).* To a precooled solution (0 °C) of **37a** (0.09 g, 0.19 mmol) in dry THF (2 mL) was added TBAF (0.30 mL of 1.0 M solution in THF, 0.28 mmol) dropwise under nitrogen atmosphere. The resulting solution was gradually warmed to room temperature and was stirred at the same temperature for 2 h. After completion of reaction (as indicated by TLC), the reaction mixture was diluted with brine (5 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over anhyd. Na_2SO_4, and the crude residue obtained after evaporation of solvent was purified by silica gel column chromatography using petroleum ether:EtOAc (4:1) as an eluent to afford **33** (0.065 g, 95%) as a colorless oil. $[\alpha]_D$: −34.2 (*c* 0.55, $CHCl_3$); IR (Neat): ν_{max} 3440, 2934, 2819, 1724, 1451 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.44−7.19 (m, 5H), 6.38−6.23 (m, 1H), 5.88 (d, *J* = 11.0 Hz, 1H), 5.78 (ddt, *J* = 16.8, 10.2, 6.8 Hz, 1H), 5.46 (dd, *J* = 15.4, 7.6 Hz, 1H), 4.96 (dd, *J* = 18.0, 14.4 Hz, 2H), 4.74 (dd, *J* = 6.8, 2.1 Hz, 1H), 4.63 (d, *J* = 6.0 Hz, 1H), 4.57 (d, *J* = 6.8 Hz, 1H), 4.21 (t, *J* = 7.0 Hz, 1H), 3.41 (t, *J* = 6.4 Hz, 1H), 3.25 (s, 3H), 3.14 (s, 3H), 2.03 (d, *J* = 13.4, 6.8 Hz, 2H), 1.57 (s, 3H), 1.50−1.33 (m, 2H), 1.32−1.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.2, 138.6, 130.1, 128.4, 128.0, 127.7, 126.9 (2 × C), 126.2, 114.5, 94.1, 86.8, 81.5, 77.6, 56.0, 55.5, 33.5, 33.0, 25.0, 11.0; HRMS: *m*/*z* calcd for $C_{22}H_{32}O_4$ + Na 383.2198; found 383.2196.

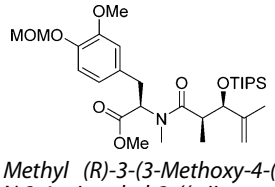
*Preparation of Methyl ((R)-3-(3-Methoxy-4-(methoxymethoxy)-phenyl)-2-((2R,3R)-N,2,4-trimethyl-3-((triisopropylsilyl)oxy)pent-4-enamido)propanoyl)-L-valinate (**38**).* Compound **38** was prepared from the acid **34** (0.052 g, 0.2 mmol) and amine **8** (0.07 g, 0.18 mmol) in 58% yield (0.070 g) as a colorless oil, following the same procedure described for the synthesis of **25**. $[\alpha]_D$: +52.9 (c 0.45, $CHCl_3$); IR (neat): ν_{max} 2944, 2869, 1823, 1746, 1614 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.00 (d, *J* = 8.0 Hz, 1H), 6.76 (s, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 6.25 (d, *J* = 8.8 Hz, 1H), 5.70 (dd, *J* = 10.6, 5.8 Hz, 1H), 5.17 (q, *J* = 6.8 Hz, 2H), 4.91 (s, 1H), 4.79 (s, 1H), 4.49 (dd, *J* = 8.8, 5.4 Hz, 1H), 4.42 (d, *J* = 9.4 Hz, 1H), 3.85 (s, 3H), 3.73 (s, 3H), 3.47 (s, 3H), 3.35 (dd, *J* = 14.6, 5.6 Hz, 1H), 2.85 (s, 3H), 2.80 (dd, *J* = 9.2, 2.0 Hz, 1H), 2.19−2.06 (m, 1H), 1.90 (bs, 1H), 1.75 (s, 3H), 1.04 (bs, 21H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 176.2, 172.0, 170.4, 149.6, 146.4, 144.9, 131.1, 121.2, 116.3, 113.6, 112.4, 95.5, 78.8, 57.2, 55.94 (2 × C), 55.92, 55.8, 42.0, 33.4, 31.0, 30.8, 18.9, 18.12 (3 × C), 18.07 (3 × C), 17.7, 17.1, 14.9, 12.6 (3 × C); HRMS: *m*/*z* for $C_{35}H_{60}N_2O_8Si$ + Na calcd: 687.4017; found: 687.4013.



*Preparation of ((R)-3-(3-Methoxy-4-(methoxymethoxy)phenyl)-2-((2R,3R)-N,2,4-trimethyl-3-((triisopropylsilyl)oxy)pent-4-enamido)-propanoyl)-L-valine (**39**).* Compound **39** was prepared by hydrolysis of ester **38** (0.125 g, 0.19 mmol) using a procedure described for the synthesis of **30**, afforded **39** (0.094 g, 77%) as a colorless oil. $[\alpha]_D$: +43.2 (c 0.75, $CHCl_3$); IR (neat): ν_{max} 3394, 2928, 1738, 1635, 1560 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.00 (d, *J* = 8.0 Hz, 1H), 6.75 (s, 1H), 6.67 (d, *J* = 8.0 Hz, 1H), 6.39 (d, *J* = 8.4 Hz, 1H), 5.71 (dd, *J* = 10.2, 6.0 Hz, 1H), 5.17 (q, *J* = 6.6 Hz, 2H), 4.87 (s, 1H), 4.74 (s, 1H), 4.49 (dd, *J* = 8.4, 4.8 Hz, 1H), 4.38 (d, *J* = 9.4 Hz, 1H), 3.84 (s, 3H), 3.46 (s, 3H), 3.31 (dd, *J* = 14.8, 6.0 Hz, 1H), 2.86 (s, 3H), 2.95−2.70 (m, 2H), 2.25−2.17 (m, 1H), 1.68 (s, 3H), 1.02 (bs, 21H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H), 0.79 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 176.4, 175.5, 170.6, 149.5, 146.1, 145.0, 130.8, 121.2, 116.1, 113.6, 112.2, 96.4, 78.7, 57.1, 56.0, 55.9, 55.7, 42.0, 33.7, 31.2, 30.7, 18.9, 18.12 (3 × C), 18.08 (3 × C), 17.6, 17.0, 14.9, 12.5 (3 × C); HRMS: *m*/*z* for $C_{34}H_{58}N_2O_8Si$ + Na calcd: 673.3860; found: 673.3857.



*Preparation of Methyl (R)-3-(3-Methoxy-4-(methoxymethoxy)-phenyl)-2-(methylamino)propanoate (**40**).* To a solution of **22a** (0.472 g, 1.09 mmol) in MeOH (8 mL) was added 10% palladium on activated charcoal (0.06 g) under argon atmosphere. The reaction mixture was stirred for 1 h under hydrogen atmosphere. After completion of the reaction (TLC), it was filtered through a short pad of Celite, and the Celite pad was washed with EtOAc (20 mL). Evaporation of solvent followed by silica gel column chromatography of the resulting crude residue using EtOAc as eluent yielded **40** (0.284 g, 92%) as a colorless oil. $[\alpha]_D^{24}$ −14.4 (*c* 1.23, $CHCl_3$); IR (Neat): ν_{max} 3335, 2946, 1735, 1591, 1513 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.06 (d, *J* = 8.0 Hz, 1H), 6.73 (s, 1H), 6.69 (d, *J* = 8.4 Hz, 1H), 5.20 (s, 2H), 3.86 (s, 3H), 3.70 (s, 3H), 3.51 (s, 3H), 3.43 (t, *J* = 6.8 Hz, 1H), 3.02−2.81 (m, 2H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.7, 149.5, 145.2, 131.3, 121.2, 116.4, 112.6, 96.5, 64.6, 56.1, 56.8, 51.7, 39.1, 34.7; HRMS: *m*/*z* calcd for $C_{14}H_{21}NO_5$+H 284.1498; found 284.1498.



*Preparation of Methyl (R)-3-(3-Methoxy-4-(methoxymethoxy)-phenyl)-2-((2R,3R)-N,2,4-trimethyl-3-((triisopropylsilyl)oxy)pent-4-enamido)propanoate (**41**).* Compound **41** was prepared from the acid **34** (0.060 g, 0.23 mmol) and amine **40** (0.055 g, 0.19 mmol) in 52% yield (0.054 g) as a colorless oil, following the same procedure described for the synthesis of **25**. $[\alpha]_D^{24}$: +16.2 (c 0.30, $CHCl_3$); IR (neat): ν_{max} 2944, 2867, 1740, 1646, 1514 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.02 (d, *J* = 8.0 Hz, 1H), 6.76 (s, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 5.34 (dd, *J* = 10.8, 5.2 Hz, 1H), 5.27−5.13 (m, 2H), 4.95 (s, 1H), 4.83 (s, 1H), 4.39 (d, *J* = 8.8 Hz, 1H), 3.86 (s, 3H), 3.70 (s, 3H), 3.49 (s, 3H), 3.33 (dd, *J* = 14.6, 5.2 Hz, 1H), 2.95−2.85 (m, 1H), 2.84 (s, 3H), 2.81−2.70 (m, 1H), 1.71 (s, 3H), 1.05 (bs, 21H), 0.94 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 175.1, 171.3, 149.5, 145.4, 145.0, 131.3, 121.1, 116.2, 113.8, 112.2, 96.4, 78.8, 57.3, 56.0, 55.8, 52.0, 42.0, 34.5, 32.9, 18.14 (3 × C),

DOI: 10.1021/acs.joc.6b02535
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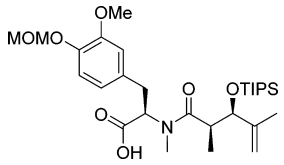
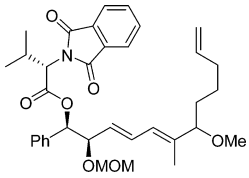
18.08 (3 × C), 17.3, 15.0, 12.5 (3 × C); HRMS: *m*/*z* for $C_{30}H_{51}NO_7Si$ + Na calcd: 588.3333; found: 588.3335.

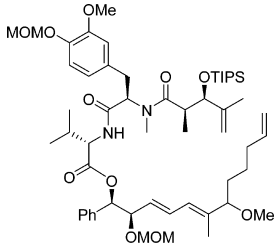


*Preparation of (R)-3-(3-Methoxy-4-(methoxymethoxy) phenyl)-2-((2R,3R)-N,2,4-trimethyl-3-((triisopropylsilyl)oxy)pent-4-enamido) Propanoic Acid (**32**).* Compound **32** was prepared by hydrolysis of ester **41** (0.051 g, 0.09 mmol) using a procedure described for the synthesis of **30**, afforded **32** (0.040 g, 81%) as a colorless oil. $[\alpha]_D^{24}$: +6.3 (c 0.30, $CHCl_3$); IR (neat): ν_{max} 3424, 2944, 1738, 1633, 1513 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.02 (d, *J* = 8.0 Hz, 1H), 6.77 (s, 1H), 6.74−6.60 (m, 2H), 5.26−5.14 (m, 3H), 4.96 (s, 1H), 4.83 (s, 1H), 4.40 (d, *J* = 9.0 Hz, 1H), 3.86 (s, 3H), 3.49 (s, 3H), 3.36 (dd, *J* = 15.2, 5.4 Hz, 1H), 2.93 (dd, *J* = 9.6, 4.8 Hz, 1H), 2.88 (s, 3H), 2.83−2.72 (m, 1H), 1.70 (s, 3H), 1.05 (bs, 21H), 0.97 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 175.9, 174.9, 149.7, 145.2, 145.1, 131.2, 121.2, 116.3, 114.2, 112.3, 95.5, 78.7, 58.6, 56.0, 55.9, 42.1, 34.4, 33.7, 18.2 (3 × C), 18.1 (3 × C), 17.2, 15.0, 12.6 (3 × C); HRMS: *m*/*z* for $C_{29}H_{49}NO_7Si$ + Na calcd: 574.3176; found: 574.3177.

