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Construction of the *Myrioneuron* Alkaloids: A Total Synthesis of (±)-Myrioneurinol

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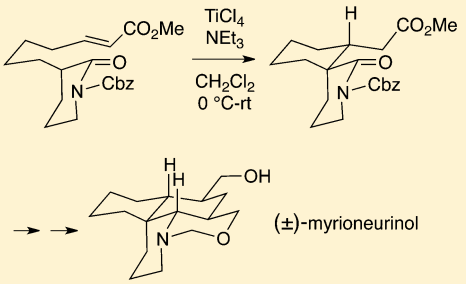
Supporting Information

ABSTRACT: A strategy has been developed that culminated in a stereoselective total synthesis of the tetracyclic antimalarial *Myrioneuron* alkaloid myrioneurinol. The synthesis relies on three highly diastereoselective reactions, including an intramolecular chelation-controlled Michael spirocyclization of an *N*-Cbz-lactam titanium enolate to an *α,β*-unsaturated ester for construction of the A/D-ring system and the attendant C5 (quaternary), C6 relative stereochemistry; a malonate enolate conjugate addition to a nitrosoalkene in order to install the appropriate functionality and establish the configuration at C7; and an intramolecular aza-Sakurai reaction to form the B-ring and the accompanying C9 and C10 stereocenters.



INTRODUCTION

The *Myrioneuron* alkaloids are a small but growing group of plant metabolites that have a common biosynthesis starting from lysine.[1] These alkaloids generally have a *cis*-decahydroquinoline moiety embedded in their structures and also incorporate 1,3-oxazine and/or 1,3-diazine rings (Figure 1).

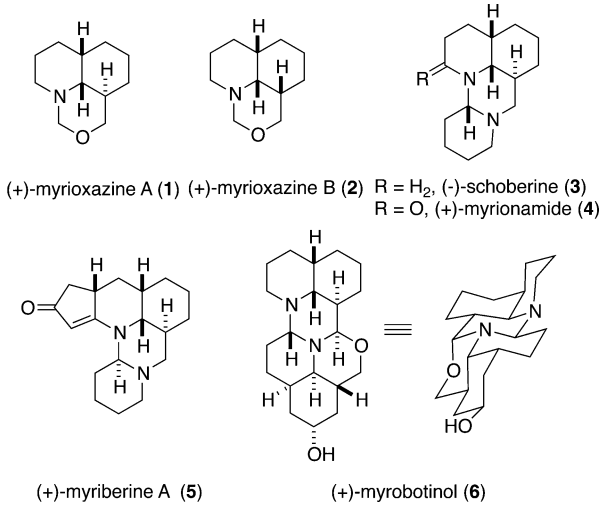


Figure 1. Structures of some representative *Myrioneuron* alkaloids.

These metabolites range from simple tricyclic systems such as (+)-myrioxazine A (**1**) and B (**2**)[2] to tetracyclic compounds such as (−)-schoberine (**3**) and (+)-myrionamide (**4**),[3] pentacycles such as (+)-myriberine A (**5**),[4] and the hexacyclic compound (+)-myrobotinol (**6**).[5] An architecturally pleasing feature of these molecules is the fact that they contain a series of tightly fused chair six-membered rings, as can be seen in the conformational depiction of (+)-myrobotinol (**6**).

In 2007, Bodo and co-workers[6] isolated a new tetracyclic alkaloid, (+)-myrioneurinol, from the leaves of the northern Vietnamese plant *Myrioneuron nutans*. Using a variety of spectral methods, they proposed the absolute stereostructure and conformation of **7** for this metabolite (Figure 2).

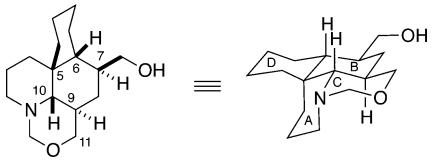


Figure 2. Structure and conformation of (+)-myrioneurinol (**7**).

Myrioneurinol has some of the same structural features as other *Myrioneuron* alkaloids (i.e., *cis*-decahydroquinoline, 1,3-oxazine) but also has some significant differences, including a quaternary carbon at C5 and a hydroxymethyl group at C7 along with five contiguous stereogenic centers.

Myrioneuron alkaloids display a number of different types of biological activity. For example, (+)-myriberine A (**5**) was reported to effectively inhibit the hepatitis C virus.[4] Moreover, some alkaloids, including an ester derivative of (+)-myrobotinol (**6**),[5] have cytotoxicity against KB cells.[7] (+)-Myrioneurinol (**7**) showed only weak inhibitory activity against KB cells but does have moderate antimalarial activity against *Plasmodium falciparum*.[6]

Relatively little synthetic work has appeared in this area to date. Bodo et al. described syntheses of both the natural and unnatural enantiomers of myrioxazines A and B.[2] In addition, this group synthesized a similar tricyclic alkaloid, (−)-myrionine,[8] from a myrioxazine A intermediate and converted

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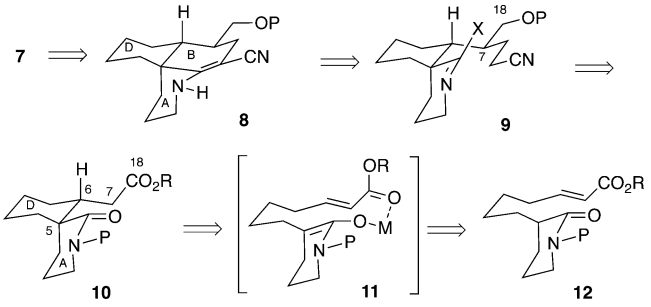
myrionine into (−)-schoberine (**3**) as well as the closely related amidinium alkaloid (−)-myrionidine.[9] In 2009, Burrell and co-workers reported a total synthesis of racemic myrioxazine A.[10] Shortly thereafter, the same group published an approach to a model compound incorporating the A/B/C-ring system of myrioneurinol.[11]

Because of the unique structural features of myrioneurinol (**7**) along with its reported antimalarial activity, we became interested in this metabolite as a challenging target for synthesis. In a brief communication that appeared in 2014, we reported a successful stereoselective total synthesis of racemic myrioneurinol.[12] In this paper, we now describe the full details of these studies.

RESULTS AND DISCUSSION

Synthesis Plan. Our initial retrosynthetic analysis for the synthesis of alkaloid **7** is outlined in Scheme 1. The plan was to

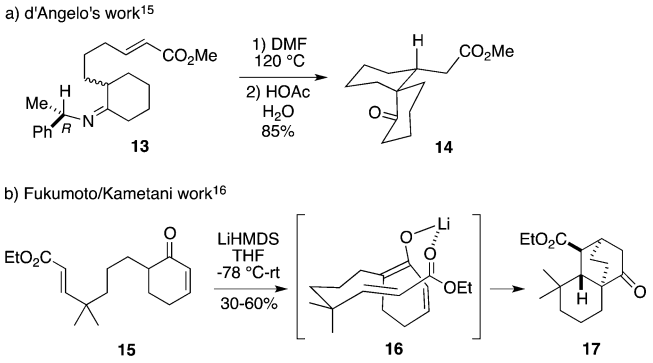
Scheme 1. First-Generation Retrosynthetic Analysis for Myrioneurinol (7)



prepare a key intermediate **8** having the A/B/D-rings of the natural product and then reduce the cyanoenamine moiety to set the C9,C10 stereochemistry and establish the attendant C11 hydroxymethyl group, ultimately leading to myrioneurinol. Compound **8** would be produced by cyclization of the anion of nitrile **9** onto an appropriate lactam imidate derivative to produce the B-ring of the alkaloid.[13] Intermediate **9** would in turn be accessed by alkylation at C7 of the enolate of spirocyclic ester **10** followed by reduction of the C18 carboxylate to the corresponding hydroxymethyl group. A key step in the synthesis was to be an intramolecular Michael spirocyclization of a 2-piperidone-derived α,β-unsaturated ester such as **12** to form **10**.[14] We anticipated that it should be possible to control the relative stereochemistry at C5 (quaternary) and C6 in this process via metal-chelated enolate intermediate **11**, for which there was some literature precedent (vide infra).

Studies of the Construction of the A/D Spirocyclic Ring System of Myrioneurinol via a Diastereoselective Intramolecular Michael Reaction. Our first goal was to effect a diastereoselective spirocyclization of a substrate such as **12** to generate the A/D-ring system **10** of the alkaloid (cf. Scheme 1). Intramolecular Michael reactions are now well-documented,[14] and some literature examples provided good support for this proposed transformation. d'Angelo and Ferroud demonstrated that thermal cyclization of imine **13**, followed by acidic hydrolysis, provided the single keto ester spirocycle **14** in high yield with the relative and absolute stereochemistry shown (Scheme 2).[15] Moreover, Fukumoto, Kametani, and co-workers reported that treatment of substrate **15** with lithium hexamethyldisilazide led to one diastereomeric

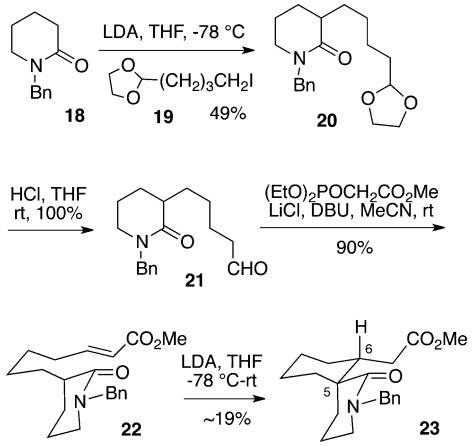
Scheme 2. Relevant Intramolecular Michael Cyclizations



product **17** by an intramolecular double Michael reaction.[16,17] It was proposed that this interesting transformation occurs via Li-chelated intermediate **16**. Support for this supposition was the observation that addition of some HMPA significantly lowered the product yield.

It was decided initially to explore the feasibility of effecting the desired Michael reaction using *N*-benzyl-protected lactam substrate **22** (Scheme 3). This compound was easily prepared

Scheme 3. Synthesis and Studies of the Cyclization of *N*-Benzyllactam Enoate 22



via a short sequence starting from *N*-benzyl-2-piperidone (**18**), which was alkylated with iodide **19**[18] to afford lactam **20**. Hydrolysis of the acetal then led to aldehyde **21**, which was subjected to a Wadsworth–Emmons–Horner olefination to produce the desired (*E*)-α,β-unsaturated ester **22**.

A number of experimental conditions were examined in attempts to convert enoate **22** into spirocycle **23**. It was eventually found that treatment of substrate **22** with LDA at −78 °C and subsequent warming to room temperature did indeed produce spirocycle **23**, but at best in only ~19% isolated yield along with starting material and some decomposition products. Addition of anhydrous $ZnCl_2$ to the mixture led to no reaction. Other bases such as KHMDS, NaH, and KO*t*-Bu in various solvents yielded only decomposition products. Although disappointed in the yield of **23**, we were pleased to find that only one stereoisomer had formed, and this material was determined by ^{1}H NMR NOE experiments and eventual correlation with a later intermediate (vide infra) to have the desired C5,C6 relative configuration.

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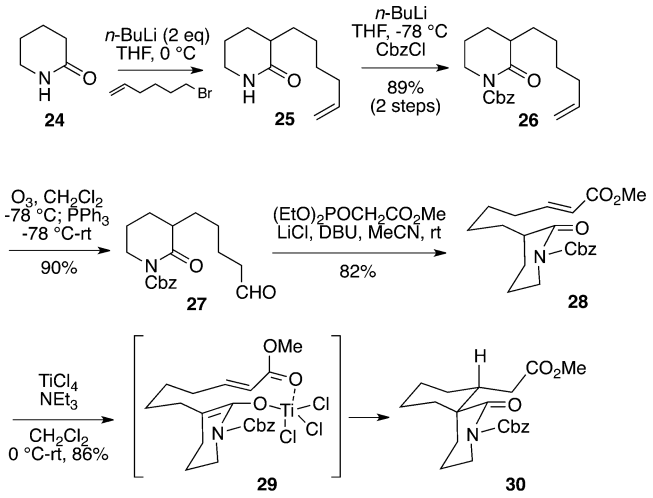
The formation of Michael adduct **23**, albeit in only low yield, provided some glimmer of hope that our conjugate addition strategy might in fact be viable. On the basis of work by Evans et al.[19] demonstrating that *N*-acyloxazolidones undergo facile Michael reactions, we decided to explore the possibility of cyclizing an *N*-acyllactam derivative analogous to the *N*-benzyl system **22**. The requisite substrate could be prepared by a route similar to that in Scheme 3, but one that proved to be more scalable. Thus, the dianion of valerolactam (**24**) was *C*-alkylated with 6-bromo-1-hexene to afford lactam **25** (Scheme 4).[20] A

Scheme 4. Diastereoselective Intramolecular Michael Reaction To Form the Spirocyclic A/D-Ring System 30 of Myrioneurinol



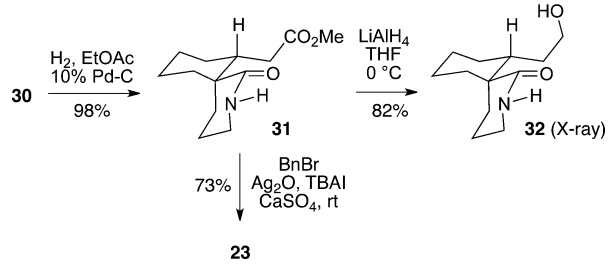
Cbz group was then installed on the nitrogen of intermediate **25** to yield *N*-acyllactam **26**. Ozonolysis of olefin **26** led to aldehyde **27**, which upon Wadsworth–Emmons–Horner olefination afforded the (*E*)-α,β-unsaturated ester substrate **28**.

