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Studies toward Total Synthesis of (±)-Caldaphnidine C via One-Pot Sequential Intramolecular Vilsmeier−Haack and Azomethine Ylide 1,3-Dipolar Cycloaddition

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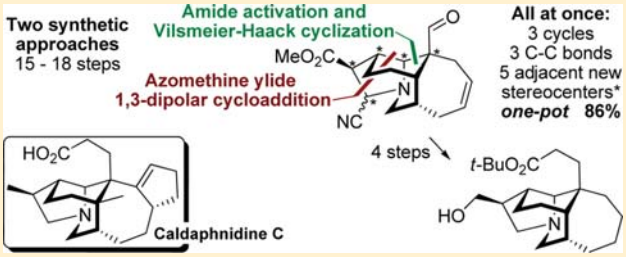
Supporting Information

ABSTRACT: An application of a one-pot sequential Vilsmeier−Haack cyclization and intramolecular azomethine ylide 1,3-dipolar cycloaddition toward the total synthesis of (±)-caldaphnidine C is presented. It allowed an efficient formation of three cycles with perfect control of four of the five newly created stereogenic centers including one all-carbon quaternary center. Two synthetic strategies to produce the key-step precursor, the investigation and optimization of the cyclization partners (nucleophile, azomethine ylide, and dipolarophile), and further derivatization of the cycloadduct are reported.



INTRODUCTION

Some of the most architecturally complex and synthetically challenging alkaloid natural products are found in the *Daphniphyllum* family.[1] Several impressive syntheses of many members of the 14 different types of *Daphniphyllum* alkaloids have been reported over the years,[2] but daphnilactone B-type and yuzurimine-type alkaloids still resist the efforts of synthetic chemists. These alkaloids share the same rigid and compact tetracyclic core **1** that could be regarded as a common synthetic intermediate to many alkaloids of these types (Figure 1).

So far, only five research groups have reported synthetic approaches toward members of daphnilactone B-type and yuzurimine-type alkaloids.[3] The group of Denmark used a cascade of intramolecular hetero-Diels−Alder and nitronate cycloadditions approach, followed by reductive amination to assemble the tricyclic core **4** of these alkaloids in 27 steps (Scheme 1, top left).[4] It should be noted that this approach is nonracemic and that the two contiguous quaternary centers (C3 and C4) were set in the key step. Hayakawa and Kigoshi reported last year a radical cyclization with compound **6** to set the tetracarbocyclic core **7** of yuzurimine-type alkaloids (Scheme 1, bottom left).[5] In a model study, the group of Coldham used a cascade of condensation of aldehyde **8** with ethyl glycinate, intramolecular imine alkylation, and azomethine ylide cycloaddition to build the bridged bicyclic portion **9** of the natural products (Scheme 1, top right).[6] Through a Dieckman cyclization and decarboxylation sequence, the group of Hanessian assembled the seven-membered ring and completed four of the five cycles of daphnilactone B-type alkaloids from compound **10** (Scheme 1, middle right).[7] Finally, our group developed one-pot sequential cyclizations to access four of the five rings common to daphnilactone B-type and yuzurimine-type alkaloids (see **13**, Scheme 1, bottom right).[8] Herein, we report a full account of this synthetic approach, with an extensive study of the key step, as well as our efforts to install proper functionalization on the polycyclic adduct in a premise to the completion of the total synthesis of caldaphnidine C.

RESULTS AND DISCUSSION

We embarked on this journey with the goal to prepare the common intermediate **1** depicted in Figure 1 that should allow the synthesis of both daphnilactone B-type and yuzurimine-type *Daphniphyllum* alkaloids. We felt that this common intermediate could be accessed using a new synthetic strategy we developed in our group,[9] namely, a sequential Vilsmeier−Haack cyclization and intramolecular azomethine ylide 1,3-dipolar cycloaddition as shown in Scheme 2. This one-pot process allows the formation of three cycles of the tetracyclic core, with perfect control of four of the five newly generated stereogenic centers, the fifth one being destroyed later on. Additionally, adduct **1** bears proper functional groups to further advance toward the targeted alkaloids. The substrate for the key transformation is a cycloheptane ring **14** bearing an amide branch, a nucleophilic (Nü) alkene, and a dipolarophile branch (alkene).

We anticipated several challenges with this approach. First, the seven-membered ring key-step substrate **14** requires a *cis* relationship between the amide and the dipolarophile branches, which may be hard to control on conformationally flexible seven-membered rings (Scheme 2). Secondly, with such a densely functionalized substrate, chemoselectivity in the amide activation, as well as for all ensuing steps, could rapidly become

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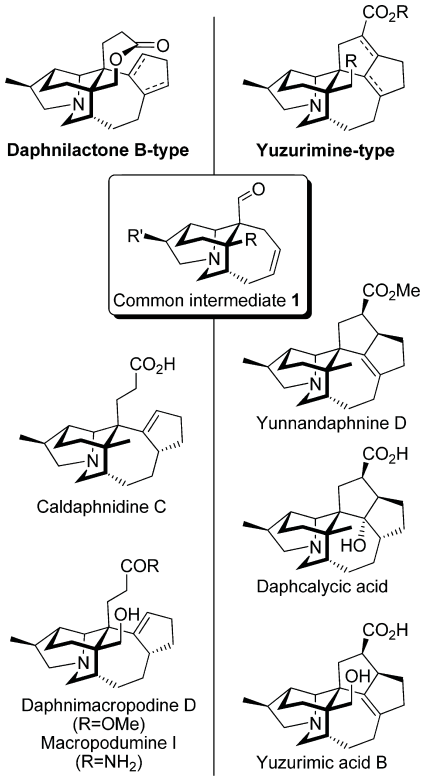
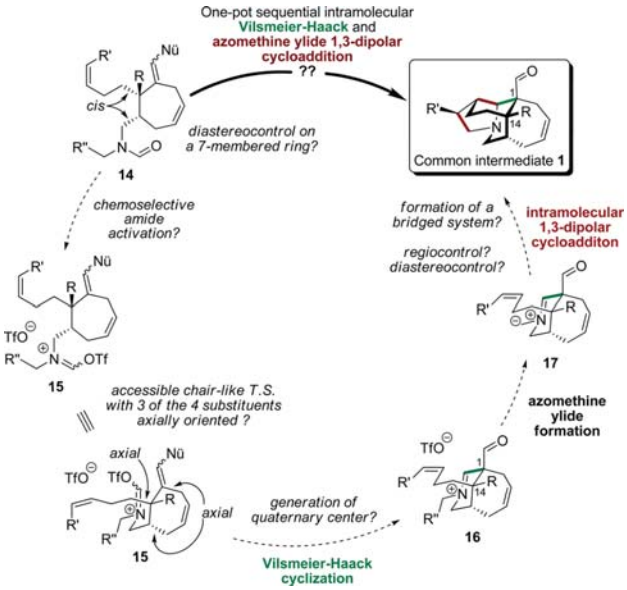


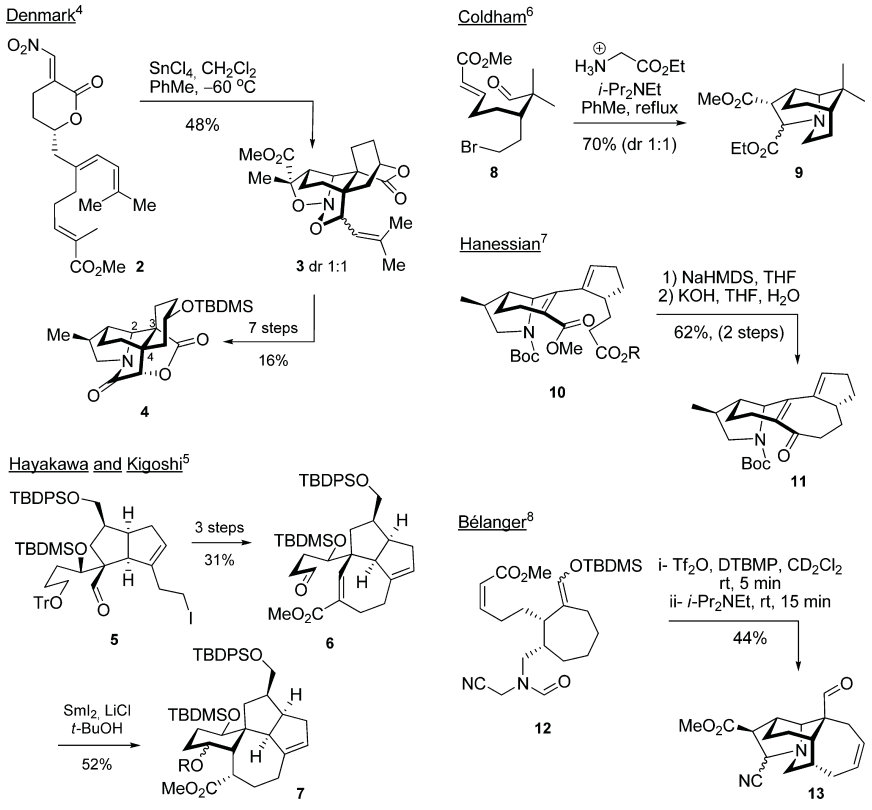
Figure 1. Representative daphnilactone B-type and yuzurimine-type *Daphniphyllum* alkaloids.

Scheme 2. Key Step and Challenges toward Common Intermediate 1



an issue. Thirdly, the transition state for the Vilsmeier−Haack cyclization is a chairlike conformation with three of the four substituents on the chair axially oriented. We could, therefore, anticipate a low concentration of the reactive conformation, usually translated in a low reaction rate and ultimately in low yield. This raised the question about the stability of triflyliminium ion **15** in these conditions. Fourthly, the

Scheme 1. Efforts toward the Total Synthesis of Daphnilactone B-Type and Yuzurimine-Type *Daphniphyllum* Alkaloids



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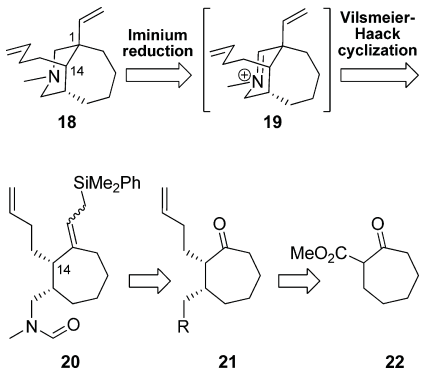
Vilsmeier–Haack cyclization will generate a congested quaternary center (C1), adjacent to another quaternary center (C14). Fifthly, after the generation of the azomethine ylide **17**, the intramolecular 1,3-dipolar cycloaddition will create a bridged system with three new stereogenic centers. Regio- and diastereoselectivity will be controlled mainly by conformational restrictions imposed by the intramolecularity of the process. To maximize our chances of success in using this key transformation for the synthesis of daphnilactone B-type and yuzurimine-type alkaloids, we addressed each of these challenges separately with model systems.

First Model Study: Generation of a Quaternary Center in the Vilsmeier–Haack Cyclization. As an initial study, we decided to concentrate our efforts on the generation of the quaternary center in the Vilsmeier–Haack cyclization (Scheme 3). We opted to design a model compound **20** lacking the quaternary center at C14 and functionalization on the amide to prepare the azomethine ylide. We hoped to confirm this first step in the sequence after reduction of the transient iminium ion **19**. The key-step precursor **20** would be obtained after the installation of an allylsilane, the nucleophile chosen for this first study. Side chains would be incorporated on cycloheptanone in a *cis* relationship through 1,4-addition and alkylation reactions.

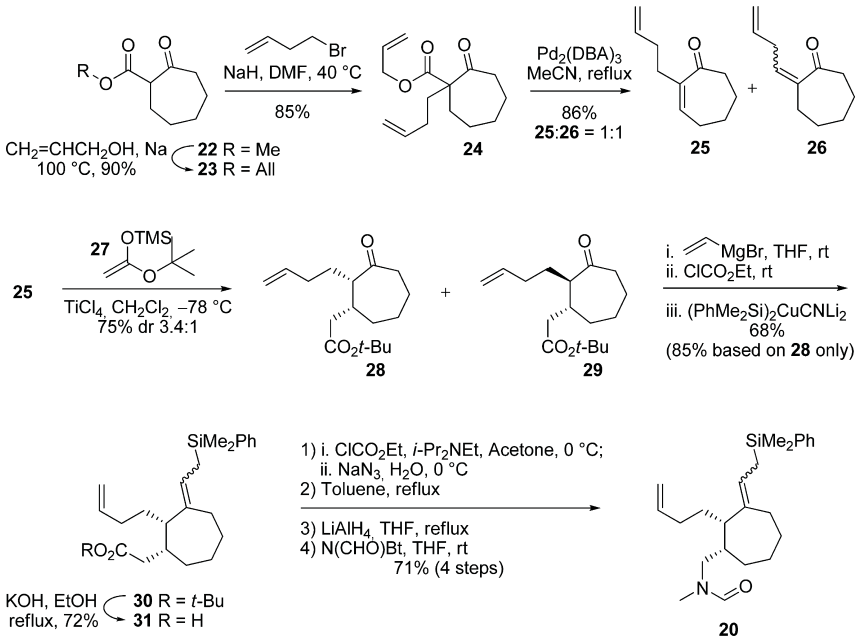
Scheme 3. Retrosynthetic Analysis of Model Compound 18



The synthesis of compound **20** started with the transesterification of known methyl ester **22** using allyl alcohol (Scheme 4).[10] After alkylation with 4-bromobutene, treatment of allyl β-ketoester **24** in oxidative deallyloxycarbonylation conditions[11] using $Pd_2(dba)_3$ generated a 1:1 mixture of *endo* and *exo* enones **25** and **26**, respectively. Fortunately, careful separation of these isomers led to the isolation of pure *endo* enone **25** that was used in the next steps. A Mukaiyama–Michael addition of silyl ketene acetal **27**[12] in the presence of $TiCl_4$,[13] followed by kinetic protonation of the resulting enolate at low temperature with acetic acid, produced a 3.4:1 mixture of two hardly separable diastereomers **28** and **29**. Unfortunately, we have not been able to prove the relative stereochemistry beyond any doubt,[14] but related examples in the literature on five- and six-membered rings present a good selectivity for *cis* isomers.[12] One-pot addition of vinylmagnesium bromide to ketone, trapping of the resulting alcoholate with ethyl chloroformate, and S_N2' displacement of the allylcarbonate with silyl organocuprate $(PhMe_2Si)_2CuCNLi_2$ gave allylsilane **29** in good yield. Only the major diastereomer **28** reacted in these conditions. Saponification of *tert*-butyl ester **30**, followed by Curtius rearrangement,[15] reduction of the resulting isocyanate,[16] and formylation using Katritzky reagent, *N*-formylbenzotriazole,[17] furnished compound **20** in 71% yield over four steps.

At this point, installation of the quaternary center and preparation of the bridged azabicyclo[4.3.1]decane unit **18** using the intramolecular Vilsmeier–Haack cyclization was tested (Scheme 5). We planned to reduce the iminium ion **19** *in situ* to be able to isolate and characterize the product. Although the activation of formamide **20** with triflic anhydride in the presence of 2,6-di-*t*-butyl-4-methylpyridine (DTBMP) gave triflyliminium ion **32**, no cyclization was observed at room temperature. Pushing the conditions to refluxing 1,2-dichloro-

Scheme 4. Synthesis of the Vilsmeier–Haack Cyclization Precursor 20 with Allylsilane



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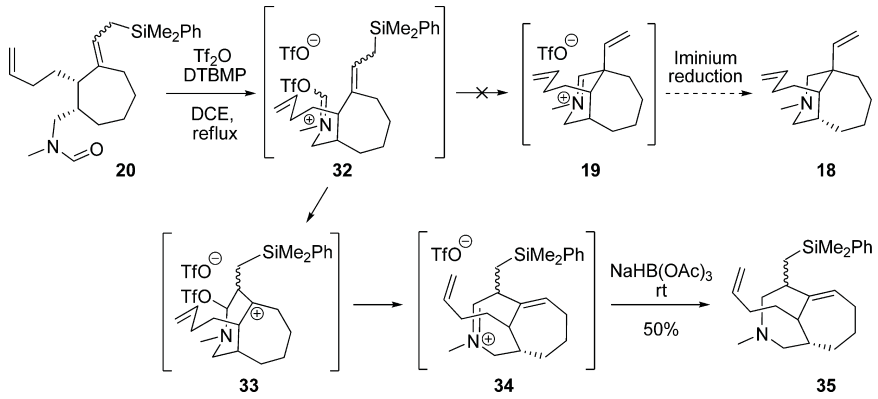
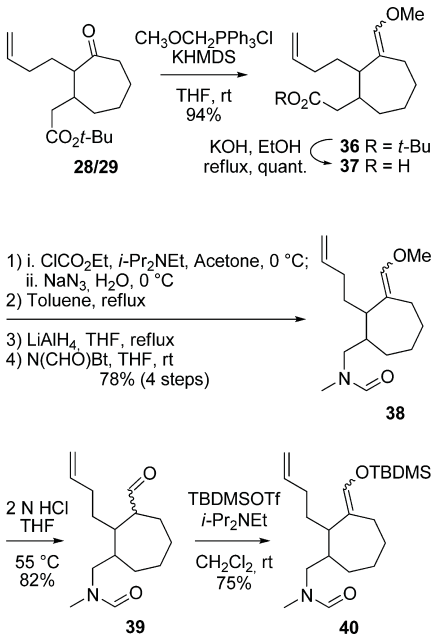
Scheme 5. Vilsmeier–Haack Cyclization with Allylsilane 20



ethane (DCE) resulted in a quite unusual cyclization: after iminium reduction, cycloadduct **35** was obtained, corresponding to an unexpected regioselectivity for the reaction of the allylsilane. Facing the steric constraint due to the generation of the quaternary center in the anticipated adduct **19**, the allylsilane reacted with the least nucleophilic site (β to Si) to generate a tertiary center as in **33**. This result convinced us that the allylsilane was not nucleophilic enough for the Vilsmeier–Haack cyclization on substrate **20** and stronger carbon nucleophiles are needed in order to force the generation of the hindered quaternary carbon.

The choice of a silyl enol ether as a stronger nucleophile was obvious.[18] Installation of the latter was performed on a mixture of ketones **28** and **29** synthesized in the first model study. Hence, a Wittig olefination afforded methyl enol ether **36** (Scheme 6).[19] Unlike the case for the installation of the allylsilane, this time, both diastereomers **28** and **29** reacted and a mixture of four partially separable isomers of **36** was obtained. The next steps up to compound **38** followed the sequence previously developed. Hydrolysis of methyl enol ether **38**,[20,21]

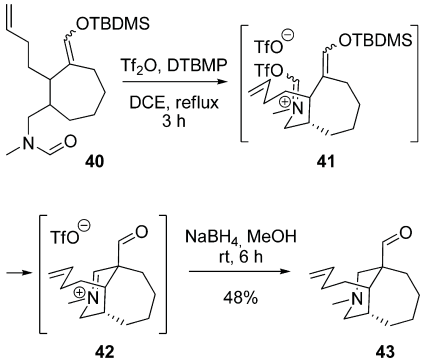
Scheme 6. Synthesis of the Vilsmeier–Haack Cyclization Precursor 40 with Silyl Enol Ether



followed by enolization of aldehyde **39** with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf), afforded silyl enol ether **40**.[22,23]

Upon activation of formamide **40** with triflic anhydride, the intramolecular Vilsmeier–Haack reaction proceeded smoothly at room temperature over 18 h. Triflyliminium ion **41** can even be observed by ^{1}H NMR considering the slow rate of the cyclization, and refluxing conditions were necessary to get a complete conversion to iminium ion **42** (Scheme 7). The latter

Scheme 7. Vilsmeier–Haack Cyclization with Silyl Enol Ether 40



was reduced *in situ* with $NaBH_4$ to provide bicyclic compound **43** in an unoptimized 48% yield. Surprisingly, the aldehyde was not reduced. This result definitely confirmed the possibility to create a quaternary center during the formation of the piperidine ring using a silyl enol ether as the nucleophile in the intramolecular Vilsmeier–Haack reaction.

Second Model Study: Preparation of the Azomethine Ylide and Intramolecular 1,3-Dipolar Cycloaddition. The next objective of this study was to evaluate the feasibility of the second cyclization, a 1,3-dipolar cycloaddition. The most direct route to daphnilactone B congeners was to opt for an unstabilized azomethine ylide (R″ = $SiMe_3$ or $SnBu_3$, Scheme 2) as a dipole since the latter leads to a methylene β to nitrogen in the pyrrolidine ring, as in the natural products.[24] As shown in Scheme 8, a Curtius rearrangement on the previously synthesized carboxylic acid **37** and treatment of the resulting isocyanate with 9-fluorenemethanol in the presence of Ti(O-*t*-Bu)$_4$ furnished *N*-Fmoc protected amine **44** in good yield (92% over 3 steps).[25] Formamide **45** was obtained following deprotection of the Fmoc group with NaH, *in situ* alkylation

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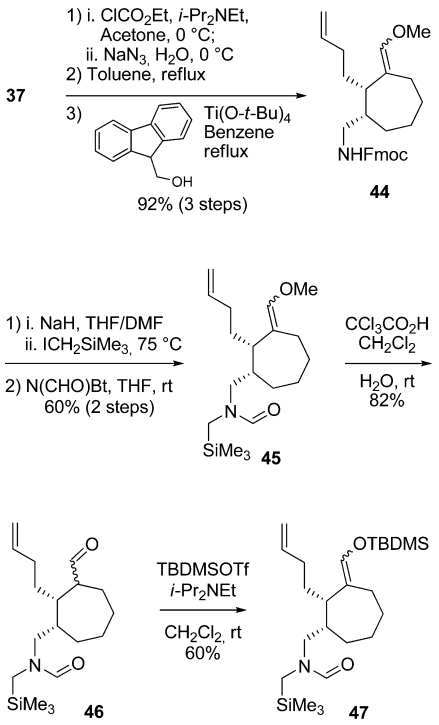
Scheme 8. Synthesis of Cyclization Precursor 47 with Silyl Enol Ether



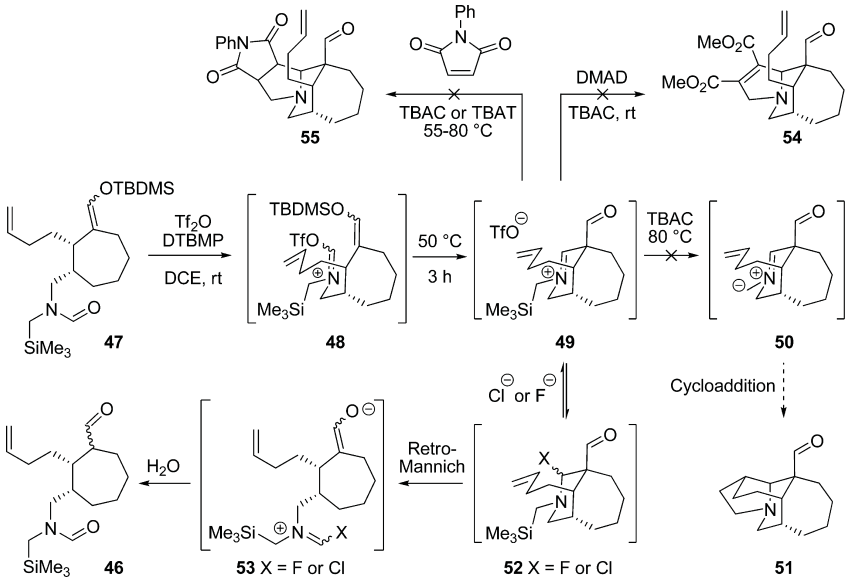
of the sodium amide with iodomethyltrimethylsilane, and formylation[17] in 60% overall yield. Hydrolysis of the methyl enol ether **45** was more problematic, and previous conditions (2 N HCl) failed probably due to the sensitivity of the trimethylsilyl group to acidic conditions and to chloride anions. Diluted aqueous trichloroacetic acid worked best, and aldehyde **46** was obtained in good yield (82%).[26] Finally, enolization[22] of the latter furnished the compound **47** that was then tested in the full cyclization sequence.

Formamide **47** was activated with triflic anhydride in the presence of DTBMP, and after 3 h at 50 °C, a complete Vilsmeier–Haack cyclization was observed by ^{1}H NMR (Scheme 9). However, when a source chloride was added to *N*-trimethylsilylmethyliminium ion **49** to promote desilylation and generation of the unstabilized azomethine ylide **50**, no cycloadduct **51** was obtained. To verify the formation and reactivity of azomethine ylide **50**, addition of an excess of an external dipolarophile such as dimethyl acetylenedicarboxylate (DMAD) or *N*-phenylmaleimide, using tetrabutylammonium chloride (TBAC) or tetrabutylammonium triphenyldifluorosilicate (TBAT) to promote desilylation also failed to produce the expected cycloadducts **54** or **55**, respectively. In all cases, only aldehyde **46** was recovered after workup. We postulated that there was a reversible addition of halide to the iminium ion **49** which resulted in a retro-Mannich reaction, thus releasing ring strain in the bridged bicyclic system of **52**, to produce aldehyde **46** as the sole isolated product.

At this point, two possible solutions were envisaged to circumvent this reactivity issue and favor conversion of the cascade precursor to the desired tetracyclic adduct. The first one was to weaken the carbon–metal bond in compound **47** by replacing silicon with tin.[9b,27] This way, the demetalation rate should increase[28] and the desired azomethine ylide **50** may be formed and trapped prior to any addition to the iminium ion and retro-Mannich reaction. Unfortunately, the carbon–tin bond is too labile and incorporation of a stannane at different points in the synthesis never led to the desired tin-containing key-step precursor.