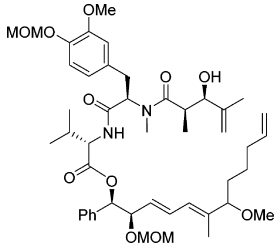


*Preparation of (1R,2R,3E,5E)-7-Methoxy-2-(methoxymethoxy)-6-methyl-1-phenyldodeca-3,5,11-trien-1-yl (2S)-2-(1,3-dioxoisoindolin-2-yl)-3-methylbutanoate (**43**).* To a solution of the acid **42** (0.050 g, 0.2 mmol) in CH_2Cl_2 (1 mL) were added Et_3N (0.04 mL, 0.26 mmol) and 2,4,6-trichlorobenzoyl chloride (0.03 mL, 0.22 mmol) at room temperature. After stirring the reaction mixture for 1 h, a solution of alcohol **33** (0.049 g, 0.14 mmol) and DMAP (0.08 g, 0.64 mmol) in CH_2Cl_2 (2 mL) was added to the reaction mixture at room temperature and stirred for 3 h. After completion of the reaction (TLC), it was quenched with saturated NH_4Cl solution (5 mL) and extracted with Et_2O (2 × 10 mL). The combined organic extracts were washed with brine (10 mL) and dried over anhyd. Na_2SO_4. Evaporation of the solvent followed by silica gel column chromatography of the crude residue using petroleum ether:EtOAc (4:1) as eluent to afford **43** (0.049g, 60%) as a colorless oil. $[\alpha]_D^{24}$: −39.9 (*c* 1.54, $CHCl_3$); IR (Neat): ν_{max} 2932, 2362, 1720, 1646, 1384 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 3.0 Hz, 2H), 7.74 (d, *J* = 2.6 Hz, 2H), 7.32−7.10 (m, 5H), 6.33 (dd, *J* = 14.6, 11.4 Hz, 1H), 5.95−5.71 (m, 3H), 5.32 (dd, *J* = 15.4, 7.4 Hz, 1H), 5.12−4.89 (m, 2H), 4.65 (t, *J* = 7.2 Hz, 2H), 4.49 (d, *J* = 6.8 Hz, 1H), 4.38 (t, *J* = 6.8 Hz, 1H), 3.53−3.33 (m, 1H), 3.18 (s, 3H), 3.14 (s, 3H), 2.83 (td, *J* = 13.8, 6.8 Hz, 1H), 2.03 (dd, *J* = 12.8, 6.2 Hz, 2H), 1.56 (s, 3H), 1.50−1.30 (m, 2H), 1.35−1.22 (m, 2H), 1.18 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 167.5 (2 × C), 138.8, 138.5, 136.4, 134.1 (2 × C), 131.6 (2 × C), 130.3, 128.0, 127.9 (2 × C), 127.5, 127.3 (2 × C), 126.1, 123.4 (2 × C), 114.5, 93.8, 86.7, 78.6, 77.6, 58.0, 56.0, 55.3, 33.5, 32.9, 28.2, 25.0, 20.9, 19.5, 11.0; HRMS: *m*/*z* calcd for $C_{35}H_{43}NO_7$ + Na 612.2937; found 612.2935.

*Preparation of (1R,2R,3E,5E)-7-Methoxy-2-(methoxymethoxy)-6-methyl-1-phenyldodeca-3,5,11-trien-1-yl L-valinate (**44**).* To a stirred solution of ester **43** (0.065 g, 0.11 mmol) in MeOH (1 mL) was added hydrazine hydrate (0.006 mL of 80% aq. solution, 0.16 mmol) at rt. The reaction mixture was stirred at rt for 2 h. After completion of the reaction (TLC), MeOH was evaporated off in vacuo and purified by neutral alumina column chromatography using petroleum ether:EtOAc (3:2) as an eluent to afford amine **44** (0.033 g, 65%) as a colorless oil. $[\alpha]_D^{24}$: −67.9 (*c* 1.25, $CHCl_3$); IR (Neat): ν_{max} 3387, 3327, 2934, 1737, 1624 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.41−7.18 (m, 5H), 6.43 (dd, *J* = 14.8, 11.4 Hz, 1H), 5.95−5.84 (m, 2H), 5.84−5.70 (m, 1H), 5.43 (dd, *J* = 15.2, 7.4 Hz, 1H), 5.05−4.89 (m, 2H), 4.66 (dd, *J* = 6.8, 1.4 Hz, 1H), 4.49 (d, *J* = 6.4 Hz, 1H), 4.45 (t, *J* = 6.4 Hz, 1H), 3.48−3.35 (m, 2H), 3.15 (s, 3H), 3.08 (s, 3H), 2.24−2.10 (m, 1H), 2.09−1.95 (m, 2H), 1.77 (bs, 2H), 1.61 (s, 3H), 1.50−1.35 (m, 2H), 1.35−1.20 (m, 2H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.7, 138.9, 138.5, 137.2, 130.1, 128.1 (2 × C), 128.0 (2 × C), 127.1, 126.1, 126.0, 114.5, 94.0, 86.8, 77.9, 77.7, 59.8, 56.0, 55.3, 33.5, 33.0, 25.02, 25.0, 19.5, 16.6, 11.2; HRMS: *m*/*z* calcd for $C_{27}H_{41}NO_5$+H 460.3063; found 460.3064.



*Preparation of (1R,2R,3E,5E)-7-Methoxy-2-(methoxymethoxy)-6-methyl-1-phenyldodeca-3,5,11-trien-1-yl ((R)-3-(3-Methoxy-4-(methoxymethoxy) phenyl)-2-((2R,3R)-N,2,4-trimethyl-3-((triisopropylsilyl)oxy)pent-4-enamido)propanoyl)-L-valinate (**31**).* To a solution of the acid **32** (0.017 g, 0.03 mmol) in dry CH_2 Cl_2 (1 mL) were added amine **44** (0.012 g, 0.026 mmol), EDCl·HCl (0.012 g, 0.078 mmol), and HOBT (0.011 g, 0.073 mmol) sequentially at room temperature, and the resulting reaction mixture was stirred at the same temperature for 2 h. After completion of the reaction (TLC), it was washed with water and extracted with ethyl acetate (2 × 5 mL). The combined organic layers were washed with brine (5 mL) and dried over anhyd. Na_2SO_4. The solvent was removed in vacuo, and silica gel column chromatography of the resulting crude residue using petroleum ether:EtOAc (3:2) as eluent afforded **31** (0.024 g, 93%) as a colorless oil. $[\alpha]_D^{24}$: −47.5 (*c* 0.2, $CHCl_3$); IR (Neat): ν_{max} 3389, 2927, 2342, 1748, 1601 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.42−7.23 (m, 6H), 6.99 (dd, *J* = 8.0, 5.2 Hz, 1H), 6.73−6.59 (m, 2H), 6.41 (t, *J* = 12.6 Hz, 1H), 5.86 (dd, *J* = 12.4, 8.0 Hz, 2H), 5.82−5.68 (m, 1H), 5.50−5.30 (m, 2H), 5.20 (s, 1H), 5.16 (t, *J* = 6.8 Hz, 1H), 5.02−4.90 (m, 2H), 4.80−4.70 (m, 2H), 4.70−4.64 (m, 1H), 4.62−4.52 (m, 1H), 4.52−4.34 (m, 3H), 3.81 (s, 3H), 3.49 (s, $1.5H_{dia1}$), 3.46 (s, $1.5H_{dia2}$), 3.45−3.35 (m, 2H), 3.26 (d, *J* = 5.0 Hz, 1H), 3.15 (s, $2H_{dia1}$), 3.13 (s, $2H_{dia2}$), 3.11 (s, $1H_{dia1}$), 3.07 (s, $1H_{dia2}$), 2.84 (s, $1H_{dia2}$), 2.88−2.80 (m, 1H), 2.69 (s, $2H_{dia1}$), 2.35−2.20 (m, 1H), 2.03 (q, *J* = 6.4 Hz, 2H), 1.61 (s, 6H), 1.50−1.35 (m, 2H), 1.35−1.20 (m, 3H), 1.15 (d, *J* = 6.8 Hz, 2H), 1.10−0.90 (m, 24H), 0.90−0.80 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.8, 170.9, 170.8, 149.5, 145.0, 144.7, 139.1, 138.5, 136.7, 131.3, 128.2, 128.0 (2 × C), 127.9, 127.7, 127.1 (2 × C), 126.1, 121.1, 120.9, 116.1, 114.6, 112.0, 95.3, 94.0, 86.8, 78.3, 78.5, 78.0, 57.0, 56.1, 56.0, 55.9, 55.7, 55.4, 42.4, 33.6, 33.1, 30.6, 30.4, 25.0, 19.3, 18.13, 18.08 (6 × C), 16.1, 14.9, 12.5 (3 × C), 11.2; HRMS: *m*/*z* calcd for $C_{56}H_{88}N_2O_{11}Si$ + Na 1015.6055; found 1015.6055.



*Preparation of (1R,2R,3E,5E)-7-Methoxy-2-(methoxymethoxy)-6-methyl-1-phenyldodeca-3,5,11-trien-1-yl ((R)-2-((2R,3R)-3-Hydroxy-N,2,4-trimethylpent-4-enamido)-3-(3-methoxy-4-(methoxymethoxy)phenyl)propanoyl)-L-valinate (**31a**).* To a precooled solution (0 °C) of **31** (0.045 g, 0.045 mmol) in dry THF (1 mL) was added TBAF (0.07 mL of 1.0 M solution in THF, 0.06 mmol) dropwise under nitrogen atmosphere. The resulting solution was gradually

DOI: 10.1021/acs.joc.6b02535
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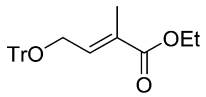
warmed to room temperature and was stirred at the same temperature for 2 h. After completion of reaction (as indicated by TLC), the reaction mixture was diluted with brine (5 mL) and extracted with EtOAc (2 × 5 mL). The combined organic layers were dried over anhyd. Na_2SO_4, and the crude residue obtained after evaporation of solvent was purified by silica gel column chromatography using petroleum ether:EtOAc (1:1) as an eluent to afford **31a** (0.027 g, 73%) as a colorless oil. $[\alpha]_D^{24}$: −69.8 (*c* 0.5, $CHCl_3$); IR (Neat): ν_{max} 3403, 3068, 2922, 1604, 1371 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.43−7.21 (m, 5H), 7.00 (t, *J* = 7.8 Hz, 1H), 6.80−6.65 (m, 2H), 6.60−6.50 (m, 1H), 6.50−6.35 (m, 1H), 5.92−5.82 (m, 2H), 5.80−5.70 (m, 1H), 5.55−5.44 (m, 1H), 5.77 (dd, *J* = 15.4, 8.4 Hz, 1H), 5.25−5.10 (m, 2H), 5.01 (d, *J* = 11.2 Hz, 1H), 4.98−4.90 (m, 2H), 4.76−4.57 (m, 2H), 4.53−4.37 (m, 3H), 4.01 (d, *J* = 11.2 Hz, 1H), 3.82 (s, $2H_{dia1}$), 3.79 (s, $1H_{dia2}$), 3.48 (s, $2H_{dia1}$), 3.46 (s, $1H_{dia2}$), 3.44−3.38 (m, 1H), 3.30−322 (m, 1H), 3.14 (s, $2H_{dia1}$), 3.13 (s, $1H_{dia2}$), 3.10 (s, $1H_{dia2}$), 3.06 (s, $2H_{dia2}$), 3.20−3.05 (m, 1H), 2.89 (s, $2H_{dia1}$), 2.75 (s, $1H_{dia2}$), 2.64−2.55 (m, 1H), 2.35−2.22 (m, 1H), 2.10−1.96 (m, 2H), 1.84 (bs, 1H), 1.64 (s, $1H_{dia2}$), 1.54 (s, $4H_{dia1}$), 1.52 (s, $1H_{dia2}$), 1.50−1.35 (m, 2H), 1.34−1.20 (m, 2H), 1.05−0.88 (m, 6H), 0.88−0.80 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.6, 170.9 (dia1), 170.6 (dia2), 170.0 (dia1), 169.7 (dia2), 149.7, 145.1, 143.0, 142.8, 139.2, 138.6, 136.9, 131.0, 130.3, 128.2 (2 × C), 128.1 (2 × C), 127.7, 127.1, 127.0, 120.9, 116.4, 114.6, 112.2, 95.4, 94.0, 86.8, 78.5, 78.2, 77.9, 74.2, 73.6, 57.0, 56.1, 55.8, 55.4, 37.4, 33.6, 33.0, 31.2, 30.6, 20.0, 19.6, 19.3, 19.2, 19.1, 17.0, 11.2; HRMS: *m*/*z* calcd for $C_{47}H_{68}N_2O_{11}$ + Na 859.4721; found 859.4725.