Since the Evans group had utilized titanium enolates for their *N*-acyloxazolidone Michael reactions,[19] we explored a similar set of conditions with our system. It was eventually found that treatment of substrate **28** with titanium tetrachloride/triethylamine in methylene chloride, starting at 0 °C and then warming to room temperature prior to an aqueous quench, led to the single spirocycle **30** in excellent 86% yield. Using titanium tetraisopropoxide or dichlorotitanium diisopropoxide did not afford the desired product **30** in acceptable yield and purity. In addition, replacement of the triethylamine by Hunig's base gave no reaction. It might also be noted that *N*-benzyllactam substrate **22** was unreactive toward these soft enolization conditions. We believe that spirocycle **30** is probably formed via a chelated titanium enolate intermediate like **29**.

In order to unambiguously confirm the structure and stereochemistry of product **30**, the Cbz group was first removed by hydrogenolysis to afford NH lactam **31**, and the ester moiety was reduced to yield alcohol **32** (Scheme 5). The structure of this compound was found to be as indicated via X-ray crystallography (see the Supporting Information). Moreover, *N*-benzylation of **31** gave *N*-benzyllactam **23**, which was identical to the material formed via cyclization of Michael substrate **22** (cf. Scheme 3).

Before proceeding further with the total synthesis of myrioneurinol, we decided to investigate some additional features of the intramolecular Michael reaction. Since our

Scheme 5. Confirmation of the Stereochemistry of Spirocycle 30



synthetic strategy was predicated upon eventually having a substituent at C7 of the spirocycle (cf. **9** in Scheme 1), attempts were made at this point to test the feasibility of incorporating an appropriate group directly into the intramolecular conjugate addition substrate. Therefore, standard Wadsworth–Emmons–Horner chemistry was used to convert aldehyde **27** into the three Michael precursors shown in Figure 3. Unfortunately, exposure of these compounds to the soft enolization conditions successfully used for substrate **28** led to no reaction.

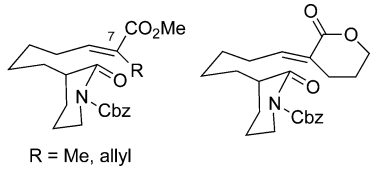


Figure 3. Attempted incorporation of a C7 substituent into the intramolecular Michael cyclization.

We also briefly investigated the possibility of preparing a suitable spirocycle in enantioenriched form by incorporating a chiral auxiliary into the Michael substrate. Thus, in the first system examined, a chiral carbamate group derived from (−)-menthol was installed to provide precursor **33** (Figure 4).

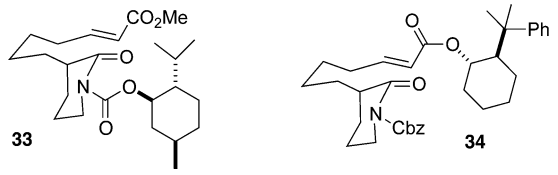


Figure 4. Cyclizations of substrates bearing chiral auxiliaries.

Although this substrate cyclized under the usual soft enolization conditions, unfortunately a 1:1 mixture of diastereomeric products was formed. Another substrate **34** bearing a chiral ester moiety was also prepared, but this system did not undergo an intramolecular Michael reaction, perhaps for steric reasons.

Attempts To Homologate the Spirocyclic Lactam A/D-Ring System at C7. Since we were unable to incorporate a C7 substituent into the intramolecular conjugate addition reaction (vide supra), we turned to post-Michael introduction of such a substituent. Therefore, a number of attempts were made to alkylate ester enolates of various spirocycles. In the case of ester **30**, all attempts to generate the corresponding enolate led only to the loss of the *N*-Cbz group. Subjection of the *N*-benzyl analogue **23** to LDA followed by methyl acrylate yielded only unchanged starting material. Attempted deprotonations of **23** with LDA/THF/HMPA or KHMDS/18-crown-6 followed by a

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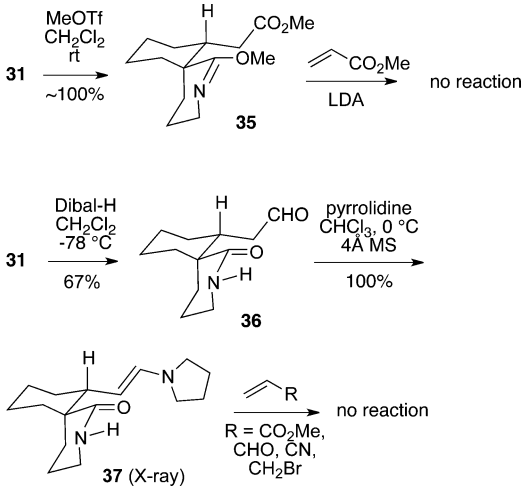
D_2O quench gave back the starting ester with no incorporation of deuterium.

Additional attempts were made to alkylate at C7 with imidate ester **35**, which was prepared in high yield from lactam **31** (Scheme 6). Treatment of ester **35** with LDA with or without

Scheme 6. Attempted Alkylations of Spirocyclic Systems at C7



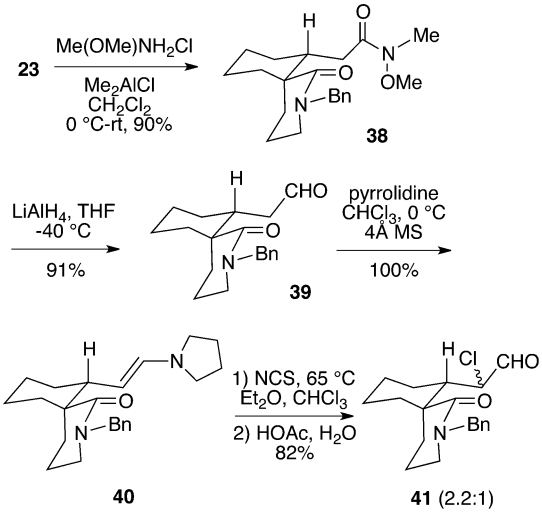
an additive such as HMPA or 18-crown-6 followed by addition of an electrophile such as methyl acrylate, TMSCl, or TBSCl led to recovered starting material. D_2O quenches again did not result in any incorporation of deuterium into the starting material.

In view of these inexplicable results, we turned to the possibility of effecting an enamine alkylation. Thus, ester **31** was reduced to the aldehyde **36**, which could be converted in high yield to the stable, isolable pyrrolidinoenamine **37** (Scheme 6).[21] The structure of this compound was secured by X-ray crystallography (see the Supporting Information). This compound proved to be unreactive toward electrophiles, including various acrylate derivatives and allyl bromide, at temperatures ranging from 80 to 140 °C as well as under microwave irradiation.

The *N*-benzyllactam derivative corresponding to enamine **37** was also prepared (Scheme 7). To access this material, ester **23** was first transformed to *N*-methoxy-*N*-methylamide **38** in high yield using a combination of *N*,*O*-dimethylhydroxylamine hydrochloride and dimethylaluminum chloride.[22] Reduction of this amide with lithium aluminum hydride then afforded aldehyde **39**,[23] which was cleanly converted to pyrrolidinoenamine **40**.[21] This enamine proved to be unreactive toward alkylation at C7 under the same sets of conditions as noted above for the NH-lactam enamine **37**. It was found, however, that the reaction of enamine **40** with *N*-chlorosuccinimide in a chloroform/ether mixture followed by hydrolysis with aqueous acetic acid produces α-chloroaldehyde **41** as a 2.2:1 mixture of diastereomers.[24]

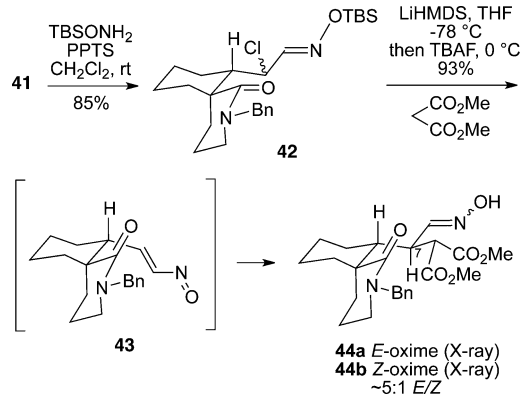
In recent years we have been involved in exploring the scope and applications of both inter- and intramolecular conjugate additions of carbon nucleophiles to nitrosoalkenes.[25,26] This methodology provides an attractive "umpolung" approach to α-alkylation of aldehydes and ketones. With α-chloroaldehyde **41** in hand, we decided to see whether this chemistry might solve the intractable C7 alkylation problem. Thus, compound **41** was

Scheme 7. Conversion of Spirocyclic Ester 23 to α-Chloroaldehyde 41



converted to *O*-TBS-α-chlorooxime **42** in high yield using *O*-TBS-hydroxylamine (Scheme 8). According to the experimen-

Scheme 8. Alkylation at C7 via a Diastereoselective Nitrosoalkene Conjugate Addition



tal protocol that we previously developed,[26b] chlorooxime derivative **42** was first combined with the lithium enolate of dimethyl malonate at −78 °C. TBAF was then slowly added at that temperature, and the reaction mixture was warmed to 0 °C prior to an aqueous quench. These reaction conditions led to the formation of a ~5:1 *E*/*Z* mixture of oximes **44a** and **44b** in excellent combined yield. It was possible to obtain pure crystalline samples of each of these compounds (see the Experimental Section), and each was analyzed by X-ray crystallography. We were pleased to find that *both* of these adducts had the desired myrioneurinol stereochemistry at C7 and differed only in the oxime geometry, with the major isomer **44a** having the *E* configuration and the minor isomer **44b** having the *Z* configuration. It seems reasonable to assume that this transformation proceeds via attack of the malonate anion onto the least hindered face of a nitrosoalkene conformer like **43**, which would produce the observed product configuration at C7. However, at this stage we are unable to rationalize why this particular conformation seems to be the reactive one. In addition, we can only speculate that the (*E*)-nitrosoalkene shown is involved here since the geometry of such a highly

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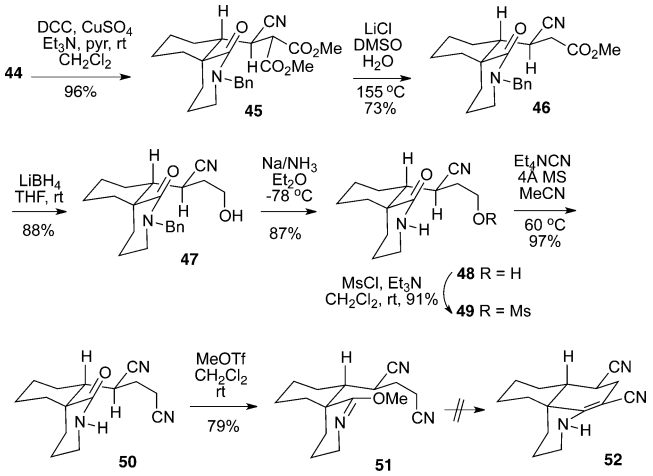
reactive, transient species formed via this process is presently unknown.

Approaches to the Formation of the Myrioneurinol B-Ring. With the C7 alkylation problem finally solved, we next turned to the construction of the B-ring of the alkaloid via a plan similar to the one shown in Scheme 1. Toward this end, the mixture of oximes **44a** and **44b** was dehydrated[27] to form nitrile **45** (Scheme 9). Subjection of malonate **45** to Krapcho

Scheme 9. Attempted Formation of the B-Ring by an Imidate Nitrile Anion Cyclization



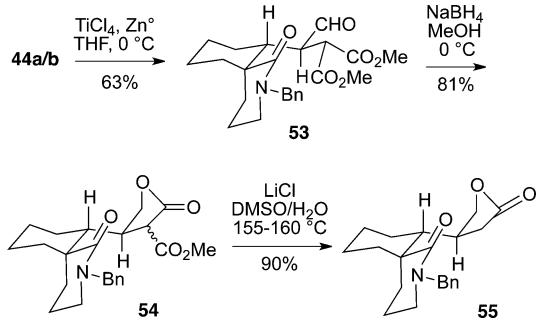
decarboxylation conditions then led to ester **46**.[28] Selective reduction of this ester with lithium borohydride yielded alcohol **47**, and the *N*-benzyl group was subsequently removed by a dissolving metal reduction to produce NH lactam alcohol **48**. The alcohol was then converted to the corresponding mesylate **49**, and displacement with cyanide afforded dinitrile **50**. It was then possible to convert lactam **50** to the *O*-methyl imidate **51** using methyl triflate. Unfortunately, treatment of nitrile imidate **51** with a variety of amide bases such as LDA and LiHMDS failed to produce any of the desired tricyclic cyanoenamine **52**. Rather, only extensive decomposition of the starting material was observed in these attempts. Since our original approach was unsuccessful, it became necessary to investigate other strategies to form the alkaloid B-ring.