The second solution was to avoid the use of a nucleophile to generate the azomethine ylide. Instead, the latter would be prepared by deprotonation α to the iminium nitrogen on a substrate bearing an electron-withdrawing group (cf. **49**, Me_3Si = nitrile or ester). However, additional steps are expected to cleave off this electron-withdrawing group after the cycloaddition since no substitution is present in the natural products on methylene β to nitrogen in the pyrrolidine ring. As shown in Scheme 10, installation of a nitrile group was performed on

Scheme 9. Attempted Key Sequential Cyclizations with Silyl Enol Ether 47



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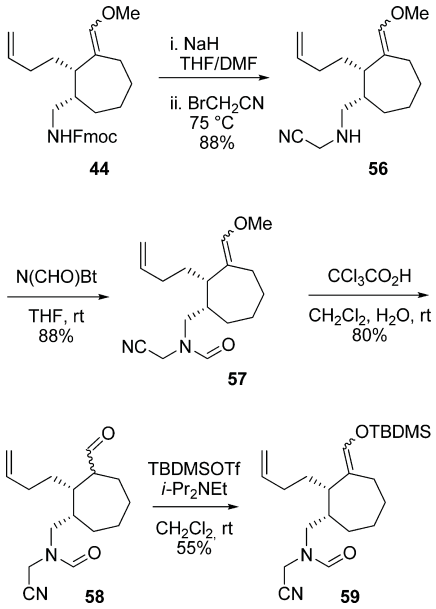
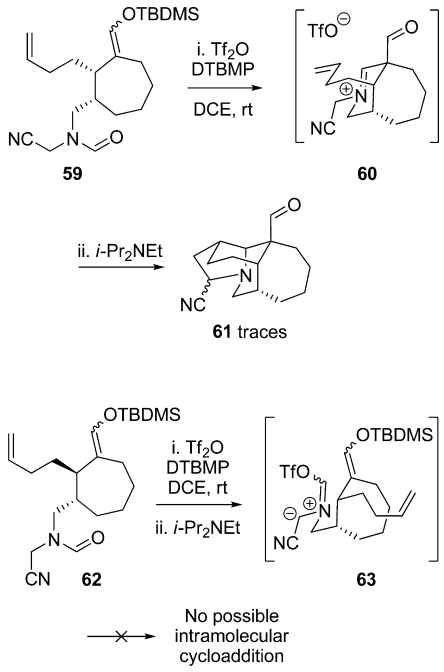
intermediate **44** and the same subsequent reaction sequence was applied.

Scheme 10. Synthesis of Cyclization Precursor 59 with a Nitrile



Formamide **59** was treated with triflic anhydride, and formation of triflyliminium ion **60** was confirmed by ^{1}H NMR (Scheme 11). Hunig's base (*i*-Pr$_2$NEt) was then added to generate the corresponding stabilized azomethine ylide, but the desired cycloadduct **61** was observed only in traces by ^{1}H NMR spectrometry on the crude material. This result may be explained by one or more of the following three plausible

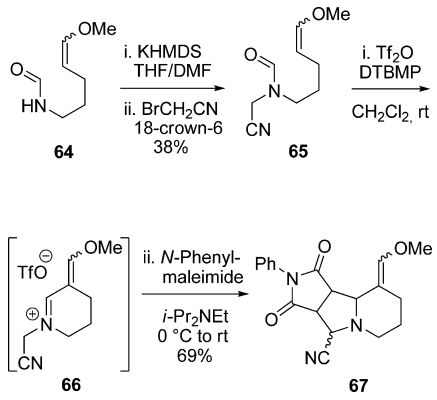
Scheme 11. Attempted Key Sequential Cyclizations with Silyl Enol Ether-Nitrile 59



hypotheses. (1) The nitrile was not compatible with the activation conditions. (2) The major isomer obtained from the 1,4-addition of silyl ketene acetal **27** to heptenone **25**, followed by a kinetic protonation (Scheme 4), was not the *cis* isomer **28** leading to **59** as expected but rather the *trans* product **29** leading to **62** (Scheme 11). The latter could not undergo intramolecular cycloaddition because the butenyl side chain would point in the wrong direction (cf. **63**). (3) The terminal alkene was not activated enough to react with the stabilized azomethine ylide.[29]

Compatibility of the nitrile in the key cyclization sequence was tested on model substrate **65** prepared straightforwardly from known formamide **64** (Scheme 12).[9a] Alkylation with

Scheme 12. Synthesis and Key Sequential Cyclizations with Model Substrate 65



bromoacetonitrile was not optimal but nonetheless furnished enough material to test our hypothesis. Iminium **66** was observed after treatment of formamide **65** with triflic anhydride without affecting the nitrile group. The ensuing azomethine ylide formation and 1,3-dipolar cycloaddition with *N*-phenylmaleimide produced cycloadduct **67** in good yield (69%) as a mixture of four diastereomers. Compatibility of the nitrile group in this sequence of cyclization was thus demonstrated, and the unsuccessful key sequential cyclizations of Scheme 11 could only be explained by the wrong *trans* diastereomer (cf. **62**) and/or the lack of reactivity of the terminal alkene in the cycloaddition.

To address both of these issues, a completely new synthesis of the key reaction substrate was designed. The route will unequivocally establish the correct and needed relative stereochemistry between the amide and the dipolarophile. It will also allow modulation of the dipolarophile reactivity: according to the work of Coldham, a dramatic increase in reactivity (lower temperature and higher yield) is observed for stabilized azomethine ylide cycloadditions when an ester-substituted alkene is used as the dipolarophile instead of a nonsubstituted terminal alkene.[29]

Third Model Study: Preparation of an Azomethine Ylide Stabilized with an Ester and Evaluation of Intramolecular 1,3-Dipolar Cycloaddition. To better control the relative stereochemistry on cycloheptane **69**, we envisaged the preparation of the substituted seven-membered ring using a ring-closing metathesis on diene **71** (Scheme 13). The latter would be obtained from a Claisen rearrangement of allyl enol ether **72**. Relative stereochemistry would be secured by a diastereocontrolled alkylation of the five-membered

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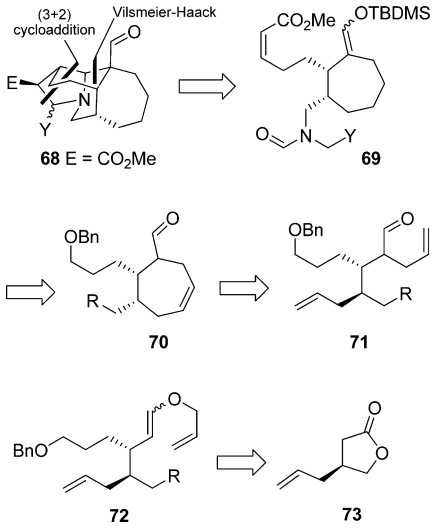
Scheme 13. Retrosynthetic Analysis for the Core of Daphnilactone B-Type and Yuzurimine-Type *Daphniphyllum* Alkaloids

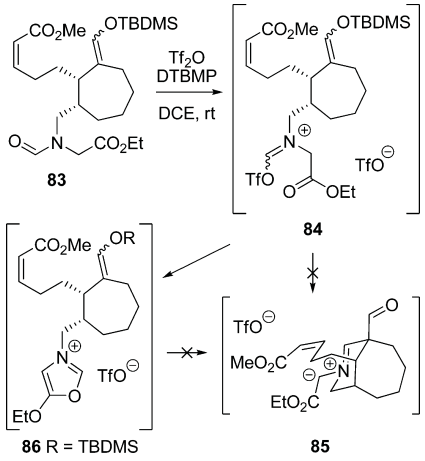


lactone **73**.[30] This new approach also ensures a certain variation of the dipolarophile since it is installed last in the sequence (**70** to **69**).

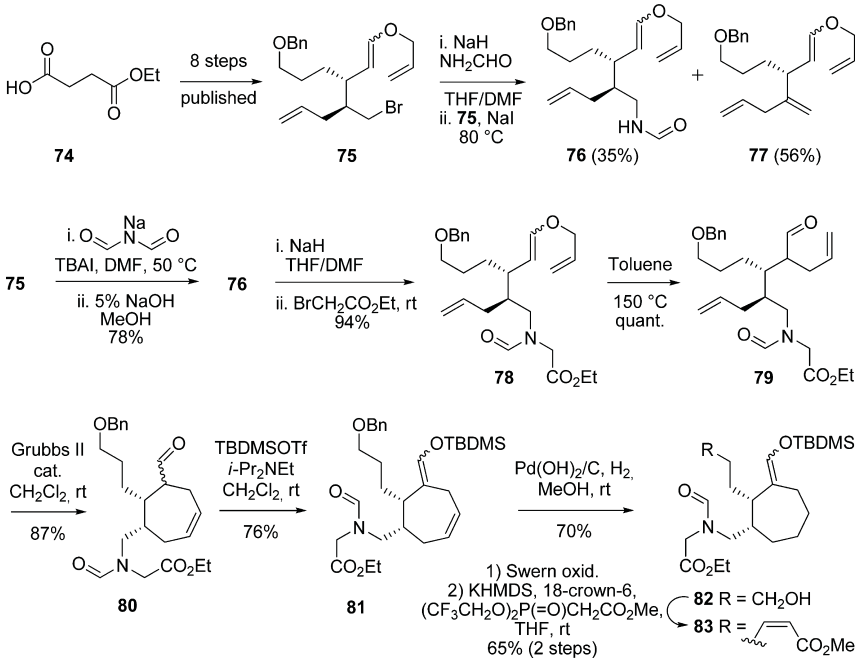
This new synthesis started with a sequence we already published.[31] Formamide was alkylated with bromide **75**, but a large amount of the elimination product **77** was observed (Scheme 14). To avoid this problem, a less basic nucleophile was necessary. Alkylation of sodium formimide, followed by hydrolysis, produced the desired amide **76** in good yield (78%) with no elimination side product.[32] Due to a complicated alkylation of formamide **64** with bromoacetonitrile (Scheme 12) in the model study, we chose to install an ester instead of a nitrile as an electron-withdrawing group. Alkylation of formamide **76** with ethyl bromoacetate generated compound **78**, which was then heated to induce the Claisen rearrangement[33] that quantitatively furnished diene **79** (Scheme 14). The latter was subjected to ring-closing metathesis with the second-generation Grubbs' catalyst,[34] and the resulting aldehyde **80** was silylated. Finally, benzyl ether deprotection, Swern oxidation of alcohol **82**, and olefination of the resulting aldehyde using Still–Gennari conditions[35] gave the key-step precursor **83**.

Unfortunately, upon activation of formamide **83** with triflic anhydride in the presence of DTBMP, no Vilsmeier–Haack cyclization product **85** was observed (Scheme 15). ^{1}H NMR analysis showed a fast protonation of the base (DTBMP) and signals corresponding to an oxazolium ion **86** that could be generated after the formation of triflyliminium ion **84**. Oxazolium ion **86** was not electrophilic enough to be trapped

Scheme 15. Attempted Key Sequential Cyclizations with Silyl Enol Ether 83



Scheme 14. Synthesis of the Cyclization Precursor 83



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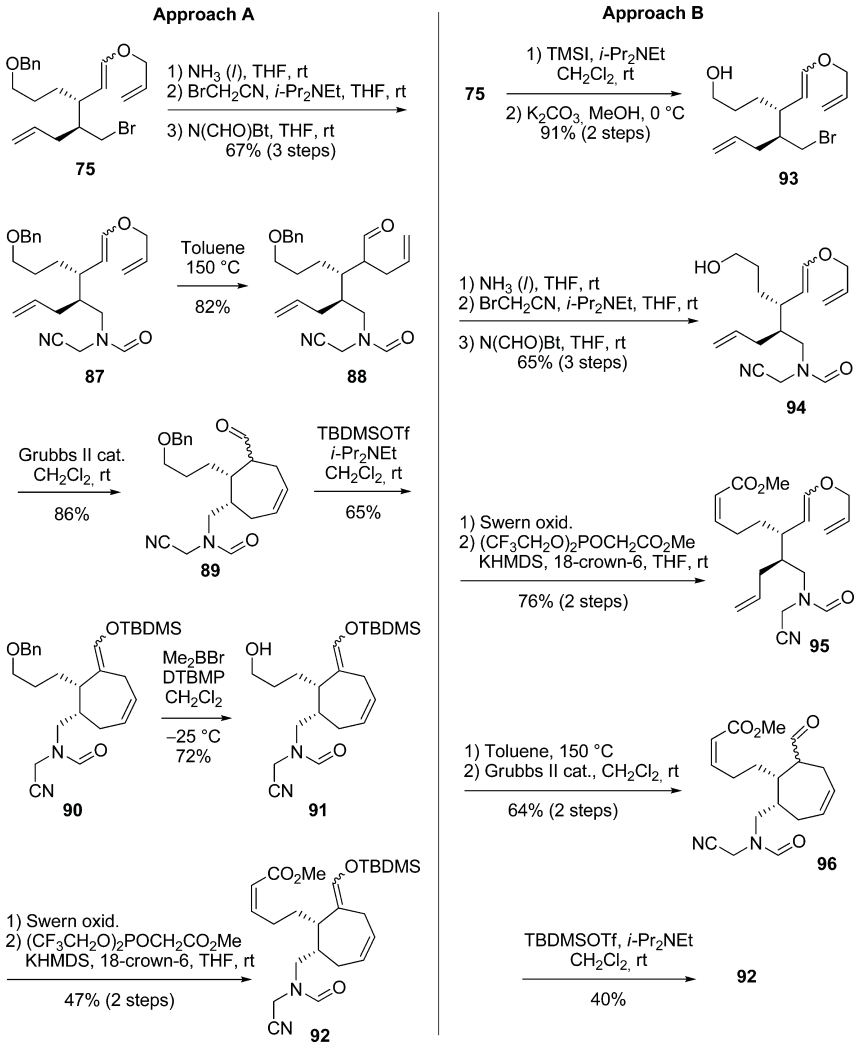
Scheme 16. Synthesis of the Cyclization Precursor 92 with Two Different Approaches



with the internal silyl enol ether despite heating to reflux.[36] Hence, we decided to reinvestigate the installation of a nitrile as an electron-withdrawing group to avoid this problem.

Fourth Model Study: Preparation of an Azomethine Ylide Stabilized with a Nitrile and Intramolecular 1,3-Dipolar Cycloaddition. Installation of the cyanomethyl onto the formamide is always low yielding, presumably because of proton exchange between formamide anion, bromoacetonitrile, and/or the alkylated *N*-(cyanomethyl)formamide. Alkylation of the primary amine prior to formylation seemed to be more promising. Moreover, because we had in the past some enol ether hydrolysis issues, we designed two similar routes to prepare either the silyl enol ether or the dipolarophile in the last steps (approaches A and B, respectively, Scheme 16). Both approaches start with bromide displacement with ammonia,[37] followed by alkylation with bromoacetonitrile, then formylation. This sequence is performed on benzyl ether **75** in approach A, or on free alcohol **93** in approach B without affecting the hydroxyl group.

In the approach A, a Claisen rearrangement on compound **87**, followed by a ring-closing metathesis, allowed us to incorporate the silyl enol ether group on aldehyde **89** prior to the dipolarophile. Deprotection of benzyl ether **90** was not as easy as in the sequence presented in Scheme 15 (cf. **75** to **77**).[38] The nitrile group on **90** interfered with the hydrogenolysis of the benzyl group (Scheme 16). We found that conditions using Guindon's reagent worked best to smoothly cleave the benzyl group while preserving the nitrile, the formamide, and even the very sensitive silyl enol ether.[39] Interestingly, these conditions allowed keeping the endocyclic alkene in place, which could later be used to incorporate the cyclopentene ring present in the natural products. Finally, oxidation of alcohol **91** and olefination installed the dipolarophile in moderate yields (47% over two steps).

In the approach B, alcohol **94** was oxidized and olefinated in a much better yield (76%, two steps). A Claisen rearrangement and ring-closing metathesis furnished aldehyde **96**.[40] The sequence ended with a silylation to generate the cyclization precursor **92**, albeit in moderate yield (40%). These two approaches count 9−10 steps from intermediate **75** and gave similar overall yields (8−10%).

We were finally pleased to find out that activation of formamide **92** with triflic anhydride allowed a clean Vilsmeier−Haack cyclization at room temperature in less than 5 min (Scheme 17). Iminium ion **97** was then deprotonated with *i*-Pr_2NEt at different temperatures (40 °C in DCE, 110 °C in

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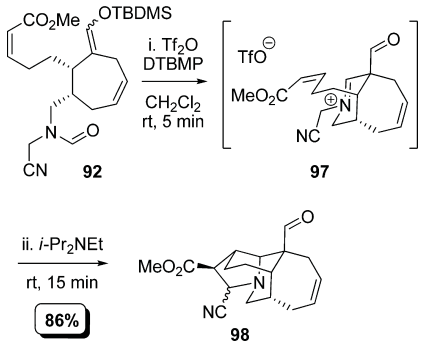
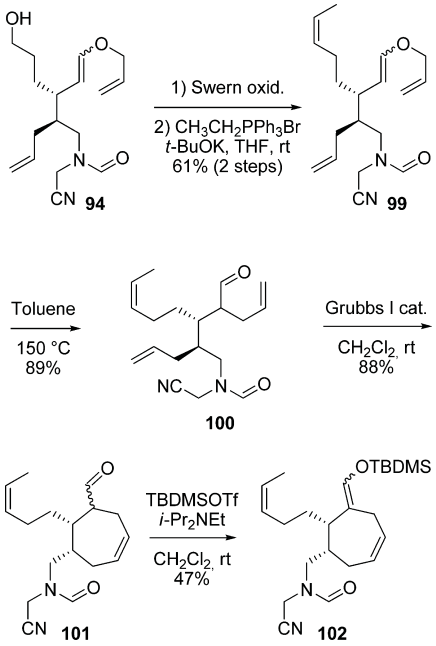
Scheme 17. Key Sequential Cyclizations with Silyl Enol Ether 92



toluene, or 120 °C in chlorobenzene) to form the azomethine ylide that engaged in the intramolecular 1,3-dipolar cycloaddition. While higher temperatures seemed to cause degradation of the ylide, the cycloaddition smoothly occurred at room temperature to form the highly congested tetracyclic product **98** in an impressive 86% yield.

Fifth Model Study: Intramolecular 1,3-Dipolar Cycloaddition between Nitrile-Stabilized Azomethine Ylide and Methyl-Substituted Alkene. A structural analysis of daphnilactone B-type and yuzurimine-type *Daphniphyllum* alkaloids shows a methyl on the pyrrolidine ring (**1**, R′ = Me, Figure 1) instead of an ester group (**98**, Scheme 17). A more direct access to the core of these alkaloids would involve a methyl-substituted dipolarophile (cf. **92**, CO_2Me = Me) even though we were aware that this dipolarophile could present a reactivity issue. As shown in Scheme 18, Swern oxidation of alcohol **94**, followed by Wittig olefination, gave the desired dipolarophile **99** with a *cis* geometry.[41] The same three steps used previously in approach B (Scheme 16) furnished the key-step compound **100** (Scheme 18). It is worth mentioning that the second-generation Grubbs' catalyst for the ring-closing

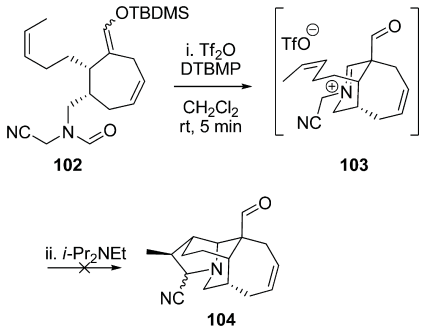
Scheme 18. Synthesis of the Cyclization Precursor 102



metathesis on substrate **100** induced a problematic isomerization of the *cis*-dipolarophile, while the first-generation Grubbs' catalyst preserved the integrity of the *cis*-alkene.[42]

Unfortunately, after activation of formamide **102** and Vilsmeier–Haack cyclization, no cycloaddition product **104** was observed, even when the temperature was increased to 160 °C (Scheme 19). It thus seems that the dipolarophile really needs to be activated for the cycloaddition to occur.

Scheme 19. Attempted Key Sequential Cyclizations with Silyl Enol Ether 102



Further Derivatization of the Key Tetracyclic Product. Functionalization of cycloadduct **98** was then undertaken. Homologation of the aldehyde, reduction of the methyl ester, and cleavage of the nitrile were required to advance toward caldaphnidine C (Figure 2).[43]

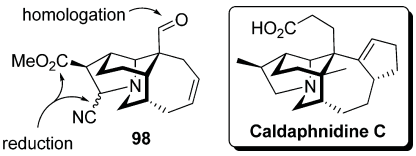
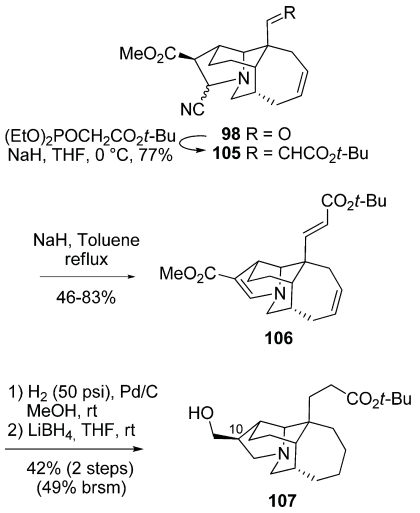


Figure 2. Planned functionalization of cycloadduct **98**.

A Horner–Wadsworth–Emmons olefination was realized on aldehyde **98** to install the required number of carbons on this chain (Scheme 20).[44] Only the *trans*-isomer of the ester **105**

Scheme 20. Derivatization of the Key Tetracyclic Product 98



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was formed, but as a mixture of three diastereomers. Epimerization α to the methyl ester (1:1) for one of the two diastereomers of **105** in the course of the olefination explains this result. Any attempt to reductively remove the nitrile group failed (Na in NH_3,[45] $NaBH_4$[46] or $NaBH_3CN$ in MeOH or MeCN, with or without Bronsted − AcOH[47] − or Lewis − $ZnBr_2$,[48] $AgBF_4$[49] − acids). We thus decided to rather eliminate the nitrile group using NaH, and vinylogous carbamate **106** was obtained as a single diastereomer.[50] Finally, all three alkenes on **106** were hydrogenated[51] and the methyl ester was reduced with $LiBH_4$. Compound **107** was isolated without reduction of *tert*-butyl ester, and the relative stereochemistry at C10 was explained by hydrogenation from the convex face of this crowded cage compound.[52]

CONCLUSION

This work establishes clearly the efficiency of one-pot sequential cyclizations to build rapidly complex architectures corresponding to the cores of natural products. The sequence of intramolecular Vilsmeier−Haack reaction and azomethine ylide 1,3-dipolar cycloaddition allowed the assembly of three new cycles in a constrained bridged system, as well as the perfect control of four of the five new stereogenic centers. The Vilsmeier−Haack cyclization successfully generated the congested quaternary center when using a reactive enol ether nucleophile. Chemoselectivity proved to be very high when a non-nucleophilic base was used to generate the stabilized azomethine ylide; otherwise, nucleophiles (such as halides used to promote desilylation to unstabilized azomethine ylides) provoked an unwanted opening of the bridged bicyclic iminium intermediate. Further functional group manipulations brought the cycloadduct to what could be seen as the closest to the natural products in the daphnilactone B-type and yuzurimine-type *Daphniphyllum* family so far reported. Future work will address the design of a nonracemic route and the installation of the required additional quaternary center (see **1**, C14) at the ring junction of the six- and seven-membered rings, as well as the installation of the cyclopentene ring on the cycloadduct.

EXPERIMENTAL SECTION

General Information. All reactions requiring anhydrous conditions were conducted in flame-dried glassware under a dry nitrogen or argon atmosphere. THF and Et_2O were distilled from Na and benzophenone under nitrogen immediately prior to use. MeCN, benzene, DCM, DCE, *i*-Pr_2NH, *i*-Pr_2NEt, and toluene were distilled from CaH_2 under nitrogen immediately prior to use. MeOH was distilled over 4 Å molecular sieves. Tf_2O and $CDCl_3$ were distilled over a small amount of phosphorus pentoxide (P_2O_5) under nitrogen immediately prior to use. Ethyl chloroformate and TBDMSOTf were distilled under nitrogen immediately prior to use. All other required fine chemicals were used directly without purification. Thin layer chromatography (TLC) was conducted with precoated 60 Å 250 μm silica gel plates with F-254 indicator and visualized using a combination of UV and anisaldehyde, ceric ammonium molybdate, iodine on silica, or potassium permanganate staining. Flash column chromatography was performed using silica gel (230−400 mesh). Melting points are uncorrected. IR spectra were recorded with a FTIR instrument by applying substrates as thin films onto a KBr plate. ^1H and ^{13}C NMR spectra were recorded on 300 MHz and/or 400 MHz spectrometers. All chemical shifts are referenced to residual non-deuterated solvent. Data for proton spectra are reported as follows: chemical shift (multiplicity [singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), and multiplet (m)], coupling constants [Hz], integration). Carbon spectra were recorded with complete proton decoupling, and the chemical shifts are reported in ppm.

Usual Reaction Workup and Purification. After addition of the indicated aqueous solution, layers were separated. The aqueous phase was extracted with the indicated solvent, and the combined organic phases were washed with the indicated aqueous solution (if needed), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure using a rotary evaporator. The crude material was purified by flash chromatography using silica gel with the indicated eluent.

Allyl 2-Oxocycloheptane-1-carboxylate (23). Na^0 (small cube) was added to a solution of **22** (47 g, 0.28 mol) in allyl alcohol (300 mL) at rt. The mixture was heated to 100 °C (with a condenser) over 5 days and was allowed to cool to rt; then water was added. The usual workup (EtOAc) and purification (5% EtOAc in hexanes) afforded a mixture of **23** and its enolic form (50 g, 91%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 12.66 (s) and 3.58 (dd, J = 10.5, 4.0 Hz) (1H), 6.03−5.84 (m, 1H), 5.32 (d, J = 17.0 Hz, 1H), 5.25 (dd, J = 10.5, 1.0 Hz, 1H), 4.66−4.61 (m, 2H), 2.63−2.58 (m, 1H), 2.46−2.40 (m, 2H), 2.15−2.07 (m) and 1.99−1.81 (m) (2H), 1.77−1.70 (m) and 1.67−1.56 (m) (2H), 1.54−1.41 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 208.7, 179.9, 172.5, 170.1, 132.3, 131.7 118.3, 117.6, 101.3, 65.5, 64.8, 58.8, 43.0, 35.3, 31.9, 29.5, 27.9, 27.5, 27.3, 24.5, 24.3; IR (film) ν (cm^{-1}) 2929, 2854, 1744, 1705, 1637, 1610, 1239, 1213; MS m/z (rel %) 196 (7) [M^+], 139 (26), 81 (100), 55 (99), 41 (90); HRMS (IE) calcd for $C_{11}H_{16}O_3$ 196.1099, found 196.1104.