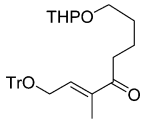


*Preparation of Ethyl (E)-2-Methyl-4-(trityloxy) but-2-enoate (**54**).* To a solution of the trityl ether **51** (3.0 g, 10.0 mmol) in Et_2O:H_2O (25 mL, 4:1) were added OsO_4 (0.003 g, 0.01 mmol) followed by NMO (2.30 g, 20 mmol) at room temperature, and the solution was allowed to stir for 8 h at the same temperature. After completion of the reaction (monitored by TLC), saturated solution of Na_2SO_3 (10 mL) was added and stirred for 0.5 h. The reaction mixture was extracted with EtOAc (2 × 20 mL), and the combined organic layers were washed with brine (15 mL) and dried over anhyd. Na_2SO_4. Evaporation of the solvent gave the crude residue which was used as such in the next reaction without further purification.

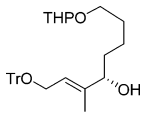
To a precooled (0 °C) solution of the diol obtained above in MeOH/H_2O (20 mL, 9:1) was added $NaIO_4$ (3.2 g, 15 mmol), and it was allowed to stir at the same temperature for 1 h. After completion of the reaction (monitored by TLC), the reaction mixture was filtered through a short pad of Celite, and the Celite pad was washed with CH_2Cl_2 (20 mL). Evaporation of the solvent gave the crude aldehyde which was used as such in the next reaction without further purification.

To a stirred solution of the aldehyde (obtained above) in dry toluene (50 mL) was added (carbethoxyethylidene)-triphenylphosphorane (5.4 g, 15 mmol) and refluxed for 1 h. After completion of the reaction (TLC), most of the solvent was evaporated off, and the crude residue thus obtained was purified by column chromatography using petroleum ether:EtOAc (10:1) as eluent to afford **54** (3.09 g, 80% for 3 steps) as a white solid. Mp: 91−92 °C; IR: ν_{max} 2929, 1957, 1489, 1443 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.59−7.44(m, 6H), 7.40−7.20 (m, 9H), 6.94 (t, *J* = 5.2 Hz, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 3.84 (d, *J* = 5.6 Hz, 2H), 1.70 (s, 3H), 1.13 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 143.8 (3 × C), 138.5, 128.6 (6 × C), 127.88, 127.86 (6 × C), 127.1 (3 × C), 87.0, 61.5, 60.6, 14.3, 12.8; HRMS: *m*/*z* for $C_{26}H_{26}O_3$ + Na calcd: 409.1780; found: 409.1781.

*Preparation of Ethyl (E)-2-Methyl-4-(trityloxy)but-2-enoate (**55**).* To a stirred solution of the ester **54** (3.01 g, 7.79 mmol) in THF (20 mL) was added *N*,*O*-dimethylhydroxylamine hydrochloride (1.15 g, 11.68 mmol) at 0 °C. Isopropylmagnesium chloride (23.37 mmol, 33.4 mL of 0.7 M solution in THF) was added to the reaction mixture dropwise at 0 °C, and the stirring was continued at the same temperature for 1 h. After completion of the reaction (TLC), it was quenched by addition of saturated NH_4Cl solution (30 mL) and was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (20 mL), dried over anhyd. Na_2SO_4, and concentrated to give the crude residue which was purified by silica gel column chromatography using petroleum ether:EtOAc (5:1) as eluent to furnish the pure amide **55** (2.18 g, 72%) as a white solid. Mp: 105−106 °C; IR (KBr): ν_{max} 2931, 1739, 1647, 1488, 1444 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.49−7.23 (m, 15H), 6.07 (t, *J* = 5.4 Hz, 1H), 3.73 (d, *J* = 6.0 Hz, 2H), 3.66 (s, 3H), 3.23 (s, 3H), 1.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 143.9 (3 × C), 132.6, 130.0, 128.6 (6 × C), 127.8 (6 × C), 127.0 (3 × C), 86.9 (C), 61.1, 60.7, 33.6, 14.3; HRMS: *m*/*z* for $C_{26}H_{27}NO_3$ + Na calcd: 424.1889; found: 424.1886.



*Preparation of (E)-3-Methyl-8-((tetrahydro-2H-pyran-2-yl)oxy)-1-(trityloxy)oct-2-en-4-one (**56**).* Compound **56** was prepared by the addition of (4-((tetrahydro-2H-pyran-2- yl)oxy)butyl)magnesium bromide (10 mL of 0.60 M solution in THF, 5.99 mmol) to Weinreb amide **55** (2.0 g, 4.99 mmol) using a procedure described for the synthesis of **36** and afforded **56** (1.84 g, 74%) as a colorless oil. IR (neat): ν_{max} 2939, 2856, 1671, 1446, 1277 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.55−7.44 (m, 6H), 7.40−7.28 (m, 6H), 7.28−7.20 (m, 3H), 6.65 (t, *J* = 4.8 Hz, 1H), 4.62−4.55 (m, 1H), 3.94 (d, *J* = 5.2 Hz, 2H), 3.86 (dd, *J* = 13.2, 6.0 Hz, 1H), 3.76 (ddd, *J* = 15.8, 9.6, 4.6 Hz, 1H), 3.52−3.45 (m, 1H), 3.45−3.32 (m, 1H), 2.67 (t, *J* = 7.2 Hz, 2H), 1.85−1.45 (m, 10H), 1.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.3, 143.7 (3 × C), 139.0, 136.6, 128.6 (6 × C), 127.9 (6 × C), 127.1 (3 × C), 98.8, 87.2, 67.3, 62.3, 61.9, 36.7, 30.7, 29.3, 25.4, 21.5, 19.6, 11.6; HRMS: *m*/*z* for $C_{33}H_{38}O_4$ + Na calcd: 521.2668; found: 521.2665.



*Preparation of (4S,E)-3-Methyl-8-((tetrahydro-2H-pyran-2-yl)-oxy)-1-(trityloxy)oct-2-en-4-ol (**57**).* To a stirred solution of (*R*)-2-methyl-CBS-oxazaborolidine (2.3 mL, 1.0 M solution in toluene, 2.27 mmol) in THF (5 mL) was added $BH_3{\cdot}SMe_2$ (5.2 mL, 2.0 M solution in THF, 10.36 mmol) at room temperature and stirred for 10 min. Then the reaction mixture was cooled to −20 °C, and the solution of ketone **56** (3.80 g, 7.63 mmol) in THF (20 mL) was added dropwise over a period of 5 h and stirred at the same temperature for an additional 5 h. After completion of the reaction (TLC), it was quenched by the addition of MeOH (5 mL), followed by evaporation of MeOH in vacuo furnished the crude residue. This was dissolved in EtOAc (10 mL) to which 1 N cold HCl (10 mL) was added and was extracted with EtOAc (2 × 20 mL). The combined organic layer was washed with brine (30 mL) and dried over anhyd. Na_2SO_4 and concentrated. The crude residue obtained after evaporation of solvent was purified by silica gel column chromatography with petroleum ether:EtOAc (5:1) as eluent to give desired alcohol **57** (3.09 g, 81%) as a colorless oil. $[\alpha]_D^{24}$: +0.4 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 3054, 2986, 2307, 1423, 1264 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, *J* = 7.6 Hz, 6H), 7.39−7.16 (m, 9H), 5.64 (t, *J* = 5.4 Hz, 1H), 4.57 (s, 1H), 4.01 (t, *J* = 6.4 Hz, 1H), 3.85 (t, *J* = 9.2 Hz, 1H), 3.74 (dd, *J* = 16.2, 7.0 Hz, 1H), 3.74 (dd, *J* = 16.2, 7.0 Hz, 1H), 3.67 (t, *J* = 5.6 Hz, 2H), 3.55−3.44 (m, 1H), 3.44−3.34 (m, 1H), 1.85−1.46 (m, 12H), 1.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.2 (3 × C), 139.7 (C), 128.6 (6 × C), 127.7 (6 × C), 126.9 (3 × C), 123.1, 98.8, 86.7, 77.2, 67.4, 62.3, 61.0, 34.5, 30.7, 29.5, 25.4, 22.5, 19.6, 11.8; HRMS: *m*/*z* for $C_{33}H_{40}O_4$ + Na calcd: 523.2824; found: 523.2823.

DOI: 10.1021/acs.joc.6b02535
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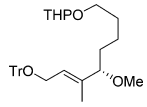
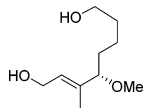
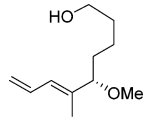


*Preparation of 2-(((S,E)-5-Methoxy-6-methyl-8-(trityloxy)oct-6-en-1-yl)oxy)tetrahydro-2H-pyran (**58**).* Compound **58** was prepared by methylation of alcohol **57** (2.80 g, 5.6 mmol) using a procedure described for the synthesis of **37a**, afforded **58** (2.64 g, 92%) as a colorless oil. $[\alpha]_D^{24}$: −5.0 (*c* 0.8, $CHCl_3$); IR (neat): ν_{max} 2985, 2307, 1445, 1264, 1029 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, J = 7.6 Hz, 6H), 7.35−7.18 (m, 9H), 5.64 (t, *J* = 5.6 Hz, 1H), 4.57 (s, 1H), 3.85 (t, *J* = 9.4 Hz, 1H), 3.78−3.60 (m, 3H), 3.52−3.43 (m, 2H), 3.38 (dd, *J* = 15.8, 6.6 Hz, 1H), 3.19 (s, 3H), 1.90−1.39 (m, 12H), 1.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.2 (3 × C), 136.9, 128.6 (6 × C), 127.7 (6 × C), 126.8 (3 × C), 125.6, 98.8, 86.8, 86.7, 67.4, 62.3, 60.8, 55.9, 33.3, 30.7, 29.6, 25.4, 22.5, 19.6, 10.7; HRMS: *m*/*z* for $C_{34}H_{42}O_4$ + Na calcd: 537.2981; found: 537.2980.

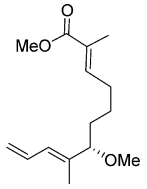


*Preparation of (S,E)-4-Methoxy-3-methyloct-2-ene-1,8-diol (**59**).* To a stirred solution of the masked triol **58** (2.60 g, 5.05 mmol) in MeOH (15 mL) was added PPTS (2.5 g, 10.11 mmol) at room temperature and stirred for 8 h. After completion of the reaction (TLC), it was quenched with solid $NaHCO_3$ (0.05 g). It was then filtered through a short pad of Celite, and the Celite pad was washed with CH_2Cl_2 (20 mL). The solvent was evaporated off, and the crude residue thus obtained was purified by silica gel column chromatography using petroleum ether:EtOAc (3:2) as an eluent to afford **59** (0.71 g, 75%) as a colorless oil. $[\alpha]_D^{24}$: −20.7 (*c* 0.4, $CHCl_3$); IR (neat): ν_{max} 3360, 2935, 2865, 1445, 1090 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.54 (dd, *J* = 11.6, 6.0 Hz, 1H), 4.18 (d, *J* = 6.4 Hz, 2H), 3.63−3.49 (m, 2H), 3.49−3.35 (m, 1H), 3.15 (s, 3H), 2.65 (bs, 2H), 1.53 (s, 3H), 1.70−1.17 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.1, 127.5, 86.8, 62.4, 58.6, 55.9, 32.8, 32.3, 21.9, 10.5; HRMS: *m*/*z* for $C_{10}H_{20}O_3$ + Na calcd: 211.1310; found: 211.1307.