The initial alternative B-ring strategy that was investigated was based upon the application of an *N*-sulfonyllactam/olefin ring-closing metathesis reaction of the type developed by Zhou and Rainier.[29] In order to prepare the required substrate for this metathesis, the mixture of oximes **44a** and **44b** was first converted to aldehyde **53** via a reductive cleavage (Scheme 10). Sodium borohydride reduction of the aldehyde yielded α-carbomethoxylactone **54**, which when subjected to Krapcho decarboxylation conditions[28] provided γ-lactone **55**.

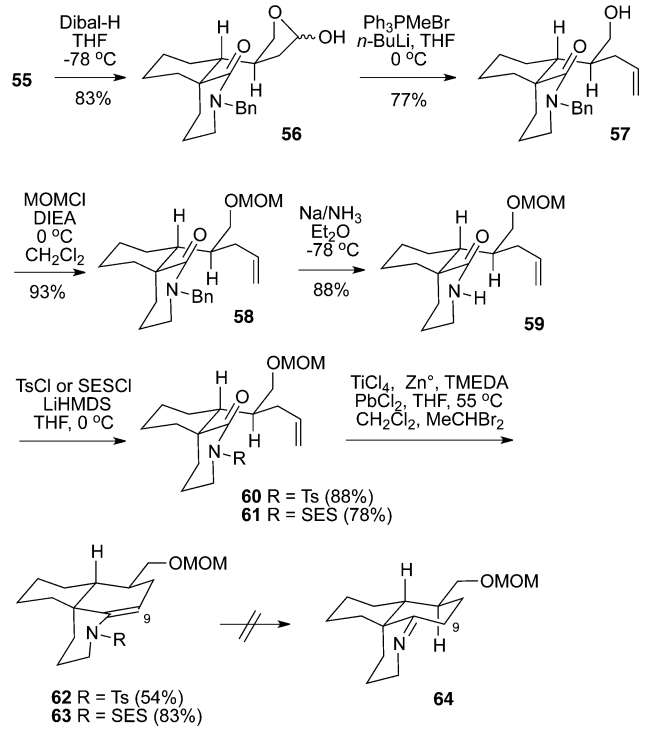
Partial reduction of lactone **55** with diisobutylaluminum hydride gave lactol **56**, and a subsequent Wittig reaction led to terminal olefin **57** (Scheme 11). The alcohol moiety in **57** was protected as the MOM derivative **58**, and the benzyl group on the lactam nitrogen was removed by a dissolving metal reduction, leading to NH lactam **59**. Two different sulfonyl groups were then installed on the nitrogen of lactam **59**, resulting in the *N*-tosyl compound **60** and the corresponding SES-functionalized[30] derivative **61**.

We were pleased to find that by the use of the experimental conditions described by Zhou and Rainier[29] it was possible to

Scheme 10. Conversion of Oximes 44 into Lactone 55



Scheme 11. Rainier-Type Olefin/*N*-Sulfonyllactam Metathesis for Formation of the B-Ring



transform *N*-sulfonyllactams **60** and **61** into the desired tricyclic *N*-sulfonylenamines **62** and **63**, respectively. In order for this route to be viable, however, it would be necessary to introduce a carbon substituent into the system at C9. The plan here was to first remove the *N*-sulfonyl group from **62** and/or **63** to form imine **64**, which would then be deprotonated and the resulting anion alkylated or acylated at C9. Unfortunately, all attempts to cleave the sulfonyl groups from **62** and **63** failed. In addition, direct acylation or alkylation of the *N*-sulfonylenamines also was unsuccessful since these intermediates proved unreactive toward various electrophiles.

In view of these disappointing results, we explored another approach based upon an intramolecular aza-Sakurai reaction, which we anticipated would generate the B-ring and also concurrently introduce a C9 substituent (vide infra). The substrate needed for this transformation was prepared via the sequence shown in Scheme 12. γ-Lactone **55** was cleanly ring-opened with *N*,*O*-dimethylhydroxylamine hydrochloride and dimethylaluminum chloride to afford amide alcohol **65**.[22] The alcohol was protected as the MOM ether **66**, and reduction of the *N*-methoxy-*N*-methylamide moiety with lithium aluminum

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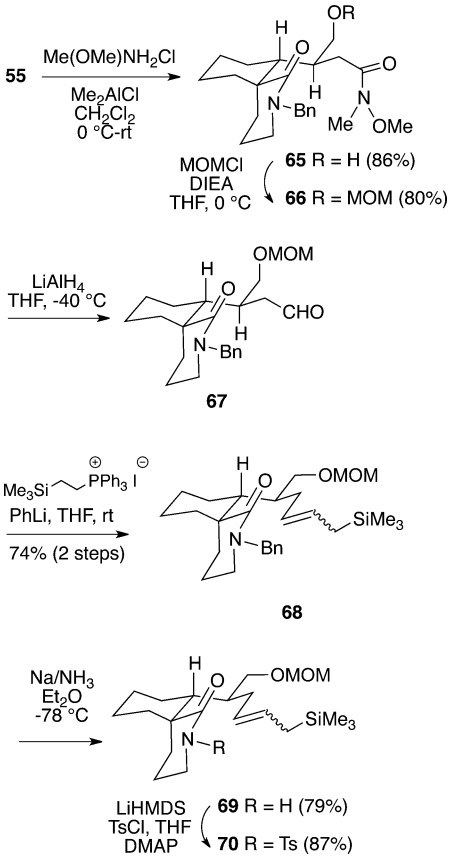
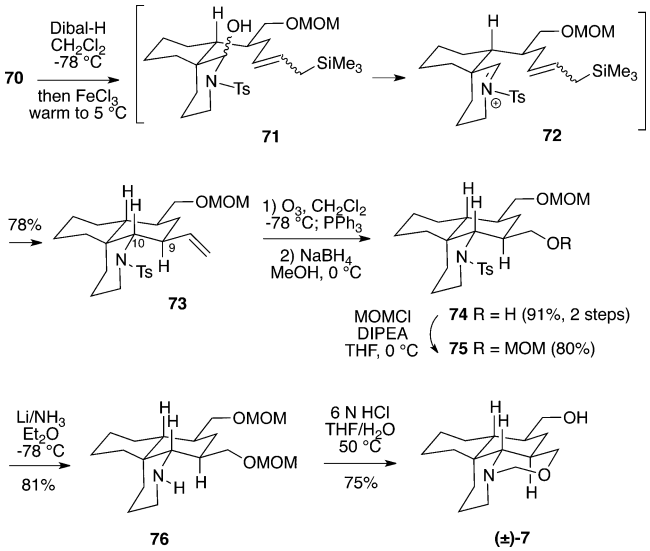
Scheme 12. Preparation of Allyl Silane Precursor 70 for the Aza-Sakurai Reaction



Scheme 13. Aza-Sakurai Reaction and Completion of the Myrioneurinol Total Synthesis



hydride then afforded aldehyde **67**.[23] This aldehyde underwent a Wittig reaction with the Seyferth β-trimethylsilylethyl ylide[31] to give allyl silane **68** as a 2.5:1 mixture of *E* and *Z* geometric isomers, which proved to be of no consequence to the synthesis. Cleavage of the *N*-benzyl group of **68** with sodium/ammonia gave NH lactam **69**, which was then converted to *N*-tosyllactam **70**.

The plan for the intramolecular aza-Sakurai reaction was to generate allyl silane *N*-sulfonyliminium ion **72** (Scheme 13). We anticipated that this species would then cyclize via a conformation such as that shown, where the incipient B-ring would be a chairlike conformer and the allyl silane moiety would be in a quasi-equatorial position, resulting in tricyclic product **73** having the desired C9,C10 relative configuration. It was found that the experimental conditions that we had previously applied to effect a related aza-Sakurai cyclization worked well here.[32] Thus, partial reduction of *N*-sulfonyllactam **70** with diisobutylaluminum hydride at low temperature to form **71** followed by addition of anhydrous ferric chloride gave the desired tricyclic compound **73** in good yield as a single stereoisomer now having the five contiguous stereogenic centers of the alkaloid in place. The structure and stereochemistry of this product were established by 2D NMR analysis (see the Supporting Information), and its subsequent conversion to myrioneurinol was carried out (vide infra).

To complete the total synthesis of the alkaloid, the vinyl group of tricycle **73** was cleaved by ozonolysis, and the intermediate aldehyde product was immediately reduced with sodium borohydride to yield alcohol **74**. A MOM group was installed on the hydroxymethyl group to form bis-MOM ether **75**, and the *N*-tosyl group was subsequently cleaved by a dissolving metal reduction to give amine **76**. Finally, exposure of **76** to HCl in aqueous THF led to hydrolytic cleavage of one of the MOM groups to give the corresponding alcohol and cyclization of the other to form the 1,3-oxazine, producing racemic myrioneurinol (**7**). This material had proton and carbon NMR spectra (including 2D spectra) identical to those of the natural product (see the Supporting Information).[33]

CONCLUSION

We have described the details of the first total synthesis of racemic myrioneurinol (**7**) via a route that requires approximately 25 operations starting from simple valerolactam (**24**). Notable steps in the synthetic strategy include (1) a diastereoselective intramolecular chelation-controlled Michael spirocyclization that serves to establish the stereogenic centers at C5 (quaternary) and C6 along with the A/D-rings of the alkaloid; (2) a diastereoselective intermolecular addition of dimethyl malonate anion to a transient nitrosoalkene to generate the desired chirality at C7; (3) and a diastereoselective intramolecular aza-Sakurai cyclization involving a *N*-sulfonyliminium ion to form the B-ring and C9 substituent along with the associated C9 and C10 stereogenic centers. Myrioneurinol is the most complex *Myrioneuron* alkaloid synthesized to date. Hopefully the work described here will stimulate further research in this interesting area.

EXPERIMENTAL SECTION

General Methods. All nonaqueous reactions were carried out in oven- or flame-dried glassware under an atmosphere of argon. All reagents were purchased from commercial vendors and used as received, unless otherwise specified. Anhydrous tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), diethyl ether (Et_2O), and acetonitrile (MeCN) were obtained from a solvent purification system. Reaction mixtures were stirred magnetically, and the reactions were monitored by thin-layer chromatography (TLC) with 250 μm EMD 60 F_{254} precoated silica gel plates. Flash chromatographic separations were performed using silica gel (240–400 mesh). ^{1}H and ^{13}C NMR chemical shifts are reported relative to chloroform (δ 7.24 and 77.0, respectively). High-resolution mass spectra were recorded on a time-of-flight (TOF) mass spectrometer.

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3-(4-(1,3-Dioxolan-2-yl)butyl)-1-benzylpiperidin-2-one (20). *n*-Butyllithium (2.5 M in hexanes, 1.25 mL, 3.12 mmol) was added to diisopropylamine (0.42 mL, 2.92 mmol) at 0 °C, and the resulting light-yellow gel was diluted with anhydrous THF (0.1 mL) and stirred for 45 min at that temperature. This solution of LDA was added dropwise at −78 °C to a stirred solution of 1-benzylpiperidin-2-one (**18**) (509 mg, 2.7 mmol) in dry THF (5 mL), and the mixture was warmed to 0 °C and stirred for 1 h. Neat 2-(4-iodobutyl)-1,3-dioxolane (**19**) (2.07 g, 8.1 mmol) was added dropwise, and the mixture was warmed to rt and stirred overnight. The mixture was diluted with saturated NH_4Cl(aq) and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (gradient 20% to 50% EtOAc/hexanes) to afford lactam **20** as a clear colorless gum (416 mg, 49%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15−7.26 (m, 5H), 4.78 (t, J = 4.6 Hz, 1H), 4.57 (d, J = 10.4 Hz, 1H), 4.51 (d, J = 10.4 Hz, 1H), 3.89−3.91 (m, 2H), 3.76−3.77 (m, 2H), 3.11 (t, J = 5.9 Hz, 2H), 2.28−2.29 (m, 1H), 1.89−1.93 (m, 2H), 1.19−1.62 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 137.9, 128.9, 128.3, 127.6, 104.9, 65.2, 50.7, 47.8, 41.9, 34.2, 32.4, 27.5, 26.9, 24.5, 22.0; HRMS-ES+ ($C_{19}H_{28}NO_3$) calcd 318.2069 (MH^+), found 318.2054.