Allyl 1-(But-3-enyl)-2-oxocycloheptane-1-carboxylate (24). NaH (60% in mineral oil, 251 mg, 6.30 mmol) was added to a solution of **23** (1.03 g, 0.52 mmol) in DMF (14 mL) at rt. The mixture was stirred 10 min at rt; then bromobut-3-ene (582 μL, 5.72 mmol) was added. The resulting mixture was stirred to 40 °C for 24 h and then was allowed to cool to rt. DMF was removed on a rotary evaporated using a mechanical pump; then water was added. The usual workup (Et_2O) and purification (2% EtOAc in hexanes) afforded **24** (1.1 g, 85%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.94−5.71 (m, 2H), 5.32 (d, J = 17.0 Hz, 1H), 5.24 (d, J = 10.5, 1H), 5.01 (d, J = 18.5 Hz, 1H), 4.95 (d, J = 10.5 Hz, 1H), 4.62 (d, J = 5.0 Hz, 2H), 2.67−2.59 (m, 1H), 2.52−2.45 (m, 1H), 2.21−1.96 (m, 4H), 1.81−1.47 (m, 8H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 208.9, 171.9, 137.8, 131.5, 118.5, 114.7, 65.4, 62.4, 41.9, 34.5, 32.7, 29.8, 28.8, 25.5, 24.7; IR (film) ν (cm^{-1}) 3078, 2932, 2860, 1737, 1710, 1453, 1201, 1148, 993, 939; MS m/z (rel %) 250 (1) [M^+], 209 (18), 196 (100), 138 (67), 84 (47); HRMS (IE) calcd for $C_{15}H_{22}O_3$ 250.1569, found 250.1576.

2-(But-3-enyl)cyclohept-2-enone (25) and 2-(But-3-enylidene)cycloheptanone (26). A solution of $Pd_2(dba)_3$ (40 mg, 0.07 mmol, weighed in a glovebox) in MeCN (3 mL) was heated to reflux; then a solution of **24** (3.5 g, 14 mmol) in MeCN (3 mL) was added dropwise. After 2 h at reflux, the mixture was allowed to cool to rt and was filtered on Florisil. The solution was concentrated under reduced pressure, and the usual purification (2% Et_2O in hexanes) afforded **25** (0.98 g, 43%) and **26** (0.98 g, 43%) as colorless oils. **25**: ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.46 (t, J = 6.5 Hz, 1H), 5.74 (ddt, J = 16.5, 10.0, 6.5 Hz, 1H), 4.96 (dd, J = 15.5, 1.5 Hz, 1H), 4.92 (d, J = 8.0 Hz, 1H), 2.55 (t, J = 6.5 Hz, 2H), 2.38−2.29 (m, 4H), 2.12 (q, J = 7.0 Hz, 2H), 1.77−1.67 (m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 205.0, 142.9, 141.8, 138.1, 114.8, 42.5, 33.3, 32.4, 27.3, 25.0, 21.4; IR (film) ν (cm^{-1}) 3580−3077, 1656, 1637; MS m/z (rel %) 164 (25) [M^+], 149 (30), 135 (32), 121 (27), 107 (39), 95 (100), 79 (57), 67 (93); HRMS (IE) calcd for $C_{11}H_{16}O_1$ 164.1201, found 164.1204. **26**: ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) δ 6.58 (t, J = 7.0 Hz, 1H), 5.81 (ddt, J = 16.5, 10.0, 6.0 Hz, 1H), 5.09−5.02 (m, 2H), 2.91 (t, J = 6.0 Hz, 2H), 2.62−2.59 (m, 2H), 2.45−2.41 (m, 2H), 1.78−1.61 (m, 6H).

***t*-Butyl *syn*-(2-(But-3-enyl)-3-oxocycloheptyl)acetate (28) and *t*-Butyl *anti*-(2-(But-3-enyl)-3-oxocycloheptyl)acetate (29).** A solution of *n*-BuLi (50.0 mL, 2.45 M in hexanes, 123 mmol) was added dropwise to a solution of *i*-Pr_2NH (20.3 mL, 143 mmol) in THF (26 mL) at 0 °C. The mixture was stirred for 15 min at 0 °C and then was cooled to −78 °C, and *t*-BuOAc (15.0 mL, 111 mmol) was added. The mixture was stirred for 3 h at −78 °C, then warmed up to −35 °C (critical), and TMSCl (16.9 mL, 134 mmol) was added. The mixture was stirred for 3 h; then a distillation

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apparatus was installed directly on the reaction flask. Distillation under reduced pressure (~10−15 mmHg, fraction collected at 65−74 °C) furnished a 1.0:2.0 mixture of C-silylated product and O-silylated product **27** (15.9 g, 57%) as a colorless oil. The mixture (7.2 g, 63% pure, 24 mmol) was added to a solution of **25** (2.8 g, 17 mmol) in THF (300 mL). The mixture was cooled to −78 °C, and $TiCl_4$ (285 μL, 2.60 mmol) was added dropwise. The mixture was stirred for 3 h at −78 °C; then acetic acid (3.0 mL, 52 mmol) was added. The resulting mixture was stirred for 20 min; then water was added. The usual workup (DCM) and purification (DCM) afforded a hardly separable 4:1 mixture of **28** and **29** (3.59 g, 75%) as a colorless oil. A small fraction of pure compounds was obtained and characterized. **28**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.75 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H), 5.00 (d, *J* = 17.0 Hz, 1H), 4.96 (d, *J* = 7.0 Hz, 1H), 2.90−2.85 (m, 1H), 2.51 (t, *J* = 5.0 Hz) and 2.46 (t, *J* = 5.0 Hz) (1H), 2.39−2.27 (m, 2H), 2.20 (dd, *J* = 15.5, 3.5 Hz, 1H), 2.06−1.63 (m, 9H), 1.48−1.25 (m, 2H), 1.42 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 213.6 (s), 171.9 (s), 138.0 (d), 114.8 (t), 80.0 (s), 53.0 (d), 44.1 (t), 36.0 (d), 34.8 (t), 33.8 (t), 31.8 (t), 27.8 (q), 23.8 (t), 23.2 (t); IR (film) ν (cm^{-1}) 2976, 2930, 1728, 1699, 1146; MS *m*/*z* (rel %) 280 (1) [M^+], 224 (32) [$M^+ - C_4H_8$], 170 (100), 152 (44), 111 (98); HRMS calcd for $C_{17}H_{28}O_3$: 280.2038, found: 280.2044. **29**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.75 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H), 5.00 (d, *J* = 17.0 Hz, 1H), 4.96 (d, *J* = 7.0 Hz, 1H), 2.61 (dt, *J* = 11.5, 3.5 Hz, 1H), 2.40 (dd, *J* = 15.5, 3.5 Hz, 1H), 2.34−2.26 (m, 1H), 2.21 (dt, *J* = 10.0, 4.0 Hz, 1H), 2.13−2.05 (m, 1H), 2.03−1.76 (m, 4H), 1.74−1.52 (m, 4H), 1.49−1.42 (m, 2H), 1.45 (s, 9H), 1.27−1.78 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 215.1 (s), 171.9 (s), 137.7 (d), 115.2 (t), 80.6 (s), 57.4 (d), 41.0 (t), 40.4 (t), 37.7 (d), 32.9 (t), 31.5 (t), 30.2 (d), 28.1 (q), 27.8 (t), 26.0 (t); IR (film) ν (cm^{-1}) 2978, 2931, 2854, 1728, 1703, 1367, 1250, 1151; MS *m*/*z* (rel %) 280 (2) [M^+], 223 (31) [$M^+ - C_4H_9$], 170 (100), 152 (38), 111 (50); HRMS calcd for $C_{17}H_{28}O_3$: 280.2038, found: 280.2044.

***t*-Butyl 2-(2-(But-3-enyl)-3-(2-(dimethylphenylsilyl)ethylidene)cycloheptyl)acetate (30).** $PhMe_2SiCl$ (8.2 mL, 49 mmol) was added to a suspension of Li^0 (2.0 g, 290 mmol) in THF (49 mL) at 0 °C. The mixture was stirred for 18 h at 0 °C; then 39 mL of this solution was transferred to a flask containing a suspension of CuCN (1.9 g, 21 mmol, weighed in a glovebox) in THF (40 mL) at 0 °C. The mixture was stirred for 4.5 h at 0 °C. Meanwhile, in a separate flask, vinylmagnesium bromide (11 mL, 1 M in THF, 11 mmol) was added dropwise to a solution of **28** and **29** (2.0 g, 4:1 *syn*: *anti*, 7.1 mmol) in THF (120 mL) at rt. The mixture was stirred for 2.25 h at rt; then $ClCO_2Et$ (1.4 mL, 18 mmol) was added. After 15 min of stirring at 0 °C, the solution was transferred via canula to the solution of silylcuprate. The resulting mixture was allowed to warm to rt over 3 h; then a saturated aqueous NH_4Cl solution was added. The usual workup (EtOAc) and purification (5% Et_2O in hexanes) afforded an inseparable mixture of *E*/*Z* isomers (4.0:1.0) of **30** (2.1 g, 68%; 85% based on **28** only) as a colorless oil:[53] ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.53−7.50 (m, 2H), 7.36−7.33 (m, 3H), 5.84−5.71 (m, 1H), 5.16 (t, *J* = 8.5 Hz, 1H), 4.98−4.90 (m, 2H), 2.25−1.78 (m, 8H), 1.74−1.60 (m, 2H), 1.58−1.17 (m, 8H), 1.43 (s, 9H), 0.29 (s) and 0.28 (s) (6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 173.0, 139.2, 138.3, 133.6, 129.0, 127.7, 123.4, 121.6, 114.3, 79.8, 50.0, 41.5, 41.1, 40.9, 39.8, 39.8, 34.2, 32.7, 32.6, 32.3, 32.0, 28.2, 27.7, 27.2, 26.4, 25.8, 25.0, 17.7, 17.2, −3.0; IR (film) ν (cm^{-1}) 3069, 2926, 2864, 1723, 1144, 909, 734; MS *m*/*z* (rel %) 426 (5) [M^+], 353 (7), 176 (14), 135 (100); HRMS calcd for $C_{27}H_{42}O_2Si$: 426.2954, found: 426.2950.

2-(2-(But-3-enyl)-3-(2-(dimethylphenylsilyl)ethylidene)-cycloheptyl)acetic Acid (31). KOH (340 mg, 71.3 mmol) was added to a solution of **30** (2.08 g, 4.88 mmol) in a mixture of EtOH (240 mL) and water (5 mL). The resulting mixture was heated to reflux for 5 days and then allowed to cool to rt. Part of the EtOH was removed under reduced pressure on the rotary evaporator. pH was adjusted to 1 at 0 °C with 1 N H_2SO_4. The usual workup (EtOAc) and purification (5 to 50% EtOAc in hexanes) afforded an inseparable mixture of *E*/*Z* isomers (4.0:1.0) of **31** (1.3 g, 72%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.55−7.52 (m, 2H), 7.37−7.35 (m, 3H), 5.79 (ddt, *J* = 17.0, 10.5, 6.5 Hz, 1H), 5.19 (t, *J* = 8.5 Hz, 1H), 4.97 (d, *J* = 17.0 Hz, 1H), 4.94 (d, *J* = 10.0 Hz, 1H), 2.44−2.25 (m), 2.19−2.11 (m), 2.07−1.82 (m), and 1.79−1.21 (m) (17H), 0.57 (s) and 0.49−0.37 (m) (1H), 0.31 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 180.5 (s), 139.0 (d), 137.8 (s), 133.6 (d), 129.0 (d), 127.8 (d), 123.6 (d), 121.8 (d), 114.5 (d), 49.8 (d), 41.6 (d), 40.3 (d), 38.1 (t), 34.3 (t), 32.5 (t), 32.2 (t), 32.0 (t), 28.6 (t), 28.1 (t), 27.1 (t), 26.3 (t), 25.4 (t), 24.9 (t), 17.7 (t), 17.2 (t), −3.0 (q); IR (film) ν (cm^{-1}) 3358−2511 (br), 2924, 1705, 1425, 1248, 833; MS *m*/*z* (rel %) 370 (4) [M^+], 251 (8), 176 (10), 135 (100); HRMS calcd for $C_{23}H_{34}O_2Si$: 370.2328, found: 370.2321.

***N*-(2-(But-3-enyl)-3-(2-(dimethylphenylsilyl)ethylidene)-cycloheptyl)methyl-*N*-methyl-formamide (20).** $ClCO_2Et$ (195 μL, 2.07 mmol) was added to a solution of **31** (750 mg, 2.03 mmol) and *i*-Pr_2NEt (439 μL, 2.52 mmol) in acetone (7.5 mL) at 0 °C, and the mixture was stirred for 30 min at 0 °C. Then an aqueous solution of NaN_3 (5.9 M, 690 μL, 4.08 mmol) was added. The resulting mixture was stirred for 1 h at 0 °C, and cold water was added. After the usual workup (toluene), anhydrous toluene (2 mL) was added and the mixture was heated to reflux for 1 h and then allowed to cool to rt. Toluene was removed under reduced pressure. Crude isocyanate was dissolved in THF (25 mL), and $LiAlH_4$ (745 mg, 2.03 mmol) was added. The mixture was heated to reflux for 16 h and then allowed to cool to rt. Water (400 μL) was added (*exotherm!*). After 5 min, an aqueous solution of NaOH (15%, 400 μL) was added. After 5 min, another portion of water (1.16 mL) was added. The mixture was stirred for 30 min, and $MgSO_4$ was added. After an additional 10 min of stirring, the mixture was filtered and concentrated under reduced pressure. Crude *N*-methylamine was dissolved in THF (14 mL), and *N*-formylbenzotriazole (390 mg, 2.65 mmol) was added. The mixture was stirred at rt for 15 h, and aqueous NaOH (2 N) was added. Stirring was continued for 10 min; then water was added. The usual workup (DCM) and purification (30 to 50% EtOAc in hexanes) afforded an inseparable mixture of *E*/*Z* isomers (4.0:1.0) and rotamers of **20** (555 mg, 71%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.06 (s), 7.98 (s), and 7.92 (s) (1H), 7.52−7.50 (m, 2H), 7.36−7.34 (m, 3H), 5.83−5.69 (m, 1H), 5.17 (t, *J* = 8.5 Hz) and 4.98−4.89 (m) (3H), 3.23−3.20 (m), 3.10−2.90 (m) and 2.60−2.55 (m) (2H), 2.86 (s), 2.83 (s), 2.80(s), and 2.77 (s) (3H), 2.31−1.85 (m), 1.82−1.40 (m), and 1.33−1.14 (m) (14H), 0.28 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 162.9, 139.2, 138.7, 138.0, 133.6, 124.0, 127.7, 123.0, 122.2, 122.0, 114.7, 114.3, 54.2, 52.8, 48.0, 47.4, 41.3, 41.0, 39.0, 34.6, 32.3, 32.1, 29.6, 28.7, 28.1, 27.7, 27.2, 27.0, 26.8, 26.3, 26.0, 25.1, 17.7, 17.4, −3.0; IR (film) ν (cm^{-1}) 3073, 2924, 2859, 1681, 834; MS *m*/*z* (rel %) 383 (9) [M^+], 342 (63) [$M^+ - C_3H_5$], 328 (13), 234 (16), 135 (100); HRMS calcd for $C_{24}H_{37}N_1O_1Si$: 383.2644, found: 383.2634.

***rel*-(1*S*,2*S*)-*N*-(2-(But-3-en-1-yl)-3-(2-(dimethylphenylsilyl)-ethylidene)cycloheptylmethyl)-(trifluoromethanesulfonyl-methylene)methanaminium Trifluoromethanesulfonate (32).** Tf_2O (10 μL, 0.061 mmol) was added to **20** (20 mg, 0.056 mmol) and *i*-Pr_2NEt (11 μL, 0.061 mmol) in $CDCl_3$ (1.5 mL) at 0 °C in a NMR tube. The ^{1}H NMR spectrum of **32** was recorded after 15 min at rt (see the SI).

***N*-Methyl-5-(dimethylphenylsilylmethyl-11-(but-3-enyl)-3-azabicyclo[4.4.1]undec-6-ene (35).** Tf_2O (14 μL, 0.0831 mmol) was added to **20** (30 mg, 0.078 mmol) and DTBMP (32 mg, 0.16 mmol) in DCE (1.5 mL) at 0 °C. The mixture was stirred for 5 min at rt, heated to reflux for 1 h, and then allowed to cool to rt. $NaHB(OAc)_3$ (83 mg, 0.39 mmol) was added, the mixture was stirred vigorously for 17 h at rt, and then saturated aqueous $NaHCO_3$ was added. The usual workup (EtOAc) and purification (50 to 100% EtOAc in hexanes) afforded an inseparable mixture of diastereomers of **35** (14 mg, 50%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.51−7.48 (m, 2H), 7.34−7.32 (m, 3H), 5.77 (ddt, *J* = 17.0, 10.5, 6.5 Hz, 1H), 5.63 (t, *J* = 7.0 Hz, 1H), 4.94 (d, *J* = 17.0 Hz, 1H), 4.91 (d, *J* = 6.5 Hz, 1H), 2.89 (t, *J* = 7.5 Hz, 1H), 2.77 (dd, *J* = 11.0, 5.5 Hz, 1H), 2.64−2.57 (m, 1H), 2.42−2.23 (m, 3H), 2.14 (s) and 2.06 (s) (3H), 2.01−1.81 (m, 2H), 1.79−1.17 (m, 8H), 0.99−0.88 (m, 2H), 0.76 (d, *J* = 7.0 Hz) and 0,71 (t, *J* = 7.0 Hz) (2H), 0.27 (s) and 0.25 (s) (6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 146.9, 139.3,

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133.5, 128.7, 127.7, 122.7, 114.1, 73.9, 61.2, 49.5, 43.8, 34.6, 34.5, 33.6, 32.5, 26.1, 20.7, 17.1, −1.6, −2.0. IR (film) ν (cm^{-1}) 2926, 2921; MS m/z (rel %) 367 (28) [M^+], 326 (11), 313 (47), 232 (51), 135 (100). HRMS calcd for $C_{24}H_{37}N_1Si$: 367.2695, found: 367.2703.

***tert*-Butyl 2-(2-(But-3-en-1-yl)-3-(methoxymethylene)cycloheptyl)acetate (36).** A solution of KHMDS (0.5 M in toluene, 42.8 mL, 21.4 mmol) was added to a solution of Ph_3PCH_2OMeCl (7.33 g, 21.4 mmol) in THF (120 mL) at 0 °C. The mixture was stirred for 30 min at rt. A solution of **28**/**29** (2.91 g, 10.4 mmol) in THF (30 mL) was added at 0 °C, and the resulting mixture was stirred at rt for 23 h. Saturated aqueous $NaHCO_3$ was added, THF was removed under reduced pressure, and water was added. The usual workup (EtOAc) and purification (30 to 100% toluene in hexanes) gave a hardly separable mixture of *E*/*Z* and *syn*/*anti* isomers of **36** (3.02 g, 94%) as a colorless oil. A small portion of the mixture of diastereomers was separated for characterization. Two portions containing two different diastereomers were characterized: Portion 1 as a 3:2 mixture of diastereomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.89 (s) and 5.62 (s) (1H), 5.88−5.70 (m, 1H), 5.01−4.89 (m, 2H), 3.56 (s) and 3.49 (s) (3H), 2.56−2.48 (m), 2.40 (dd, J = 15.5, 4.0 Hz), and 2.34 (dd, J = 15.0, 4.0 Hz) (2H), 2.10−1.65 (m, 7H), 1.60−1.25 (m, 7 H), 1.44 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 172.9, 144.6, 143.6, 139.5, 139.0, 120.6, 119.9, 114.3, 113.9, 80.0, 79.9, 59.3, 59.0, 46.8, 41.7, 41.0, 40.6, 32.7, 32.3, 32.2, 31.9, 31.6, 29.6, 28.8, 28.1, 27.7, 23.9; IR (film) ν (cm^{-1}) 2977, 2928, 2854, 1729, 1663, 1458, 1369, 1142, 1126; MS m/z (rel %): 308 (1) [M^+], 251 (26) [$M^+ - C_4H_9$], 194 (90), 159 (86), 134 (100); HRMS (EI) calcd for $C_{15}H_{23}O_3$ [$M^+ - C_4H_9$]: 251.1647, found 251.1657. Portion 2 as a 8:1 mixture of diastereomers, only the major diastereomer reported: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.85−5.72 (m) and 5.76 (s) (2H), 4.98 (d, J = 17.0 Hz, 1H), 4.93 (d, J = 10.5 Hz, 1H), 3.55 (s, 3H), 2.54−2.44 (m, 1H), 2.22−1.98 (m, 6H), 1.96−1.80 (m, 1H), 1.72−1.23 (m, 8H), 1.44 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 173.4, 143.9, 139.4, 119.8, 114.6, 79.9, 59.1, 45.0, 42.0, 40.3, 31.9, 31.6, 27.8, 26.1, 26.0, 25.7, 24.6; IR (film) ν (cm^{-1}) 2977, 2928, 2854, 1729, 1663, 1458, 1369, 1142, 1126; MS m/z (rel %): 251 (20) [$M^+ - C_4H_9$], 220 (22), 194 (73), 159 (71), 134 (100), 57 (95), 41 (76); HRMS (EI) calcd for $C_{15}H_{23}O_3$ [$M^+ - C_4H_9$] 251.1647, found 251.1655.

2-(2-(But-3-en-1-yl)-3-(methoxymethylene)cycloheptyl)-acetic Acid (37). KOH (2.11 g, 37.6 mmol) was added to a solution of **36** (1.16 g, 3.76 mmol) in a mixture of EtOH (145 mL) and water (3 mL). The resulting mixture was refluxed for 5 days. Then, a buffer solution (pH 7.4, 20 mL) was added and EtOH was removed under reduced pressure. Aqueous citric acid (10%) was added at 0 °C until an acidic pH (3) was obtained. The usual workup (EtOAc, washed with brine) afforded **37** (949 mg, 100%) as brown oil. For characterization, a small portion was purified by flash chromatography using silica gel (0 to 2% MeOH in DCM). An inseparable mixture of *E*/*Z* and *syn*/*anti* isomers of **37** was obtained as a brown oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.91 (s), 5.89−5.73 (m), 5.78 (s), and 5.64 (s) (2H), 4.99 (d, J = 17.5 Hz, 1H), 4.94 (d, J = 10.5 Hz, 1H), 3.57 (s), 3.56 (s), and 3.50 (s) (3H), 2.79 (dt, J = 11.5, 3.5 Hz) and 2.60−2.40 (m) (1H), 2.40−1.22 (m, 15H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 180.8, 145.0, 144.0, 139.6, 139.4, 139.1, 120.2, 119.7, 119.5, 114.7, 114.4, 114.2, 59.1, 58.8, 46.6, 45.0, 41.3, 41.0, 40.6, 40.2, 40.0, 39.7, 39.6, 38.7, 32.2, 32.0, 31.7, 31.6, 31.2, 29.1, 28.8, 28.4, 27.8, 27.3, 26.1, 25.8, 25.7, 25.2, 24.9, 24.6, 23.4; IR (film) ν (cm^{-1}) 3081, 2927, 2856, 1706, 1452, 1408, 1217, 1125; MS m/z (rel %): 252 (4) [M^+], 220 (9), 197 (53), 134 (100), 119 (46); HRMS (EI) calcd for $C_{15}H_{24}O_3$ [M^+] 252.1725, found 252.1727.