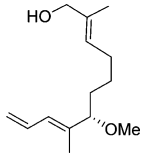
*Preparation of (S,E)-5-Methoxy-6-methylnona-6,8-dien-1-ol (**60**).* To a stirred solution of the diol **59** (0.24 g, 1.28 mmol) in CH_2Cl_2 (5 mL) was added MnO_2 (1.1 g, 12.8 mmol) at room temperature, and the resulting suspension was refluxed for 2 h. The reaction mixture was filtered through a Celite pad and concentrated to afford the crude aldehyde, which was used as such in the next step without further purification.

To a precooled (0 °C) solution of $CH_3P^+(PPh)_3Br^-$ (1.6 g, 4.48 mmol) in THF (10 mL) was added *n*-BuLi (1.6 M solution in cyclohexane, 2.4 mL, 3.84 mmol) and was stirred for 0.5 h. The reaction mixture was then cooled to −20 °C, and a solution of the aldehyde obtained above in THF (5 mL) was added dropwise and allowed to stir for a further 1.5 h. After completion of the reaction (indicated by TLC), it was quenched with sat. NH_4Cl solution (10 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (10 mL) and dried over anhyd. Na_2SO_4. Evaporation of the solvent gave the crude residue which on purification by silica gel column chromatography using petroleum ether:EtOAc (3:2) as an eluent afforded the diene **60** (0.215 g, 70% for 2 steps) as a colorless oil. $[\alpha]_D^{24}$: −26.5 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 3471, 1606, 1213, 929, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.52 (dt, *J* = 16.8, 10.6 Hz, 1H), 5.91 (d, *J* = 10.8 Hz, 1H), 5.12 (d, *J* = 16.8 Hz, 1H), 5.04 (d, *J* = 10.2 Hz, 1H), 3.52 (td, *J* = 6.6, 2.4 Hz, 2H), 3.40 (t, *J* = 6.6 Hz, 1H), 3.10 (s, 3H), 2.63 (bs, 1H), 1.60 (s, 3H), 1.58−1.12 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.6, 132.3, 128.2, 116.9, 87.0, 62.2, 55.8, 33.2, 32.3, 21.9, 10.5; HRMS: *m*/*z* for $C_{11}H_{20}O_2$ + Na calcd: 207.1361; found: 207.1361.



*Preparation of Ethyl (S,2E,8E)-7-Methoxy-2,8-dimethylundeca-2,8,10-trienoate (**61**).* To a stirred solution of alcohol **60** (0.125 g, 0.68 mmol) in EtOAc (4 mL) was added IBX (0.58 g, 2.06 mmol) and refluxed for 3 h. After completion of the reaction, it was filtered through a short pad of Celite, and the Celite pad was washed with EtOAc (25 mL). The organic layer was washed with saturated $NaHCO_3$ solution (15 mL), brine (15 mL), dried over anhyd. Na_2SO_4, and concentrated. The crude aldehyde obtained was used in the next step without further purification.

To a stirred solution of the aldehyde (obtained above) in dry toluene (20 mL) was added (carbethoxyethylidene)-triphenylphosphorane (0.49 g, 1.36 mmol) and refluxed for 1 h. After completion of the reaction (TLC), most of the solvent was evaporated off, and the crude residue thus obtained was purified by column chromatography using petroleum ether:EtOAc (6:1) as eluent to afford **61** (0.146 g, 81% for 2 steps) as a colorless oil. $[\alpha]_D^{24}$: −20.0 (*c* 0.5, $CHCl_3$); IR (neat): ν_{max} 2933, 2304, 1707, 1262, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.74 (t, *J* = 7.0 Hz, 1H), 6.61 (dt, *J* = 16.8, 10.6 Hz, 1H), 5.99 (d, *J* = 10.8 Hz, 1H), 5.20 (d, *J* = 16.8 Hz, 1H), 5.12 (d, *J* = 10.2 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.47 (t, *J* = 6.4 Hz, 1H), 3.18 (s, 3H), 2.18 (dd, *J* = 14.2, 7.2 Hz, 2H), 1.82 (s, 3H), 1.68 (s, 3H), 1.66−1.58 (m, 1H), 1.56−1.36 (m, 3H), 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.2, 141.8, 137.7, 132.4, 128.3, 127.7, 117.0, 86.8, 60.3, 56.0, 33.3, 28.5, 24.9, 14.2, 12.3, 11.0; HRMS: *m*/*z* for $C_{16}H_{26}O_3$ + Na calcd: 289.1780; found: 289.1780.



*Preparation of (S,2E,8E)-7-Methoxy-2,8-dimethylundeca-2,8,10-trien-1-ol (**62**).* To a stirred solution of the ester **61** (0.17 g, 0.64 mmol) in dry CH_2Cl_2 (8 mL) was added DIBAL-H (1.30 mL of 1.0 M solution in toluene, 1.30 mmol) dropwise at −78 °C for a period of 5 min under argon atmosphere. The reaction mixture was stirred at the same temperature for 30 min. After completion of the reaction (TLC), it was quenched by the addition of a saturated aqueous solution of potassium sodium tartrate (10 mL), diluted with Et_2O (10 mL), and stirred for 1 h at room temperature. The aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated to yield the crude residue, thus obtained was purified by column chromatography using petroleum ether:-EtOAc (5:1) as eluent to afford **62** (0.13 g, 92%) as a colorless oil. $[\alpha]_D^{24}$: −24.6 (*c* 0.5, $CHCl_3$); IR (neat): ν_{max} 3393, 2929, 2858, 16449, 1449 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.60 (dt, *J* = 16.8, 10.6 Hz, 1H), 5.98 (d, *J* = 10.8 Hz, 1H), 5.39 (t, *J* = 6.8 Hz, 1H), 5.20 (d, *J* = 16.8 Hz, 1H), 5.11 (d, *J* = 10.2 Hz, 1H), 3.98 (s, 2H), 3.47 (t, *J* = 6.8 Hz, 1H), 3.18 (s, 3H), 2.03 (dd, *J* = 14.4, 7.2 Hz, 2H), 1.92 (bs, 1H), 1.67 (s, 3H), 1.64 (s, 3H), 1.52−1.25 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.8, 134.9, 132.4, 128.3, 125.9, 116.9, 87.1, 68.8, 56.9, 33.2, 27.4, 25.7, 13.6, 11.0; HRMS: *m*/*z* for $C_{14}H_{24}O_2$ + Na calcd: 247.1674; found: 247.1676.

DOI: 10.1021/acs.joc.6b02535
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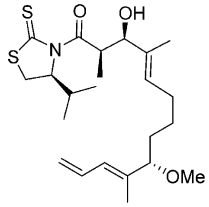
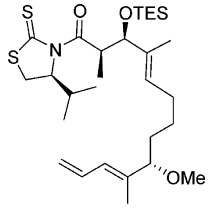


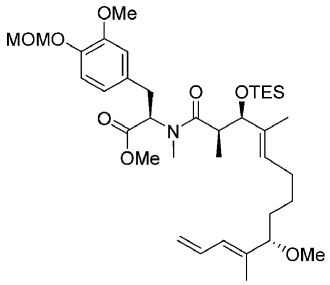
*Preparation of (2R,3R,4E,9S,10E)-3-Hydroxy-1-((S)-4-isopropyl-2-thioxothiazolidin-3-yl)-9-methoxy-2,4,10-trimethyltrideca-4,10,12-trien-1-one (**63**).* To a stirred solution of the alcohol **62** (0.12 g, 0.53 mmol) in dry CH_2Cl_2 (2 mL) were added $NaHCO_3$ (0.089 g, 1.06 mmol) and Dess−Martin periodinane (0.341 g, 0.80 mmol) at 0 °C under nitrogen atmosphere. The reaction mixture was warmed to room temperature and stirred for 1 h. After completion of the reaction (TLC), it was washed with saturated aqueous solutions of $NaHCO_3$ (5 mL) and $Na_2S_2O_3$ (5 mL) and diluted with EtOAc (10 mL). The aqueous phase was extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over anhyd. Na_2SO_4, and concentrated to give crude aldehyde as a colorless oil which was used in the next step without further purification.

To a stirred solution of thiazolidine thione **18** (0.172 g, 0.79 mmol) in freshly distilled CH_2Cl_2 (25 mL) was added $TiCl_4$ (0.08 mL, 0.79 mmol) dropwise at −25 °C under inert atmosphere and was stirred for 5 min. Diisopropylethylamine (0.2 mL, 1.18 mmol) was introduced into the reaction mixture, and the resulting dark brown reaction mixture was stirred for 30 min at −25 °C. The solution of crude aldehyde (obtained above) in CH_2Cl_2 (5 mL) was added dropwise at −25 °C and stirred at the same temperature. After completion of the reaction (10 min), it was quenched by addition of saturated NH_4Cl solution (10 mL). The reaction mixture was extracted with EtOAc (2 × 15 mL). The organic layer was washed with brine and then dried over anhyd. Na_2SO_4. It was concentrated in vacuo to provide the crude residue which was purified by silica gel column chromatography using petroleum ether:EtOAc (5:1) as eluent to afford the pure alcohol **63** (0.198 g, 85% for 2 steps) as a yellow oil. $[\alpha]_D^{24}$: +171.5 (*c* 0.65, $CHCl_3$); IR (neat): ν_{max} 3444, 2929, 2856, 1693, 1599 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.60 (dt, *J* = 16.8, 10.4 Hz, 1H), 5.98 (d, *J* = 10.8 Hz, 1H), 5.54 (t, *J* = 6.8 Hz, 1H), 5.19 (d, *J* = 16.8 Hz, 2H), 5.10 (d, *J* = 10.2 Hz, 1H), 5.05−4.95 (m, 1H), 4.47 (bs, 1H), 3.57−3.41 (m, 2H), 3.17 (s, 3H), 3.02 (d, *J* = 11.6 Hz, 1H), 2.42−2.28 (m, 1H), 2.10−1.95 (m, 2H), 1.67 (s, 3H), 1.60 (s, 3H), 1.50−1.25 (m, 4H), 1.20−1.00 (m, 6H), 0.97 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.9, 178.0, 137.8, 133.5, 132.4, 128.2, 126.1, 116.8, 87.0, 74.9, 71.8, 55.9, 40.7, 33.2, 30.7, 29.6, 27.4, 25.7, 19.0, 17.3, 13.5, 11.0, 10.7; HRMS: *m*/*z* for $C_{23}H_{37}NO_3S_2$ + Na calcd: 462.2113; found: 462.2111.



*Preparation of (2R,3R,4E,9S,10E)-1-((S)-4-Isopropyl-2-thioxothiazolidin-3-yl)-9-methoxy-2,4,10-trimethyl-3-((triethylsilyl)oxy)-trideca-4,10,12-trien-1-one (**64**).* To a solution of **63** (0.14 g, 0.32 mmol) and pyridine (0.09 mL, 0.96 mmol) in CH_2Cl_2 (1 mL) was added TESOTf (0.09 mL, 0.45 mmol) at −50 °C. The mixture was allowed to warm up to room temperature and was stirred at room temperature for 2 h. After the reaction was complete (TLC), it was washed with saturated aqueous $NaHCO_3$ solution (10 mL) and was extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine (5 mL) and dried over Na_2SO_4, and the solvent was evaporated off to give crude residue which was purified by silica gel column chromatography using petroleum ether:EtOAc (6:1) as eluent to afford desired product **64** (0.15 g, 83%) as a yellow oil. $[\alpha]_D^{24}$: +127.4 (*c* 1.10, $CHCl_3$); IR (neat): ν_{max} 2929, 1694, 1591, 1463, 1419 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.60 (dt, *J* = 17.0, 10.6 Hz, 1H), 5.98 (d, *J* = 10.8 Hz, 1H), 5.34 (t, *J* = 6.8 Hz, 1H), 5.27−5.15 (m, 2H), 5.15−5.04 (m, 2H), 4.30 (d, *J* = 9.2 Hz, 1H), 3.52−3.36 (m, 2H), 3.17 (s, 3H), 2.90 (d, *J* = 11.6 Hz, 1H), 2.14 (dt, *J* = 12.8, 6.6 Hz, 1H), 1.98 (dt, *J* = 14.8, 7.8 Hz, 1H), 1.90−1.75 (m, 1H), 1.70 (s, 3H), 1.59 (s, 3H), 1.52−1.25 (m, 4H), 1.21 (d, *J* = 6.8 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.96−0.85 (m, 12H), 0.57 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.3, 176.0, 137.9, 135.7, 132.5, 128.6, 128.2, 116.9, 87.1, 80.2, 71.3, 56.0, 42.7, 33.6, 30.8, 28.6, 27.5, 25.5, 19.0, 17.1, 15.3, 11.4, 11.0, 6.8 (3 × C), 4.8 (3 × C); HRMS: *m*/*z* for $C_{29}H_{51}NO_3S_2Si$ + Na calcd: 576.2977; found: 576.2976.