5-(1-Benzyl-2-oxopiperidin-3-yl)pentanal (21). To a solution of lactam **20** (416 mg, 1.3 mmol) in THF (5 mL) was added 1 N HCl(aq) (5 mL), and the mixture was stirred at rt for 6 h. Saturated $NaHCO_3$(aq) was added, and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to afford aldehyde **21** (355 mg, 100%) as a clear colorless gum that was used in the subsequent step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (s, 1H), 7.22−7.33 (m, 5H), 4.62 (d, J = 14.6 Hz, 1H), 4.53 (d, J = 14.6 Hz, 1H), 3.19 (dd, J = 7.3, 4.9 Hz, 2H), 2.45 (t, J = 1.7 Hz, 2H), 2.33−2.34 (m, 1H), 1.89−2.04 (m, 2H), 1.81−1.89 (m, 1H), 1.66−1.70 (m, 3H), 1.42−1.56 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7, 172.5, 137.5, 128.5, 128.0, 127.3, 50.3, 47.4, 43.7, 41.4, 31.7, 26.6, 26.5, 22.1, 21.7; IR (neat) 1724, 1605 cm^{-1}; HRMS-ES+ ($C_{17}H_{24}NO_2$) calcd 274.1807 (MH^+), found 274.1803.

Methyl 7-(1-Benzyl-2-oxopiperidin-3-yl)hept-2-enoate (22). To a stirred suspension of anhydrous lithium chloride (81 mg, 1.9 mmol) in dry MeCN (15 mL) at rt was added methyl diethylphosphonoacetate (0.34 mL, 1.9 mmol) and DBU (0.24 mL, 1.8 mmol). A solution of aldehyde **21** (440 mg, 1.61 mmol) in dry MeCN (5 mL) was added dropwise over 5 min. The resulting cloudy suspension was stirred for 24 h at rt and then diluted with saturated NH_4Cl(aq). The reaction mixture was extracted with EtOAc (3 × 50 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (25% EtOAc/hexanes) to afford (*E*)-α,β-unsaturated ester **22** (477 mg, 90%) as a clear colorless gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15−7.26 (m, 5H), 6.89−6.96 (m, 1H), 5.75 (d, J = 15.7 Hz, 1H), 4.55 (d, J = 14.6 Hz, 1H), 4.47 (d, J = 14.6 Hz, 1H), 3.66 (s, 3H), 3.11−3.14 (m, 2H), 2.27−2.29 (m, 1H), 2.16 (q, J = 6.9 Hz, 2H), 1.20−1.76 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 167.5, 149.9, 137.9, 128.9, 128.3, 127.6, 121.3, 51.7, 50.7, 47.7, 41.9, 32.5, 32.1, 28.4, 27.2, 26.8, 22.1; HRMS-ES+ ($C_{20}H_{28}NO_3$) calcd 330.2069 (MH^+), found 330.2070.

Methyl 2-Benzyl-1-oxo-2-azaspiro[5.5]undecan-7-yl)acetate (23). *Method A.* To a stirred solution of (*E*)-α,β-unsaturated ester **22** (215 mg, 0.65 mmol) in anhydrous THF (7 mL) was added dropwise freshly prepared LDA (1.7 M in THF, 0.45 mL, 0.78 mmol) at −78 °C. The resulting bright-yellow reaction mixture was slowly warmed to rt over 24 h and then diluted with saturated NH_4Cl(aq). The mixture was extracted with EtOAc (3 × 25 mL), and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography (gradient 10% to 30% EtOAc/hexanes) to afford spirocycle **23** (41 mg, 19%) as a light-yellow gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15−7.25 (m, 5H), 4.66 (d, J = 14.5 Hz, 1H), 4.36 (d, J = 14.5 Hz, 1H), 3.59 (s, 3H), 3.08−3.12 (m, 2H), 2.69 (t, J = 10.7 Hz, 1H), 2.12 (dd, J = 14.4, 3.2 Hz, 1H), 1.96 (dd, J = 14.5, 10.6 Hz, 1H), 1.05−1.75 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 173.6, 138.1, 128.9, 128.4, 127.6, 52.0, 51.1, 47.5, 46.2, 39.9, 37.8, 34.9, 27.2, 26.0. 23.4, 20.9, 19.7; IR (neat) 1733, 1675, 1172 cm^{-1}; HRMS-ES+ ($C_{20}H_{28}NO_3$) calcd 330.2069 (MH^+), found 330.2065.

Method B. To a stirred solution of NH lactam **31** (11.68 g, 48.7 mmol) in benzyl bromide (120 mL) was added silver(I) oxide (32.91 g, 146 mmol), tetra-*n*-butylammonium iodide (18.25 g, 48.7 mmol), and anhydrous calcium sulfate (33.90 g, 244 mmol). The reaction flask was covered with aluminum foil, and the mixture was stirred at rt for 44 h. The mixture was filtered through a Celite pad, which was washed with Et_2O, and the total filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (gradient 100% hexanes to 30% EtOAc/hexanes) to afford the *N*-Bn-lactam ester **23** as a greenish gum (11.59 g, 73%). This material had spectroscopic data identical to those of the material prepared by method A.

Benzyl 3-(Hex-5-en-1-yl)-2-oxopiperidine-1-carboxylate (26). To a stirred solution of valerolactam (**24**) (6.12 g, 61.7 mmol) in dry THF (250 mL) was added *n*-butyllithium (2.5 M in hexanes, 52 mL, 129.6 mmol) at 0 °C. The resulting yellowish-orange solution was stirred at 0 °C for 1 h, and then 6-bromohex-1-ene (10.00 g, 61.7 mmol) was added rapidly in one portion. The reaction mixture was stirred for 1 h and gradually warmed to rt. Brine was added, and the organic layer was separated. The aqueous layer was extracted with dichloromethane (2 × 250 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo to provide lactam **25** as a yellowish solid.

The crude lactam **25** was dissolved in dry THF (250 mL), and *n*-butyllithium (2.5 M in hexanes, 27.2 mL, 67.9 mmol) was added at −78 °C, after which the reaction mixture was stirred for 30 min. Benzyl chloroformate (13.3 mL, 92.6 mmol) was added dropwise, and the resulting bright-yellow solution was slowly warmed to rt over 1 h. Saturated NH_4Cl(aq) was added, and the mixture was extracted with ethyl acetate (3 × 250 mL). The organic phase was washed with brine and dried over anhydrous $MgSO_4$. The solution was concentrated in vacuo to afford a viscous yellowish oil that was purified by flash column chromatography on silica gel (15% EtOAc/hexanes) to yield N-Cbz-lactam **26** (17.37 g, 89%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29−7.48 (m, 5H), 5.76−5.89 (m, 1H), 5.30 (s, 2H), 4.94−5.05 (m, 2H), 3.81−3.89 (m, 1H), 3.67−3.75 (m, 1H), 2.41−2.45 (m, 1H), 1.72−2.12 (m, 6H), 1.28−1.59 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 154.8, 139.2, 136.0, 129.0, 128.6, 128.4, 114.9, 68.9, 46.5, 44.3, 34.1, 31.4, 29.3, 26.9, 26.2, 21.8; HRMS-ES+ ($C_{19}H_{26}NO_3$) calcd 316.1913 (MH^+), found 316.1909.

Benzyl 2-Oxo-3-(5-oxopentyl)piperidine-1-carboxylate (27). A solution of N-Cbz-lactam **26** (17.37 g, 55.1 mmol) in dry CH_2Cl_2 (500 mL) was cooled to −78 °C, and ozone was bubbled through the reaction mixture for 1 h until a light-blue coloration was achieved. The mixture was then purged with argon for 5 min, followed by the portionwise addition of triphenylphosphine (17.36 g, 66.2 mmol). The reaction mixture was warmed to rt over 6 h and then concentrated in vacuo to afford a yellowish oil. This material was purified by flash column chromatography on silica gel (gradient 25% to 40% EtOAc/hexanes) to afford aldehyde **27** (15.86 g, 90%) as a clear colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.70−9.75 (m, 1H), 7.31−7.45 (m, 5H), 5.27 (s, 2H), 3.69−3.82 (m, 1H), 3.47−3.67 (m, 1H), 2.42−2.47 (m, 3H), 1.62−1.88 (m, 5H), 1.23−1.49 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.0, 174.5, 154.6, 135.9, 129.0, 128.6, 128.5, 68.8, 46.4, 44.0, 31.2, 26.9, 26.3, 22.4, 21.9, 21.4; HRMS-ES+ ($C_{18}H_{24}NO_4$) calcd 318.1705 (MH^+), found 318.1696.

(*E*)-Benzyl 3-(7-Methoxy-7-oxohept-5-en-1-yl)-2-oxopiperidine-1-carboxylate (28). Anhydrous LiCl (2.63 g, 62.0 mmol) was flame-dried under a stream of argon and then suspended in dry MeCN (420 mL), to which was added methyl diethylphosphonoacetate (11.0 mL, 62.2 mmol) and DBU (7.9 mL, 56.9 mmol) at rt. A solution of aldehyde **27** (16.43 g, 51.8 mmol) in dry MeCN (150 mL) was added dropwise over 1 h, and the resulting cloudy white reaction mixture was stirred for 48 h at rt. Saturated NH_4Cl(aq) was added, and the organic layer was separated. The aqueous layer was extracted with

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EtOAc (3 × 250 mL), and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to afford a brownish oil. This crude material was purified by flash column chromatography on silica gel (20% EtOAc/hexanes) to provide (*E*)-α,β-unsaturated ester **28** (15.83 g, 82%) as a clear colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29−7.72 (m, 5H), 6.97 (dt, *J* = 15.6, 7.0 Hz, 1H), 5.83 (d, *J* = 15.6 Hz, 1H), 5.29 (s, 2H), 3.80−3.89 (m, 1H), 3.65−3.75 (m, 4H), 2.36−2.48 (m, 1H), 2.21 (q, *J* = 7.2 Hz, 2H), 1.81−1.95 (m, 4H), 1.28−1.52 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 167.5, 154.7, 149.8, 135.9, 129.0, 128.7, 128.4, 121.5, 68.8, 51.8, 46.4, 44.2, 32.4, 31.3, 28.4, 27.0, 26.4, 22.0; HRMS-ES+ ($C_{21}H_{28}NO_5$) calcd 374.1967 (MH^+), found 374.1958.

Benzyl 7-(2-Methoxy-2-oxoethyl)-1-oxo-2-azaspiro[5.5]-undecane-2-carboxylate (30). $TiCl_4$ (10.1 mL, 91.4 mmol) and dry Et_3N (12.7 mL, 91.4 mmol) were dissolved in dry CH_2Cl_2 (275 mL) at 0 °C, and the resulting deep-maroon solution was stirred for 15 min. A solution of (*E*)-α,β-unsaturated ester **28** (16.95 g, 45.5 mmol) in dry CH_2Cl_2 (120 mL) was added dropwise over 10 min, and the reaction mixture was subsequently stirred at rt for 1 h. Saturated $NaHCO_3$(aq) was carefully added at 0 °C, and the mixture was stirred for 30 min and then extracted with CH_2Cl_2 (4 × 250 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo to afford a yellow oil that was purified by flash chromatography on silica gel (gradient 20% to 35% EtOAc/hexanes) to give spirocyclic ester **30** (14.58 g, 86%) as a light-yellow gum. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28−7.41 (m, 5H), 5.23 (s, 2H), 3.66−3.79 (m, 1H), 3.55−3.62 (m, 4H), 2.65 (t, *J* = 9.6 Hz, 1H), 2.22 (dd, *J* = 12.4, 2.9 Hz, 1H), 2.02 (dd, *J* = 18.9, 7.7 Hz, 1H), 1.56−1.86 (m, 9H), 1.19−1.26 (m, 2H), 1.09 (q, *J* = 9.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.4, 173.2, 155.0, 136.0, 128.9, 128.4, 128.3, 68.7, 51.9, 49.4, 47.5, 39.8, 37.4, 35.6, 27.3, 25.8, 24.2, 20.9, 20.2; HRMS-ES + ($C_{21}H_{28}NO_5$) calcd 374.1967 (MH^+), found 374.1968.