***N*-((2-(But-3-en-1-yl)-3-(methoxymethylene)cycloheptyl)-methyl)-*N*-methylformamide (38).** Following the procedure used to prepare **20**, a solution of **37** (1.01 g, 3.98 mmol) in acetone (14.0 mL) was treated with $ClCO_2Et$ (395 μL, 4.18 mmol) and *i*-Pr_2NEt (0.87 mL, 5.0 mmol) for 30 min at 0 °C and then with an aqueous solution of NaN_3 (5.9 M, 1.35 mL, 7.96 mmol) for 1 h at 0 °C. Crude acylazide was then refluxed in toluene (14.0 mL) for 1.5 h to afford the corresponding isocyanate (993 mg) as a brown oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.91 (s), 5.82 (s), 5.78 (s), and 5.67 (s) (1H), 5.87−5.72 (m, 1H), 5.03−4.92 (m, 2H), 3.57 (s), 3.56 (s), 3.52 (s), and 3.50 (s) (3H), 3.41−3.09 (m) and 3.18 (dd, J = 7.5, 3.5 Hz) (2H), 2.97 (d, J = 12.0 Hz) and 2.65−2.49 (m) (1H), 2.22−1.19 (m, 13H). A solution of crude isocyanate (993 mg, 3.98 mmol) in THF (25 mL) was treated with $LiAlH_4$ (755 mg, 19.9 mmol) at reflux for 20 h and then with water (750 μL), aqueous NaOH (15%, 750 μL), and water (2.25 mL) to afford *N*-methylamine (845 mg, 89%) as pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.91−5.70 (m), 5.80 (s), and 5.63 (s) (2H), 4.99 (d, J = 19.0 Hz, 1H), 4.94 (d, J = 10.5 Hz, 1H), 3.56 (s), 3.54 (s), 3.50 (s), and 3.49 (s) (3H), 2.62−2.46 (m), 2.44−2.31 (m), 2.42 (s), and 2.41 (s) (4H), 2.21−1.78 (4H), 1.72−1.18 (m, 11H), 0.98−0.75 (m, 1H); IR (film) ν (cm^{-1}) 3358, 3325, 3073, 2925, 2852, 2788, 1661, 1639, 1461, 1444, 1247, 1220, 1125, 907. A solution of crude *N*-methylamine (845 mg, 3.56 mmol) in THF (24 mL) was treated with *N*-formylbenzotriazole (680 mg, 4.63 mmol) for 18 h at rt and then with aqueous NaOH (2 N). The usual workup (DCM) and purification (10 to 40% EtOAc in hexanes) afforded an inseparable mixture of diastereomers and rotamers of **38** (820 mg, 78% over 4 steps) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.09 (s), 8.07 (s), 8.01 (s), 7.99 (s), and 7.98 (s) (1H), 5.92−5.64 (m) and 5.77 (s) (2H), 5.06−4.89 (m, 2H), 3.57 (s), 3.56 (s), 3.55 (s), 3.54 (s), and 3.50 (s) (3H), 3.30 (dd, J = 13.5, 7.5 Hz), 3.20 (dd, J = 13.5, 8.0 Hz), 3.14 (dd, J = 14.0, 8.0 Hz), and 3.02 (dd, J = 14.0, 7.5 Hz) (2H), 2.92 (s), 2.92 (s), 2.90 (s), 2.87 (s), and 2.83 (s) (3H), 2.62−2.47 (m) and 2.24−1.07 (m) (14H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 163.7, 163.5, 163.2, 145.2, 144.2, 143.8, 143.5, 139.4, 139.3, 139.0, 138.8, 119.9, 119.4, 119.3, 119.0, 115.0, 114.6, 114.5, 114.2, 59.1, 58.9, 54.2, 53.3, 53.0, 48.4, 47.5, 47.1, 45.7, 44.9, 44.5, 43.9, 43.4, 42.9, 42.1, 41.8, 41.0, 40.2, 40.0, 37.9, 36.0, 34.4, 33.8, 32.7, 32.4, 32.2, 31.9, 31.7, 31.5, 31.3, 31.1, 29.6, 29.3, 29.2, 29.1, 28.7, 28.3, 28.2, 27.5, 27.2, 26.9, 26.8, 26.5, 26.3, 25.6, 25.4, 25.1, 24.9, 24.6, 24.5, 24.4, 24.2, 24.0, 23.5; IR (film) ν (cm^{-1}) 3073, 2924, 2850, 1666, 1453, 1395, 1222, 1123; MS m/z (rel %): 264 (1) [M^+], 250 (4), 206 (9), 174 (15), 151 (100); HRMS (EI) calcd for $C_{16}H_{26}NO_2$ [M^+ − H] 264.1963, found 264.1967.

***N*-((2-(But-3-en-1-yl)-3-formylcycloheptyl)methyl)-*N*-methylformamide (39).** An aqueous HCl solution (2 N, 5.20 mL, 10.4 mmol) was added to a solution of **38** (527 mg, 1.99 mmol) in THF (10 mL). The reaction mixture was heated at 55 °C for 3 h; then saturated aqueous $NaHCO_3$ was added. The usual workup (Et_2O) and purification (40 to 70% EtOAc in hexanes) afforded a mixture of diastereomers and rotamers of **39** (410 mg, 82%) as a pale yellow oil. Only the major fraction containing two diastereomers was characterized: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.63 (s) and 9.62 (s) (1H), 8.09 (s) and 8.00 (s) (1H), 5.87−5.70 (m, 1H), 5.09−4.90 (m, 2H), 3.47 (dd, J = 13.5, 8.5 Hz) and 3.22−3.00 (m) (2H), 2.92 (s) and 2.85 (s) (3H), 2.54−2.46 (m, 1H), 2.24−1.27 (m, 14H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 205.6, 204.9, 163.5, 163.4, 138.7, 138.0, 115.8, 115.1, 53.7, 53.3, 47.4, 35.6, 35.3, 35.0, 34.3, 31.8, 31.6, 29.4, 27.1, 27.0, 26.8, 26.4, 25.9, 25.6, 25.4, 24.4; IR (film) ν (cm^{-1}) 2928, 2861, 1721, 1674, 1452, 1395, 1076; MS m/z (rel %): 252 (14) [MH^+], 251 (8) [M^+], 222 (30) [M^+ − CHO], 192 (58), 172 (55), 95 (82), 81 (100); HRMS (EI) calcd for $C_{15}H_{25}NO_2$ [M^+] 251.1885, found 251.1896.

***N*-((2-(But-3-en-1-yl)-3-(((*tert*-butyldimethylsilyl)oxy)methylene)cycloheptyl)methyl)-*N*-methylformamide (40).** TBDMSOTf (201 μL, 0.877 mmol) was added to a solution of **39** (147 mg, 0.585 mmol) and *i*-Pr_2NEt (153 μL, 0.877 mmol) in DCM (10 mL) at 0 °C. The solution was stirred for 18 h at rt; then saturated aqueous Na_2CO_3 and saturated aqueous NaCl were added. The usual workup (DCM) and purification using silica gel saturated with Et_3N (25% EtOAc in hexanes) afforded a mixture of diastereomers and rotamers of **40** (160 mg, 75%) as a pale yellow oil, separable in two different portions for characterization: Portion 1: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.09 (s), 8.05 (s), 8.00 (s), and 7.98 (s) (1H), 6.20 (s), 6.07 (s), and 6.04 (s) (1H), 5.88−5.72 (m, 1H), 5.05−4.84 (m, 2H), 3.42 (dd, J = 13.5, 8.5 Hz), 3.18 (dd, J = 14.0, 7.0 Hz), 3.14 (dd, J = 13.5, 7.0 Hz), and 3.06 (dd, J = 14.0, 8.0 Hz) (2H), 2.91 (s) and 2.85 (s) (3H), 2.24−2.10 (m) and 2.08−1.04 (m) (14H), 0.91 (s, 9H), 0.11 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 163.7,

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163.2, 139.7, 139.2, 135.9, 135.5, 122.7, 121.6, 114.7, 114.3, 54.6, 53.8, 47.6, 41.3, 40.1, 39.9, 38.0, 36.5, 36.0, 34.3, 33.1, 32.3, 32.1, 31.7, 31.4, 29.4, 29.3, 28.7, 28.4, 27.8, 27.4, 27.1, 26.9, 25.3, 24.9, 24.7, 24.3, 17.8, −5.8, −5.9; IR (film) ν (cm^{-1}) 2953, 2928, 2857, 1682, 1462, 1387, 1254, 1164; MS (EI) m/z (rel %): 365 [M^+] (1), 350 [$M^+ - CH_3$] (3), 308 [$M^+ - C_4H_9$] (100), 251 (66); HRMS (EI) calcd for $C_{21}H_{38}NO_2Si$ [$M^+ - H$] 364.2672, found 364.2680. Portion 2: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.09 (s), 8.07 (s), 7.99 (s), and 7.97 (s) (1H), 6.07 (s) and 5.92 (s) (1H), 5.84−5.69 (m, 1H), 5.04−4.90 (m, 2H), 3.32 (dd, J = 13.5, 7.5 Hz), 3.22−3.08 (m), 3.15 (dd, J = 14.0, 8.0 Hz), and 3.01 (dd, J = 14.0, 7.5 Hz) (2H), 2.91 (s), 2.88 (s), 2.84 (s), and 2.82 (s) (3H), 2.70−2.55 (m), 2.13−1.90 (m), and 1.87−1.17 (m) (14H), 0.91 (s, 9H), 0.11 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 163.6, 163.3, 139.5, 139.0, 136.2, 135.8, 123.7, 123.1, 115.0, 114.5, 54.3, 53.3, 47.6, 44.4, 42.9, 42.1, 41.9, 34.3, 32.6, 32.4, 31.9, 31.7, 31.5, 29.9, 29.4, 29.3, 29.2, 28.3, 27.9, 26.7, 26.5, 25.7, 25.5, 25.3, 24.7, 24.6, 23.5, 17.9, −5.9; IR (film) ν (cm^{-1}) 3074, 2927, 2856, 1681, 1392, 1253, 1163; MS (EI) m/z (rel %): 365 [M^+] (1), 35 [$M^+ - CH_3$] (2), 308 [$M^+ - C_4H_9$] (100), 251 (56); HRMS (EI) calcd for $C_{21}H_{38}NO_2Si$ [$M^+ - H$] 364.2672, found 364.2666.

***rel*-(1*S*,6*S*)-10-(But-3-en-1-yl)-8-methyl-8-azabicyclo[4.3.1]decane-1-carbaldehyde (43).** Tf_2O (41 μL, 0.24 mmol) was added to a solution of **40** (81 mg, 0.22 mmol) and DTBMP (50 mg, 0.24 mmol) in DCE (3.0 mL) at rt. After 15 min, the solution was heated at 80 °C for 3 h. Progression of the reaction was monitored by ^{1}H NMR. The mixture was concentrated under reduced pressure, and the product was solubilized in MeOH (3.0 mL). $NaBH_4$ (42 mg, 1.1 mmol) was added at 0 °C, and the mixture was stirred at rt for 6 h. Aqueous NaOH (1 N) was added, and solvent was removed under reduced pressure. Water was added. The usual workup (DCM) and purification (0 to 5% EtOAc in hexanes) afforded a hardly separable mixture of diastereomers of **43** (25 mg, 48%) as a yellow oil. A small portion of the major diastereomer was isolated and characterized: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.32 (s, 1H), 5.74 (ddt, J = 17.0, 10.0, 7.0 Hz, 1H), 5.00 (d, J = 17.0 Hz) and 4.97 (d, J = 10.0 Hz) (2H), 2.41 (d, J = 12.5 Hz) and 2.38 (d, J = 12.5 Hz) (2H), 2.24−2.10 (m) and 2.21 (s) (6H), 2.02−1.85 (m, 5H), 1.80−1.70 (m, 2H), 1.67−1.46 (m, 5H), 1.15−1.07 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 203.2, 138.0, 115.2, 57.6, 57.5, 52.0, 47.1, 36.3, 35.7, 35.5, 34.5, 32.8, 29.3, 26.7, 26.6; IR (film) ν (cm^{-1}) 2933, 2846, 2792, 2692, 1723, 1465, 1446; MS (EI) m/z (rel %): 235 [M^+] (32), 206 (100); HRMS (EI) calcd for $C_{15}H_{25}NO$ [M^+] 235.1936, found 235.1935.

(9*H*-Fluoren-9-yl)methyl *N*-((2-(But-3-en-1-yl)-3-(methoxymethylene)cycloheptyl)methyl)carbamate (44). Following the procedure used to prepare **20**, a solution of **37** (819 mg, 3.24 mmol) in acetone (11 mL) was treated with $ClCO_2Et$ (321 μL, 3.41 mmol) and *i*-Pr_2NEt (0.70 mL, 4.1 mmol) for 30 min at 0 °C and then with an aqueous solution of NaN_3 (5.9 M, 1.10 mL, 6.50 mmol) for 1 h at 0 °C. Crude acylazide was then refluxed in toluene (11.0 mL) for 1.5 h to afford the corresponding isocyanate. The latter was dissolved in benzene (24 mL); then 9-fluorenemethanol (954 mg, 4.86 mmol) and Ti(O*t*-Bu)$_4$ (248 μL, 0.648 mmol) were added at 0 °C. The mixture was refluxed for 3 h; then saturated aqueous NH_4Cl was added. The usual workup (Et_2O) and purification (5 to 25% EtOAc in hexanes) afforded an inseparable mixture of diastereomers of **44** (1.32 g, 92%) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.77 (d, J = 7.5 Hz, 2H), 7.60 (d, J = 7.5 Hz, 2H), 7.41 (t, J = 7.5 Hz, 2H), 7.32 (t, J = 7.5 Hz, 2H), 5.90−5.72 (m) and 5.63 (s) (2H), 5.05−4.89 (m, 2H), 4.78−4.70 (m, 1H), 4.46−4.35 (m, 2H), 4.23 (t, J = 7.0 Hz, 1H), 3.56 (s), 3.54 (s), 3.50 (s), and 3.48 (s) (3H), 3.20−2.82 (m, 2H), 2.59−2.46 (m) and 2.18−1.78 (m) (4H), 1.77−1.13 (m, 10H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 157.0 (s), 156.7 (s), 144.5 (s), 144.2 (s), 143.8 (s), 143.6 (d), 143.3 (d), 141.5 (s), 139.3 (d), 139.2 (d), 127.7 (d), 127.1 (d), 125.1 (d), 120.0 (d), 119.6 (s), 114.6 (t), 114.4 (t), 114.3 (t), 66.5 (t), 66.1 (t), 59.0 (q), 58.9 (q), 46.9 (d), 45.2 (d), 45.0 (d), 44.5 (t), 44.4 (t), 43.3 (d), 43.2 (d), 43.0 (d), 37.6 (d), 37.4 (d), 32.4 (t), 32.1 (t), 31.9 (t), 31.6 (t), 31.4 (t), 31.0 (t), 30.0 (t), 29.6 (t), 29.4 (t), 29.2 (t), 28.5 (t), 28.3 (t), 27.4 (t), 26.7 (t), 26.1 (t), 25.6 (t), 25.4 (t), 25.0 (t), 24.9 (t), 24.3 (t), 23.5 (t); IR (film) ν (cm^{-1}) 3420, 3340, 3067, 3008, 2927, 2859, 1722, 1694, 1537, 1519, 1449, 1249, 1124; MS (EI) m/z (rel %): 445 [M^+] (1), 178 (100), 151 (20), 148 (18); HRMS (EI) calcd for $C_{29}H_{35}NO_3$ [M^+] 445.2617, found 445.2626.

***N*-((2-(But-3-en-1-yl)-3-(methoxymethylene)cycloheptyl)methyl)-*N*-((trimethylsilyl)methyl)formamide (45).** NaH (60% in mineral oil, 143 mg, 3.58 mmol) was added to a solution of **44** (1.06 g, 2.38 mmol) in THF (28 mL) and DMF (14 mL) at rt. The reaction mixture was stirred at 75 °C for 1 h; then TMSI (530 μL, 3.57 mmol) was added. The solution was stirred at 75 °C for 3.5 h, and aqueous NaOH (1 N) was added. The usual workup (Et_2O) afforded the corresponding secondary amine as a yellow oil. The latter was solubilized in THF (20 mL); then *N*-formylbenzotriazole (454 mg, 3.09 mmol) was added. The resulting solution was stirred at rt for 15 h. Aqueous NaOH (1 N) was added, and solvent was removed under reduced pressure. The usual workup (DCM) and purification (0 to 5% Et2O in DCM) afforded a hardly separable mixture of diastereomers and rotamers of **45** (485 mg, 60% over 2 steps) as a pale yellow oil. Only one fraction containing two diastereomers was characterized: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.06 (s), 8.05 (s), 7.97 (s), and 7.96 (s) (1H), 5.85−5.70 (m) and 5.77 (s) (2H), 5.03−4.89 (m, 2H), 3.56 (s), 3.55 (s), and 3.50 (s) (3H), 3.28−2.93 (m, 2H), 2.88−2.70 (m), 2.85 (d, J = 14.0 Hz), and 2.75 (d, J = 15.0 Hz) (2H), 2.61−2.50 (m) and 2.22−1.09 (m) (14H), 0.11 (s) and 0.09 (s) (9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 163.0, 162.4, 143.9, 143.6, 139.6, 139.4, 139.2, 139.0, 120.2, 119.6, 115.0, 114.7, 114.4, 59.2, 58.9, 53.3, 52.9, 47.6, 47.2, 43.1, 42.4, 41.8, 41.5, 39.9, 37.9, 37.4, 36.8, 36.5, 33.2, 33.0, 32.2, 32.0, 31.9, 31.7, 29.3, 29.1, 28.5, 28.3, 27.0, 26.6, 26.5, 25.7, 25.5, 25.2, 24.8, 24.6, 24.3, −1.9, −2.4; IR (film) ν (cm^{-1}) 2931, 2869, 1664, 1646, 1452, 1249, 853; MS (EI) m/z (rel %): 337 [M^+] (1), 322 [$M^+ - CH_3$] (100), 306 (23), 151 (66); HRMS (IE) calcd for $C_{18}H_{32}NO_2Si$ [$M^+ - CH_3$] 322.2202, found: 322.2207.

***N*-((2-(But-3-en-1-yl)-3-formylcycloheptyl)methyl)-*N*-((trimethylsilyl)methyl)formamide (46).** Trichloroacetic acid (1.38 g, 8.45 mmol) was added to a solution of **45** (569 mg, 1.69 mmol) in DCM (45 mL). Water (3−4 drops) was added, and the resulting solution was stirred for 15 h at rt. Saturated aqueous $NaHCO_3$ and saturated aqueous NaCl were added. The usual workup (DCM) and purification (30% EtOAc in hexanes) afforded a mixture of diastereomers and rotamers of **46** (448 mg, 82%) as a colorless oil, separable in two different portions for characterization: Portion 1: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.72 (s), 9.63 (s), and 9.62 (s) (1H), 8.07 (s), 8.00 (s), and 7.98 (s) (1H), 5.85−5.71 (m, 1H), 5.08−4.91 (m, 2H), 3.43 (dd, J = 13.5, 8.0 Hz), 3.14 (dd, J = 14.0, 7.0 Hz), and 3.05 (dd, J = 14.0, 7.5 Hz) (2H), 2.86 (s), 2.79 (d, J = 9.0 Hz), and 2.72 (d, J = 7.5 Hz) (2H), 2.52−2.46 (m, 1H), 2.18−1.20 (m, 14H), 0.11 (s) and 0.09 (s) (9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 205.6, 205.0, 163.3, 162.4, 138.7, 138.1, 115.8, 115.2, 53.4, 53.2, 47.4, 37.7, 35.8, 34.9, 33.4, 31.8, 31.6, 28.6, 27.3, 27.1, 26.8, 26.5, 26.1, 25.5, 24.6, 24.3, −1.9, −2.4; IR (film) ν (cm^{-1}) 2929, 2856, 1721, 1667, 1452, 1390, 1249; MS (EI) m/z (rel %): 323 [M^+] (2), 308 [$M^+ - CH_3$] (92), 294 [$M^+ - CHO$] (44), 282 (55), 145 (100); HRMS (IE) calcd for $C_{18}H_{33}NO_2Si$ [M^+] 323.2280, found: 323.2290. Portion 2: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.77 (s), 9.72 (s), and 9.62 (s) (1H), 8.08 (s), 8.06 (s), 8.00 (s), and 7.98 (s) (1H), 5.82−5.63 (m, 1H), 5.06−4.93 (m, 2H), 3.39−2.96 (m), 3.32 (t, J = 8.0 Hz), 3.20 (dd, J = 14.0, 6.5 Hz), and 3.10 (dd, J = 14.0, 8.0 Hz) (2H), 2.85 (d, J = 15.0 Hz), 2.79 (d, J = 15.5 Hz), 2.75 (s), and 2.55−2.47 (m) (2H), 2.38−2.20 (m) and 2.17−0.85 (m) (15H), 0.13 (s), 0.11 (s), and 0.10 (s) (9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 205.8, 205.6, 205.1, 163.1, 162.6, 162.4, 138.6, 138.1, 138.0, 115.7, 115.3, 57.1, 54.5, 54.1, 53.9, 49.0, 42.7, 42.4, 41.3, 38.6, 38.0, 37.7, 37.1, 34.2, 33.8, 32.9, 28.7, 28.5, 28.0, 27.7, 26.9, 25.2, 25.0, 24.6, 23.0, −1.8, −2.4; IR (film) ν (cm^{-1}) 3075, 2931, 2861, 1721, 1666, 1443, 1390, 1249; MS (EI) m/z (rel %): 323 [M^+] (2), 308 [$M^+ - CH_3$] (33), 294 [$M^+ - CHO$] (23), 145 (100); HRMS (EI) calcd for $C_{18}H_{33}NO_2Si$ [M^+] 323.2280, found: 323.2287.

***N*-((2-(But-3-en-1-yl)-3-(((*tert*-butyldimethylsilyl)oxy)methylene)cycloheptyl)methyl)-*N*-((trimethylsilyl)methyl)formamide (47).** Following the procedure used to prepare **40**, a solution of **46**

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(228 mg, 0.705 mmol) in DCM (12 mL) was treated with TBDMSOTf (260 μL, 1.13 mmol) and *i*-Pr_2NEt (197 μL, 1.13 mmol) for 20 h at rt to afford, after the usual purification using silica gel saturated with Et_3N (10% EtOAc in hexanes), an inseparable mixture of diastereomers and rotamers of **47** (184 mg, 60%) as a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.08 (s), 8.05 (s), 8.03 (s), 7.97 (s), 7.97 (s), and 7.95 (s) (1H), 6.07 (s) and 5.92 (s) (1H), 5.85−5.70 (m, 1H), 5.03−4.89 (m, 2H), 3.32 (dd, *J* = 13.5, 7.5 Hz), 3.21 (dd, *J* = 13.5, 8.0 Hz), 3.17−2.57 (m), 3.12 (dd, *J* = 14.0, 7.5 Hz), 3.00 (dd, *J* = 14.0, 7.5 Hz), 2.86 (d, *J* = 15.0 Hz), 2.73 (d, *J* = 15.0 Hz), and 2.51 (d, *J* = 15.0 Hz) (4H), 2.17−1.06 (m, 14H), 0.92 (s) and 0.91 (s) (9H), 0.12 (s), 0.10 (s), 0.09 (s), and 0.08 (s) (15 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 163.1, 162.6, 162.4, 162.2, 139.7, 139.6, 139.3, 139.1, 136.4, 136.2, 136.0, 135.8, 123.9, 123.3, 122.0, 121.5, 115.0, 114.7, 114.6, 114.3, 54.2, 53.6, 53.0, 47.6, 45.0, 44.6, 43.0, 42.3, 41.8, 41.7, 41.5, 39.6, 37.7, 37.0, 33.8, 33.3, 33.1, 32.4, 32.2, 31.9, 31.7, 31.5, 29.3, 28.5, 28.4, 27.9, 27.2, 26.9, 26.6, 25.8, 25.5, 25.4, 24.8, 24.7, 23.6, 17.9, −1.8, −1.9, −2.4, −5.8; MS (EI) *m*/*z* (rel %): 437 [M^+] (2), 422 [$M - CH_3]^+$ (23), 380 [$M^+ - C_4H_9$] (100), 251 (49); HRMS (EI) calcd for $C_{24}H_{47}NO_2Si_2$ [M^+] 437.3145, found 437.3138.

***rel*-(1*S*,6*S*)-10-(But-3-en-1-yl)-1-formyl-8-((trimethylsilyl)-methyl)-8-aza-bicyclo[4.3.1]dec-8-en-8-ium Trifluoromethanesulfonate (49).** Tf_2O (12 μL, 73 μmol) was added to a solution of **47** (29 mg, 66 μmol) and DTBMP (15 mg, 73 μmol) in DCE (0.75 mL) at rt. After 15 min, additional DCE (7.5 mL) and DMAD (24 μL, 0.20 mmol) were added. Then, the solution was heated at 55 °C for 3 h. ^1H NMR analysis of an aliquot showed the formation of the iminium ion **49**: ^1H NMR (300 MHz, $CDCl_3$) characteristic signals δ (ppm) 9.70 (s) and 9.63 (s) (1H), 8.46 (s, 1H), 5.83−5.69 (m, 1H), 5.02 (d, *J* = 10.0 Hz, 1H), 5.01 (d, *J* = 18.0 Hz, 1H), 3.94−3.77 (m, 1H), 3.45−3.31 (m, 1H), 3.14−3.08 (m) and 2.60−2.53 (m) (2H), 2.17−1.18 (m, 14H), 0.16 (s, 9H).

2-(((2-(But-3-en-1-yl)-3-(methoxymethylene)cycloheptyl)-methyl)amino)acetonitrile (56). NaH (60% in mineral oil, 237 mg, 5.92 mmol) was added to a solution of **44** (1.32 g, 2.96 mmol) in THF (34 mL) and DMF (17 mL) at rt. The mixture was stirred at 75 °C for 1 h; then $BrCH_2CN$ (395 μL, 5.92 mmol) was added. The resulting solution was stirred at 75 °C for 2 h, and saturated aqueous $NaHCO_3$ was added. The usual workup (EtOAc) and purification using silica gel saturated with Et_3N (10 to 40% EtOAc in hexanes) afforded an inseparable mixture of diastereomers of **56** (683 mg, 88%) as an orange oil: ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.91 (s), 5.88−5.73 (m), 5.80 (s), 5.75 (s), and 5.64 (s) (2H), 5.00 (d, *J* = 17.5 Hz, 1H), 4.95 (d, *J* = 10.5 Hz, 1H), 3.61 (s), 3.58 (s), 3.56 (s), 3.55 (s), and 3.51 (s) (5H), 2.66 (dd, *J* = 11.5, 6.5 Hz) and 2.58−2.49 (m) (3H), 2.18−2.00 (m, 3H), 1.92−1.79 (m, 1H), 1.73−1.06 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 144.2, 143.2, 142.9, 142.8, 138.8, 138.8, 138.6, 138.5, 119.7, 119.3, 119.3, 119.2, 117.7, 117.7, 114.0, 113.8, 113.7, 58.9, 58.8, 58.7, 58.6, 53.4, 53.4, 52.4, 52.3, 44.9, 44.8, 44.4, 43.5, 43.0, 42.6, 38.1, 37.2, 37.1, 37.0, 36.7, 36.7, 32.5, 32.2, 32.0, 31.7, 31.6, 31.5, 31.3, 30.5, 29.9, 29.8, 29.7, 29.1, 28.6, 28.2, 28.0, 27.3, 27.0, 26.4, 25.6, 25.5, 25.3, 24.5, 24.2, 23.5; IR (film) ν (cm^{-1}) 2927, 2854, 1663, 1459, 1222, 1124; MS (CI:NH_3) *m*/*z* (rel %): 262 [M^+] (8), 220 (27), 161 (35), 148 (100); HRMS (CI:NH_3) calcd for $C_{16}H_{26}N_2O$ [M^+] 262.2045, found: 262.2045.