*Preparation of (2R,3R,4E,9S,10E)-9-Methoxy-2,4,10-trimethyl-3-((triethylsilyl)oxy)trideca-4,10,12-trienoic acid (**65**).* To a stirred solution of thione **64** (0.12 g, 0.22 mmol) in THF (4 mL) were added LiOH (0.7 mL of 1.0 M aq.solution, 0.66 mmol) followed by H_2O_2 (1.2 mL of 30% w/v solution in water). The reaction mixture was stirred for 2 h at room temperature and was acidified to pH = 7 carefully with 2 N HCl. The reaction mixture was extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine (5 mL), dried over anhyd. Na_2SO_4, and concentrated. The crude residue thus obtained was purified by silica gel column chromatography using EtOAc as eluent to afford **65** (0.07 g, 75%) as a colorless oil. $[\alpha]_D^{24}$: −17.4 (*c* 1.10, $CHCl_3$); IR (neat): ν_{max} 3583, 3356, 2931, 2374, 1470 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.79 (bs, 1H), 6.60 (dt, *J* = 16.8, 10.4 Hz, 1H), 5.98 (d, *J* = 10.8 Hz, 1H), 5.36 (t, *J* = 7.2 Hz, 1H), 5.20 (d, *J* = 9.2 Hz, 1H), 5.11 (d, *J* = 10.2 Hz, 1H), 4.19 (d, *J* = 7.0 Hz, 1H), 3.47 (t, *J* = 6.4 Hz, 1H), 3.18 (s, 3H), 2.63 (p, *J* = 6.8 Hz, 1H), 2.13−1.90 (m, 2H), 1.67 (s, 3H), 1.58 (s, 3H), 1.51−1.23 (m, 4H), 1.12 (d, *J* = 6.8 Hz, 3H), 0.93 (t, *J* = 7.8 Hz, 9H), 0.58 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.0, 137.7, 135.0, 132.4, 128.3, 127.9, 116.9, 87.2, 79.8, 56.0, 44.6, 33.1, 27.2, 25.5, 12.4, 11.4, 11.0, 6.74 (3 × C), 4.68 (3 × C); HRMS: *m*/*z* for $C_{23}H_{42}O_4Si$ + Na calcd: 433.2750; found: 433.2753.



*Preparation of Methyl (2R)-3-(3-Methoxy-4-(methoxymethoxy)-phenyl)-2-((2R,4E,9S,10E)-9-methoxy-N,2,4,10-tetramethyl-3-((triethylsilyl)oxy) trideca-4,10,12-trienamido)propanoate (**66**).* Compound **66** was prepared from the acid **65** (0.07 g, 0.17 mmol) and amine **40** (0.101 g, 0.26 mmol) in 52% yield (0.055 g) as a colorless oil, following the same procedure described for the synthesis of **25**. $[\alpha]_D^{24}$: +6.0 (*c* 0.75, $CHCl_3$); IR (neat): ν_{max} 2923, 2375, 1742, 1654, 1438 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.01 (d, *J* = 8.0 Hz, 1H), 6.75 (s, 1H), 6.65 (d, *J* = 7.6 Hz, 1H), 6.62−6.45 (m, 1H), 5.96 (d, *J* = 10.4 Hz, 1H), 5.42−5.30 (m, 2H), 5.25−5.30 (m, 3H), 5.10 (d, *J* = 10.2 Hz, 1H), 4.11 (d, *J* = 9.0 Hz, 1H), 3.85 (s, 3H), 3.69 (s, 3H), 3.48 (s, 3H), 3.46−3.39 (m, 1H), 3.31 (dd, *J* = 14.2, 4.4 Hz, 1H), 3.15 (s, 3H), 2.95−2.70 (m, 2H), 2.80 (s, 3H), 2.10−1.82 (m, 2H), 1.65 (s, 3H), 1.55 (s, 3H), 1.50−1.10 (m, 4H), 1.00−0.80 (m, 12H), 0.54 (q, *J* = 7.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.1, 171.4, 149.6, 145.1, 138.0, 135.0, 132.5, 131.3, 128.5, 128.1, 121.2, 116.8, 116.2, 112.3, 95.5, 87.1, 80.4, 57.1, 56.1, 56.0, 55.9, 52.1, 41.3, 34.7, 33.5, 32.8, 27.5, 25.4, 14.9, 11.3, 11.0, 6.8 (3 × C), 4.8 (3 × C); HRMS: *m*/*z* for $C_{37}H_{61}NO_8Si$ + Na calcd: 698.4064; found: 698.4068.

DOI: 10.1021/acs.joc.6b02535
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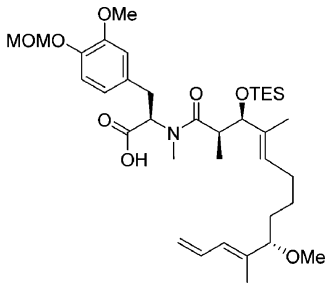
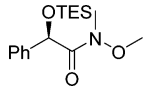
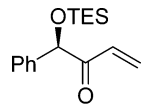


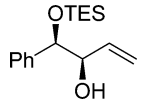
*Preparation of (2R)-3-(3-Methoxy-4-(methoxymethoxy)phenyl)-2-((2R,4E,9S,10E)-9-methoxy-N,2,4,10-tetramethyl-3-((triethylsilyl)oxy)trideca-4,10,12-trienamido)propanoic acid (**48**).* Compound **48** was prepared by the hydrolysis of ester **66** (0.029 g, 0.04 mmol) using a procedure described for the synthesis of **30**, affording **48** (0.024 g, 89%) as a colorless oil. $[\alpha]_D^{24}$: −1.2 (*c* 0.4, $CHCl_3$); IR (neat): ν_{max} 3387, 2927, 1616, 1513, 1264 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.02 (d, *J* = 8.0 Hz, 1H), 6.75 (s, 1H), 6.67 (d, *J* = 8.0 Hz, 1H), 6.65−6.52 (m, 1H), 5.97 (d, *J* = 10.2 Hz, 1H), 5.52 (bs, 1H), 5.35 (t, *J* = 7.2, 1H), 5.26−5.16 (m, 1H), 5.18 (s, 2H), 5.12 (d, *J* = 10.0 Hz, 1H), 4.16 (d, *J* = 9.2 Hz, 1H), 3.85 (s, 3H), 3.55 (t, *J* = 6.8 Hz, 1H), 3.49 (s, 3H), 3.32 (dd, *J* = 14.6, 5.4 Hz, 1H), 3.21 (s, 3H), 2.92−2.72 (m, 2H), 2.83 (s, 3H), 2.10−1.85 (m, 2H), 1.66 (s, 3H), 1.57 (s, 3H), 1.50−1.10 (m, 4H), 0.90 (t, *J* = 7.6 Hz, 9H), 0.97−0.80 (m, 3H), 0.55 (q, *J* = 7.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.2, 175.9, 149.6, 145.1, 137.2, 135.6, 132.4, 131.1, 128.7, 128.1, 121.0, 117.3, 116.3, 112.0, 95.5, 87.9, 80.2, 56.1, 55.8, 55.3, 41.0, 34.0, 32.6, 31.9, 29.7, 27.3, 25.3, 15.3, 11.3, 11.0, 6.8 (3 × C), 4.8 (3 × C); HRMS: *m*/*z* for $C_{36}H_{59}NO_8Si$ + Na calcd: 684.3908; found: 684.3904.



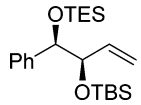
*Preparation of (R)-N-Methoxy-N-methyl-2-phenyl-2-((triethylsilyl)oxy)acetamide (**67**).* To a stirred solution of the Weinreb amide **67a**[13] (2.5 g, 12.88 mmol) in CH_2Cl_2 (15 mL) were added imidazole (1.7 g, 25.76 mmol), 4-(dimethylamino)pyridine (0.314 g, 2.58 mmol), and TESCl (2.6 mL, 15.46 mmol) at 0 °C. The reaction mixture was slowly warmed to room temperature and stirred at same temperature for 5 h. After completion of the reaction (TLC), it was poured into water (20 mL) and was extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with brine (10 mL) and dried over anhyd. Na_2SO_4. Silica gel column chromatography of the residue obtained after evaporation of the solvent, using petroleum ether:EtOAc (4:1) as an eluent, afforded the desired product **67** (3.8 g, 95%) as a colorless oil. $[\alpha]_D^{24}$: −25.3 (*c* 0.3, $CHCl_3$); IR (neat): ν_{max} 2956, 2879, 1721, 1604, 1375 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.48−7.43 (m, 2H), 7.36−7.30 (m, 2H), 7.27 (ddd, *J* = 7.4, 3.6, 1.2 Hz, 1H), 5.60 (s, 1H), 3.49 (s, 3H), 3.13 (s, 3H), 0.93 (t, *J* = 8.0 Hz, 9H), 0.63 (q, *J* = 7.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.3, 139.9, 128.3 (2 × C), 127.9, 127.3, 126.9, 90.4, 61.1, 29.7, 6.7 (3 × C), 4.7 (3 × C); HRMS: *m*/*z* for $C_{16}H_{27}NO_3Si$ + Na calcd: 332.1658; found: 332.1660.



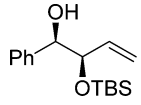
*Preparation of (R)-1-Phenyl-1-((triethylsilyl)oxy)but-3-en-2-one (**68**).* To a solution of the Weinreb amide **67** (0.86 g, 2.78 mmol) in dry THF (8 mL) was added vinylmagnesium bromide (4.2 mL of 1.0 M solution in THF, 4.17 mmol) at 0 °C. Progress of the reaction was monitored by TLC, and after the reaction was complete (∼1 h), it was cautiously quenched by addition of 1 M aq. HCl (5 mL), and the organic layer was extracted with EtOAc (2 × 15 mL). The combined organic extracts were washed with brine (10 mL) and dried (anhyd. Na_2SO_4). Evaporation of solvent followed by silica gel column chromatography of the resultant crude residue with petroleum ether:EtOAc (10:1) as eluent yielded **68** (0.67 g, 82%) as a colorless oil. $[\alpha]_D^{24}$: +58.7 (*c* 0.3, $CHCl_3$); IR (neat): ν_{max} 2957, 2878, 1701, 1615, 1455 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, *J* = 7.4 Hz, 2H), 7.33 (ddd, *J* = 6.2, 2.4, 0.8 Hz, 2H), 7.30−7.23 (m, 1H), 6.82 (dd, *J* = 17.4, 10.6 Hz, 1H), 6.36 (dd, *J* = 17.4, 1.8 Hz, 1H), 5.66 (dd, *J* = 10.6, 1.6 Hz, 1H), 5.22 (s, 1H), 0.93 (t, *J* = 8.0 Hz, 9H), 0.62 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.1, 138.4, 130.2, 129.6, 128.4 (2 × C), 128.0, 125.9 (2 × C), 80.1, 6.6 (3 × C), 4.6 (3 × C); HRMS: *m*/*z* for $C_{16}H_{24}O_2Si$ + Na calcd: 299.1443; found: 299.1443.