Methyl 2-(1-Oxo-2-azaspiro[5.5]undecan-7-yl)acetate (31). To a stirred solution of spirocyclic ester **30** (14.57 g, 39.1 mmol) in EtOAc (150 mL) was added 10% palladium on carbon (20% w/w, 2.91 g). The reaction flask was purged and filled with hydrogen gas at 1 atm (supplied via two balloons). The resulting suspension was stirred for 36 h at rt and then filtered through a pad of Celite, which was washed with EtOAc. The filtrate was concentrated in vacuo to afford NH lactam **31** as a slightly yellowish gum (9.21 g, 98%) which was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.56 (br s, 1H), 3.26 (s, 3H), 3.23−3.25 (m, 2H), 2.62 (t, *J* = 10.7 Hz, 1H), 2.23 (dd, *J* = 14.5, 3.2 Hz, 1H), 2.05 (dd, *J* = 14.6, 10.7 Hz, 1H), 1.25−1.87 (m, 11H), 1.06 (q, *J* = 13.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7, 173.5, 51.9, 45.7, 42.5, 39.4, 37.7, 34.6, 26.8, 25.9, 23.2, 20.7, 19.7; HRMS-ES+ ($C_{13}H_{22}NO_3$) calcd 240.1600 (MH^+), found 240.1579.

7-(2-Hydroxyethyl)-2-azaspiro[5.5]undecan-1-one (32). To a stirred suspension of $LiAlH_4$ (20 mg, 0.40 mmol) in anhydrous THF (1 mL) at 0 °C was added dropwise NH lactam **31** (25 mg, 0.10 mmol) as a solution in THF (1 mL) over 5 min. The reaction mixture was stirred for 4 h at 0 °C and then carefully quenched with MeOH. The mixture was diluted with 1 N HCl(aq) and extracted with $CHCl_3$ (3 × 25 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to provide alcohol **32** as a white crystalline solid. The crude alcohol **32** was recrystallized from a minimal amount of refluxing Et_2O/MeOH to afford clear prisms that were suitable for X-ray analysis (17 mg, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.24 (br s, 1H), 3.57 (t, *J* = 5.9 Hz, 2H), 3.22−3.31 (m, 2H), 2.80 (br s, 1H), 2.18−2.29 (m, 1H), 1.07−1.98 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.7, 61.0, 42.6, 38.4, 36.7, 34.6, 30.1, 28.0, 26.3, 22.6, 20.8, 19.3; IR (neat) 3290, 1636, 1049 cm^{-1}; HRMS-ES+ ($C_{12}H_{22}NO_2$) calcd 212.1651 (MH^+), found 212.1670.

2-(1-Oxo-2-azaspiro[5.5]undecan-7-yl)acetaldehyde (36). To a stirred solution of NH lactam **31** (355 mg, 1.48 mmol) in dry CH_2Cl_2 (35 mL) at −78 °C was added dropwise DIBAL-H (1.5 M in PhMe, 2.96 mmol, 2.0 mL) over 5 min. The reaction mixture was stirred for 2 h at −78 °C, carefully quenched with MeOH, and then warmed to rt. An equal volume of saturated aqueous potassium sodium tartrate solution was added, and the mixture was stirred at rt for 1 h. The mixture was separated, and the aqueous layer extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (20% CH_2Cl_2/Et_2O + 1% MeOH) to furnish aldehyde **36** as a clear gum (208 mg, 67%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.63−9.67 (m, 1H), 6.37 (br s, 1H), 3.25−3.48 (m, 2H), 2.72−2.80 (m, 1H), 2.31 (ddd, *J* = 17.1, 3.5, 1.6 Hz, 1H), 1.91 (ddd, *J* = 15.0, 9.1, 3.7 Hz, 1H), 1.67−1.98 (m, 6H), 1.04−1.66 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.0, 177.7, 47.3, 45.8, 42.5, 37.1, 34.5, 27.4, 26.1, 23.3, 20.6, 19.6; IR (neat) 1720, 1645 cm^{-1}; HRMS-ES+ ($C_{12}H_{20}NO_2$) calcd 210.1494 (MH^+), found 210.1495.

7-((*E*)-2-(Pyrrolidin-1-yl)vinyl)-2-azaspiro[5.5]undecan-1-one (37). To a stirred solution of aldehyde **36** (50 mg, 0.24 mmol) in $CHCl_3$ (1 mL) at 0 °C was added 4 Å molecular sieves (300 mg) and pyrrolidine (0.29 mmol, 0.024 mL). The reaction mixture was stirred for 1.5 h at 0 °C, filtered through a Celite pad, and concentrated in vacuo to give pyrrolidinoenamine **37** as a white solid that was used without further purification (63 mg, 100%). A small sample (ca. 5 mg) of enamine **37** was recrystallized from Et_2O to afford clear prisms that were suitable for X-ray analysis. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.08−6.19 (m, 2H), 3.95 (dd, *J* = 13.8, 7.6 Hz, 1H), 2.85−3.25 (m, 6H), 2.62−2.73 (m, 1H), 1.11−2.05 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.6, 136.9, 100.2, 49.6, 47.4, 43.8, 42.7, 34.3, 28.1, 26.3, 25.2, 23.5, 20.8, 20.4; HRMS-ES+ ($C_{16}H_{27}N_2O$) calcd 263.2123 (MH^+), found 263.2131.

2-(2-Benzyl-1-oxo-2-azaspiro[5.5]undecan-7-yl)-*N*-methoxy-*N*-methylacetamide (38). To a stirred suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (10.16 g, 105.7 mmol) in dry CH_2Cl_2 (300 mL) at 0 °C was added dropwise dimethylaluminum chloride (1 M in hexane, 105.7 mL, 105.7 mmol). The reaction mixture was warmed to rt and stirred for 2 h. A solution of *N*-Bn-lactam **23** (11.59 g, 35.2 mmol) in dry CH_2Cl_2 (60 mL) was added, and the mixture was stirred for 24 h at rt. An equal volume of saturated aqueous potassium sodium tartrate solution was added, and the resulting biphasic mixture was stirred for 2 h at rt. The aqueous layer was extracted with CH_2Cl_2 (3 × 250 mL), and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to afford a brownish oil. This material was purified via flash column chromatography on silica gel (50% EtOAc/hexanes) to afford *N*-methoxy-*N*-methylamide **38** as a light-yellow gum (11.34 g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21−7.31 (m, 5H), 4.68 (d, *J* = 14.6 Hz, 1H), 4.46 (d, *J* = 14.6 Hz, 1H), 3.65 (s, 3H), 3.16−3.27 (m, 5H), 2.75 (br s, 1H), 2.27 (m, 1H), 2.12 (m, 1H), 1.10−1.94 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.4, 138.2, 128.9, 128.3, 127.6, 61.6, 51.1, 47.7, 46.3, 39.6, 35.6, 35.1, 32.6, 27.2, 26.1, 23.5, 20.9, 19.7; HRMS-ES+ ($C_{21}H_{31}N_2O_3$) calcd 359.2335 (MH^+), found 359.2335.

2-(2-Benzyl-1-oxo-2-azaspiro[5.5]undecan-7-yl)-acetaldehyde (39). To a stirred solution of *N*-methoxy-*N*-methylamide **38** (11.34 g, 31.7 mmol) in dry THF (300 mL) at −40 °C was added lithium aluminum hydride (4.79 g, 126.6 mmol) in portions over 5 min. The resulting dark-gray suspension was stirred for 1 h at −40 °C and then carefully diluted with methanol followed by 1 N NaOH(aq). The mixture was warmed to rt, and additional 1 N NaOH(aq) solution was added. The mixture was extracted with EtOAc (4 × 200 mL), and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude material was purified via flash column chromatography on silica gel (gradient 25% to 35% EtOAc/hexanes) to afford aldehyde **39** as a waxy yellowish solid (8.62 g, 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.61 (dd, *J* = 3.7, 1.6 Hz, 1H), 7.17−7.34 (m, 5H), 4.67 (d, *J* = 14.5 Hz, 1H), 4.37 (d, *J* = 14.5 Hz, 1H), 3.05−3.21 (m, 2H), 2.78−2.86 (m, 1H), 2.15 (ddd, *J* = 14.4, 3.6, 1.5 Hz, 1H), 2.04 (ddd, *J* = 14.5, 10.3, 3.8 Hz, 1H), 1.65−2.00 (m, 7H), 1.34−1.64 (m, 6H), 1.17 (qd, *J* = 12.5, 4.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.3, 175.3, 137.9, 129.1, 128.4, 127.8, 51.2, 47.6, 47.4, 46.2, 37.7, 34.8, 27.7, 26.1, 23.5, 20.8, 19.6; HRMS-ES+ ($C_{19}H_{26}NO_2$) calcd 300.1964 (MH^+), found 300.1956.

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2-(2-Benzyl-1-oxo-2-azaspiro[5.5]undecan-7-yl)-2-chloroacetaldehyde (41). To a stirred solution of aldehyde **39** (8.62 g, 28.8 mmol) in dry $CHCl_3$ (175 mL) at 0 °C were added powdered 4 Å molecular sieves (38.2 g) and pyrrolidine (2.82 mL, 34.5 mmol). The reaction mixture was stirred for 1.5 h at 0 °C and then filtered through a pad of Celite, which was washed with dry Et_2O (1 × 50 mL) and dry CH_2Cl_2 (2 × 50 mL) to afford a solution of pyrrolidinoenamine **40**. ^{1}H NMR (obtained on a sample of crude material after concentration in vacuo; 300 MHz, $CDCl_3$) δ 7.23−7.36 (m, 5H), 6.20 (d, J = 13.7 Hz, 1H), 5.13 (d, J =14.7 Hz, 1H), 4.12 (d, J = 14.7 Hz, 1H), 3.96 (dd, J = 13.6, 7.8 Hz, 1H), 3.02−3.23 (m, 2H), 2.92−3.01 (m, 4H), 2.80−2.88 (m, 1H), 1.14−1.93 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.2, 138.2, 136.9, 128.8, 128.4, 127.4, 100.2, 51.3, 49.4, 47.9, 44.6, 34.5, 28.6, 26.5, 25.3, 23.9, 21.1, 20.4.

To the above stirred $CHCl_3$/Et_2O solution of enamine **40** (10.14 g, 28.8 mmol) was added *N*-chlorosuccinimide (3.81 g, 28.5 mmol) in one portion. The reaction mixture was heated at reflux for 30 min and then stirred at rt for 5 h. Aqueous acetic acid (10% v/v) was added, and the resulting biphasic mixture was stirred for 30 min. The aqueous layer was extracted with EtOAc (2 × 50 mL), and the combined organic layers were washed with 1 N HCl(aq), saturated $NaHCO_3$(aq), and brine, dried over anhydrous $MgSO_4$, and then concentrated in vacuo. The resulting brownish oil was purified by flash column chromatography on silica gel (gradient 7.5% to 15% EtOAc/hexanes) to afford α-chloroaldehyde **41** as an inseparable ∼2.2:1 mixture of C7 diastereomers (7.84 g, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.37 (d, J = 4.8 Hz, 1H), 9.30 (d, J = 3.6 Hz, 1H), 7.21−7.35 (m, 5H), 5.05 (d, J = 14.7 Hz, 1H), 4.93 (d, J = 14.5 Hz, 1H), 4.72 (s, 1H), 4.22 (d, J = 14.5 Hz, 1H), 3.98−4.04 (m, 2H), 3.87 (dd, J = 8.4, 4.8 Hz, 1H), 2.98−3.31 (m, 4H), 1.22−2.04 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.4, 193.9, 175.3, 175.2, 137.7, 137.7, 129.0, 128.9, 128.7, 128.4, 127.4, 127.3, 68.3, 66.3, 65.8, 65.7, 51.4, 51.0, 47.4, 47.1, 46.3, 45.3, 43.9, 43.6, 35.5, 35.4, 25.9, 25.8, 25.1, 24.1, 23.5, 23.1, 20.7, 20.6, 19.6, 19.2, 15.7; HRMS-ES+ ($C_{19}H_{25}NO_2Cl$) calcd 334.1574 (MH^+), found 334.1574.