***N*-((2-(But-3-en-1-yl)-3-(methoxymethylene)cycloheptyl)-methyl)-*N*-(cyanomethyl)formamide (57).** *N*-Formylbenzotriazole (288 mg, 1.96 mmol) was added to a solution of **56** (427 mg, 1.63 mmol) in THF (22 mL). The resulting mixture was stirred at rt for 18 h. Aqueous NaOH (2 N) was added, and solvent was removed under reduced pressure. The usual workup (DCM) and purification (30 to 40% EtOAc in hexanes) afforded an inseparable mixture of diastereomers and rotamers of **57** (415 mg, 88%) as a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.09 (s), 7.98 (s), 7.96 (s), and 7.94 (s) (1H), 5.87 (s), 5.83−5.51 (m), 5.76 (s), and 5.59 (s) (2H), 5.04−4.79 (m, 2H), 4.33−4.03 (m, 2H), 3.49 (s), 3.48 (s), 3.47 (s), and 3.44 (s) (3H), 3.34−3.02 (m, 2H), 2.53−2.38 (m, 1H), 2.14−1.08 (m, 13H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 162.8, 162.5, 162.3, 162.1, 144.9, 143.9, 143.7, 143.4, 138.6, 138.5, 138.1, 118.1, 118.0, 114.9, 114.7, 114.5, 114.4, 59.1, 58.9, 52.2, 51.1, 46.1, 44.5, 42.9, 42.2, 41.9, 41.0, 37.7, 35.8, 32.8, 32.3, 31.8, 31.6, 31.4, 31.3, 30.1, 28.9, 28.5, 28.4, 28.3, 27.2, 26.7, 26.4, 26.2, 25.9, 25.5, 24.7, 23.7; IR (film) ν (cm^{-1}) 2929, 2863, 1681, 1429, 1223, 1179, 1123; MS (EI) *m*/*z* (rel %): 290 [M^+] (2), 275 [$M^+ - CH_3$] (4), 206 (26), 174 (34), 148 (100); HRMS (EI) calcd for $C_{17}H_{26}N_2O_2$ [M^+] 290.1994, found: 290.1995.

***N*-((2-(But-3-en-1-yl)-3-formylcycloheptyl)methyl)-*N*-(cyanomethyl)formamide (58).** Trichloroacetic acid (1.16 g, 7.11 mmol) was added to a solution of **57** (413 mg, 1.42 mmol) in DCM (36 mL). Water (4−5 drops) was added, and the resulting solution was stirred for 18 h at rt. Saturated aqueous $NaHCO_3$ and saturated aqueous NaCl were added. The usual workup (DCM) and purification (80 to 100% Et_2O in hexanes) afforded a mixture of diastereomers and rotamers of **58** (315 mg, 80%) as a pale yellow oil separable in two different portions for characterization: Portion 1: ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.76 (s) and 9.61 (s) (1H), 8.14 (s), 8.04 (s), and 7.99 (s) (1H), 5.79−5.63 (m, 1H), 5.02−4.89 (m, 2H), 4.69 (d, *J* = 17.5 Hz), 4.39 (d, *J* = 18.0 Hz), 4.34 (d, *J* = 17.5 Hz), 4.30 (d, *J* = 18.0 Hz), 4.15 (d, *J* = 17.5 Hz), and 4.14 (d, *J* = 17.5 Hz) (2H), 3.79 (dd, *J* = 14.0, 10.0 Hz), 3.35 (dd, *J* = 7.0, 5.5 Hz), 3.27 (dd, *J* = 14.5, 8.5 Hz), 3.20 (dd, *J* = 14.5, 7.0 Hz), and 2.98 (dd, *J* = 14.0, 6.0 Hz) (2H), 2.57−2.48 (m, 1H), 2.14−1.97 (m, 3H), 1.93−1.78 (m, 3H), 1.68−1.52 (m, 3H), 1.50−1.31 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 206.4, 205.9, 205.5, 163.3, 162.9, 162.8, 138.5, 137.8, 137.7, 116.0, 115.9, 115.2, 115.0, 53.7, 52.8, 52.7, 52.6, 51.0, 44.9, 41.7, 36.4, 35.1, 34.3, 34.1, 34.1, 33.8, 31.6, 31.3, 31.1, 29.9, 29.4, 27.9, 27.7, 26.8, 26.4, 26.3, 26.3, 26.0, 25.8, 25.7, 25.5, 25.4, 24.4, 24.0, 23.9; IR (film) ν (cm^{-1}) 2930, 2863, 1719, 1680, 1432, 1399; MS (EI) *m*/*z* (rel %): 276 [M^+] (9), 247 [M-CHO]$^+$ (10), 233 [$M^+ - CH_2CN$] (8), 192 (57), 137 (62), 95 (100); HRMS (EI) calcd for $C_{16}H_{24}N_2O_2$ [M^+] 276.1838, found: 276.1836. Portion 2: ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.68 (s) and 9.67 (s) (1H), 8.16 (s) and 8.03 (s) (1H), 5.72−5.61 (m, 1H), 4.99−4.90 (m, 2H), 4.36 (d, *J* = 17.5 Hz), 4.22 (d, *J* = 4.5 Hz), and 4.17 (d, *J* = 17.5 Hz) (2H), 3.55 (dd, *J* = 14.0, 8.0 Hz), 3.38 (dd, *J* = 14.5, 7.5 Hz), 3.30 (dd, *J* = 14.0, 8.0 Hz), and 3.23 (dd, *J* = 14.5, 8.0 Hz) (2H), 2.39−2.23 (m, 2H), 2.07−1.88 (m, 3H), 1.80−1.49 (m, 7H), 1.44−1.19 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 204.6, 204.1, 162.4, 137.9, 137.4, 115.6, 115.1, 114.9, 114.7, 56.7, 52.8, 47.7, 42.7, 37.8, 37.3, 36.3, 33.1, 33.0, 30.6, 29.0, 28.7, 25.3, 25.1, 24.8, 24.8, 24.7, 24.7, 23.2; IR (film) ν (cm^{-1}) 2931, 2864, 1719, 1679, 1433, 1402, 1181; MS (EI) *m*/*z* (rel %): 276 [M^+] (8), 247 [M^+ − CHO] (9), 233 [$M^+ - CH_2CN$] (7), 192 (65), 95 (96), 81 (100); HRMS (EI) calcd for $C_{16}H_{24}N_2O_2$ [M^+] 276.1838, found: 276.1839.

***N*-((2-(But-3-en-1-yl)-3-(((*tert*-butyldimethylsilyl)oxy)methylene)cycloheptyl)methyl)-*N*-(cyanomethyl)formamide (59).** Following the procedure used to prepare **40**, a solution of **58** (145 mg, 0.525 mmol) in DCM (9 mL) was treated with TBDMSOTf (193 μL, 0.839 mmol) and *i*-Pr_2NEt (146 μL, 0.839 mmol) for 7 h at rt to afford, after the usual purification using silica gel saturated with Et_3N (0 to 40% EtOAc in hexanes), a mixture of diastereomers and rotamers of **59** (113 mg, 55%) as a pale yellow oil separable in two different portions for characterization: Portion 1: ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.11 (s), 8.04 (s), and 8.01 (s) (1H), 6.24 (s), 6.07 (s), and 6.05 (s) (1H), 5.77 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H), 5.01−4.88 (m, 2H), 4.58 (d, *J* = 17.5 Hz), 4.36 (d, *J* = 17.5 Hz), 4.25 (d, *J* = 17.5 Hz), 4.15 (d, *J* = 18.0 Hz), 4.14 (d, *J* = 17.5 Hz), and 4.10 (d, *J* = 17.5 Hz) (2H), 3.69 (dd, *J* = 14.0, 9.5 Hz), 3.39 (dd, *J* = 14.5, 4.5 Hz), 3.32 (dd, *J* = 14.5, 8.5 Hz), 3.23 (dd, *J* = 14.5, 7.5 Hz), and 3.19−3.14 (m) (2H), 2.80 (d, *J* = 12.0 Hz), 2.75−2.70 (m), and 2.67−2.63 (m) (1H), 2.19−2.13 (m, 1H), 2.02−1.93 (m, 2H), 1.83−1.45 (m) and 1.42−1.33 (m) (8H), 1.26−1.11 (m, 2H), 0.91 (s) and 0.90 (s) (9H), 0.12 (s) and 0.11 (s) (6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.7, 162.2, 161.8, 138.9, 138.8, 138.5, 137.2, 135.9, 135.4, 121.8, 120.8, 114.9, 114.4, 114.3, 52.6, 50.8, 45.2, 41.4, 40.1, 39.9, 38.0, 35.9, 35.7, 35.4, 33.3, 32.4, 32.3, 31.6, 31.5, 30.3, 29.8, 29.7, 29.5, 28.9, 28.7, 28.6, 27.5, 27.3, 27.1, 25.7, 25.4, 25.2, 24.8, 24.4, 18.2, −5.2, −5.4; IR (film) ν (cm^{-1}) 2960, 2929, 2859, 1687, 1463, 1429, 1387, 1254, 1164, 1141; MS (EI) *m*/*z* (rel %): 390 [M^+] (1), 333 [$M^+ - C_4H_9$] (100), 306 (25), 251 (45); HRMS (EI) calcd for $C_{22}H_{38}N_2O_2Si$ [M^+]

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390.2702, found: 390.2703. Portion 2: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.14 (s), 8.01 (s), and 8.00 (s) (1H), 6.10 (s), 6.07 (s), and 5.93 (s) (1H), 5.79−5.69 (m, 1H), 4.97 (dd, J = 17.0, 1.5 Hz, 1H), 4.96 (d, J = 10.0 Hz, 1H), 4.22 (s), 4.14 (s), and 4.13 (s) (2H), 3.42 (dd, J = 14.0, 7.5 Hz), 3.35 (dd, J = 14.5, 8.5 Hz), 3.30 (dd, J = 14.5, 7.5 Hz), and 3.19 (dd, J = 14.5, 8.0 Hz) (2H), 2.66−2.58 (m, 1H), 2.09−1.98 (m, 3H), 1.87−1.77 (m, 2H), 1.75−1.66 (m, 2H), 1.63−1.44 (m, 3H), 1.41−1.22 (m, 3H), 0.91 (s, 9H), 0.11 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.4, 162.1, 138.8, 138.3, 136.3, 135.9, 122.6, 121.9, 115.1, 114.6, 114.4, 51.3, 46.4, 43.1, 42.4, 42.2, 42.1, 35.8, 32.0, 31.8, 30.1, 28.7, 28.6, 26.7, 26.5, 26.1, 25.9, 25.7, 25.6, 24.9, 24.8, 18.2, −5.3; IR (film) ν (cm^{-1}) 2953, 2929, 2858, 1685, 1432, 1254, 1164, 1136; MS (EI) m/z (rel %): 390 [M$^+$] (1), 375 [M$^+$ − CH_3] (7), 333 [M − C_4H_9]$^+$ (100), 306 (17), 251 (58); HRMS (EI) calcd for $C_{22}H_{38}N_2O_2Si$ [M$^+$] 390.2702, found: 390.2705.

***rel*-(1*S*,6*S*)-10-(But-3-en-1-yl)-8-(cyanomethyl)-1-formyl-8-azabicyclo[4.3.1]dec-8-en-8-ium Trifluoromethanesulfonate (60).** Tf_2O (13 μL, 77 μmol) was added to a solution of **59** (25 mg, 64 μmol) and DTBMP (14.5 mg, 70.4 μmol) in DCE (1.0 mL) at rt. After 20 min, the mixture was heated at 80 °C for 3 h. ^{1}H NMR analysis of an aliquot showed the formation of the iminium ion **60**: ^{1}H NMR (400 MHz, $CDCl_3$) characteristic signals δ (ppm) 9.99 (s) and 9.91 (s) (1H), 9.70 (s) and 9.45 (s) (1H), 6.24−6.05 (m, 1H), 5.90 (d, J = 17.5 Hz), 5.80 (d, J = 17.5 Hz), 5.68 (d, J = 17.5 Hz), and 5.57 (d, J = 17.5 Hz) (2H), 5.46−5.26 (m, 2H), 4.83 (d, J = 5.5 Hz), 4.27 (d, J = 16.0 Hz), 3.87 (d, J = 14.0 Hz), and 3.64 (bs) (2H), 3.20−2.98 (m, 2H), 2.81−1.54 (m, 12H).

***N*-(Cyanomethyl)-*N*-(5-methoxypent-4-en-1-yl)formamide (65).** A solution of KHMDS (0.5 M in toluene, 7.68 mL, 3.84 mmol) was added dropwise to a solution of **64**[9a] (499 mg, 3.49 mmol) in THF (14.0 mL) and DMF (7.0 mL) at rt. The reaction mixture was stirred for 1 h; then a solution of 18-crown-6 ether (1.01 g, 3.84 mmol) in THF (1.0 mL) and $BrCH_2CN$ (345 μL, 5.18 mmol) were added. The solution was stirred for 18 h at rt; then saturated aqueous $NaHCO_3$ was added. The usual workup (EtOAc) and purification (60 to 70% EtOAc in hexanes) afforded a mixture of E/Z isomers and rotamers of **65** (238 mg, 38%) as a brown oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.10 (s), 8,07 (s), and 8.05 (s) (1H), 6.30 (d, J = 12.5 Hz), and 5.95 (d, J = 6.0 Hz) (1H), 4.64 (dt, J = 12.5, 7.5 Hz, 1H), 4.27 (s), 4.26 (s), and 4.17 (s) (2H), 3.58 (s) and 3.50 (s) (3H), 3.48−3.37 (m) and 3.40 (t, J = 7.0 Hz) (2H), 2.07 (q, J = 7.0 Hz) and 1.97 (q, J = 7.0 Hz) (2H), 1.72−1.62 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.4 (d), 162.1 (d), 161.8 (d), 147.8 (d), 147.5 (d), 147.2 (d), 115.0 (s), 114.8 (s), 114.7 (s), 103.6 (d), 100.8 (d), 100.3 (d), 59.2 (q), 55.6 (q), 55.5 (q), 46.6 (t), 46.5 (t), 42.2 (t), 35.6 (t), 29.8 (t), 29.7 (t), 28.1 (t), 27.2 (t), 27.1 (t), 24.5 (t), 23.9 (t), 19.9 (t); IR (film) ν (cm^{-1}) 3059, 2937, 2856, 1681, 1429, 1397, 1209, 1181, 1143, 1108, 934; MS (EI) m/z (rel %): 182 [M$^+$] (10), 152 (9), 98 (100), 85 (29); HRMS (EI) calcd for $C_9H_{14}N_2O_2$ [M$^+$] 182.1055, found 182.1057.

***rel*-9-(Methoxymethylene)-1,3-dioxo-2-phenyldecahydro-1*H*-pyrrolo[3,4-*a*]indolizine-4-carbonitrile (67).** Tf_2O (61 μL, 0.36 mmol, freshly distilled over P_2O_5) was added to a solution of **65** (60 mg, 0.33 mmol) and DTBMP (74 mg, 0.36 mmol) in DCM (5.0 mL) at rt. After 30 min, *N*-phenylmaleimide (342 mg, 1.97 mmol), followed by *i*-Pr_2NEt (230 μL, 1.32 mmol), was added at 0 °C. The mixture was then stirred for 2 h at rt. Saturated aqueous Na_2CO_3 was added. The usual workup (DCM) and purification using silica gel saturated with Et_3N (20 to 60% EtOAc in hexanes) afforded two separable portions of two diastereomers of **67**: portion 1 (42 mg, 1.5:1 d.r.) as a yellow oil and portion 2 (34 mg, 2:1 d.r.) as a brown oil (79% global yield). Portion 1 (two diastereomers): ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.49−7.36 (m, 3H), 7.27−7.18 (m, 2H), 6.78 (s) and 6.36 (s) (1H), 4.41 (s), 3.80 (dd, J = 9.5, 6.0 Hz), and 3.64−3.49 (m) (3H), 3.65 (s) and 3.62 (s) (3H), 3.47−3.42 (m) and 3.39−3.31 (m) (1H), 3.04−2.76 (m, 2H), 2.45 (td, J = 11.0, 2.5 Hz) and 2.32 (td, J = 11.0, 3.5 Hz) (1H), 1.79−1.60 (m) and 1.58−1.46 (m) (3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 175.0, 174.6, 174.4, 174.2, 145.9, 143.3, 131.9, 131.4, 129.6, 129.5, 129.3, 126.7, 126.5, 117.7, 115.4, 111.8, 108.4, 66.2, 63.4, 59.8, 59.6, 56.9, 54.7, 50.5, 48.8, 48.5, 48.1, 45.7, 45.1, 23.8, 23.0, 22.4, 21.5; IR (film) ν (cm^{-1}) 3019, 2942, 2831, 1716, 1498, 1386, 1181, 1129; MS (EI) m/z (rel %): 392 (21), 360 [MNa^+] (100), 333 (35); HRMS (EI) calcd for $C_{19}H_{19}N_3O_3Na$ [MNa^+] 360.1319, found 360.1327. Portion 2 (two diastereomers): ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.52−7.38 (m, 3H), 7.33−7.21 (m, 2H), 6.80 (s) and 6.25 (s) (1H), 4.44 (d, J = 8.5 Hz), 3.79 (t, J = 9.0 Hz), and 3.60−3.24 (m) (4H), 3.63 (s, 3H), 3.08−2.99 (m) and 2.94−2.81 (m) (2H), 2.65 (td, J = 11.5, 2.5 Hz) and 2.03 (t, J = 11.0 Hz) (1H), 1.84−1.50 (m, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 174.9, 174.1, 173.5, 173.4, 145.8, 143.1, 131.9, 131.6, 129.6, 129.5, 129.4, 129.2, 126.9, 126.9, 115.4, 113.9, 112.4, 108.3, 66.4, 63.3, 59.8, 59.7, 56.9, 55.3, 51.4, 48.7, 46.8, 46.1, 45.5, 44.8, 23.6, 23.2, 22.3, 21.8; IR (film) ν (cm^{-1}) 3019, 2939, 2836, 1717, 1499, 1384, 1194, 1130; MS (EI) m/z (rel %): 392 (22), 360 [MNa^+] (100), 333 (29); HRMS (EI) calcd for $C_{19}H_{19}N_3O_3Na$ [MNa^+] 360.1319, found 360.1327.

***N*-(*rel*-(2*S*,3*S*)-2-Allyl-3-(2-(allyloxy)vinyl)-6-(benzyloxy)-hexyl)formamide (76).** TBAI (1.51 g, 4.09 mmol) and diformylimide sodium salt (1.16 g, 12.3 mmol) were added to a solution of **75**[8] (1.61 g, 4.09 mmol) in DMF (41 mL). The solution was stirred at 50 °C for 24 h and then cooled at rt. 5% NaOH solution in MeOH (6.0 mL) was added, and the mixture was stirred at rt for 45 min. The usual workup (Et_2O) and purification using silica gel saturated with Et_3N (10 to 80% EtOAc in hexanes) afforded **76** (1.13 g, 78%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.10 (d, J = 1.5 Hz), 7.96 (d, J = 12.0 Hz), and 7.92 (d, J = 12.0 Hz) (1H), 7.37−7.25 (m, 5H), 6.17 (d, J = 12.5 Hz), 6.16 (d, J = 12.5 Hz), 6.10 (d, J = 5.0 Hz), and 6.08 (d, J = 6.0 Hz) (1H), 5.97−5.87 (m, 1H), 5.87−5.68 (m, 1H), 5.55 (bs, 1H), 5.35−5.21 (m, 2H), 5.09−5.02 (m, 2H), 4.56−4.46 (m), 4.49 (s), and 4.27−4.07 (m) (5H), 3.63 (ddd, J = 13.0, 8.0, 4.5 Hz), 3.48−3.34 (m), and 3.31−3.00 (m) (4H), 2.58−2.44 (m) and 2.22−1.86 (m) (3H), 1.71−1.13 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 164.7 (d), 161.2 (d), 146.9 (d), 146.7 (d), 145.5 (d), 145.4 (d), 138.2 (s), 136.6 (d), 136.5 (d), 136.4 (d), 136.0 (d), 133.4 (d), 133.2 (d), 128.0 (d), 127.3 (d), 127.2 (d), 117.6 (t), 117.2 (t), 117.1 (t), 116.9 (t), 116.7 (t), 116.4 (t), 116.2 (t), 108.6 (d), 108.4 (d), 104.9 (d), 104.4 (d), 72.5 (d), 72.3 (d), 70.0 (d), 69.8 (d), 69.6 (d), 43.3 (d), 42.5 (d), 42.4 (d), 42.0 (t), 39.1 (d), 38.7 (d), 38.5 (t), 38.4 (t), 35.0 (d), 34.7 (d), 34.2 (t), 33.9 (t), 33.4 (t), 33.0 (t), 29.2 (t), 29.1 (t), 28.9 (t), 27.5 (t), 27.3 (t), 27.1 (t); IR (film) ν (cm^{-1}) 3299, 3066, 3028, 2930, 2858, 1665, 1536, 1453, 1385, 1163, 1100; MS (CI: NH_3) m/z (rel %): 316 [M$^+$ − C_3H_5] (30), 208 (35), 163 (100); HRMS (CI: NH_3) calcd for $C_{22}H_{32}NO_3$ [MH^+] 358.2382, found 358.2390.

(((4-(2-(Allyloxy)vinyl)-5-methyleneoct-7-en-1-yl)oxy)-methyl)benzene (77). NaH (60% in mineral oil, 24 mg, 0.58 mmol) was added to a solution of formamide (770 μL, 19.2 mmol) in THF (1.5 mL) and DMF (0.7 mL) at 0 °C. The solution was stirred for 1 h at rt; then NaI (72 mg, 0.48 mmol) and a solution of **75** (175 mg, 0.445 mmol) in THF (1.5 mL) were added. The mixture was stirred for 48 h at 80 °C; then water was added. The usual workup (EtOAc) and purification using silica gel saturated with Et_3N (0 to 60% EtOAc in hexanes) afforded **76** (56 mg, 35%) as a colorless oil and **77** (78 mg, 56%) as a colorless oil: **77**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.38−7.24 (m, 5H), 6.22 (d, J = 12.5 Hz) and 6.00 (d, J = 6.5 Hz) (1H), 5.97−5.73 (m, 2H), 5.32 (dd, J = 17.0, 1.5 Hz), 5.29 (dd, J = 17.5, 1.5 Hz), 5.23 (dd, J = 8.0, 1.0 Hz), and 5.20 (dd, J = 10.5, 1.5 Hz) (2H), 5.08 (m, 2H), 4.84−4.83 (m) and 4.77−4.75 (m) (2H), 4.66 (dd, J = 12.5, 9.0 Hz) and 4.27−4.18 (m) (3H), 4.50 (s, 2H), 3.47 (td, J = 6.0, 5.0 Hz, 2H), 3.24 (td, J = 9.5, 4.5 Hz) and 2.55−2.47 (m) (1H), 2.77 (t, J = 7.5 Hz, 2H), 1.70−1.35 (m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 151.1 (s), 150.9 (s), 146.1 (d), 144.7 (d), 138.6 (s), 138.5 (s), 136.6 (d), 136.5 (d), 133.9 (d), 133.4 (d), 128.2 (d), 127.5 (d), 127.3 (d), 117.2 (t), 116.8 (t), 116.1 (t), 115.9 (t), 109.8 (d), 109.5 (t), 108.9 (t), 107.4 (d), 72.7 (t), 72.4 (t), 70.3 (t), 70.2 (t), 69.8 (t), 44.3 (d), 40.0 (d), 39.0 (t), 38.6 (t), 30.3 (t), 30.1 (t), 27.6 (t), 27.5 (t); IR (film) ν (cm^{-1}) 3081, 3032, 2982, 2940, 2856, 1661, 1643, 1454; MS (EI) m/z (rel %): 312 [M$^+$] (2), 221 (8), 163 (100), 91 (100); HRMS (EI) calcd for $C_{21}H_{28}O_2$ [M$^+$] 312.2089, found 312.2084

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Ethyl 2-(*N*-(*rel*-(2*S*,3*S*)-2-Allyl-3-(2-(allyloxy)vinyl)-6-(benzyloxy)hexyl)formamido)acetate (78). NaH (60% in mineral oil, 190 mg, 4.74 mmol) was added to a solution of **76** (1.13 g, 3.16 mmol) in THF (7.0 mL) and DMF (2.5 mL) at rt, and the solution was stirred for 1 h. $BrCH_2CO_2Et$ (525 μL, 4.74 mmol) was added. The mixture was stirred for 18 h at rt; then water was added and THF was removed under reduced pressure. The usual workup (EtOAc) and purification (20 to 80% EtOAc in hexanes) afforded **78** (1.32 g, 94%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.07 (s), 8.07 (s), and 8.06 (s) (1H), 7.37−7.25 (m, 5H), 6.16 (d, *J* = 12.5 Hz) and 6.06 (d, *J* = 6.5 Hz) (1H), 5.99−5.57 (m, 2H), 5.35−5.18 (m, 2H), 5.07−4.98 (m, 2H), 4.48 (s, 2H), 4.52−4.43 (m) and 4.22−3.84 (m) (7H), 3.44 (t, *J* = 6.0 Hz) and 3.43 (t, *J* = 6.0 Hz) (2H), 3.39−3.29 (m) and 3.23−3.06 (m) (2H), 2.67−2.59 (m), 2.25−2.22 (m), and 2.11−1.94 (m) (3H), 1.71−1.41 (m, 4H), 1.30−1.24 (m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 168.9 (s), 168.2 (s), 168.1 (s), 163.6 (d), 163.3 (d), 163.2 (d), 147.3 (d), 147.0 (d), 146.0 (d), 145.7 (d), 138.4 (s), 138.2 (s), 136.7 (d), 136.5 (d), 135.7 (d), 133.6 (d), 133.1 (d), 128.1 (d), 127.3 (d), 117.2 (t), 117.1 (t), 116.9 (t), 116.4 (t), 116.0 (t), 107.6 (d), 107.3 (d), 104.0 (d), 72.6 (t), 72.4 (t), 72.2 (t), 70.1 (t), 69.9 (t), 69.8 (t), 69.7 (t), 61.4 (t), 61.3 (t), 61.1 (t), 61.0 (t), 48.9 (t), 48.5 (t), 44.1 (t), 44.0 (t), 43.8 (t), 43.6 (t), 40.4 (d), 40.3 (d), 40.0 (d), 39.9 (d), 38.7 (d), 38.1 (d), 34.2 (d), 33.9 (d), 33.7 (t), 33.6 (t), 33.2 (t), 33.1 (t), 28.9 (t), 28.2 (t), 27.7 (t), 27.6 (t), 27.3 (t), 13.8 (q); IR (film) ν (cm^{-1}) 3073, 3035, 2986, 2936, 2861, 1749, 1679, 1453, 1435, 1197, 1098; MS (CI: NH_3) *m*/*z* (rel %): 444 [MH^+] (100), 416 (13), 402 (16), 358 (23); HRMS (CI: NH_3) calcd for $C_{26}H_{38}NO_5$ [MH^+] 444.2750, found 444.2757.