*Preparation of (1R,2R)-1-Phenyl-1-((triethylsilyl)oxy)but-3-en-2-ol (**69**).* To a solution of the ketone **68** (1.05 g, 3.59 mmol) in methanol (15 mL) was added $CeCl_3.7H_2O$ (2.67 g, 7.18 mmol) at room temperature, and the solution was stirred at the same temperature for 0.5 h. The reaction mixture was cooled to −78 °C, $NaBH_4$ (0.20 g, 5.30 mmol) was added portion wise over a period of 15 min, and the reaction mixture was stirred at −78 °C for 1 h. After completion of the reaction (TLC), it was cautiously quenched by addition of water (1 mL). After evaporation of MeOH in vacuo, the crude residue was washed with water and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried over anhyd. Na_2SO_4, and concentrated. Silica gel column chromatography of the crude residue obtained after evaporation of the solvent, with petroleum ether:EtOAc (10:1) as an eluent, gave desired alcohol **69** (0.96 g, 91%; 96:4 dr) as a colorless oil. $[\alpha]_D^{24}$: +1.30 (*c* 1.25, $CHCl_3$); IR (neat): ν_{max} 3455, 2956, 2878, 1638, 1604 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38−7.23 (m, 5H), 5.65 (ddd, *J* = 17.2, 10.6, 5.4 Hz, 1H), 5.19 (d, *J* = 17.2 Hz, 1H), 5.08 (d, *J* = 10.6 Hz, 1H), 4.42 (d, *J* = 7.2 Hz, 1H), 4.10 (t, *J* = 6.0 Hz, 1H), 2.94 (s, 1H), 0.86 (t, *J* = 8.0 Hz, 9H), 0.61−0.40 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.0, 136.0, 128.0 (2 × C), 127.8, 127.1 (2 × C), 116.5, 79.0, 77.3, 6.6 (3 × C), 4.7 (3 × C); HRMS: *m*/*z* for $C_{16}H_{26}O_2Si$ + Na calcd: 301.1600; found: 301.1612.



*Preparation of (5R,6R)-8,8-Diethyl-2,2,3,3-tetramethyl-6-phenyl-5-vinyl-4,7-dioxa-3,8-disiladecane (**70**).* To a stirred solution of the Weinreb amide **69** (0.96 g, 3.26 mmol) in CH_2Cl_2 (5 mL) were added imidazole (0.43 g, 6.52 mmol), 4-(dimethylamino)pyridine (0.079 g, 0.65 mmol), and TBSCl (0.73 g, 4.89 mmol) at 0 °C. The reaction mixture was slowly warmed to room temperature and stirred at the same temperature for 8 h. After completion of the reaction (TLC), it was poured into water (20 mL) and was extracted with EtOAc (2 × 10 mL). The combined organic layer was washed with brine (10 mL) and dried over anhyd. Na_2SO_4. Silica gel column chromatography of the residue obtained after evaporation of the solvent, using petroleum ether:EtOAc (4:1) as an eluent, afforded the desired product **70** (1.2 g, 94%) as a colorless oil. $[\alpha]_D^{24}$: −39.7 (*c* 0.65, $CHCl_3$); IR (neat): ν_{max} 2927, 1723, 1639, 1601, 1454 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.32−7.14 (m, 5H), 5.61 (ddd, *J* = 17.2, 10.5, 5.4 Hz, 1H), 5.02 (d, *J* = 17.2 Hz, 1H), 4.95 (d, *J* = 10.6 Hz, 1H), 4.57 (d, *J* = 5.4 Hz, 1H), 4.20 (t, *J* = 5.4 Hz, 1H), 0.89 (s, 9H), 0.87−0.83 (m, 9H), 0.50 (q, *J* = 7.8, Hz, 6H), 0.04 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.5, 137.5, 127.5 (2 × C), 127.2 (2 × C), 127.0, 115.5, 78.1, 77.9, 25.9 (3 × C), 18.3, 6.8 (3 × C), 4.8 (3 × C), −2.9, −4.7; HRMS: *m*/*z* for $C_{22}H_{40}O_2Si_2$ + Na calcd: 415.2465; found: 415.2467.



*Preparation of (1R,2R)-2-((tert-Butyldimethylsilyl)oxy)-1-phenylbut-3-en-1-ol (**52**).* To a stirred solution of the masked diol **70** (1.3 g, 3.32 mmol) in CH_2Cl_2:MeOH (10 mL, 1:1) was added PPTS

DOI: 10.1021/acs.joc.6b02535
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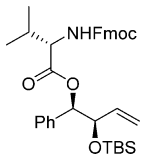
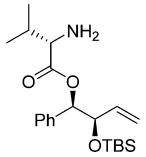
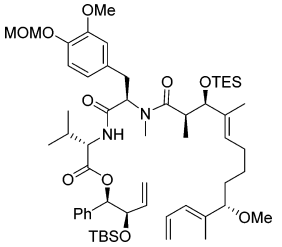
(0.416 g, 1.66 mmol) at 5 °C, and the solution was stirred at the same temperature for 4 h. After completion of the reaction (TLC), it was stirred with solid $NaHCO_3$ (0.05 g) for 5 min. It was then filtered through a short pad of Celite, and the Celite pad was washed with CH_2Cl_2 (20 mL). The solvent was evaporated off, and the crude residue thus obtained was purified by silica gel column chromatography using petroleum ether:EtOAc (10:1) as eluent to afford **52** (0.78 g, 80%) as a colorless oil. $[\alpha]_D^{24}$: −27.5 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3020, 2400, 2046, 1213, 784 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.37−7.24 (m, 5H), 5.78 (ddd, *J* = 17.0, 10.6, 6.2 Hz, 1H), 5.14 (dt, *J* = 2.6, 1.6 Hz, 1H), 5.11 (d, *J* = 1.2 Hz, 1H), 4.49 (dd, *J* = 5.8, 3.6 Hz, 1H), 4.15 (t, *J* = 6.0 Hz, 1H), 3.06 (d, *J* = 4.0 Hz, 1H), 0.91 (s, 9H), −0.00 (s, 3H), −0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.5, 137.6, 128.0 (2 × C), 127.6, 126.9 (2 × C), 116.8, 78.9, 77.4, 25.8 (3 × C), 18.1, −4.4, −5.2; HRMS: *m*/*z* for $C_{16}H_{26}O_2Si$ + Na calcd: 301.1600; found: 301.1604.



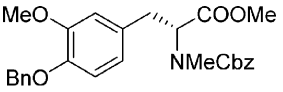
*Preparation of (1R,2R)-2-((tert-Butyldimethylsilyl)oxy)-1-phenylbut-3-en-1-yl(((9H-fluoren-9-yl)methoxy)carbonyl)-L-valinate (**71**).* To a solution of the acid (0.17 g, 0.51 mmol) in CH_2Cl_2 (5 mL) were added Et_3N (0.11 mL, 0.69 mmol) and 2,4,6-trichlorobenzoyl chloride (0.08 mL, 0.59 mmol) at room temperature. After stirring the reaction mixture for 1 h, a solution of alcohol **52** (0.10 g, 0.34 mmol) and DMAP (0.214 g, 1.7 mmol) in CH_2Cl_2 (2 mL) was added to the reaction mixture at room temperature and stirred for 4 h. After completion of the reaction (TLC), it was quenched with saturated NH_4Cl solution (10 mL) and extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with brine (10 mL) and dried over anhyd. Na_2SO_4. Evaporation of the solvent followed by silica gel column chromatography of the crude residue using petroleum ether:EtOAc (6:1) as eluent to afford **71** (0.145 g, 81%) as a colorless oil. $[\alpha]_D^{24}$: −22.0 (*c* 0.15, $CHCl_3$); IR (neat): ν_{max} 3355, 2959, 1726, 1510, 1252 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 7.4 Hz, 2H), 7.62 (dd, *J* = 7.4 Hz, 2H), 7.44−7.28 (m, 9H), 5.70 (d, *J* = 6.8 Hz, 1H), 5.59 (ddd, *J* = 16.4, 10.4, 5.6 Hz, 1H), 5.35 (d, *J* = 9.0 Hz, 1H), 5.19 (d, *J* = 17.2 Hz, 1H), 5.08 (d, *J* = 10.4 Hz, 1H), 4.49−4.34 (m, 4H), 4.24 (t, *J* = 6.9 Hz, 1H), 2.31−2.17 (m, 1H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.90 (s, 9H), 0.74 (d, *J* = 6.8 Hz, 3H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 156.1, 143.9, 143.8, 141.3 (2 × C), 136.7, 136.4, 128.3, 128.1 (2 × C), 127.7 (2 × C), 127.6 (2 × C), 127.3, 127.0 (2 × C), 125.1, 119.9 (2 × C), 117.1, 80.2, 75.3, 67.0, 58.8, 47.2, 31.5, 25.7 (3 × C), 19.0, 18.1, 17.1, −4.7, −5.0; HRMS: *m*/*z* for $C_{36}H_{45}NO_5Si$ + Na calcd: 622.2965; found: 622.2966.



*Preparation of (1R,2R)-2-((tert-Butyldimethylsilyl)oxy)-1-phenylbut-3-en-1-yl -L-valinate (**49**).* To a stirred solution of the ester **71** (0.107 g, 0.178 mmol) in DMF was added 20% pipiridine at room temperature, and the stirring was continued at the same temperature for 0.5 h. After completion of the reaction (TLC), DMF was evaporated off in vacuo to give crude residue, which was purified by silicagel column chromatography using petroleum ether:EtOAc (1:1) as an eluent to afford **49** (0.062 g, 93%) as a colorless oil. $[\alpha]_D^{24}$: −23.0 (*c* 0.10, $CHCl_3$); IR (KBR): ν_{max} 3393, 2856, 2358, 1735, 1604 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.31−7.16 (m, 5H), 5.61 (d, *J* = 6.8 Hz, 1H), 5.60−5.45 (m, 1H), 5.12 (d, *J* = 17.2 Hz, 1H), 5.01 (d, *J* = 10.4 Hz, 1H), 4.36 (t, *J* = 6.0 Hz, 1H), 3.32 (d, *J* = 4.2 Hz, 1H), 2.11−1.95 (m, 1H), 1.41 (bs, 2H), 0.88 (d, *J* = 6.8 Hz, 3H), 0.84 (s, 9H), 0.67 (d, *J* = 6.8 Hz, 3H), −0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.8, 137.0, 136.6, 128.0, 127.9 (2 × C), 127.6 (2 × C), 116.7, 79.3, 75.3, 59.6, 31.7, 25.6 (3 × C), 19.3, 18.1, 16.5, −4.8, −5.2; HRMS: *m*/*z* for $C_{21}H_{35}NO_3Si$ + Na calcd: 400.2284; found: 400.2288.