(*E*)-2-(2-Benzyl-1-oxo-2-azaspiro[5.5]undecan-7-yl)-2-chloroacetaldehyde *O*-(*tert*-Butyldimethylsilyl)oxime (42). To a stirred solution of α-chloroaldehyde **41** (∼2.2:1 C7 diastereomeric mixture, 7.84 g, 23.54 mmol) in dry CH_2Cl_2 (110 mL) was added *O*-TBS-hydroxylamine (6.85 g, 47.08 mmol), powdered 4 Å molecular sieves (650 mg), and PPTS (1.00 g, 3.97 mmol). The reaction mixture was stirred for 24 h at rt and then filtered through a pad of Celite, which was washed with CH_2Cl_2. The combined filtrates were concentrated to afford a colorless oil that was purified by flash column chromatography on silica gel (gradient 2.5% to 5% EtOAc/hexanes) to provide the *O*-TBS-oxime **42** as a separable ∼2.2:1 mixture of diastereomers (9.25 g total, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) (major) δ 7.48 (d, J = 9.3 Hz, 1H), 7.19−7.36 (m, 5H), 5.53 (d, J = 15.0 Hz, 1H), 4.35 (t, J = 9.3 Hz, 1H), 3.63 (d, J = 15.0 Hz, 1H), 3.10−3.21 (m, 2H), 2.74−2.86 (m, 1H), 2.20−2.25 (m, 1H), 1.13−2.05 (m, 11H), 0.98 (s, 9H), 0.23 (s, 3H), 0.21 (s, 3H); ^{1}H NMR (minor) δ 7.18−7.65 (m, 5H), 7.04 (d, J = 8.8 Hz, 1H), 5.09−5.18 (m, 2H), 3.86 (d, J = 14.7 Hz, 1H), 3.01−3.13 (m, 2H), 2.74−2.80 (m, 1H), 2.17−2.31 (m, 1H), 1.16−1.87 (m, 11H), 0.95 (s, 9H), 0.22 (s, 3H), 0.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) (major) δ 175.4, 155.0, 138.2, 129.0, 128.1 127.6, 62.7, 51.0, 47.1, 46.8, 46.1, 35.3, 26.4, 25.8, 25.4, 22.4, 20.9, 19.4, 18.4, −4.5, −4.8; ^{13}C NMR (minor) δ 175.3, 153.3, 137.8, 128.9, 128.1, 127.6, 53.8, 51.0, 47.1, 46.9, 46.2, 35.3, 26.3, 25.8, 25.5, 22.3, 20.9, 19.3, 18.4, −4.7, −4.9; HRMS-ES+ ($C_{25}H_{40}N_2O_2SiCl$) (major) calcd 463.2548 (MH^+), found 463.2551; (minor) calcd 463.2548 (MH^+), found 463.2543.

Dimethyl 2-((*E*/*Z*)-1-(2-Benzyl-1-oxo-2-azaspiro[5.5]undecan-7-yl)-2-(hydroxyimino)ethyl)malonate (44a/44b). To a stirred solution of dimethyl malonate (1.21 mL, 10.6 mmol) in dry THF (60 mL) at −78 °C was added dropwise LiHMDS (1 M in THF, 10.6 mL, 10.6 mmol), and the resulting yellow solution was stirred for 30 min at that temperature. A solution of *O*-TBS-oxime **42** (∼2.2:1 mixture of C7 diastereomers, 4.10 g, 8.9 mmol) in dry THF (30 mL) was added dropwise over 5 min, followed by the dropwise addition of TBAF (1 M in THF, 17.7 mL, 17.7 mmol) over 5 min. The reaction mixture was immediately warmed to 0 °C via transfer to an ice bath and stirred for 4 h at that temperature. The mixture was diluted with saturated NH_4Cl(aq) and extracted with EtOAc (3 × 200 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give an oil that was purified by flash chromatography on silica gel (10% Et_2O in CH_2Cl_2) to afford oximes **44a** and **44b** as a white solid (∼5:1 mixture of (*E*)- and (*Z*)-oxime geometric isomers, 3.66 g, 93%). The geometric isomers **44a** (*E*) and **44b** (*Z*) (∼5 mg of solid from column fractions near the beginning and end of the elution, respectively) were each recrystallized from a minimal amount of Et_2O via slow evaporation to afford clear prisms that were analyzed by X-ray crystallography. All attempts to purify a sufficient quantity of the minor isomer (**44b**) by chromatography for NMR analysis were unsuccessful. ^{1}H NMR (300 MHz, $CDCl_3$) (major (**44a**)) δ 7.72−7.77 (m, 2H), 7.23−7.36 (m, 5H), 4.80 (d, J = 14.6 Hz, 1H), 4.39 (d, J = 14.6 Hz, 1H), 3.90 (d, J = 5.6 Hz, 1H), 3.77 (s, 3H), 3.73 (s, 3H), 3.14−3.31 (m, 2H), 2.79−2.86 (m, 1H), 2.55 (dt, J = 13.1, 3.2 Hz, 1H), 1.06−1.93 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) (major (**44a**)) δ 175.2, 169.1, 168.9, 152.6, 137.8, 129.0, 128.4, 127.7, 55.7, 53.1, 52.7, 51.1, 47.8, 47.4, 44.1, 42.2, 35.1, 26.5, 25.1, 23.1, 20.8, 19.5; HRMS-ES+ ($C_{24}H_{33}N_2O_6$) (mixture) calcd 445.2339 (MH^+), found 445.2342.

Dimethyl 2-((2-Benzyl-1-oxo-2-azaspiro[5.5]undecan-7-yl)-(cyano)methyl)malonate (45). To a stirred solution of oximes **44a** and **44b** (284 mg, 0.64 mmol) in dry CH_2Cl_2 (8 mL) were added $CuSO_4$·$5H_2O$ (100 mg), Et_3N (0.16 mL, 1.54 mmol), and pyridine (0.51 mL, 6.4 mmol). DCC (158 mg, 0.77 mmol) was then added in one portion, and the reaction mixture was stirred for 14 h at rt and then diluted with 1 N HCl(aq). The mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (20% EtOAc/hexanes) to provide nitrile **45** as a white waxy solid (263 mg, 96%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21−7.61 (m, 5H), 4.57 (dd, J = 19.4, 14.5 Hz, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 3.77 (d, J = 5.9 Hz, 1H), 3.16−3.33 (m, 2H), 3.07 (dd, J = 7.8, 1.2 Hz, 1H), 2.51 (dd, J = 12.1, 3.1 Hz, 1H), 2.04−2.15 (m, 1H), 1.32−1.94 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 167.4, 166.7, 137.7, 129.1, 128.3, 127.8, 119.2, 54.3, 53.7, 53.4, 51.3, 47.8, 47.5, 42.0, 34.8, 34.5, 26.0, 24.7, 23.5, 20.6, 19.2; IR (neat) 2242, 1741, 1625, 1201 cm^{-1}; HRMS-ES+ ($C_{24}H_{31}N_2O_5$) calcd 427.2233 (MH^+), found 427.2215.

Methyl 3-(2-Benzyl-1-oxo-2-azaspiro[5.5]undecan-7-yl)-3-cyanopropanoate (46). To a stirred solution of nitrile **45** (2.22 g, 5.2 mmol) in DMSO (50 mL) and H_2O (25 mL) was added LiCl (2.21 g, 52.1 mmol), and the reaction mixture was heated at 155 °C for 24 h and then cooled to rt. The mixture was extracted with EtOAc (3 × 200 mL), and the combined organic layers were washed with H_2O and brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (20% EtOAc/hexanes) to furnish ester **46** as a clear colorless gum (1.41 g, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18−7.32 (m, 5H), 4.64 (d, J = 14.5 Hz, 1H), 4.44 (d, J = 14.5 Hz, 1H), 3.71 (s, 3H), 3.14−3.25 (m, 2H), 2.80 (dd, J = 10.6, 3.6 Hz, 1H), 2.75 (d, J = 10.6 Hz, 1H), 2.59 (dd, J = 14.6, 3.5 Hz, 1H), 2.40 (dd, J = 12.8, 3.6 Hz, 1H), 1.23−2.07 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 170.2, 137.3, 128.2, 127.9, 127.4, 120.7, 52.1, 50.9, 47.2, 47.1, 43.6, 37.6, 34.4, 30.5, 25.6, 23.8, 22.9, 20.2, 18.7; IR (neat) 2239, 1739, 1623, 1203 cm^{-1}; HRMS-ES+ ($C_{22}H_{29}N_2O_3$) calcd 369.2178 (MH^+), found 369.2188.

2-(2-Benzyl-1-oxo-2-azaspiro[5.5]undecan-7-yl)-4-hydroxybutanenitrile (47). To a stirred suspension of $LiBH_4$ (21 mg, 0.95 mmol) in dry THF (3 mL) at rt was added dropwise a solution of ester **46** (250 mg, 0.68 mmol) in dry THF (5 mL). The reaction mixture was stirred for 15 h at rt and diluted with brine. The mixture was extracted with EtOAc (3 × 50 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (40% EtOAc/hexanes) to afford alcohol **47** as a clear gum (203 mg, 88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20−7.37 (m, 5H), 4.77 (d, J = 14.5 Hz, 1H), 4.37 (d, J =

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14.5 Hz, 1H), 3.84−3.93 (m, 1H), 3.61−3.72 (m, 1H), 3.49−3.59 (m, 1H), 3.21−3.36 (m, 2H), 2.53−2.59 (m, 2H), 1.30−2.18 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3, 137.2, 129.2, 128.3, 128.0, 122.6, 59.0, 51.6, 47.7, 47.6, 40.4, 34.7, 30.2, 26.1, 23.5, 23.1, 20.7, 18.8; HRMS-ES+ ($C_{21}H_{29}N_2O_2$) calcd 341.2229 (MH^+), found 341.2219.

4-Hydroxy-2-(1-oxo-2-azaspiro[5.5]undecan-7-yl)butanenitrile (48). Liquid ammonia (ca. 10 mL) was condensed at −78 °C, and Na metal (83 mg, 3.6 mmol) was added until the reaction mixture developed a deep-purple coloration. A solution of alcohol **47** (122 mg, 0.36 mmol) in dry Et_2O (10 mL) was added dropwise, and the reaction mixture was stirred for 45 min and then quenched by the addition of solid NH_4Cl (∼200 mg). The mixture was warmed to rt, and saturated NH_4Cl(aq) was added. The resulting biphasic mixture was extracted with EtOAc (3 × 50 mL), and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (gradient 5% to 10% MeOH/EtOAc) to afford N−H lactam alcohol **48** as a white solid (76 mg, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.15 (br s, 1H), 3.82−3.93 (m, 1H), 3.71 (dt, J = 12.3, 4.9 Hz, 1H), 3.28−3.46 (m, 2H), 2.66 (dd, J = 10.2, 4.9 Hz, 1H), 2.45 (dd, J = 12.6, 3.4 Hz, 1H), 2.07−2.15 (m, 1H), 1.24−2.06 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.6, 122.4, 59.1, 47.3, 42.5, 40.7, 34.8, 34.5, 30.2, 26.1, 23.3, 23.1, 20.6, 18.8; HRMS-ES+ ($C_{14}H_{23}N_2O_2$) calcd 251.1760 (MH^+), found 251.1752.

3-Cyano-3-(1-oxo-2-azaspiro[5.5]undecan-7-yl)propyl Methanesulfonate (49). To a stirred solution of NH lactam alcohol **48** (76 mg, 0.31 mmol) in dry CH_2Cl_2 (5 mL) at rt were added Et_3N (0.083 mL, 0.62 mmol) and MsCl (0.047 mL, 0.37 mmol), and the mixture was stirred for 4 h at that temperature. The reaction mixture was diluted with brine and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (5% MeOH/EtOAc) to furnish mesylate **49** as a clear gum (92 mg, 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.61 (br s, 1H), 4.28−4.43 (m, 2H), 3.23−3.36 (m, 2H), 3.07 (s, 3H), 2.59 (td, J = 7.8, 1.3 Hz, 1H), 2.28 (ddd, J = 12.7, 3.5, 1.2 Hz, 1H), 2.03−2.10 (m, 3H), 1.20−1.88 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.1, 121.0, 67.5, 47.0, 43.3, 42.3, 37.8, 34.6, 32.4, 30.9, 26.0, 23.8, 23.1, 20.5, 19.0; HRMS-ES+ ($C_{15}H_{25}N_2O_4S$) calcd 329.1535 (MH^+), found 329.1536.

2-(1-Oxo-2-azaspiro[5.5]undecan-7-yl)pentanedinitrile (50). To a solution of mesylate **49** (92 mg, 0.28 mmol) in dry MeCN (10 mL) were added Et_4NCN (308 mg, 1.96 mmol) and 4 Å molecular sieves (100 mg). The reaction mixture was heated at 60 °C for 12 h and cooled to rt. The mixture was filtered through a Celite pad, which was rinsed with EtOAc. The combined filtrates were washed with 1 M $NaHCO_3$(aq) and brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting orange oil was purified by flash column chromatography on silica gel (40% EtOAc/Et_2O) to afford dinitrile **50** as a yellowish gum (71 mg, 97%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.59 (br s, 1H), 3.30−3.41 (m, 2H), 2.49−2.68 (m, 3H), 2.29 (dd, J = 12.8, 2.9 Hz, 1H), 1.18−2.13 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.1, 120.5, 118.7, 47.0. 43.2, 42.4, 34.4, 33.6, 29.0, 26.0, 24.0, 23.2, 20.5, 19.0, 15.8; IR (neat) 2242, 2159, 1649 cm^{-1}; HRMS-ES+ ($C_{15}H_{22}N_3O$) calcd 260.1763 (MH^+), found 260.1750.