Ethyl 2-(*N*-(*rel*-(2*S*,3*S*)-2-Allyl-3-(3-(benzyloxy)propyl)-4-formylhept-6-en-1-yl)formamido)acetate (79). A solution of **78** (703 mg, 1.58 mmol) in toluene (31 mL) was heated at 150 °C in a sealed tube for 96 h. The solution was concentrated under reduced pressure to afford an inseparable mixture of diastereomers and rotamers of **79** (703 mg, 100%) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.70−9.61 (m, 1H), 8.08 (s) and 8.06 (s) (1H), 7.40−7.24 (m, 5H), 5.76−5.59 (m, 2H), 5.11−4.98 (m, 4H), 4.49 (s, 2H), 4.23−4.16 (m, 2H), 4.03 (d, *J* = 17.5 Hz), 4.01 (d, *J* = 17.5 Hz), 3.95−3.80 (m), 3.90 (d, *J* = 17.5 Hz), and 3.87 (d, *J* = 17.5 Hz) (2H), 3.60−3.38 (m), 3.31−3.17 (m), and 3.15−3.07 (m) (4H), 2.56−2.39 (m, 2H), 2.31−1.85 (m, 4H), 1.83−1.38 (m, 5H), 1.31−1.22 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 205.8 (d), 205.5 (d), 205.4 (d), 205.0 (d), 169.6 (s), 168.9 (s), 164.6 (d), 164.5 (d), 164.0 (d), 164.0 (d), 138.9 (s), 138.7 (s), 136.7 (d), 136.6 (d), 136.0 (d), 135.9 (d), 135.9 (d), 135.4 (d), 135.4 (d), 128.7 (d), 128.7 (d), 128.0 (d), 127.8 (d), 118.0 (t), 117.9 (t), 117.9 (t), 117.7 (t), 117.5 (t), 117.3 (t), 117.3 (t), 117.3 (t), 72.9 (t), 72.8 (t), 72.8 (t), 70.2 (t), 70.1 (t), 69.6 (t), 69.5 (t), 61.7 (t), 61.3 (t), 61.3 (t), 52.6 (d), 52.5 (d), 49.5 (t), 49.4 (t), 48.8 (t), 48.7 (t), 44.8 (t), 44.6 (t), 43.9 (t), 43.9 (t), 38.1 (d), 37.7 (d), 37.4 (d), 37.1 (d), 36.9 (d), 36.6 (d), 33.0 (t), 32.9 (t), 32.5 (t), 32.5 (t), 31.4 (t), 31.1 (t), 30.8 (t), 30.7 (t), 28.6 (t), 28.4 (t), 28.4 (t), 28.2 (t), 23.9 (t), 23.7 (t), 23.5 (t), 13.6(q); IR (film) ν (cm^{-1}) 3073, 2982, 2936, 2864, 1748, 1720, 1678, 1436, 1400, 1198; MS (EI) *m*/*z* (rel %): 443 [M^+] (3), 398 [$M - OC_2H_5$]$^+$ (7), 342 (36), 264 (33), 116 (90), 91 (100); HRMS (EI) calcd for $C_{26}H_{37}NO_5$ [M^+] 443.2672, found 443.2661.

Ethyl 2-(*N*-((*rel*-(1*S*,7*S*)-7-(3-(Benzyloxy)propyl)-6-formylcyclohept-3-en-1-yl)methyl)formamido)acetate (80). Second-generation Grubbs' catalyst (40 mg, 5 mol %) was added to a solution of **79** (423 mg, 0.954 mmol) in DCM (160 mL). The solution was stirred for 18 h at rt and then concentrated under reduced pressure. The usual purification (50% EtOAc in hexanes) afforded a mixture of diastereomers and rotamers of **80** (344 mg, 87%) as a brown oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.72 (s), 9.70 (s), 9.62 (s), and 9.61 (s) (1H), 8.11 (s), 8.07 (s), and 8.05 (s) (1H), 7.42−7.23 (m, 5H), 5.78−5.56 (m, 2H), 4.48 (s) and 4.45 (s) (2H), 4.24−4.11 (m), 4.07 (s), 3.98 (d, *J* = 17.0 Hz), 3.95 (s), and 3.90 (d, *J* = 17.0 Hz) (4H), 3.52−3.12 (m, 4H), 2.62−2.34 (m) and 2.33−2.16 (m) (4H), 2.12−1.77 (m, 3H), 1.71−1.30 (m, 4H), 1.28−1.22 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 205.8 (d), 205.1 (d), 204.9 (d), 204.6 (d), 169.7 (s), 169.7 (s), 168.9 (s), 168.9 (s), 164.4 (d), 164.3 (d), 163.9 (d), 163.8 (d), 138.8 (s), 138.7 (s), 131.3 (d), 130.8 (d), 129.2 (d), 129.0 (d), 128.7 (d), 128.6 (d), 128.6 (d), 128.6 (d), 128.5 (d), 128.3 (d), 127.9 (d), 127.9 (d), 127.8 (d), 127.8 (d), 127.7 (d), 72.9 (t), 72.8 (t), 72.7 (t), 72.6 (t), 70.2 (t), 70.2 (t), 69.6 (t), 69.6 (t), 61.7 (t), 61.6 (t), 61.3 (t), 61.2 (t), 56.6 (d), 56.3 (d), 52.4 (t), 51.7 (d), 51.6 (d), 51.0 (t), 49.2 (t), 48.2 (t), 47.9 (t), 46.0 (t), 44.4 (t), 43.5 (t), 41.9 (d), 41.6 (d), 38.6 (d), 38.0 (d), 37.2 (d), 37.1(d), 34.3 (d), 34.2 (d), 28.5 (t), 28.2 (t), 28.1 (t), 28.0 (t), 27.5 (t), 27.0 (t), 27.0 (t), 26.9 (t), 23.7 (t), 23.6 (t), 23.4 (t), 23.2 (t), 22.6 (t), 22.4 (t), 20.7 (t), 20.6 (t), 13.6 (q), 13.6 (q); IR (film) ν (cm^{-1}) 2986, 2938, 2869, 1746, 1720, 1676, 1439, 1401, 1371, 1203; MS (EI) *m*/*z* (rel %): 416 [MH^+] (17), 402 (10), 388 (45), 218 (100); HRMS (EI) calcd for $C_{24}H_{33}NO_5$ [M^+] 415.2359, found 415.2361.

Ethyl 2-(*N*-((*rel*-(1*S*,7*S*)-7-(3-(Benzyloxy)propyl)-6-(((*tert*-butyldimethylsilyl)oxy)methylene)cyclohept-3-en-1-yl)-methyl)formamido)acetate (81). Following the procedure used to prepare **40**, a solution of **80** (49 mg, 0.12 mmol) in DCM (2.0 mL) was treated with TBDMSOTf (65 μL, 0.28 mmol) and *i*-Pr_2NEt (49 μL, 0.28 mmol) for 18 h at rt to afford, after the usual purification using silica gel saturated with Et_3N (0 to 40% EtOAc in hexanes), one geometrical isomer of **81** (as a mixture of rotamers) of unidentified stereochemistry (48 mg, 76%) as a colorless oil: ^{1}H NMR (400 MHz, C_6D_6) δ (ppm) 7.96 (s) and 7.81 (s) (1H), 7.43−7.32 (m, 2H), 7.27−7.07 (m, 3H), 6.23 (s, 1H), 5.81−5.73 (m, 1H), 5.58−5.44 (m, 1H), 4.42−4.34 (AB quartet, 2H), 3.95−3.79 (m), 3.72 (d, *J* = 17.0 Hz), and 3.46−3.22 (m) (7H), 3.55 (dd, *J* = 14.0, 7.0 Hz), 3.12 (dd, *J* = 14.0, 7.5 Hz), 2.85 (dd, *J* = 14.5, 7.5 Hz), and 2.76−2.62 (m) (3H), 2.21−2.12 (m, 1H), 1.84−1.31 (m, 6H), 1.28−1.15 (m, 1H), 0.94 (s, 9H), 0.88 (t, *J* = 7.0 Hz, 3H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, C_6D_6) δ (ppm) 169.5 (s), 168.8 (s), 163.6 (d), 163.4 (d), 139.8 (s), 139.5 (s), 135.2 (d), 134.8 (d), 129.7 (d), 129.5 (d), 128.6 (d), 128.5 (d), 128.3 (d), 128.2 (d), 128.0 (d), 127.8 (d), 127.7 (d), 127.5 (d), 122.2 (s), 121.1 (s), 72.7 (t), 72.5 (t), 70.3 (t), 69.5 (t), 60.8 (t), 60.6 (t), 50.7 (t), 48.2 (t), 46.6 (t), 44.0 (t), 43.9 (t), 42.7 (d), 40.5 (d), 40.1 (d), 28.6 (t), 28.2 (t), 27.6 (t), 27.2 (t), 25.4 (q), 25.2 (q), 24.6 (t), 24.5 (t), 21.6 (t), 21.2 (t), 17.8 (s), 13.3 (q), −6.1 (q), −6.1 (q); IR (film) ν (cm^{-1}) 3024, 2952, 2930, 2857, 1751, 1682, 1435, 1253, 1198, 838; MS (ESI) *m*/*z* (rel %): 552 [MNa^+] (100); HRMS (ESI) calcd for $C_{30}H_{47}NO_5SiNa$ [MNa^+] 552.3116, found 552.3127.

Ethyl 2-(*N*-((*rel*-(1*S*,2*S*)-3-(((*tert*-Butyldimethylsilyl)oxy)-methylene)-2-(3-hydroxypropyl)cycloheptyl)methyl)formamido)acetate (82). A mixture of **81** (89 mg, 0.17 mmol) and $Pd(OH)_2/C$ (20%, 12 mg, 10 mol %) in MeOH (5.0 mL) was stirred under a hydrogen atmosphere for 2.5 h. The mixture was filtered on Celite and concentrated under reduced pressure. The usual purification (40 to 100% EtOAc in hexanes) afforded a mixture of rotamers of **82** (52 mg, 70%) as a colorless oil: ^{1}H NMR (400 MHz, C_6D_6) δ (ppm) 8.09 (s) and 7.78 (s) (1H), 6.30 (s, 1H), 3.92 (q, *J* = 7.0 Hz), 3.89−3.78 (m), 3.36 (d, *J* = 17.5 Hz), and 3.26 (d, *J* = 17.5 Hz) (4H), 3.73−3.61 (m) and 3.59−3.44 (m) (2H), 3.02 (dd, *J* = 14.5, 8.5 Hz), 2.92−2.81 (m), and 2.74 (dd, *J* = 14.5, 7.0 Hz) (2H), 2.26 (bs) and 2.18−2.05 (m) (2H), 1.85−1.49 (m, 5H), 1.47−1.11 (m, 6H), 1.02−0.86 (m), 0.96 (s), and 0.92 (t, *J* = 7.0 Hz) (14H), 0.09 (s, 6H); ^{13}C NMR (100 MHz, C_6D_6) δ (ppm) 169.5 (s), 168.9 (s), 164.4 (d), 163.9 (d), 136.4 (d), 136.2 (d), 123.9 (s), 123.3 (s), 61.5 (t), 61.0 (t), 60.9 (t), 60.6 (t), 51.7 (t), 48.2 (t), 47.0 (t), 44.0 (t), 43.0 (d), 42.9 (d), 42.1 (d), 41.7 (d), 30.7 (t), 30.6 (t), 28.8 (t), 28.3 (t), 26.9 (t), 26.6 (t), 25.6 (t), 25.6 (t), 25.2 (q), 24.7 (t), 24.5 (t), 21.8 (t), 21.3 (t), 17.7 (s), 13.3 (q), 13.3 (q), −6.0 (q), −6.1 (q); IR (film) ν (cm^{-1}) 3592−3188, 2930, 2858, 1751, 1675, 1442, 1401, 1253, 1198; MS (ESI) *m*/*z* (rel %): 464 [MNa^+] (100); HRMS (ESI) calcd for $C_{23}H_{43}NO_5SiNa$ [MNa^+] 464.2830, found 464.2809.

(2*Z*)-Methyl 5-(*rel*-(1*S*,7*S*)-2-(((*tert*-Butyldimethylsilyl)oxy)-methylene)-7-((*N*-(2-ethoxy-2-oxoethyl)formamido)methyl)-cycloheptyl)pent-2-enoate (83). Oxalyl chloride (19 μL, 0.22 mmol) was added to a solution of DMSO (27 μL, 0.40 mmol) in DCM (1.0 mL) at −78 °C. After 10 min at −78 °C, a solution of **82** (89 mg, 0.20 mmol) in DCM (3.0 mL) was added, and the mixture was stirred 45 min at −78 °C. Et_3N (141 μL, 1.01 mmol) was added, and the reaction mixture was allowed to warm up to rt over 2 h.

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Saturated aqueous $NaHCO_3$ was added; then the usual workup (DCM) afforded the corresponding aldehyde (90 mg of crude material). A solution of KHMDS (0.5 M in toluene, 0.40 mL, 0.20 mmol) was added to a solution of methyl bis(2,2,2-trifluoroethyl)-phosphonoacetate (67 mg, 0.20 mmol) and 18-crown-6 ether (133 mg, 0.505 mmol) in THF (2.0 mL) at −78 °C. After 30 min at −78 °C, a solution of crude aldehyde (90 mg of crude material) in THF (2.0 mL) was added and the reaction mixture was allowed to warm up to rt over 2 h. Saturated aqueous $NaHCO_3$ was added. The usual workup (DCM) and purification (5 to 15% acetone in toluene) afforded a mixture of rotamers of **83** (65 mg, 65% over 2 steps) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.09 (s, 1H), 6.26−6.18 (m, 1H), 6.09 (s) and 6.06 (s) (1H), 5.77 (d, J = 11.5 Hz) and 5.74 (d, J = 11.5 Hz) (1H), 4.21 (q, J = 7.0 Hz) and 4.19 (q, J = 7.0 Hz) (2H), 4.05 (d, J = 17.5 Hz), 3.98 (d, J = 17.5 Hz), 3.96 (d, J = 17.5 Hz), and 3.89 (d, J = 17.5 Hz) (2H), 3.69 (s) and 3.68 (s) (3H), 3.35 (dd, J = 14.0, 7.5 Hz), 3.26 (dd, J = 14.5, 7.5 Hz), and 3.15 (dd, J = 14.5, 8.0 Hz) (2H), 2.60 (ddd, J = 16.5, 9.0, 5.5 Hz, 1H), 2.49 (q, J = 7.5 Hz, 2H), 2.15−2.02 (m) and 1.99−1.93 (m) (2H), 1.74−1.45 (m, 6H), 1.42−1.21 (m), 1.28 (t, J = 7.0 Hz), and 1.26 (t, J = 7.0 Hz) (6H), 0.91 (s, 9H), 0.11 (s), 0.11 (s), and 0.10 (s) (6H); ^{13}C NMR (100 MHz, C_6D_6) δ (ppm) 169.6 (s), 168.9 (s), 166.7 (s), 166.6 (s), 163.6 (d), 163.3 (d), 151.3 (d), 150.4 (d), 136.5 (d), 136.3 (d), 123.4 (s), 122.8 (s), 120.0 (d), 119.5 (d), 60.8 (t), 60.6 (t), 51.5 (t), 50.2 (q), 50.0 (q), 48.1 (t), 46.7 (t), 44.0 (t), 43.6 (d), 43.1 (d), 42.6 (d), 42.5 (d), 28.7 (t), 28.2 (t), 27.5 (t), 27.2 (t), 26.8 (t), 26.4 (t), 26.0 (t), 25.6 (t), 25.3 (q), 25.2 (q), 24.8 (t), 17.7 (s), 13.3 (q), −6.0 (q), −6.1 (q); IR (film) ν (cm^{-1}) 3024, 2950, 2929, 2857, 1752, 1723, 1682, 1646, 1437, 1254, 1197, 1167, 837; MS (ESI) m/z (rel %): 518 [MNa^+] (100); HRMS (ESI) calcd for $C_{26}H_{45}NO_6SiNa$ [MNa^+] 518.2908, found 518.2910.

Oxazolium Ion 86. Tf_2O (4.3 μL, 26 μmol) was added to a solution of **83** (11.5 mg, 23.2 μmol) and DTBMP (5.2 mg, 26 μmol) in $CDCl_3$ (0.6 mL) at rt. After 5 min, ^{1}H NMR analysis showed the formation of oxazolium ion **86**: ^{1}H NMR (300 MHz, $CDCl_3$) characteristic signals δ (ppm) 9.60 (s, 1H), 7.26 (d, 1H, J = 2.0 Hz), 6.33 (dt, J = 11.5, 8.0 Hz, 1H), 6.04 (s, 1H), 5.78 (d, J = 11.5 Hz, 1H), 4.42 (qd, J = 7.0, 2.0 Hz, 2H), 4.25 (d, J = 7.5 Hz, 2H), 3.68 (s, 3H), 2.70−2.48 (m, 2H), 2.39−2.27 (m, 1H), 2.13−2.01 (m, 2H), 1.98−1.90 (m, 1H), 1.73−1.22 (m, 8H), 1.49 (t, J = 7.0 Hz, 3H), 0.89 (s, 9H), 0.10 (s), and 0.09 (s) (6H).

***N*-(*rel*-(2*S*,3*S*)-2-Allyl-3-(2-(allyloxy)vinyl)-6-(benzyloxy)-hexyl)-*N*-(cyanomethyl)formamide (87).** NH_3 gas was condensed (60 mL) in a solution of **75** (1.52 g, 3.86 mmol) in THF (15 mL) in a sealed tube at −78 °C. The tube was sealed, and the solution was stirred for 72 h at rt and then cooled at −78 °C to decrease pressure. The sealed tube was opened, and the mixture was allowed to warm up to rt. After complete NH_3 evaporation, saturated aqueous $NaHCO_3$ was added and THF was removed under reduced pressure. Water was added; then the usual workup (EtOAc) afforded a mixture of E/Z isomers and rotamers of the corresponding primary amine (1.27 g, 100%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.34−7.23 (m, 5H), 6.14 (d, J = 12.5 Hz) and 6.04 (d, J = 6.5 Hz) (1H), 5.99−5.69 (m, 2H), 5.34−5.17 (m, 2H), 5.08−4.98 (m, 2H), 4.53 (dd, J = 12.5, 10.0 Hz) and 4.11 (dd, J = 10.5, 6.5 Hz) (1H), 4.49 (s, 2H), 4.22−4.17 (m, 2H), 3.46 (t, J = 6.0 Hz) and 3.44 (t, J = 6.0 Hz) (2H), 2.79−2.48 (m, 2H), 2.19−2.04 (m, 2H), 1.97−1.89 (m) and 1.71−1.20 (m) (6H). $BrCH_2CN$ (270 μL, 4.05 mmol) was added to a solution of primary amine (1.27 g, 3.86 mmol) and i-Pr_2NEt (0.71 mL, 4.1 mmol) in THF (70 mL). The solution was stirred for 18 h at rt. Water was added, and THF was removed under reduced pressure. Saturated aqueous $NaHCO_3$ was added; then the usual workup (EtOAc) afforded a mixture of E/Z isomers and rotamers of the secondary amine (1.46 g) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.38−7.23 (m, 5H), 6.16 (d, J = 12.5 Hz) and 6.07 (d, J = 6.5 Hz) (1H), 6.00−5.67 (m, 2H), 5.35−5.19 (m, 2H), 5.07−4.99 (m, 2H), 4.53 (dd, J = 12.5, 10.0 Hz) and 4.12 (dd, J = 10.5, 6.5 Hz) (1H), 4.49 (s, 2H), 4.23 (d, J = 5.5 Hz) and 4.20 (d, J = 5.5 Hz) (2H), 3.60−3.41 (m, 4H), 2.78−2.49 (m, 2H), 2.23−2.09 (m, 2H), 2.00−1.90 (m) and 1.73−1.43 (m) (5H), 1.38−1.19 (m, 2H). A solution of secondary amine (1.42 g, 3.86 mmol) in THF (84 mL) was treated with *N*-formylbenzotriazole (738 mg, 5.02 mmol). The mixture was stirred for 20 h at rt; then aqueous NaOH (2 N) was added. The solution was stirred for 15 min at rt; then water was added and THF was removed under reduced pressure. The usual workup (DCM) and purification (0 to 40% EtOAc in hexanes) afforded a mixture of E/Z isomers and rotamers of **87** (1.02 g, 67% over 3 steps) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.11 (s) and 8.00 (s) (1H), 7.38−7.26 (m, 5H), 6.19 (d, J = 12.5 Hz) and 6.08 (d, J = 6.5 Hz) (1H), 6.00−5.84 (m, 1H), 5.75−5.60 (m, 1H), 5.36−5.21 (m, 2H), 5.11−5.03 (m, 2H), 4.53−4.46 (m, 1H), 4.49 (s, 2H), 4.37−4.04 (m, 4H), 3.47−3.13 (m, 2H), 3.45 (t, J = 6.0 Hz, 2H), 2.64−2.55 (m), and 2.17−1.95 (m) (3H), 1.80−1.65 (m, 2H), 1.63−1.44 (m, 2H), 1.40−1.24 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 162.6 (d), 162.5 (d), 162.4 (d), 147.5 (d), 147.2 (d), 146.1 (d), 138.3 (s), 138.3 (s), 136.2 (d), 136.0 (d), 135.2 (d), 135.1 (d), 133.5 (d), 133.1 (d), 128.1 (d), 127.4 (d), 127.3 (d), 117.5 (t), 117.3 (t), 117.2 (t), 116.8 (t), 114.5 (s), 107.3 (d), 103.8 (d), 72.6 (t), 72.5 (t), 70.0 (t), 69.6 (t), 48.7 (t), 48.5 (t), 43.7 (t), 43.2 (t), 39.9 (d), 39.6 (d), 38.8 (d), 38.2 (d), 35.8 (t), 35.4 (t), 35.3 (t), 34.1 (d), 33.8 (d), 33.6 (t), 33.3 (t), 33.0 (t), 32.8 (t), 30.2 (t), 29.8 (t), 28.8 (t), 27.8 (t), 27.6 (t), 27.5 (t), 27.3 (t); IR (film) ν (cm^{-1}) 3077, 3032, 2937, 2861, 1681, 1428, 1163, 1096, 920; MS (EI) m/z (rel %) 355 [$M^+ - C_3H_5$] (2), 311 (10), 247 (19), 163 (62), 91 (100); HRMS (EI) calcd for $C_{24}H_{32}N_2O_3$ [M^+] 396.2413, found 396.2417.

***N*-(*rel*-(2*S*,3*S*)-2-Allyl-3-(3-(benzyloxy)propyl)-4-formylhept-6-enyl)-*N*-(cyanomethyl)formamide (88).** A solution of **87** (1.40 g, 3.53 mmol) in toluene (75 mL) was heated at 150 °C in a sealed tube for 120 h. The solution was concentrated under reduced pressure. The usual purification using silica gel saturated with Et_3N (30 to 40% EtOAc in hexanes) afforded an inseparable mixture of diastereomers and rotamers of **88** (1.15 g, 82%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.66 (d, J = 2.0 Hz) and 9.63 (d, J = 2.5 Hz) (1H), 8.08 (s), 8.07 (s), 7.97 (s), and 7.96 (s) (1H), 7.36−7.26 (m, 5H), 5.77−5.60 (m, 2H), 5.11−5.03 (m, 4H), 4.48 (s) and 4.47 (s) (2H), 4.28−4.01 (m, 2H), 3.49−3.42 (m, 2H), 3.26 (t, J = 7.0 Hz, 2H), 2.52−2.41 (m, 2H), 2.35−2.05 (m, 2H), 1.99−1.80 (m, 3H), 1.70−1.41 (m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 205.0 (d), 204.8 (d), 204.4 (d), 204.0 (d), 162.5 (d), 138.3 (s), 138.1 (s), 135.8 (d), 135.1 (d), 134.7 (d), 128.3 (d), 127.6 (d), 127.4 (d), 117.9 (t), 117.7 (t), 117.5 (t), 117.4 (t), 117.2 (t), 114.5 (s), 72.9 (t), 72.7 (t), 70.0 (t), 70.0 (t), 69.7 (t), 69.4 (t), 52.4 (d), 52.3 (d), 52.0 (d), 49.2 (t), 49.1 (t), 44.4 (t), 44.2 (t), 37.8 (d), 37.4 (d), 37.0 (d), 36.7 (d), 36.6 (d), 36.3 (d), 35.8 (t), 33.1 (t), 32.9 (t), 32.8 (t), 32.7 (t), 31.7 (t), 31.2 (t), 31.0 (t), 30.1 (t), 28.7 (t), 28.4 (t), 28.3 (t), 23.9 (t), 23.8 (t), 23.6 (t), 23.5 (t); IR (film) ν (cm^{-1}) 3073, 2936, 2863, 1719, 1681, 1430, 1101, 918; MS (EI) m/z (rel %) 396 [M^+] (2), 367 [M^+ − CHO] (7), 328 (15), 277 (18), 91 (100); HRMS (EI) calcd for $C_{24}H_{32}N_2O_3$ [M^+] 396.2413, found 396.2401.