*Preparation of (1R,2R)-2-((tert-Butyldimethylsilyl)oxy)-1-phenylbut-3-en-1-yl ((R)-3-(3-Methoxy-4-(methoxymethoxy)phenyl)-2-((2R,3R,4E,9S,10E)-9-methoxy-N,2,4,10-tetramethyl-3-((triethylsilyl)oxy)trideca-4,10,12-trienamido)propanoyl)-L-valinate (**47**).* To a solution of the acid **48** (0.024 g, 0.036 mmol) in dry CH_2Cl_2 (1 mL) were added amine **49** (0.020 g, 0.054 mmol), EDCl·HCl (0.014 g, 0.094 mmol) and HOBT (0.013 g, 0.088 mmol) sequentially at room temperature, and the resulting reaction mixture was stirred at the same temperature for 2 h. After completion of the reaction (TLC), it was washed with water and extracted with ethyl acetate (2 × 5 mL). The combined organic layer was washed with brine (5 mL) and dried over anhyd. Na_2SO_4. The solvent was removed in vacuo, and silica gel column chromatography of the resulting crude residue using petroleum ether:EtOAc (3:2) as eluent afforded **47** (0.018 g, 50%) as a colorless oil. $[\alpha]_D^{24}$: −10.0 (*c* 0.25, $CHCl_3$); IR (neat): ν_{max} 3349, 2925, 1650, 1598, 1424 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.40−7.20 (m, 5H), 7.10−6.98 (m, 1H), 6.74 (s, 1H), 6.70−6.52 (m, 2H), 5.95 (d, *J* = 10.6 Hz, 1H), 5.80−5.60 (m, 3H), 5.40−5.25 (m, 2H), 5.22−5.02 (m, 6H), 4.48 (dd, *J* = 8.5, 4.6 Hz, 1H), 4.45−4.30 (m, 1H), 4.10 (t, *J* = 10.2 Hz, 1H), 3.82 (s, 3H), 3.48 (s, 3H), 3.45−3.40 (m, 1H), 3.15 (s, 3H), 3.25−3.10 (m, 1H), 2.95−2.80 (m, 1H), 2.74 (s, 3H), 2.21 (bs, 1H), 2.10−1.70 (m, 3H), 1.65 (s, 3H), 1.55−1.40 (m, 2H), 1.29 (s, 3H), 1.38−1.15 (m, 2H), 1.08 (d, *J* = 6.0 Hz, 3H), 0.95−0.80 (m, 24H), 0.55 (q, *J* = 7.6 Hz, 6H), 0.08 (s, 3H), −0.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9, 170.8,170.5, 154.0, 149.5, 145.0, 138.0, 136.9, 135.0, 132.5, 131.7, 128.2, 128.1, 128.0, 127.7 (2 × C), 127.4 (2 × C), 120.8, 116.8, 116.5, 115.8, 112.7, 95.5, 87.0, 84.4, 80.6, 79.0, 75.3, 57.2, 56.0, 55.9, 55.8, 41.9, 33.4, 31.1, 27.4, 25.8, 25.7 (3 × C), 25.6, 19.3, 18.1, 17.3, 17.0, 14.7, 11.0, 10.9, 6.8 (3 × C), 4.8 (3 × C), −4.8, −5.3



74

*Preparation of methyl (R)-3-(4-(Benzyloxy)-3-methoxyphenyl)-2-(((benzyloxy)carbonyl)(methyl) amino)propanoate (**74**).* Compound **74** was prepared (1.72 g, 90%) as a colorless oil as a mixture of rotamers by the methylation of phenol **73** (2.0 g, 4.25 mmol) using a procedure described for the synthesis of **22a**. $[\alpha]_D^{24}$: +22.2 (*c* 1.75, $CHCl_3$); IR (Neat): ν_{max} 1742, 1705, 1513, 1457, 1140 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.46−7.37 (m, $2H_{maj+min}$), 7.37−7.15 (m, $8H_{maj+min}$), 6.79−6.72 (m, $1.37H_{maj+min}$), 6.67−6.54 (m, $1.56H_{maj+min}$), 5.10 (s, $2H_{maj+min}$), 5.11−5.05 (m, $1.2H_{maj}$), 5.00 (s, $0.8H_{min}$), 5.05−4.95 (m, $0.6H_{maj}$), 4.74 (d, *J* = 10.4, 4.8 Hz, $0.4H_{min}$), 3.79 (s, $1.8H_{maj}$), 3.74 (s, $1.2H_{min}$), 3.72 (s, $1.8H_{maj}$), 3.66 (s, $1.2H_{min}$), 3.24 (ddd, *J* = 19.0, 14.6, 5.0 Hz, $1H_{maj+min}$), 3.07−2.90 (m, $1H_{maj+min}$), 2.83 (s, $1.2H_{min}$), 1.74 (s, $1.8H_{maj}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4 (maj), 171.1(min), 156.5 (maj), 155.7 (min), 149.5 (maj+min), 147.2 (maj), 146.8 (min), 137.1 (maj), 137.0 (min), 136.5 (maj), 136.2 (min), 130.2 (maj), 130.0 (min), 128.4 (2 × C maj+min), 128.3 (2 × C maj +min), 127.9 (min), 127.82 (maj), 127.77 (min), 127.7 (maj), 127.4 (2 × C maj+min), 127.2 (maj+min), 127.1 (maj+min), 120.83 (min), 120.77 (maj), 115.9 (min), 113.9 (maj), 112.3 (min), 112.2

DOI: 10.1021/acs.joc.6b02535
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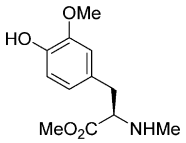
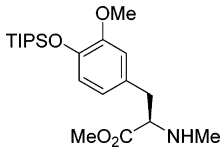
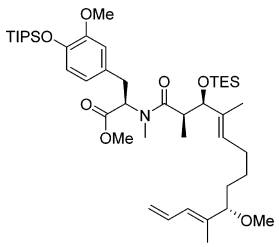
(maj), 70.9 (maj+min), 67.3 (min), 67.0 (maj), 60.7 (min), 60.0 (maj), 55.8 (maj+min), 52.2 (maj+min), 34.7 (min), 34.3 (maj), 32.1 (min), 31.5 (maj); HRMS: m/z calcd for $C_{27}H_{29}NO_6$ + Na 486.1893; found 486.1894.



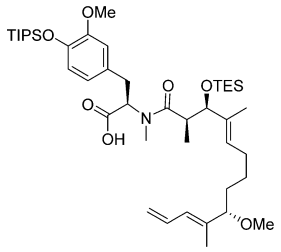
*Preparation of Methyl (R)-3-(4-Hydroxy-3-methoxyphenyl)-2-(methylamino)propanoate (**75**).* Compound **75** was prepared by the hydrogenolysis of carbamate **74** (1.3 g, 2.8 mmol) using a procedure described for the synthesis of **8**, afforded **75** (0.602 g, 92%) as a colorless sticky liquid. $[\alpha]_D^{24}$: −13.7 (c 0.76, $CHCl_3$); IR (Neat): ν_{max} 3450, 2952, 1737, 1517, 1276 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.78 (d, J = 8.0 Hz, 1H), 6.67 (s, 1H), 6.62 (d, J = 8.0 Hz, 1H), 3.82 (s, 3H), 3.68 (s, 3H), 3.43 (t, J = 6.6 Hz, 1H), 2.90 (d, J = 6.6 Hz, 2H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.5, 146.7, 144.6, 128.3, 121.6, 114.7, 111.7, 64.5, 55.6, 51.5, 38.9, 34.5; HRMS: m/z calcd for $C_{12}H_{17}NO_4$+H 240.1236; found 240.1235.



*Preparation of Methyl (R)-3-(3-Methoxy-4-((triisopropylsilyl)-oxy)phenyl)-2-(methylamino) propanoate (**76**).* To a stirred solution of the phenol **75** (0.40 g, 1.67 mmol) in CH_2Cl_2 (5 mL) were added imidazole (0.22 g, 3.34 mmol), 4-(dimethylamino)-pyridine (0.041 g, 0.33 mmol), and TIPSCl (0.34 mL, 2.0 mmol) at 0 °C. The reaction mixture was slowly warmed to room temperature and stirred at the same temperature for 3 h. After completion of the reaction (TLC), it was poured into water (20 mL) and was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (10 mL) and dried over anhyd. Na_2SO_4. Silica gel column chromatography of the residue obtained after evaporation of the solvent, using EtOAc as an eluent afforded the desired product **76** (0.54 g, 82%) as a colorless oil. $[\alpha]_D^{24}$: −8.9 (c 0.35, $CHCl_3$); IR (Neat): ν_{max} 3584, 2943, 2866, 1738, 1514 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.78 (d, J = 8.0 Hz, 1H), 6.65 (s, 1H), 6.60 (d, J = 8.0 Hz, 1H), 3.78 (s, 3H), 3.63 (s, 3H), 3.40 (t, J = 6.8 Hz, 1H), 2.96−2.83 (m, 2H), 2.36 (s, 3H), 1.68 (bs, 1H), 1.34−1.18 (m, 3H), 1.12−1.05 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 150.7, 144.3, 128.1, 121.0, 120.4, 112.8, 64.9, 55.5, 51.5, 39.3, 34.7, 17.8 (6 × C), 12.7 (3 × C); HRMS: m/z calcd for $C_{21}H_{37}NO_4Si$+H 396.2570; found 396.2567.



*Preparation of Methyl ((2R)-2-((2R,4E,9S,10E)-9-Methoxy-3-((triethylsilyl)oxy)-N,2,4,10-tetramethyltrideca-4,10,12-trienamido)-3-(3-methoxy-4-((triisopropylsilyl)oxy)phenyl)-propanoyl)-L-valinate (**77**).* Compound **77** was prepared from the acid **65** (0.075 g, 0.18 mmol) and amine **76** (0.108 g, 0.27 mmol) in 60% yield (0.085 g) as a colorless oil, following the same procedure described for the synthesis of **25**. $[\alpha]_D^{24}$: +6.8 (c 1.3, $CHCl_3$); IR (neat): ν_{max} 2928, 2312, 1702, 1680, 1465 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.74 (d, J = 8.0 Hz, 1H), 6.66 (s, 1H), 6.64−6.49 (m, 2H), 5.96 (d, J = 10.8 Hz, 1H), 5.37 (t, J = 6.8 Hz, 1H), 5.25−5.15 (m, 2H), 5.09 (d, J = 10.0 Hz, 1H), 4.13 (d, J = 9.2 Hz, 1H), 3.76 (s, 3H), 3.68 (s, 3H), 3.43 (t, J = 6.4 Hz, 1H), 3.27 (dd, J = 14.6, 5.2 Hz, 1H), 3.16 (s, 3H), 2.97−2.78 (m, 2H), 2.76 (s, 3H), 2.08−1.86 (m, 2H), 1.66 (s, 3H), 1.62 (s, 3H), 1.51−1.32 (m, 2H), 1.30−1.15 (m, 5H), 1.13−1.00 (m, 21H), 0.91 (t, J = 7.8 Hz, 9H). 0.55 (q, J = 7.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.1, 171.5, 150.1, 144.2, 138.1, 135.1, 132.5, 130.1, 128.5, 128.1, 121.2, 120.1, 116.8, 112.7, 87.1, 80.4, 57.7, 56.0, 55.5, 52.0, 41.3, 34.7, 33.5, 33.1, 27.6, 25.5, 17.9 (6 × C), 15.1, 12.8 (3 × C), 11.3, 11.1, 6.8 (3 × C), 4.8 (3 × C); HRMS: m/z for $C_{44}H_{77}NO_7Si_2$ + Na calcd: 810.5136; found: 810.5140.

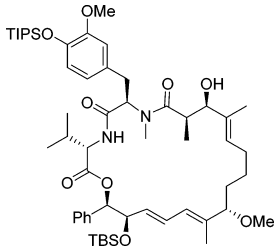


*Preparation of (R)-3-(3-Methoxy-4-((triisopropylsilyl)oxy)phenyl)-2-((2R,3R,4E,9S,10E)-9-methoxy-N,2,4,10-tetramethyl-3-((triethylsilyl)oxy)trideca-4,10,12-trienamido) Propanoic Acid (**78**).* To a stirred solution of ester **77** (0.05 g, 0.074 mmol) in THF (2 mL) was added potassium trimethylsilonate (0.014 g, 0.11 mmol) at room temperature and stirred at the same temperature. After completion of the reaction (TLC), it was evaporated off in vacuo to give crude residue which was washed with water and extracted with EtOAc (2 × 5 mL). The combined organic layer was washed with brine (10 mL) and dried over anhyd. Na_2SO_4. Silica gel column chromatography of the residue obtained after evaporation of the solvent, using petroleum ether:EtOAc (1:4) as an eluent, afforded acid **78** (0.04 g, 83%) as a colorless oil. $[\alpha]_D^{24}$: +2.7 (c 0.15, $CHCl_3$); IR (neat): ν_{max} 3418, 2939, 1736, 1610, 1515 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.76 (dd, J = 15.6, 8.0 Hz, 1H), 6.67 (s, 1H), 6.64−6.51 (m, 2H), 5.98 (t, J = 9.4 Hz, 1H), 5.45−5.30 (m, 2H), 5.20 (d, J = 16.8 Hz, 1H), 5.11 (d, J = 10.2 Hz, 1H), 4.18 (dd, J = 13.4, 6.4 Hz, 1H), 3.76 (s, 3H), 3.62- 3.44 (m, 1H), 3.23−3.09 (m, 4H), 2.98−2.85 (m, 1H), 2.79 (s, 3H), 2.75−2.68 (m, 1H), 2.10−1.82 (m, 2H), 1.60 (s, 3H), 1.55 (s, 3H), 1.55−1.45 (m, 2H), 1.35−1.17 (m, 5H), 1.15−1.0 (m, 18H), 1.01−0.80 (m, 12H), 0.55 (q, J = 7.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.9, 175.3, 150.7, 144.1, 137.5, 135.1, 132.3, 129.8, 129.0, 128.7, 120.4, 120.1, 117.2, 113.2, 87.7, 80.5, 55.6, 55.4, 55.3, 41.1, 34.0, 33.0, 27.6, 25.3, 18.7, 17.8 (6 × C), 15.3, 12.8 (3 × C), 11.0, 10.8, 6.8 (3 × C), 4.8 (3 × C); HRMS: m/z for $C_{43}H_{75}NO_7Si_2$ + Na calcd: 796.4980; found: 796.4982.