2-(1-Methoxy-2-azaspiro[5.5]undec-1-en-7-yl)pentanedinitrile (51). To a stirred solution of dinitrile **50** (7.5 mg, 0.029 mmol) in dry CH_2Cl_2 (1 mL) was added methyl trifluoromethanesulfonate (0.0144 mL, 0.087 mmol), and the reaction mixture was stirred for 10 h at rt. CH_2Cl_2 was added, and the mixture was washed with 1 M $NaHCO_3$(aq) and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel (40% EtOAc/Et_2O) to afford methyl imidate **51** as a clear gum (6.3 mg, 79%). ^{1}H NMR (850 MHz, $CDCl_3$) δ 3.64 (s, 3H), 3.62 (dd, J = 16.7, 3.6 Hz, 1H), 3.44 (pentet, J = 7.7 Hz, 1H), 2.58−2.62 (m, 1H), 2.51−2.54 (m, 1H), 2.44 (dd, J = 9.0, 8.9 Hz, 1H), 2.15 (dd, J = 12.5, 3.3 Hz, 1H), 2.05−2.08 (m, 1H), 2.02 (dt, J = 9.8, 3.9 Hz, 1H), 1.92 (pentet, J = 7.3 Hz, 1H), 1.88 (br d, J = 13.2 Hz, 1H), 1.80 (br d, J = 13.7 Hz, 1H), 1.72−1.75 (m, 1H), 1.61−1.68 (m, 5H), 1.57−1.59 (m, 1H), 1.51 (qt, J = 9.7, 3.9 Hz, 1H), 1.36 (qt, 13.2, 4.2 Hz, 1H); ^{13}C NMR (212.5 MHz, $CDCl_3$) δ 165.1, 120.0, 118.1, 52.6, 46.8, 43.3, 43.1, 33.8, 33.0, 28.8, 25.8, 23.7, 23.5, 20.2, 19.5, 15.5; HRMS-ES+ ($C_{16}H_{24}N_3O$) calcd 274.1919 (MH^+), found 274.1906.

Dimethyl 2-(1-(2-Benzyl-1-oxo-2-azaspiro[5.5]undecan-7-yl)-2-oxoethyl)malonate (53). To a stirred solution of the aldoxime E/Z isomer mixture **44a**/**44b** (1.06 g, 2.4 mmol) in dry THF (34 mL) at 0 °C was added Zn metal dust (1.58 g, 23.9 mmol) followed by the dropwise addition of $TiCl_4$ (1.37 mL, 11.9 mmol). The reaction mixture was stirred at 0 °C for 10 min and then carefully quenched with saturated $NaHCO_3$(aq). The mixture was filtered through a sintered glass frit, and the filter cake was washed with CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to yield a yellow oil that was purified by flash column chromatography on silica gel (20% EtOAc/hexanes) to give aldehyde **53** (651 mg, 63%) as a white fluffy solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.92 (s, 1H), 7.23−7.35 (m, 5H), 4.60 (d, J = 14.5 Hz, 1H), 4.50 (d, J = 14.5 Hz, 1H), 3.93 (d, J = 7.7 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.21−3.35 (m, 2H), 2.86 (dt, J = 7.7, 2.1 Hz, 1H), 2.70 (dt, J = 13.3, 2.5 Hz, 1H), 2.02−2.16 (m, 1H), 1.26−1.89 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.9, 174.8, 169.5, 169.0, 137.8, 129.2, 128.3, 127.8, 53.7, 53.4, 53.1, 52.5, 51.2, 47.6, 47.5, 43.9, 34.8, 26.7, 24.7, 24.6, 20.8, 19.5; IR (neat) 1734, 1627 cm^{-1}; HRMS-ES+ ($C_{24}H_{32}NO_6$) calcd 430.2230 (MH^+), found 430.2235.

Methyl 4-(2-Benzyl-1-oxo-2-azaspiro[5.5]undecan-7-yl)-2-oxotetrahydrofuran-3-carboxylate (54). To a stirred solution of aldehyde **53** (1.18 g, 2.7 mmol) in MeOH (60 mL) and CH_2Cl_2 (5 mL) at 0 °C was added $NaBH_4$ (102 mg, 2.7 mmol) in one portion. The reaction mixture was stirred at 0 °C for 5 min and then diluted with saturated NH_4Cl(aq). The mixture was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (20% EtOAc/hexanes) to afford α-carbomethoxylactone **54** as a white crystalline solid (879 mg, 81%). Mp 110−112 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22−7.35 (m, 5H), 5.34 (d, J = 14.6 Hz, 1H), 4.50 (t, J = 8.6 Hz, 1H), 4.02 (t, J = 9.3 Hz, 1H), 3.87 (s, 3H), 3.77 (d, J = 10.1 Hz, 1H), 3.69 (d, J = 14.7 Hz, 1H), 3.15−3.20 (m, 2H), 3.02 (pentet, J = 8.4 Hz, 1H), 2.58−2.62 (m, 1H), 1.28−2.09 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 173.0, 168.9, 137.9, 129.0, 128.2, 127.8, 71.5, 53.6, 51.3, 50.8, 47.1, 45.9, 44.8, 41.1, 35.2, 26.2, 24.8, 22.5, 20.5, 18.8; IR (neat) 1764, 1727, 1617, 1149 cm^{-1}; HRMS-ES+ ($C_{23}H_{30}NO_5$) calcd 400.2124 (MH^+), found 400.2118.

2-Benzyl-7-(5-oxotetrahydrofuran-3-yl)-2-azaspiro[5.5]undecan-1-one (55). To a solution of α-carbomethoxylactone **54** (879 mg, 2.2 mmol) in DMSO (45 mL) and H_2O (16 mL) was added LiCl (4.59 g, 110.0 mmol), and the reaction mixture was heated in an oil bath at 155−160 °C for 48 h (additional water was added periodically to maintain the solvent). The mixture was cooled to rt, and brine was added. The mixture was extracted with EtOAc (3 × 100 mL), and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give a yellowish oil that was purified by flash column chromatography on silica gel (gradient 20% to 30% EtOAc/hexanes) to furnish butyrolactone **55** as a white crystalline solid (676 mg, 90%). Mp 136−139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24−7.36 (m, 5H), 5.02 (d, J = 14.4 Hz, 1H), 4.41 (t, J = 7.3 Hz, 1H), 4.12 (d, J = 14.5 Hz, 1H), 3.94 (t, J = 8.8 Hz, 1H), 3.17−3.24 (m, 2H), 2.42−2.53 (m, 3H), 2.18 (dd, J = 16.0, 6.7 Hz, 1H), 1.97 (dt, J = 13.8, 3.2 Hz, 1H), 1.11−1.89 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 175.4, 137.4, 129.1, 128.6, 127.9, 73.2, 51.3, 47.7, 45.7, 44.5, 39.5, 35.5, 33.3, 30.1, 25.9, 23.6, 20.7, 19.5; IR (neat) 1765, 1609, 1188 cm^{-1}; HRMS-ES+ ($C_{21}H_{28}NO_3$) calcd 342.2069 (MH^+), found 342.2068.

2-Benzyl-7-(5-hydroxytetrahydrofuran-3-yl)-2-azaspiro[5.5]undecan-1-one (56). To a stirred solution of butyrolactone **55** (97 mg, 0.28 mmol) in dry THF (10 mL) at −78 °C was added dropwise DIBAL-H (1 M in THF, 2.8 mmol, 2.8 mL) over 20 min. The reaction was quenched with MeOH at −78 °C, and the mixture was warmed to rt, after which equal volumes of CH_2Cl_2 and saturated aqueous

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potassium sodium tartrate solution were added. The mixture was stirred for 1 h and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (20% Et_2O/CH_2Cl_2) to afford lactol **56** as a ~4:1 mixture of C9 diastereomers (80 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) (mixture) δ 7.23−7.33 (m, 5H), 5.35−5.38 (m, 1H), 4.88−4.93 (m, 1H), 3.95−4.31 (m, 1H), 3.71−3.94 (m, 1H), 3.47−3.55 (m, 1H), 3.21−3.32 (m, 2H), 2.30−2.52 (m, 3H), 1.18−2.03 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) (major) δ 176.0, 137.8, 128.9, 128.7, 127.7, 99.2, 73.2, 51.4, 47.8, 46.1, 44.8, 39.7, 37.9, 35.6, 27.4, 26.3, 23.5, 21.0, 19.6; ^{13}C NMR (minor) δ 176.9, 137.4, 129.0, 128.7, 127.9, 99.5, 71.3, 51.4, 47.7, 44.2, 42.2, 39.7, 38.1, 35.6, 30.1, 27.3, 23.5, 20.9, 19.4; HRMS-ES+ ($C_{21}H_{30}NO_3$) calcd 344.2226 (MH^+), found 344.2236.

2-Benzyl-7-(1-hydroxypent-4-en-2-yl)-2-azaspiro[5.5]-undecan-1-one (57). To a stirred suspension of $MePPh_3Br$ (recrystallized from THF/CH_2Cl_2, 1.22 g, 3.18 mmol) in dry THF (15 mL) at 0 °C was added *n*-butyllithium (1.6 M in hexanes, 2.1 mL, 3.2 mmol), and the resulting yellow-orange solution was stirred for 30 min at 0 °C. A solution of lactol **56** (218 mg, 0.64 mmol) in dry THF (13 mL) was added dropwise over ca. 5 min, and the mixture was slowly warmed to rt over 12 h. The mixture was diluted with saturated NH_4Cl(aq) and then extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (20% EtOAc/hexanes) to furnish terminal olefin **57** as a clear gum (169 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24−7.33 (m, 5H), 5.81−5.92 (m, 1H), 4.98−5.10 (m, 2H), 4.68 (d, *J* = 14.5 Hz, 1H), 4.47 (d, *J* = 14.5 Hz, 1H), 3.51−3.59 (m, 2H), 3.16−3.28 (m, 2H), 2.42 (dt, *J* = 9.7, 3.2 Hz, 1H), 2.24−2.28 (m, 1H), 2.10−2.13 (m, 1H), 1.87−1.96 (m, 1H), 1.19−1.86 (m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4, 138.5, 137.9, 128.8, 128.5, 127.7, 116.4, 64.0, 51.4, 47.8, 47.4, 44.2, 43.8, 37.4, 35.8, 26.9, 24.5, 24.2, 21.2, 19.6; HRMS-ES+ ($C_{22}H_{32}NO_2$) calcd 342.2433 (MH^+), found 342.2431.

2-Benzyl-7-(1-(methoxymethoxy)pent-4-en-2-yl)-2-azaspiro-[5.5]undecan-1-one (58). To a stirred solution of terminal olefin alcohol **57** (181 mg, 0.53 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C were added DIEA (0.41 mL, 2.65 mmol) and MOMCl (0.14 mL, 1.59 mmol). The mixture was stirred for 28 h at rt and then diluted with 1 M $NaHCO_3$(aq). The mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (10% EtOAc/hexanes) to furnish MOM ether **58** as a clear oil (189 mg, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24−7.31 (m, 5H), 5.81−5.95 (m, 1H), 5.01−5.11 (m, 2H), 4.67 (d, *J* = 14.5 Hz, 1H), 4.56 (s, 2H), 4.49 (d, *J* = 14.5 Hz, 1H), 3.57 (dd, *J* = 9.8, 4.0 Hz, 1H), 3.31−3.39 (m, 4H), 3.13−3.24 (m, 1H), 2.42 (dt, *J* = 12.8, 3.0 Hz, 1H), 2.21−2.28 (m, 1H), 1.84−1.96 (m, 1H), 1.16−1.83 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7, 138.2, 137.4, 128.9, 128.5, 127.5, 116.4, 96.9, 69.0, 55.6, 51.3, 47.9, 47.8, 44.3, 40.3, 38.1, 35.5, 26.8, 24.2, 23.3, 21.2, 19.7; HRMS-ES+ ($C_{24}H_{36}NO_3$) calcd 386.2695 (MH^+), found 386.2687.

7-(1-(Methoxymethoxy)pent-4-en-2-yl)-2-azaspiro[5.5]-undecan-1-one (59). Liquid ammonia (ca. 25 mL) was condensed at −78 °C, and Na metal (113 mg, 4.91 mmol) was added until the reaction developed a deep-purple coloration. A solution of MOM ether **58** (189.4 mg, 0.491 mmol) in dry Et_2O (10 mL) was added dropwise, and the mixture was stirred for 1 h. Solid NH_4Cl was added, and the mixture was warmed to rt. Brine was added, and the mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (gradient 50% to 75% Et_2O/CH_2Cl_2) to provide NH lactam **59** as a clear colorless gum (127 mg, 88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81−5.95 (m, 2H), 5.01−5.11 (m, 2H), 4.59−4.63 (m, 2H), 3.60 (dd, *J* = 9.8, 3.9 Hz, 1H), 3.27−3.41 (m, 6H), 2.23−2.34 (m, 3H), 1.11−2.01 (m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.0, 137.3, 116.5, 97.1, 69.0, 55.7, 43.9, 42.8, 40.3, 38.1, 35.3, 30.1, 26.7, 24.0, 23.0, 21.1, 19.7; HRMS-ES+ ($C_{17}H_{30}NO_3$) calcd 296.2226 (MH^+), found 296.2238.