***N*-((*rel*-(1*S*,7*S*)-7-(3-(Benzyloxy)propyl)-6-formylcyclohept-3-en-1-yl)methyl)-*N*-(cyanomethyl)formamide (89).** Second-generation Grubbs' catalyst (41 mg, 5 mol %) was added to a solution of **88** (381 mg, 0.961 mmol) in DCM (160 mL). The solution was stirred for 18 h at rt and then concentrated under reduced pressure. The usual purification (20 to 50% EtOAc in hexanes) afforded an inseparable mixture of diastereomers and rotamers of **89** (303 mg, 86%) as a brown oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.71 (s), 9.65 (s), and 9.63 (s) (1H), 8.17 (s), 8.09 (s), 8.01 (s), and 8.00 (s) (1H), 7.38−7.26 (m, 5H), 5.83−5.61 (m, 2H), 4.57 (d, J = 17.5 Hz), 4.19 (d, J = 17.5 Hz), 4.08 (d, J = 17.5 Hz), and 4.60−4.06 (m) (2H), 4.49 (s) and 4.47 (s) (2H), 3.78 (dd, J = 14.0, 10.0 Hz), 3.49−3.34 (m), 3.32−3.20 (m), and 3.07 (dd, J = 14.0, 6.0 Hz) (4H), 2.62−2.50 (m, 2H), 2.43−2.15 (m), 2.10−2.00 (m), 1.83 (dd, J = 14.0, 7.0 Hz), and 1.77−1.32 (m) (9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 205.6 (d), 204.5 (d), 203.8 (d), 203.4 (d), 162.6 (d), 162.4 (d), 162.2 (d), 138.2 (s), 131.3 (d), 130.7 (d), 129.1 (d), 128.3 (d), 128.0 (d), 127.6 (d), 127.5 (d), 114.7 (s), 114.6 (s), 72.9 (t), 72.9 (t), 72.7 (t), 70.3 (t), 70.2 (t), 69.5 (t), 56.5 (d), 56.0 (d), 51.7 (t), 51.3 (d), 50.0 (t), 47.4 (t), 44.8 (t), 43.7 (d), 41.5 (d), 41.1 (d), 38.5 (d), 38.2 (d), 36.3 (d), 36.1 (d), 35.3 (t), 33.7 (d), 33.5 (d), 30.5 (t), 29.6 (t), 28.8 (t), 28.4

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(t), 28.2 (t), 27.6 (t), 27.1 (t), 27.1 (t), 24.1 (t), 23.9 (t), 23.7 (t), 22.4 (t), 22.1 (t), 21.2 (t), 21.0 (t); IR (film) ν (cm^{-1}) 3028, 2940, 2868, 1719, 1678, 1435, 1180, 1097; MS (EI) m/z (rel %) 368 [M^+] (5), 340 (3), 277 (8), 91 (100); HRMS (EI) calcd for $C_{22}H_{28}N_2O_3$ [M^+] 368.2100, found 368.2108.

***N*-((*rel*-(1*S*,7*S*,*E*)-7-(3-(Benzyloxy)propyl)-6-((*tert*-butyldimethylsilyloxy)methylene)cyclohept-3-enyl)methyl)-*N*-(cyanomethyl)formamide (*E*-90) and *N*-((*rel*-(1*S*,7*S*,*Z*)-7-(3-(Benzyloxy)propyl)-6-((*tert*-butyldimethylsilyloxy)methylene)-cyclohept-3-enyl)methyl)-*N*-(cyanomethyl)formamide (*Z*-90).** Following the procedure used to prepare **40**, a solution of **89** (304 mg, 0.825 mmol) in DCM (16.5 mL) was treated with TBDMSOTf (284 μL, 1.24 mmol) and *i*-Pr_2NEt (287 μL, 1.65 mmol) for 18 h at rt to afford, after the usual purification using silica gel saturated with Et_3N (0 to 40% EtOAc in hexanes), *E*-**90** (187 mg) and *Z*-**90**[54] (63 mg) (63% global yield) as colorless oils. *E*-**90** and *Z*-**90** both exist as a mixture of rotamers and were separated at this stage. However, due to the instability of the products, full characterization was not possible and both isomers were carried through the sequence separately. Only the sequence with the major isomer *E*-**90** is reported thereafter: *E*-**90** (major) ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.14 (s) and 8.00 (s) (1H), 7.38−7.28 (m, 5H), 6.05 (s, 1H), 5.82−5.75 (m, 1H), 5.57−5.52 (m, 1H), 4.49 (s, 2H), 4.32 (d, J = 17.5 Hz, 1H), 4.14 (d, J = 17.5 Hz, 1H), 3.46 (t, J = 5.5 Hz, 2H), 3.33−3.19 (m, 2H), 3.10 (dd, J = 17.5, 6.5 Hz, 1H), 2.70−2.64 (m, 1H), 2.12−1.92 (m, 4H), 1.71−1.56 (m, 2H), 1.49−1.34 (m, 2H), 0.91 (s, 9H), 0.11 (s, 6H). *Z*-**90** (minor) ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.14 (s) and 8.02 (s) (1H), 7.38−7,28 (m, 5H), 6.13 (s) and 6.10 (s) (1H), 5.71−5.65 (m, 1H), 5.57−5.50 (m, 1H), 4.59 (d, J = 17.5 Hz, 1H), 4.49 (s, 2H), 4.19 (d, J = 2.0 Hz) and 4.09 (d, J = 17.5 Hz) (1H), 3.45 (t, J = 6.0 Hz, 2H), 3.38−3.23 (m, 2H), 2.99−2.95 (m, 1H), 2.79−2.73 (m, 1H), 2.47 (dd, J = 18.0, 7.0 Hz, 1H), 2.09−1.88 (m, 3H), 1.68−1.27 (m, 4H), 0.90 (s, 9H), 0.12 (s) and 0.11 (s) (6H).

***N*-((*rel*-(1*S*,7*S*,*E*)-6-((*tert*-Butyldimethylsilyloxy)methylene)-7-(3-hydroxypropyl)cyclohept-3-enyl)methyl)-*N*-(cyanomethyl)-formamide (*E*-91).** A solution of Me_2BBr (1.0 M in DCM, 3.87 mL, 3.87 mmol) was added to a solution of *E*-**90** (187 mg, 0.387 mmol) and DTBMP (795 mg, 3.87 mmol) in DCM (8.0 mL) at −25 °C. The solution was stirred for 2 h at −25 °C; then saturated aqueous $NaHCO_3$ (2.0 mL) was added at −25 °C. The mixture was stirred for 15 min at rt, and saturated aqueous NaCl was added. The usual workup (DCM) and purification using silica gel saturated with Et_3N (10 to 100% EtOAc in hexanes) afforded a mixture of rotamers of *E*-**91** (110 mg, 72%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.19 (s) and 8.03 (s) (1H), 6.07 (s) and 6.04 (s) (1H), 5.80−5.74 (m, 1H), 5.56−5.52 (m, 1H), 4.31 (d, J = 17.5 Hz), 4.17 (d, J = 17.5 Hz), and 4.17 (d, J = 3.3 Hz) (2H), 3.63−3.57 (m, 2H), 3.33 (dd, J = 14.5, 7.0 Hz, 1H), 3.24 (dd, J = 14.5, 8.0 Hz, 1H), 3.11 (dd, J = 17.5, 6.5 Hz, 1H), 2.65−2.63 (m) and 2.54−2.49 (m) (1H), 2.12−2.05 (m, 2H), 2.00−1.89 (m) and 1.78 (bs) (3H), 1.61−1.54 (m, 2H), 1.43−1.36 (m, 2H), 0.90 (s, 9H), 0.11 (s) and 0.10 (s) (6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.8 (d), 162.6 (d), 135.0 (d), 134.7 (d), 130.1 (d), 129.3 (d), 126.9 (d), 126.4 (d), 121.0 (s), 119.6 (s), 114.5 (s), 62.1 (t), 61.7 (t), 50.2 (t), 46.3 (t), 43.5 (d), 42.3 (d), 40.3 (d), 39.6 (d), 36.0 (t), 30.3 (t), 30.2 (t), 30.0 (t), 29.0 (t), 28.6 (t), 25.6 (q), 25.1 (t), 24.5 (t), 21.8 (t), 20.2 (t), 18.2 (s), −5.3 (q), −5.4 (q); IR (film) ν (cm^{-1}) 3611−3132, 2956, 2930, 2889, 2859, 1673, 1465, 1433, 1402, 1253, 1179; MS (EI) m/z (rel %) 392 [M^+] (10), 335 [$M^+ - C_4H_9$] (17), 249 (34), 74 (100); HRMS (EI) calcd for $C_{21}H_{36}N_2O_3Si$ [M^+] 392.2495, found 392.2503.

(*Z*)-Methyl 5-(*rel*-(1*S*,7*S*,*E*)-2-((*tert*-Butyldimethylsilyloxy)-methylene)-7-((*N*-(cyanomethyl)formamido)methyl)cyclohept-4-enyl)pent-2-enoate (*E*-92). Following the procedure used to prepare **83**, a solution of *E*-**91** (350 mg, 0.891 mmol) in DCM (6.0 mL) was added to a solution of oxalyl chloride (101 μL, 1.16 mmol) and DMSO (127 μL, 1.78 mmol) in DCM (12 mL), and the mixture was then treated with Et_3N (621 μL, 4.46 mmol) to afford the corresponding aldehyde (350 mg of crude material). A solution of crude aldehyde in THF (6.0 mL) was then added to a solution of KHMDS (0.5 M in toluene, 1.78 mL, 0.891 mmol), methyl bis(2,2,2-trifluoroethyl)phosphonoacetate (298 mg, 0.891 mmol), and 18-crown-6 ether (588 mg, 2.23 mmol) in THF (12 mL) to afford, after the usual workup (Et_2O) and purification (5 to 15% acetone in toluene), a mixture of rotamers of *E*-**92** (188 mg, 47% over 2 steps) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.18 (s) and 8.04 (s) (1H), 6.26 (dt, J = 11.5, 8.0 Hz, 1H), 6.06 (s, 1H), 5.82−5.79 (m, 2H), 5.56−5.51 (m, 1H), 4.38 (d, J = 17.5 Hz, 1H), 4.12 (d, J = 17.5 Hz, 1H), 3.70 (s, 3H), 3.34−3.23 (m, 2H), 3.02 (dd, J = 17.0, 6.0 Hz, 1H), 2.84−2.79 (m, 1H), 2.66−2.60 (m, 1H), 2.54−2.48 (m, 1H), 2.20−2.16 (m, 1H), 2.09−2.02 (m, 3H), 1.73−1.65 (m, 1H), 1.49−1.40 (m, 1H), 0.91 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) major rotamer δ (ppm) 166.6 (s), 162.7 (d), 149.5 (d), 135.1 (d), 130.4 (d), 126.3 (d), 120.0 (d), 119.2 (s), 114.6 (s), 51.1 (q), 49.5 (t), 44.5 (d), 38.6 (d), 30.3 (t), 28.8 (t), 27.1 (t), 26.2 (t), 25.8 (t), 25.6 (q), 18.3 (s), −5.3 (q), −5.3 (q); IR (film) ν (cm^{-1}) 2952, 2928, 2857, 1720, 1680, 1462, 1437, 1406, 1254, 1198, 1177, 1154; MS (ESI) m/z (rel %) 469 [MNa^+] (100), 353 (12), 130 (7); HRMS (ESI) calcd for $C_{24}H_{38}N_2NaO_4Si$ [MNa^+] 469.2498, found 469.2488.

***rel*-(4*R*,5*S*)-4-(2-(Allyloxy)vinyl)-5-(bromomethyl)oct-7-en-1-ol (93).** TMSI (11.2 mL, 78.5 mmol) was added to a solution of **75** (3.94 g, 8.73 mmol) and *i*-Pr_2NEt (18.2 mL, 105 mmol) in DCM (85 mL) at 0 °C. The solution was stirred for 18 h at rt; then water was added. The layers were separated, and the aqueous phase was extracted with EtOAc. Combined organic phases were washed twice with aqueous HCl (0.2 N) and with saturated aqueous NaCl, then dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was dissolved in MeOH (85 mL), and K_2CO_3 (2.41 g, 17.5 mmol) was added at 0 °C. The solution was stirred for 15 min at 0 °C; then water was added and MeOH was removed under reduced pressure. The usual workup (EtOAc, washed with brine) and purification using silica gel saturated with Et_3N (0 to 30% EtOAc in hexanes) afforded a mixture of *E*/*Z* isomers of **93** (2.19 g, 91%) as a yellow pale oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.24 (d, J = 12.5 Hz) and 6.08 (d, J = 6.5 Hz) (1H), 6.01−5.85 (m, 1H), 5.83−5.64 (m, 1H), 5.38−5.14 (m, 2H), 5.11 (d, J = 15.5 Hz) and 5.07 (d, J = 9.5 Hz) (2H), 4.47 (dd, J = 12.5, 10.5 Hz) and 4.09 (dd, J = 10.0, 6.5 Hz) (1H), 4.28−4.16 (m, 2H), 3.70−3.58 (m, 2H), 3.54 (dd, J = 10.0, 4.0 Hz) and 3.43−3.32 (m) (2H), 2.79−2.66 (m) and 2.09−1.95 (m) (1H), 2.35−2.11 (m, 2H), 1.76−1.18 (m, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) major isomer: 147.0 (d), 135.9 (d), 133.2 (d), 117.3 (t), 117.0 (t), 105.0 (d), 69.9 (t), 62.3 (t), 43.9 (d), 39.7 (d), 37.3 (t), 33.9 (t), 30.4 (t), 28.5 (t); minor isomer: 145.9 (d), 135.7 (d), 133.7 (d), 117.3 (t), 117.0 (t), 107.6 (d), 72.4 (t), 62.5 (t), 44.4 (d), 36.9 (t), 35.5 (d), 33.9 (t), 30.2 (t), 28.4 (t); IR (film) ν (cm^{-1}) 3616-3172, 3077, 3017, 2921, 2867, 1664, 1644, 1455, 1425, 1161, 921; MS (ESI) m/z (rel %) 327 [MNa^+] (92, ^{81}Br), 325 [MNa^+] (100, ^{79}Br); HRMS (ESI) calcd for $C_{14}H_{23}{}^{79}BrO_2Na$ [MNa^+] 325.0774, found 325.0779.

***N*-(*rel*-(2*S*,3*S*)-2-Allyl-3-(2-(allyloxy)vinyl)-6-hydroxyhexyl)-*N*-(cyanomethyl)formamide (94).** Following the procedure used to prepare **87**, a solution of **93** (773 mg, 2.55 mmol) in THF (6.0 mL) was treated with NH_3 gas (25 mL) for 96 h at rt to afford the corresponding primary amine (608 mg, crude product). A solution of the crude primary amine in THF (43 mL) was then treated with *i*-Pr_2NEt (465 μL, 2.67 mmol) and $BrCH_2CN$ (178 μL, 2.67 mmol) for 18 h at rt to afforded the corresponding secondary amine (707 mg, crude product) as a pale yellow oil. A solution of the crude secondary amine in THF (42 mL) was then treated with *N*-formylbenzotriazole (448 mg, 3.05 mmol) for 18 h at rt to afford, after the usual purification using silica gel saturated with Et_3N (40 to 100% EtOAc in hexanes), an inseparable mixture of *E*/*Z* isomers of **94** (504 mg, 65% over 3 steps) each in a 8:1 rotamer ratio, as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.15 (s) and 8.02 (s) (1H), 6.21 (d, J = 12.5 Hz), 6.09 (d, J = 6.0 Hz), and 6.03 (d, J = 6.0 Hz) (1H), 5.98−5.83 (m, 1H), 5.81−5.58 (m, 1H), 5.37−5.18 (m, 2H), 5.13−4.96 (m, 2H), 4.74−4.69 (m), 4.62−4.57 (m), 4.51 (dd, J = 12.5, 10.5 Hz), 4.36 (d, J = 17.5 Hz), 4.30−4.18 (m), 4.17−4.12 (m), 4.09 (d, J = 17.5 Hz), and 3.98−3.90 (m) (5H), 3.68−3.53 (m, 2H), 3.43 (dd, J = 14.5, 5.0 Hz), 3.37 (d, J = 6.0 Hz), 3.28 (dd, J = 14.5, 8.5 Hz), and 3.18 (dd, J = 14.5, 9.5 Hz) (2H), 2.73−2.49 (m) and 2.22−1.90 (m) (3H), 1.86−1.13 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) only the major rotamer

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of *E* and *Z* isomers reported δ (ppm) 163.5 (d), 163.4 (d), 148.2 (d), 146.8 (d), 135.8 (d), 135.6 (d), 133.9 (d), 133.6 (d), 118.2 (t), 118.1 (t), 118.0 (t), 118.0 (t), 114.9 (s), 114.8 (s), 107.8 (d), 104.2 (d), 72.8 (t), 70.3 (t), 62.3 (t), 62.2 (t), 48.7 (t), 48.5 (t), 40.0 (d), 39.8 (d), 38.2 (d), 33.7 (d), 33.0 (t), 32.8 (t), 30.2 (t), 30.1 (t), 30.0 (t), 29.7 (t), 28.2 (t), 27.2 (t); IR (film) ν (cm^{-1}) 3647−3156, 3080, 2933, 2871, 1672, 1431, 1285; MS (ESI) *m*/*z* (rel %) 345 [MK^+] (2), 329 [MNa^+] (100), 290 (18); HRMS (ESI) calcd for $C_{17}H_{26}N_2O_3Na$ [MNa^+] 329.1836, found 329.1836.

(2*Z*)-*rel*-(6*S*,7*S*)-Methyl 6-(2-(allyloxy)vinyl)-7-((*N*-(cyanomethyl)formamido)methyl)deca-2,9-dienoate (95). Following the procedure used to prepare **83**, a solution **94** (197 mg, 0.643 mmol) in DCM (3.0 mL) was added to a solution of oxalyl chloride (62 μL, 0.71 mmol) and DMSO (92 μL, 1.3 mmol) in DCM (10 mL), and the mixture was then treated with Et_3N (450 μL, 3.22 mmol) to afford the corresponding aldehyde (196 mg of crude material). A solution of crude aldehyde in THF (3.0 mL) was then added to a solution of KHMDS (0.5 M in toluene, 1.42 mL, 0.707 mmol), methyl bis(2,2,2-trifluoroethyl)phosphonoacetate (215 mg, 0.643 mmol), and 18-crown-6 ether (425 mg, 1.61 mmol) in THF (10 mL) to afford, after the usual workup (Et_2O) and purification using silica gel saturated with Et_3N (20 to 60% EtOAc in hexanes), an inseparable mixture of *E*/*Z* isomers and rotamers of **95** (176 mg, 76% over 2 steps) as a pale yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.12 (s) and 7.99 (s) (1H), 6.23−6.12 (m), 6.18 (d, *J* = 12.5 Hz), and 6.08 (d, *J* = 6.5 Hz) (2H), 5.95−5.81 (m, 1H), 5.76 (d, *J* = 11.5 Hz) and 5.73−5.55 (m) (2H), 5.29 (dd, *J* = 17.5, 1.5 Hz), 5.21 (dd, *J* = 10.5, 1.0 Hz), and 5.09−4.96 (m) (4H), 4.57 (d, *J* = 6.5 Hz) and 4.49 (dd, *J* = 12.5, 10.0 Hz) (1H), 4.37 (d, *J* = 17.5 Hz), 4.26 (s), and 4.13 (d, *J* = 17.5 Hz) (2H), 4.22−4.16 (m, 2H), 3.66 (s, 3H), 3.52−3.21 (m), 3.41 (dd, *J* = 14.5, 4.5 Hz), and 3.14 (dd, *J* = 14.5, 10.0 Hz) (2H), 2.75−2.46 (m, 2H), 2.12−1.92 (m, 3H), 1.85−1.73 (m, 1H), 1.62−1.52 (m, 1H), 1.47−1.30 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) *E*-isomer (major rotamer): 166.5 (s), 162.7 (d), 149.5 (d), 147.8 (d), 135.1 (d), 133.1 (d), 119.7 (d), 117.8 (t), 117.5 (t), 114.6 (s), 103.3 (d), 70.2 (t), 51.0 (q), 48.6 (t), 39.1 (d), 38.3 (d), 33.3 (t), 31.8 (t), 30.3 (t), 26.8 (t); Z-isomer (major rotamer) and *E*-isomer (minor rotamer): 166.6 (s), 162.8 (d), 162.4 (d), 150.0 (d), 149.9 (d), 147.5 (d), 146.4 (d), 136.0 (d), 135.2 (d), 133.5 (d), 133.2 (d), 119.5 (d), 119.4 (d), 117.6 (t), 117.4 (t), 117.0 (t), 114.8(s), 106.8 (d), 103.4 (d), 72.7 (t), 69.9 (t), 50.9 (q), 48.6 (t), 43.7 (t), 39.4 (d), 38.7 (d), 36.0 (t), 34.2 (d), 33.8 (t), 33.1 (t), 31.7 (t), 31.0 (t), 30.0 (t), 26.9 (t), 26.8 (t); IR (film) ν (cm^{-1}) 3083, 2982, 2927, 2876, 1719, 1680, 1644, 1437, 1407, 1203, 1175; MS (ESI) *m*/*z* (rel %) 399 [MK^+] (9), 383 [MNa^+] (100); HRMS (ESI) calcd for $C_{20}H_{28}N_2O_4Na$ [MNa^+] 383.1941, found 383.1941.

(*Z*)-Methyl 5-(*rel*-(1*S*,2*S*)-2-((*N*-(Cyanomethyl)formamido)-methyl)-7-formylcyclohept-4-en-1-yl)pent-2-enoate (96). A solution of **95** (359 mg, 1.00 mmol) in toluene (20 mL) was heated at 155 °C in a sealed tube for 96 h. The solution was concentrated under reduced pressure to afford the corresponding diene (359 mg of crude product). The crude diene (359 mg) was dissolved in DCM (165 mL), and second-generation Grubbs' catalyst (42 mg, 5 mol %) was added. The solution was stirred for 3 h at rt and then concentrated under reduced pressure. The usual purification (40 to 80% EtOAc in hexanes) afforded an inseparable mixture of diastereomers and rotamers of **96** (213 mg, 64%) as a brown oil: ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.74 (s), 9.73 (s), 9.65 (s), and 9.64 (s) (1H), 8.22 (s), 8.16 (s), 8.15 (s), and 8.07 (s) (1H), 6.21 (dt, *J* = 11.5, 8.0 Hz, 1H), 5.88−5.62 (m, 3H), 4.64 (d, *J* = 17.5 Hz), 4.49 (d, *J* = 17.5 Hz), 4.41 (d, *J* = 18.0 Hz), 4.32 (s), 4.27 (s), 4.26 (d, *J* = 17.5 Hz), and 4.18 (d, *J* = 17.5 Hz) (2H), 3.90 (dd, *J* = 14.5, 10.5 Hz), 3.47 (dd, *J* = 14.5, 6.0 Hz), 3.43−3.25 (m), and 3.01 (dd, *J* = 14.5, 5.0 Hz) (2H), 3.70 (s), 3.69 (s), and 3.67 (s) (3H), 2.79−1.77 (m, 9H), 1.71−1.40 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) only the major rotamer of each diastereomer reported δ (ppm) 205.2 (d), 204.0 (d), 167.2 (s), 167.1 (s), 163.5 (d), 163.1 (d), 149.0 (d), 148.9 (d), 131.0 (d), 129.8 (d), 129.0 (d), 128.6 (d), 121.0 (d), 120.7 (d), 115.0 (s), 114.9 (s), 55.6 (d), 51.1 (t), 51.1 (d), 51.0 (q), 50.8 (q), 49.3 (t), 40.3 (d), 39.1 (d), 36.5 (d), 33.1 (d), 30.2 (t), 29.4 (t), 28.0 (t), 27.4 (t), 27.1 (t), 25.6 (t), 25.2 (t), 24.7 (t), 24.3 (t), 24.0 (t); IR (film) ν (cm^{-1}) 3022, 2948, 2934, 1718, 1678, 1437, 1406, 1202, 1177; MS (ESI) *m*/*z* (rel %) 371 [MK^+] (29), 355 [MNa^+] (100), 333 [MH^+] (2); HRMS (ESI) calcd for $C_{18}H_{24}N_2O_4Na$ [MNa^+] 355.1628, found 355.1630.

Methyl *rel*-(1*R*,2*S*,3*R*,6*S*,11*S*,12*S*,15*S*)-4-Aza-3-cyano-11-formyltetracyclo[9.3.1.0^{4,15}.0^{6,12}]pentadec-8-ene-2-carboxylate (98α-CN) and Methyl *rel*-(1*R*,2*S*,3*S*,6*S*,11*S*,12*S*,15*S*)-4-Aza-3-cyano-11-formyltetracyclo[9.3.1.0^{4,15}.0^{6,12}]pentadec-8-ene-2-carboxylate (98β-CN). Tf_2O (84 μL, 0.50 mmol) was added to a solution of **92** (178 mg, 0.399 mmol) and DTBMP (246 mg, 1.20 mmol) in DCM (40 mL) at rt. After 15 min at rt, an additional portion of Tf_2O (84 μL, 0.50 mmol) was added and another additional portion (35 μL, 0.21 mmol) after 10 min. Progression of the Vilsmeier−Haack cyclization was monitored by TLC. *i*-Pr_2NEt (0.56 mL, 3.2 mmol) was then added at rt, and the mixture was stirred for 1 h. Saturated aqueous $NaHCO_3$ was added. The usual workup (EtOAc) and purification (2 to 10% MeCN in toluene) afforded two separable diastereomers **98α-CN** (54.5 mg) and **98β-CN** (52.5 mg) (86% global yield) as pale yellow oils: **98α-CN**: ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.39 (s, 1H), 5.70−5.59 (m, 2H), 4.31 (bs, 1H), 3.75 (s, 3H), 3.41 (dd, *J* = 14.0, 8.5 Hz, 1H), 3.33 (dd, *J* = 9.0, 6.0 Hz, 1H), 3.18 (dd, *J* = 14.0, 5.5 Hz, 1H), 3.13 (bs, 1H), 2.81−2.74 (m, 1H), 2.55−2.47 (m, 1H), 2.35−2.19 (m, 4H), 1.72−1.45 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 201.2 (d), 169.7 (s), 128.9 (d), 124.9 (d), 117.3 (s), 61.6 (d), 54.7 (d), 52.2 (q), 52.2 (d), 50.3 (s), 49.7 (t), 37.5 (d), 36.4 (t), 34.6 (d), 34.0), 32.6 (t), 28.3 (t), 19.1 (t); IR (film) ν (cm^{-1}) 3016, 2956, 2930, 2889, 1722, 1439, 1203, 1177; MS (ESI) *m*/*z* (rel %) 315 [MH^+] (100), 288 [M^+ − CN] (13), 198 (6); HRMS (ESI) calcd for $C_{18}H_{23}N_2O_3$ [MH^+] 315.1709, found 315.1704. **98β-CN**: ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.39 (s, 1H), 5.65−5.57 (m, 2H), 4.27 (d, *J* = 8.0 Hz, 1H), 3.74 (s, 3H), 3.42 (bs, 1H), 3.35 (dd, *J* = 8.0, 6.0 Hz, 1H), 3.29 (dd, *J* = 14.0, 6.5 Hz, 1H), 2.94 (dd, *J* = 14.0, 9.0 Hz, 1H), 2.75−2.63 (m, 2H), 2.31−2.11 (m, 4H), 1.64−1.52 (m, 2H), 1.50−1.35 (m, 2H), 1.15−1.03 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 201.1 (d), 170.5 (s), 128.8 (d), 124.4 (d), 120.9 (s), 61.2 (d), 57.8 (d), 55.4 (d), 53.9 (t), 52.5 (q), 50.3 (s), 38.5 (d), 36.3 (t), 34.2 (d), 33.2 (d), 31.7 (t), 28.1 (t), 18.6 (t); IR (film) ν (cm^{-1}) 3016, 2928, 2885, 1725, 1438, 1241, 1204, 1170; MS (ESI) *m*/*z* (rel %) 315 [MH^+] (100), 288 [M^+ − CN] (11), 198 (5); HRMS (ESI) calcd for $C_{18}H_{23}N_2O_3$ [MH^+] 315.1709, found 315.1714.