*Preparation of (1R,2R)-2-((tert-Butyldimethylsilyl)oxy)-1-phenylbut-3-en-1-yl ((R)-3-(3-Methoxy-4-((triisopropylsilyl)oxy)phenyl)-2-((2R,3R,4E,9S,10E)-9-methoxy-N,2,4,10-tetramethyl-3-((triethylsilyl)-oxy)trideca-4,10,12-trienamido)propanoyl)-L-valinate (**79**).* Compound **79** was prepared from the acid **78** (0.034 g, 0.05 mmol) and amine **49** (0.027 g, 0.072 mmol) in 80% yield (0.04 g) as a colorless oil, following the same procedure described for the synthesis of **31**. $[\alpha]_D^{24}$: −9.0 (c 0.2, $CHCl_3$); IR (neat): ν_{max} 2952, 2866, 1743, 1689, 1515 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.46−7.18 (m, 5H), 6.77- 6.69 (m, 1H), 6.67 (s, 1H), 6.64−6.49 (m, 2H), 6.30 (d, J = 9.0 Hz, 1H), 5.94 (t, J = 10.6 Hz, 1H), 5.69−5.59 (m, 1H), 5.58−5.55 (m, 1H), 5.45−5.28 (m, 1H), 5.17 (d, J = 17.6 Hz, 2H), 5.12−4.99 (m, 2H), 4.61 (dd, J = 9.2, 4.8 Hz, 1H), 4.49−4.32 (m, 1H), 4.11 (t, J = 9.2 Hz, 1H), 3.74 (s, 3H), 3.48−3.35 (m, 1H), 3.29 (dd, J = 14.6, 5.4 Hz, 1H), 3.12 (s, 3H), 2.88−2.82 (m, 1H), 2.81 (s, 3H), 2.77−2.70 (m, 1H), 2.25−2.05 (m, 1H), 1.95−1.75 (m, 2H), 1.72−1.60 (m, 1H), 1.62 (s, 3H), 1.47 (s, 3H), 1.42−1.30 (m, 2H), 1.28−1.17 (m, 5H), 1.15−1.00 (m, 18H), 0.98−0.82 (m, 21H), 0.82−0.70 (m, 6H), 0.62−0.45 (m, 6H), 0.04 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.2, 170.7,170.4, 150.5, 144.1, 138.0, 136.7, 136.4, 135.3, 132.5, 129.9, 128.7, 128.3, 128.1, 128.0 (2 × C), 127.8 (2 × C), 121.2, 119.9, 117.0, 116.8, 112.9, 82.2, 80.2, 80.1, 75.1, 56.6, 56.0, 55.5, 55.3, 41.3, 33.6, 33.3, 31.2, 31.1, 27.5, 27.3, 25.72 (2 × C), 25.68, 25.4, 19.1, 18.2, 17.9 (6

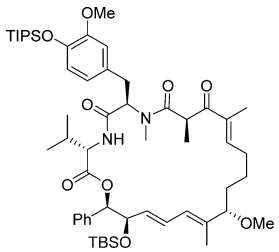
DOI: 10.1021/acs.joc.6b02535
J. Org. Chem. 2017, 82, 438−460

× C), 17.1, 15.4, 12.8 (3 × C), 11.0, 6.8 (3 × C), 4.8 (3 × C), −4.7, −4.9.



*Preparation of (3S,6R,9R,10R,11E,16S,17E,19E,21R,22R)-21-((tert-Butyldimethylsilyl)oxy)-10-hydroxy-3-isopropyl-16-methoxy-6-(3-methoxy-4-((triisopropylsilyl)oxy)benzyl)7,9,11,17-tetramethyl-22-phenyl-1-oxa-4,7-diazacyclodocosa-11,17,19-triene-2,5,8-trione (**80**).* To a solution of the tetraene **79** (0.01 g, 0.009 mmol) in toluene (20 mL) was added Hoveyda−Grubbs second-generation catalyst (0.001 g, 0.0018 mmol), and the solution was allowed to heat at reflux for 8 h. After completion of the reaction (TLC), the solvent was evaporated off, and the crude residue thus obtained was purified using silica gel column chromatography with petroleum ether:EtOAc (10:1) as an eluent furnished the RCM product as a colorless oil, ^{1}H NMR spectrum of which included some surplus peaks. Hence the compound was used as such in the next reaction.

To a stirred solution of the macrolactone (6 mg, 0.01 mmol) in CH_2Cl_2: MeOH (1 mL, 1:1) was added PPTS (3 mg, 0.01 mmol) at room temperature, and the solutionwas stirred for 2 h. After completion of the reaction (TLC), it was stirred with solid $NaHCO_3$ (0.05 g) for 5 min. It was then filtered through a short pad of Celite, and the Celite pad was washed with CH_2Cl_2 (10 mL). The solvent was evaporated off, and the crude residue thus obtained was purified by silica gel column chromatography using petroleum ether:EtOAc (4:1) as eluent to afford **80** (3 mg, 34% for 2 steps) as colorless oil. $[\alpha]_D^{24}$: +62.0 (*c* 0.15, $CHCl_3$); IR (neat): ν_{max} 3410, 2946, 1742, 1743, 1632 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40−7.20 (m, 5H), 6.75 (d, *J* = 8.0 Hz, 1H), 6.71 (s, 1H), 6.68−6.58 (m, 2H), 6.22 (t, *J* = 11.4 Hz, 1H), 5.78 (d, *J* = 8.4 Hz, 1H), 5.62 (t, *J* = 6.6 Hz, 1H), 5.57 (t, *J* = 8.0 Hz, 1H), 4.99 (dd, *J* = 11.4, 6.2 Hz, 1H), 4.66−4.56 (m, 1H), 4.32 (bs, 1H), 3.75 (s, 3H), 3.60−3.49 (m, 1H), 3.33 (bs, 1H), 3.29−3.18 (m, 1H), 3.14 (s, 3H), 2.90 (s, 3H), 2.88−2.80 (m, 2H), 2.20−2.14 (m, 2H), 2.12−2.00 (m, 1H), 1.66 (s, 3H), 1.61 (s, 3H), 1.52−1.40 (m, 3H), 1.30−1.15 (m, 5H), 1.15−1.10 (m, 18H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.90 (s, 9H), 0.73 (d, *J* = 6.6 Hz, 3H), 0.50 (d, *J* = 6.4 Hz, 3H), 0.11 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.7, 171.0,169.6, 150.7, 144.1, 140.5, 139.9, 136.7, 135.4, 135.2, 129.7, 128.4, 128.2 (2 × C), 127.9 (3 × C), 126.3, 121.1, 120.2, 112.7, 85.4, 80.4, 77.2, 75.3, 56.6, 56.2, 55.7, 55.4, 40.3, 33.0, 31.6, 31.3, 30.5, 29.7, 25.7 (3 × C), 25.1, 24.0, 18.9, 18.1, 17.9 (6 × C), 16.9, 13.7, 12.8 (3 × C), 10.8, −4.8, −4.9; HRMS: *m*/*z* for $C_{56}H_{90}N_2O_9Si_2$ + Na calcd: 1013.6083; found: 1013.6086.



*Preparation of (3S,6R,9R,11E,16S,17E,19E,21R,22R)-21-((tert-Butyldimethylsilyl)oxy)-3-isopropyl-16-methoxy-6-(3-methoxy-4-((triisopropylsilyl)oxy)benzyl)-7,9,11,17-tetramethyl-22-phenyl-1-oxa-4,7-diazacyclodocosa-11,17,19-triene-2,5,8,10-tetraone (**81**).* To a stirred solution of the alcohol **80** (3 mg, 0.003 mmol) in dry CH_2Cl_2 (1 mL) were added $NaHCO_3$ (1 mg, 0.007 mmol) and Dess−Martin periodinane (2 mg, 0.005 mmol) at 0 °C under nitrogen atmosphere. The reaction mixture was warmed to room temperature and stirred for 3 h. After completion of the reaction (TLC), it was washed with saturated aqueous solutions of $NaHCO_3$ (3 mL) and $Na_2S_2O_3$ (3 mL) and diluted with EtOAc (5 mL). The aqueous phase was extracted with EtOAc (2 × 5 mL). The combined organic layer was washed with brine (5 mL), dried over anhyd. Na_2SO_4, and concentrated to give crude residue which was purified by silica gel column chromatography to afford *β*-keto amide **81** (2.5 mg, 84%) as a colorless oil. $[\alpha]_D^{24}$: +74.4 (*c* 0.125, $CHCl_3$); IR (neat): ν_{max} 2927, 2375, 1473, 1654 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32−7.19 (m, 6H), 6.76−6.71 (m, 2H), 6.62 (d, *J* = 8.4 Hz, 1H), 6.57 (t, *J* = 7.2 Hz, 1H), 6.40 (d, *J* = 9.0 Hz, 1H), 6.27 (t, *J* = 11.2 Hz, 1H), 5.93 (d, *J* = 7.2 Hz, 1H), 5.64 (t, *J* = 8.4 Hz, 1H), 5.12 (dd, *J* = 11.2, 6.8 Hz, 1H), 4.68−4.60 (m, 2H), 4.13 (q, *J* = 6.8 Hz, 1H), 3.76 (s, 3H), 3.67 (t, *J* = 6.4 Hz, 1H), 3.29 (dd, *J* = 14.8, 7.0 Hz, 1H), 3.21 (s, 3H), 2.87 (s, 3H), 2.87−2.80 (m, 1H), 2.41 (dd, *J* = 14.6, 7.2 Hz, 1H), 2.35−2.19 (m, 1H), 2.19−2.07 (m, 1H), 1.82 (s, 3H), 1.64 (s, 3H), 1.60−1.48 (m, 2H), 1.32−1.15 (m, 5H), 1.15−1.00 (m, 21H), 0.89 (s, 9H), 0.79 (d, *J* = 6.8 Hz, 3H), 0.62 (d, *J* = 6.8 Hz, 3H), 0.08 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.7, 172.6, 170.7,169.7, 157.8, 150.8, 146.3, 144.3, 142.1, 138.7, 136.7, 136.6, 129.6, 128.2, 128.0 (2 × C), 127.9 (3 × C), 121.1, 120.1, 112.7, 79.2, 77.2, 71.8, 61.0, 56.9, 56.2, 56.1, 55.5, 44.5, 31.9, 31.1, 30.9, 29.7, 27.8, 25.7 (3 × C), 24.4, 19.0, 18.1, 17.9 (6 × C), 17.2, 13.4, 12.9 (3 × C), 12.2, −4.8, −5.0; HRMS: *m*/*z* for $C_{56}H_{88}N_2O_9Si_2$ + Na calcd: 1011.5926; found: 1011.5926.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02535.

^{1}H and ^{13}C NMR spectra of all the new compounds and HRMS spectrum of 15-*epi*-aetheramide are provided (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

O.R. thanks the Council of Scientific and Industrial Research (C.S.I.R), New Delhi and the Indian Institute of Science (I.I.Sc), Bangalore for a research fellowship.

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DOI: 10.1021/acs.joc.6b02535
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(14) Recent report by Qi et al. (ref 6) claimed that the deprotection of silyl ethers in a structurally similar lactone (epimeric at the 15th position) with TBAF produced unidentifiable products, while the deprotection of bis silylether of aetheramide B furnished aetheramide B in good yield. Kalesse et al. reported (ref 4) the deprotection of silyl ether in a structurally similar lactone with HF·pyridine.

DOI: 10.1021/acs.joc.6b02535
J. Org. Chem. 2017, 82, 438−460