***N*-(*rel*-(2*S*,3*S*)-(6*Z*)-2-Allyl-3-(2-(allyloxy)vinyl)oct-6-en-1-yl)-*N*-(cyanomethyl)formamide (99).** Following the procedure used to prepare **83**, a solution of **94** (100 mg, 0.326 mmol) in DCM (2.0 mL) was added to a solution of oxalyl chloride (32 μL, 0.36 mmol) and DMSO (46 μL, 0.65 mmol) in DCM (5 mL), and the mixture was then treated with Et_3N (227 μL, 1.63 mmol) to afford the corresponding aldehyde (107 mg of crude material). Ph_3PEtBr (145 mg, 0.390 mmol) was added to a solution of *t*-BuOK (40 mg, 0.36 mmol) in THF (4.0 mL) at 0 °C. After 20 min at rt, a solution of aldehyde (107 mg of crude material) in THF (2.5 mL) was added, and the mixture was allowed to warm up to rt and stirred 18 h. Water was added, and solvent was removed under reduced pressure. Saturated aqueous $NaHCO_3$ was added. The usual workup (EtOAc) and purification using silica gel saturated with Et_3N (30% EtOAc in hexanes) afforded a mixture of *E*/*Z* isomers (for the allyl enol ether) and rotamers of **99** (27 mg, 76% over 2 steps) as a pale yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.13 (s) and 8.01 (s) (1H), 6.19 (d, *J* = 12.5 Hz), 6.18 (d, *J* = 12.5 Hz), 6.09 (d, *J* = 6.5 Hz), and 6.06 (d, *J* = 5.5 Hz) (1H), 5.98−5.83 (m, 1H), 5.81−5.62 (m, 1H), 5.50−5.38 (m, 1H), 5.37−5.20 (m, 3H), 5.10−5.00 (m, 2H), 4.55 (dd, *J* = 12.5, 10.0 Hz), 4.51 (dd, *J* = 12.5, 10.0 Hz), and 4.14 (dd, *J* = 6.5, 3.5 Hz) (1H), 4.35 (d, *J* = 17.5 Hz), 4.28−4.17 (m), 4.09 (d, *J* = 17.5 Hz) (4H), 3.41 (dd, *J* = 14.5, 5.0 Hz), 3.36 (dd, *J* = 14.5, 6.0 Hz), 3.28 (dd, *J* = 14.5, 8.0 Hz), and 3.18 (dd, *J* = 14.5, 9.5 Hz) (2H), 2.62−2.53 (m) and 2.17−1.89 (m) (5H), 1.80−1.56 (m, 4H), 1.50−1.40 (m, 1H), 1.38−1.20 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.7 (d), 162.7 (d), 162.3 (d), 162.2 (d), 147.8 (d), 147.5 (d), 146.3 (d), 146.0 (d), 136.5 (d), 136.1 (d), 135.4 (d), 135.2 (d), 133.7 (d), 133.6 (d), 133.3 (d), 133.2 (d), 130.3 (d), 130.0 (d), 129.9 (d), 129.6 (d), 124.6 (d), 124.4 (d), 124.2 (d), 124.0 (d), 117.9 (t), 117.7 (t), 117 0.7 (t),

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117.6 (t), 117.1 (t), 116.7 (t), 114.6 (s), 114.5 (s), 108.3 (d), 107.8 (d), 104.1 (d), 72.8 (t), 72.7 (t), 70.4 (t), 70.1 (t), 48.9 (t), 48.7 (t), 44.2 (t), 43.4 (t), 40.2 (d), 40.1 (d), 40.0 (d), 39.7 (d), 38.7 (d), 38.1 (d), 38.0 (d), 36.2 (t), 35.6 (t), 34.1 (t), 34.0 (t), 33.9 (t), 33.5 (t), 33.3 (t), 33.0 (t), 32.3 (t), 31.4 (t), 30.9 (t), 30.3 (t), 29.9 (t), 25.0 (t), 24.8 (t), 24.7 (t), 24.6 (t), 17.9 (q), 12.9 (q), 12.9 (q), 12.7 (q); IR (film) ν (cm^{-1}) 3077, 3017, 2932, 2867, 1679, 1425, 1405, 1161; MS (ESI) *m*/*z* (rel %) 339 [MNa^+] (100); HRMS (ESI) calcd for $C_{19}H_{28}N_2O_2Na$ [MNa^+] 339.2043, found 339.2049.

***N*-(*rel*-(2*S*,3*S*)-(*Z*)-2-Allyl-3-(1-oxopent-4-en-2-yl)oct-6-en-1-yl)-*N*-(cyanomethyl)formamide (100).** A solution of **99** (27 mg, 85 μmol) in toluene (3.0 mL) was heated at 155 °C in a sealed tube for 144 h. The solution was concentrated under reduced pressure. The usual purification using silica gel saturated with Et_3N (20 to 40% EtOAc in hexanes) afforded an inseparable mixture of diastereomers and rotamers of **100** (24 mg, 89%) as a cololess oil: ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.71 (d, *J* = 2.0 Hz), 9.78 (d, *J* = 2.0 Hz), and 9.67 (d, *J* = 2.0 Hz) (1H), 8.15 (s), 8.14 (s), 8.11 (s), and 8.02 (s) (1H), 5.80–5.61 (m, 2H), 5.57–5.42 (m, 1H), 5.39–5.25 (m, 1H), 5.18–4.99 (m, 4H), 4.43–4.08 (m), 4.36 (d, *J* = 17.5 Hz), 4.32 (d, *J* = 16.0 Hz), 4.18 (d, *J* = 17.5 Hz), and 4.13 (d, *J* = 17.5 Hz) (2H), 3.65–3.49 (m) and 3.36–3.19 (m) (2H), 2.60–2.40 (m, 2H), 2.38–1.79 (m, 7H), 1.68–1.32 (m, 2H), 1.59 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 208.1 (d), 205.1 (d), 204.8 (d), 204.0 (d), 162.6 (d), 162.5 (d), 135.9 (d), 135.3 (d), 135.1 (d), 134.8 (d), 134.7 (d), 132.1 (d), 129.4 (d), 129.3 (d), 128.8 (d), 128.8 (d) 125.5 (d), 125.1 (d), 124.8 (d), 119.7 (t), 118.2 (t), 118.1 (t), 117.9 (t), 117.7 (t), 117.6 (t), 117.5 (t), 117.3 (t), 114.5 (s), 114.5 (s), 114.4 (s), 52.5 (d), 52.4 (d), 52.1 (d), 50.5 (t), 49.2 (t), 49.2 (t), 45.7 (d), 44.5 (t), 40.1 (d), 38.0 (d), 37.5 (d), 37.4 (d), 37.3 (d), 36.9 (d), 36.6 (d), 36.3 (d), 36.0 (t), 36.0 (t), 34.7 (t) 34.0 (t), 33.2 (t), 33.1 (t), 33.0 (t), 32.9 (t), 31.6 (t), 31.2 (t), 31.2 (t), 31.1 (t), 30.2 (t), 30.2 (t), 27.2 (t), 27.1 (t), 26.7 (t), 26.6 (t), 26.3 (t), 25.8 (t), 25.5 (t), 25.4 (t), 25.3 (t), 24.7 (t), 13.4 (q), 13.0 (q), 12.9 (q), 12.8 (q); IR (film) ν (cm^{-1}) 3077, 3012, 2927, 2862, 1724, 1672, 1430, 1395, 1180, 916; MS (ESI) *m*/*z* (rel %) 371 [MNa^+ + MeOH] (32), 355 [MK^+] (30), 339 [MNa^+] (100); HRMS (ESI) calcd for $C_{19}H_{28}N_2O_2Na$ [MNa^+] 339.2043, found 339.2046.

***N*-(Cyanomethyl)-*N*-((*rel*-(1*S*,7*S*)-6-formyl-7-((*Z*)-pent-3-en-1-yl)cyclohept-3-en-1-yl)methyl)formamide (101).** First-generation Grubbs' catalyst (5.9 mg, 5 mol %) was added to a solution of **100** (45.2 mg, 0.143 mmol) in DCM (14.5 mL). The solution was stirred for 6 h at rt with N_2 bubbling; then another portion of first-generation Grubbs' catalyst (5.9 mg, 5 mol %) was added. The solution was stirred at rt for 18 h, and water was finally added. The usual workup (DCM) and purification (0 to 40% EtOAc in hexanes) afforded an inseparable mixture of diastereomers and rotamers of **101** (36.0 mg, 88%) as a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.73 (s) and 9.65 (s) (1H), 8.22 (s), 8.17 (s), 8.06 (s), and 8.02 (s) (1H), 5.86–5.57 (m), 5.54–5.41 (m), 5.37–5.23 (m), and 5.14–4.96 (m) (4H), 4.66–4.02 (m), 4.62 (d, *J* = 17.5 Hz), 4.49 (d, *J* = 17.5 Hz), 4.22 (d, *J* = 17.5 Hz), and 4.12 (d, *J* = 17.5 Hz) (2H), 3.49–3.05 (m, 2H), 2.66–1.72 (m, 10H), 1.67–1.13 (m) and 1.08–0.83 (m) (4H); ^{13}C NMR (75.5 MHz, $CDCl_3$) only the major rotamer of each diastereomer reported δ (ppm) 204.6, 203.3, 162.4, 162.3, 130.9, 129.2, 128.9, 128.8, 128.4, 127.9, 125.4, 114.6, 114.5, 56.0, 51.8, 51.2, 50.0, 41.2, 38.2, 35.9, 33.6, 30.6, 29.6, 28.6, 27.3, 25.5, 25.2, 24.9, 24.2, 24.0, 23.9, 12.8; MS (ESI) *m*/*z* (rel %) 343 [MNa^+ + MeOH] (19), 311 [MNa^+] (100), 297 (41); HRMS (ESI) calcd for $C_{17}H_{24}N_2O_2Na$ [MNa^+] 311.1730, found 311.1734.

***N*-((*rel*-(1*S*,7*S*)-6-(((*tert*-Butyldimethylsilyl)oxy)methylene)-7-((*Z*)-pent-3-en-1-yl)cyclohept-3-en-1-yl)methyl)-*N*-(cyanomethyl)formamide (102).** Following the procedure used to prepare **40**, a solution of **101** (34 mg, 0.12 mmol) in DCM (2.5 mL) was treated with TBDMSOTf (54 μL, 0.24 mmol) and *i*-Pr_2NEt (62 μL, 0.35 mmol) for 18 h at rt to afford, after the usual purification using silica gel saturated with Et_3N (0 to 40% EtOAc in hexanes), one geometrical isomer (as a mixture of rotamers) of **102** (22.5 mg, 47%) of unidentified stereochemistry as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.18 (s) and 8.01 (s) (1H), 6.07 (s, 1H), 5.85–5.70 (m, 1H), 5.61–5.27 (m, 3H), 5.05–4.94 (m), 4.33 (d, *J* = 17.5 Hz), and 4.17 (d, *J* = 17.5 Hz) (2H), 3.34–3.20 (m, 2H), 3.13 (dd, *J* = 17.0, 6.5 Hz, 1H), 2.78–2.59 (m, 1H), 2.18–1.79 (m, 6H), 1.73–1.51 (m, 1H), 1.58 (d, *J* = 7.0 Hz, 3H), 1.34–1.18 (m, 1H), 0.92 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) only the major rotamer reported δ (ppm) 162.5, 135.1, 130.2, 129.8, 126.4, 124.7, 119.5, 114.4, 50.1, 43.5, 39.6, 30.1, 28.7, 26.0, 25.6, 25.3, 24.5, 18.3, 12.9, −5.3; MS (ESI) *m*/*z* (rel %) 457 [$MNa^+ + O_2$] (45), 425 [MNa^+] (100), 411 (18); HRMS (ESI) calcd for $C_{23}H_{38}N_2O_2SiNa$ [MNa^+] 425.2595, found 425.2605.

***rel*-(1*S*,6*S*,10*S*)-8-(Cyanomethyl)-1-formyl-10-((*Z*)-pent-3-en-1-yl)-8-azabicyclo[4.3.1]deca-3,8-dien-8-ium Trifluoromethanesulfonate (103).** Tf_2O (3.0 μL, 19 μmol) was added to a solution of **102** (5.0 mg, 12 μmol) and DTBMP (7.6 mg, 37 μmol) in DCE (0.7 mL) at rt. After 10 min, an additional portion of Tf_2O (1.0 μL, 0.6 μmol) was added. ^1H NMR analysis showed the formation of the iminium ion **103**: ^1H NMR (300 MHz, CD_2Cl_2) characteristic signals δ (ppm) 9.69 (s, 1H), 9.39 (s, 1H), 6.16–6.06 (m, 1H), 5.82–5.66 (m, 1H), 5.60–5.50 (m, 1H), 5.42 (d, *J* = 17.5 Hz, 1H), 5.34–5.29 (m, 1H), 5.22 (d, *J* = 17.5 Hz, 1H), 4.13 (dd, *J* = 17.0, 4.5 Hz, 1H), 3.82 (d, *J* = 17.0 Hz, 1H), 2.92–2.58 (m), 2.40–1.89 (m), and 1.67–0.83 (m) (13H).

Methyl *rel*-(1*R*,6*S*,11*S*,12*S*,15*S*)-4-Aza-11-((*E*)-3-(*tert*-butoxy)-3-oxoprop-1-enyl)-3-cyanotetra-cyclo[9.3.1.$0^{4,15}$.$0^{6,12}$]pentadec-8-ene-2-carboxylate (105). *t*-BuOK (5.2 mg, 44 μmol) was added to a solution of *tert*-butyl diethylphosphonoacetate (14.0 mg, 55.4 μmol) in THF (1.0 mL) at 0 °C. The mixture was stirred for 30 min at 0 °C; then a solution of **98*α*/*β*-CN** (11.6 mg, 36.9 μmol) in THF (1.0 mL) was added. The reaction mixture was stirred for 2 h at 0 °C. Saturated aqueous $NaHCO_3$ was added at 0 °C. The usual workup (EtOAc) and purification (5 to 30% EtOAc in hexanes) gave three separable diastereomers **105** (11.7 mg, 77%) as a pale yellow oil: Diastereoisomer 1: ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.86 (d, *J* = 16.5 Hz, 1H), 5.67 (d, *J* = 16.5 Hz, 1H), 5.61–5.55 (m, 2H), 4.30 (d, *J* = 8.0 Hz, 1H), 3.74 (s, 3H), 3.37 (bs, 1H), 3.32 (d, *J* = 6.0 Hz, 1H), 3.28 (t, *J* = 6.0 Hz, 1H), 2.93 (dd, *J* = 14.0, 9.5 Hz, 1H), 2.81 (d, *J* = 15.5 Hz, 1H), 2.62–2.50 (m, 1H), 2.31–1.95 (m, 5H), 1.77–1.63 (m, 1H), 1.58–1.32 (m, 2H), 1.50 (s, 9H), 1.14–0.98 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 170.4 (s), 166.1 (s), 154.3 (d), 128.6 (d), 124.8 (d), 121.1 (s), 120.3 (d), 80.6 (s), 64.4 (d), 58.1 (d), 55.2 (d), 54.3 (t), 52.4 (q), 41.0 (s), 38.5 (d), 37.8 (t), 36.4 (t), 36.3 (d), 34.1 (d), 28.1 (q), 27.7 (t), 18.7 (t); IR (film) ν (cm^{-1}) 3023, 2957, 2922, 2876, 1735, 1709, 1644, 1206, 1151; MS (ESI) *m*/*z* (rel %): 435 [MNa^+] (41), 413 [MH^+] (80), 408 [MNa^+ − HCN] (100); HRMS (ESI) calcd for $C_{24}H_{33}N_2O_4$ [MH^+] 413.2435, found 413.2444. Diastereoisomer 2: ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.84 (d, *J* = 16.5 Hz, 1H), 5.82–5.68 (m, 2H), 5.67 (d, *J* = 16.5 Hz, 1H), 4.12 (d, *J* = 7.5 Hz, 1H), 3.75 (s, 3H), 3.08–3.00 (m, 3H), 2.91 (d, *J* = 5.0 Hz, 1H), 2.69–2.58 (m, 1H), 2.58 (dd, *J* = 16.0, 6.5 Hz, 1H), 2.36–2.26 (m, 2H), 2.16–1.83 (m, 5H), 1.55–1.41 (m, 1H), 1.49 (s, 9H), 1.38–1.24 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 173.1 (s), 166.2 (s), 154.5 (d), 128.5 (d), 128.1 (d), 120.5 (d), 117.7 (s), 80.6 (s), 65.3 (d), 57.7 (d), 57.7 (d), 52.6 (q), 52.3 (t), 40.5 (d), 40.0 (t), 38.6 (s), 37.3 (d), 35.5 (t), 34.9 (d), 28.4 (t), 28.2 (t), 28.1 (q); IR (film) ν (cm^{-1}) 3023, 2959, 2921, 2876, 1739, 1709, 1644, 1209, 1147; MS (ESI) *m*/*z* (rel %): 435 [MNa^+] (100), 413 [MH^+] (69); HRMS (ESI) calcd for $C_{24}H_{32}N_2O_4Na$ [MNa^+] 435.2254, found 435.2269. Diastereoisomer 3: ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.87 (d, *J* = 16.5 Hz, 1H), 5.65–5.59 (m, 2H), 5.64 (d, *J* = 16.5 Hz, 1H), 4.35 (d, *J* = 9.5 Hz, 1H), 3.75 (s, 3H), 3.40 (dd, *J* = 14.5, 8.5 Hz, 1H), 3.27 (dd, *J* = 9.0, 6.0 Hz, 1H), 3.15 (dd, *J* = 14.5, 6.5 Hz, 1H), 3.09–3.02 (m, 1H), 2.73–2.53 (m, 2H), 2.33–2.06 (m, 5H), 1.98 (bs, 1H), 1.78–1.56 (m, 2H), 1.48 (s, 9H), 1.56–1.41 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 169.7 (s), 166.2 (s), 154.9 (d), 128.7 (d), 125.3 (d), 120.2 (d), 117.6 (s), 80.6 (s), 64.8 (d), 54.8 (d), 52.4 (d), 52.1 (q), 49.6 (t), 41.2 (s), 39.0 (t), 37.7 (d), 37.2 (d), 36.4 (t), 34.6 (d), 28.1 (q), 27.9 (t), 19.0 (t); IR (film) ν (cm^{-1}) 3016, 2943, 2931, 2884, 1744, 1709, 1641, 1215, 1152; MS (ESI) *m*/*z* (rel %): 435 [MNa^+] (25), 413 [MH^+] (100), 408 [MNa^+ − HCN] (35); HRMS (ESI) calcd for $C_{24}H_{33}N_2O_4$ [MH^+] 413.2435, found 413.2447.

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Methyl *rel*-(1*R*,6*S*,11*S*,12*S*,15*S*)-4-Aza-11-((*E*)-3-(*tert*-butoxy)-3-oxoprop-1-enyl)tetracyclo[9.3.1.0^{4,15}.0^{6,12}]pentadeca-2,8-diene-2-carboxylate (1016). A solution of **105** (19.2 mg, 46.5 μmol) in toluene (2.0 mL) was added to a solution of NaH (60% in mineral oil, 93 mg, 2.3 mmol) in toluene (3.0 mL) at 0 °C. Then, the mixture was refluxed for 12 h. Water was added at 0 °C. The usual workup (EtOAc, washed with brine) and purification (0 to 30% EtOAc in hexanes) afforded **105** (14.9 mg, 83%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.11 (s, 1H), 7.09 (d, *J* = 16.0 Hz, 1H), 5.76 (d, *J* = 16.0 Hz, 1H), 5.66−5.47 (m, 2H), 3.98 (d, *J* = 10.0 Hz, 1H), 3.65 (s, 3H), 3.58 (dd, *J* = 14.0, 10.5 Hz, 1H), 3.33 (dd, *J* = 14.0, 9.0 Hz, 1H), 3.11 (t, *J* = 7.5 Hz, 1H), 2.63 (d, *J* = 16.5 Hz, 1H), 2.44 (dt, *J* = 18.5, 6.0 Hz, 1H), 2.35−2.19 (m, 2H), 2.12−1.91 (m, 3H), 1.72−1.56 (m, 1H), 1.49 (s, 9H), 1.43−1.23 (m, 1H), 1.13 (dd, *J* = 14.5, 3.0 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 166.5 (s), 166.4 (s), 154.8 (d), 153.0 (d), 131.2 (d), 122.9 (d), 118.9 (d), 104.6 (s), 80.4 (s), 65.4 (d), 50.4 (q), 50.0 (t), 42.0 (s), 40.3 (d), 40.0 (d), 38.5 (t), 34.7 (t), 34.3 (d), 28.2 (q), 26.1 (t), 23.7 (t); MS (ESI) *m*/*z* (rel %): 408 [MNa^+] (100), 386 [MH^+] (20); HRMS (ESI) calcd for $C_{23}H_{31}NO_4Na$ [MNa^+] 408.2145, found 408.2161.

***tert*-Butyl *rel*-(1*R*,2*S*,6*S*,11*S*,12*S*,15*S*)-4-Aza-2-(hydroxymethyl)tetracyclo[9.3.1.0^{4,15}.0^{6,12}]pentadecane-11-propanoate (107).** A solution of **106** (12.4 mg, 32.1 μmol) and Pd/C (10%, 3.4 mg, 10 mol %) in MeOH (1.5 mL) was stirred under a hydrogen atmosphere (50 psi) for 36 h. The mixture was filtered on Celite and concentrated under reduced pressure to afford the corresponding saturated compound (12.6 mg, quantitative) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 3.67 (s, 3H), 3.48−3.36 (m, 1H), 3.21 (dd, *J* = 11.0, 8.0 Hz, 2H), 3.00 (dd, *J* = 15.0, 8.0 Hz, 1H), 2.84 (t, *J* = 12.5 Hz, 1H), 2.72 (bs, 1H), 2.66−2.58 (m, 1H), 2.53−2.40 (m, 1H), 2.29−2.14 (m, 3H), 2.00−1.53 (m, 10H), 1.51−1.33 (m, 3H), 1.45 (s, 9H), 1.30−1.17 (m, 1H); MS (ESI) *m*/*z* (rel %): 392 [MH^+] (100); HRMS (ESI) calcd for $C_{23}H_{38}NO_4$ [MH^+] 392.2795, found 392.2808. The latter (12.6 mg, 32.1 μmol) was dissolved in THF, (2.0 mL) and a solution of $LiBH_4$ (2.0 M in THF, 32 μL, 64 μmol) was added at 0 °C. After 30 min, an additional portion of $LiBH_4$ (2.0 M in THF, 32 μL, 64 μmol) was added. The mixture was stirred for 14 h at rt; then water was added. Solvent was removed under reduced pressure, and saturated aqueous $NaHCO_3$ was added. The usual workup (EtOAc, Na_2SO_4) and purification (20 to 50% EtOAc in hexanes) gave **107** (4.9 mg, 42%, 49% brsm) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.68−3.58 (m, 2H), 3.55 (dd, *J* = 10.5, 6.5 Hz, 1H), 3.28 (dd, *J* = 15.0, 11.0 Hz, 1H), 3.20 (d, *J* = 3.5 Hz, 1H), 3.12 (t, *J* = 11.5 Hz, 1H), 2.88 (dd, *J* = 15.0, 9.5 Hz, 1H), 2.72−2.48 (m, 3H), 2.21 (dd, *J* = 9.0, 8.0 Hz, 2H), 2.13−2.04 (m, 1H), 1.86−1.64 (m, 7H), 1.60−1.40 (m, 8H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.7 (s), 80.5 (s), 72.8 (d), 67.8 (t), 59.7 (t), 58.4 (t), 42.6 (d), 37.0 (d), 36.2 (s), 35.1 (t), 34.1 (d), 33.0 (d), 32.6 (t), 32.2 (t), 28.8 (t), 27.8 (q), 25.2 (t), 24.0 (t), 23.9 (t), 15.2 (t); IR (film) ν (cm^{-1}) 3448, 2975, 2932, 2878, 1725, 1478, 1455, 1152; MS (ESI) *m*/*z* (rel %): 364 [MH^+] (100); HRMS (ESI) calcd for $C_{22}H_{38}NO_3$ [MH^+] 364.2846, found 364.2862.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01835.

Copies of ^{1}H and ^{13}C NMR spectra for all new compounds, and copies of 2D NMR spectra for compounds ***Z*-91**, **98α-CN**, **98β-CN**, and **107** (PDF)

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Notes

The authors declare no competing financial interest.

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