7-(1-(Methoxymethoxy)pent-4-en-2-yl)-2-tosyl-2-azaspiro-[5.5]undecan-1-one (60). To a stirred solution of NH lactam **59** (127 mg, 0.43 mmol) in dry THF (15 mL) at 0 °C was added LiHMDS (1 M in THF, 1.3 mL, 1.3 mmol), and the mixture was stirred for 1 h at that temperature. TsCl (278 mg, 1.3 mmol) was added, and the reaction mixture was stirred for 20 h at rt. $NaHCO_3$(aq) (1 M) was added, and the mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (20% EtOAc/hexanes) to furnish *N*-tosyllactam **60** as a white solid (170 mg, 88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 4.2 Hz, 2H), 5.35−5.48 (m, 1H), 4.82−4.92 (m, 2H), 4.52−4.54 (m, 2H), 4.16−4.21 (m, 1H), 3.59−3.68 (m, 1H), 3.43 (dd, *J* = 9.9, 4.4 Hz, 1H), 3.24−3.35 (m, 4H), 2.43 (s, 3H), 2.12 (dt, *J* = 9.8, 3.2 Hz, 1H), 1.05−1.93 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5, 144.9, 136.8, 136.7, 129.6, 129.1, 116.5, 97.0, 68.5, 55.7, 50.3, 47.5, 44.6, 40.3, 37.5, 35.7, 26.4, 23.8, 23.4, 22.0, 21.0, 20.5; HRMS-ES+ ($C_{24}H_{39}N_2O_5S$) calcd 467.2580 (MNH_4^+), found 467.2585.

7-(1-(Methoxymethoxy)pent-4-en-2-yl)-2-(2-(trimethylsilyl)-ethyl)sulfonyl-2-azaspiro[5.5]undecan-1-one (61). To a stirred solution of NH lactam **59** (45 mg, 0.15 mmol) in dry THF (5 mL) at 0 °C was added LiHMDS (1 M in THF, 0.45 mL, 0.45 mmol), and the mixture was stirred for 1 h at that temperature. SESCl (0.087 mL, 0.45 mmol) was added, and the reaction mixture was stirred for 24 h at rt. $NaHCO_3$(aq) (1 M) was added, and the mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (20% EtOAc/hexanes) to furnish *N*-sulfonyllactam **61** as a clear colorless gum (55 mg, 78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.73−5.87 (m, 1H), 5.01−5.07 (m, 2H), 4.57 (s, 2H), 3.94−3.97 (m, 1H), 3.46−3.57 (m, 3H), 3.35−3.40 (m, 4H), 2.13−2.33 (m, 3H), 0.88−1.97 (m, 19H), 0.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.1, 136.8, 131.7, 127.9, 117.0, 97.1, 68.6, 55.7, 51.4, 50.6, 47.5, 44.2, 40.7, 37.9, 36.2, 26.4, 26.4, 24.1, 23.2, 21.1, 20.5, −1.6; HRMS-ES+ ($C_{22}H_{45}N_2O_5SSi$) calcd 477.2818 (MNH_4^+), found 477.2849.

7-((Methoxymethoxy)methyl)-4-tosyl-2,3,4,6,7,7a,8,9,10,11-decahydro-1*H*-benzo[*e*]quinoline (62). $TiCl_4$ (0.37 mL, 3.3 mmol) was dissolved in dry CH_2Cl_2 (6 mL) at 0 °C, followed by the addition of dry THF (1.7 mL, 19.3 mmol) and TMEDA (2.8 mL, 19.3 mmol). The reaction mixture was stirred for 20 min at rt, followed by the addition of activated Zn dust (washed with 1 N HCl(aq) and acetone and then dried in vacuo at 100 °C for 24 h) (468 mg, 7.2 mmol) and $PbCl_2$ (104 mg, 0.38 mmol). The mixture was stirred for 5 min at rt, and a solution of *N*-tosyllactam **60** (45 mg, 0.1 mmol) and Br_2CHCH_3 (0.41 mL, 4.5 mmol) in dry CH_2Cl_2 (3 mL) was added dropwise. The reaction mixture was heated at 55 °C for 30 min, cooled to 0 °C, treated with saturated K_2CO_3(aq) (0.8 mL), and stirred for 30 min. The resulting yellowish mixture was filtered through a sintered glass frit that was washed with CH_2Cl_2. The combined filtrates were concentrated in vacuo, and the residue was chromatographed on silica gel (15% EtOAc/hexanes) to afford *N*-sulfonylenamine **62** as a white solid (23 mg, 54%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.3 Hz, 2H), 5.56 (dd, *J* = 5.9, 2.7 Hz, 1H), 4.60 (s, 2H), 4.00 (dd, *J* = 11.6, 4.1 Hz, 1H), 3.35−3.58 (m, 6H), 2.96 (td, *J* = 4.2, 3.5 Hz, 1H), 2.11−2.20 (m, 1H), 1.20−2.10 (m, 17H); ^{13}C NMR (213 MHz, $CDCl_3$) δ 144.6, 142.8, 138.8, 129.5, 127.2, 120.1, 96.7, 69.9, 65.9, 55.3, 50.2, 46.7, 39.4, 32.5, 32.2, 29.8, 29.7, 28.0, 26.3, 22.3, 21.5, 20.6, 20.6; HRMS-ES+ ($C_{23}H_{34}NO_4S$) calcd 420.2209 (MH^+), found 420.2217.

7-((Methoxymethoxy)methyl)-4-(2-(trimethylsilyl)ethyl)-sulfonyl-2,3,4,6,7,7a,8,9,10,11-decahydro-1*H*-benzo[*e*]-quinoline (63). $TiCl_4$ (0.37 mL, 3.3 mmol) was dissolved in dry CH_2Cl_2 (4 mL) at 0 °C, followed by the addition of dry THF (1.7 mL, 19.3 mmol) and TMEDA (2.7 mL, 19.3 mmol). The reaction mixture

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was stirred for 20 min at rt, followed by the addition of activated Zn dust (washed with 1 N HCl(aq) and acetone and then dried in vacuo at 100 °C for 24 h) (468 mg, 7.2 mmol) and $PbCl_2$ (104 mg, 0.38 mmol). The mixture was stirred for 5 min at rt, and a solution of *N*-sulfonyllactam **61** (43 mg, 0.1 mmol) and Br_2CHCH_3 (0.41 mL, 4.5 mmol) in dry CH_2Cl_2 (2 mL) was added dropwise. The reaction mixture was heated at 55 °C for 30 min, cooled to 0 °C, treated with saturated K_2CO_3(aq) (0.5 mL), and stirred for 30 min. The resulting yellowish mixture was filtered through a sintered glass frit that was washed with CH_2Cl_2. The combined filtrates were concentrated in vacuo, and the residue was chromatographed on silica gel (15% EtOAc/hexanes) to afford *N*-sulfonylenamine **63** as a clear gum (33 mg, 83%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.72 (dd, J = 6.3, 2.0 Hz, 1H), 4.61 (s, 2H), 3.96 (dd, J = 11.9, 4.5 Hz, 1H), 3.55 (dd, J = 9.4, 4.1 Hz, 1H), 3.36−3.40 (m, 4H), 2.95−3.07 (m, 3H), 0.79−2.29 (m, 18H), 0.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.2, 121.6, 97.1, 70.2, 55.7, 51.0, 50.2, 47.2, 33.0, 32.8, 30.3, 30.1, 28.5, 26.7, 22.7, 21.1, 20.9, 10.9, −1.56; HRMS-ES+ ($C_{21}H_{40}NO_4SSi$) calcd 430.2447 (MH^+), found 430.2453.

3-(2-Benzyl-1-oxo-2-azaspiro[5.5]undecan-7-yl)-4-hydroxy-*N*-methoxy-*N*-methylbutanamide (65). To a stirred suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (2.57 g, 29.7 mmol) in dry CH_2Cl_2 (25 mL) at 0 °C was added dropwise dimethylaluminum chloride (0.9 M in heptane, 33.0 mL, 29.7 mmol), and the resulting mixture was stirred for 2 h at rt. A solution of butyrolactone **55** (676 mg, 2.0 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise, and the reaction mixture was stirred for 24 h at rt. The mixture was diluted with an equal volume of saturated aqueous potassium sodium tartrate solution, and the resulting biphasic mixture was stirred for 1 h at rt. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified via flash column chromatography on silica gel (gradient 50% to 100% Et_2O/CH_2Cl_2) to afford amide alcohol **65** as an off-white fluffy solid (681 mg, 86%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15−7.39 (m, 5H), 4.78 (d, J = 14.6 Hz, 1H), 4.38 (d, J = 14.6 Hz, 1H), 4.10 (br s, 1H), 3.70−3.74 (m, 4H), 3.47−3.54 (m, 1H), 3.15−3.29 (m, 5H), 1.28−2.81 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.0, 175.4, 138.0, 129.1, 128.2, 127.6, 65.4, 61.8, 51.2, 47.9, 47.7, 46.2, 40.3, 35.4, 32.6, 26.9, 23.6, 23.3, 21.2, 20.7, 19.5; HRMS-ES+ ($C_{23}H_{35}N_2O_4$) calcd 403.2597 (MH^+), found 403.2600.

3-(2-Benzyl-1-oxo-2-azaspiro[5.5]undecan-7-yl)-*N*-methoxy-4-(methoxymethoxy)-*N*-methylbutanamide (66). To a stirred solution of amide alcohol **65** (681 mg, 1.7 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C were added MOMCl (0.75 mL, 8.5 mmol) and DIEA (2.62 mL, 16.9 mmol). The reaction mixture was stirred for 24 h at rt, diluted with saturated $NaHCO_3$(aq), and extracted with EtOAc (3 × 100 mL). The combined extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting crude oil was purified via flash column chromatography on silica gel (gradient 20% to 100% Et_2O/CH_2Cl_2) to afford MOM ether **66** (596 mg, 80%) as a light-yellow gum. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19−7.29 (m, 5H), 4.85 (d, J = 14.6 Hz, 1H), 4.51 (s, 2H), 4.20 (d, J = 14.6 Hz, 1H), 3.64 (s, 3H), 3.56 (dd, J = 15.9, 5.6 Hz, 1H), 3.44−3.50 (m, 1H), 3.29 (s, 3H), 3.07−3.20 (m, 5H), 2.59−2.78 (m, 1H), 2.31−2.42 (m, 2H), 1.10−2.06 (m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.9, 138.1, 128.9, 128.3, 127.5, 97.0, 69.1, 61.6, 55.7, 50.9, 47.4, 44.6, 37.3, 35.9, 35.5, 32.7, 30.7, 26.8, 23.7, 23.6, 21.1, 19.5; HRMS-ES+ ($C_{25}H_{39}N_2O_5$) calcd 447.2859 (MH^+), found 447.2870.

3-(2-Benzyl-1-oxo-2-azaspiro[5.5]undecan-7-yl)-4-(methoxymethoxy)butanal (67). To a stirred solution of MOM ether **66** (596 mg, 1.3 mmol) in dry THF (50 mL) at −40 °C was added lithium aluminum hydride (169 mg, 5.4 mmol) in one portion, and the resulting suspension was stirred for 1 h at that temperature. Methanol was added carefully followed by 1 N NaOH(aq), and the mixture was warmed to rt and further diluted with brine. The reaction mixture was extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to afford aldehyde **67** as a clear colorless gum that was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.57 (dd, J = 3.4, 1.8 Hz, 1H), 7.22−7.33 (m, 5H), 4.63 (d, J = 14.4 Hz, 1H), 4.43−4.54 (m, 3H), 3.64 (dd, J = 9.7, 3.8 Hz, 1H), 3.21−3.33 (m, 6H), 2.42−2.49 (m, 2H), 2.32−2.37 (m, 1H), 1.08−2.01 (m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.2, 175.6, 137.9, 128.9, 128.5, 127.7, 96.8, 69.7, 55.8, 51.4, 49.1, 47.8, 45.0, 36.7, 35.3, 30.7, 26.7, 23.9, 23.1, 21.0, 19.4; HRMS-ES+ ($C_{23}H_{34}NO_4$) calcd 388.2488 (MH^+), found 388.2490.

2-Benzyl-7-((*E*/*Z*)-1-(methoxymethoxy)-6-(trimethylsilyl)-hex-4-en-2-yl)-2-azaspiro[5.5]undecan-1-one (68). To a stirred solution of 2-trimethylsilylethyltriphenylphosphonium iodide (2.66 g, 5.4 mmol) in dry THF (35 mL) at rt was added dropwise PhLi (1.8 M in dibutyl ether, 3.05 mL, 5.5 mmol). The resulting deep-crimson solution was stirred at rt for 5 min, and then a solution of aldehyde **67** (519 mg, 1.3 mmol) in dry THF (5 mL) was added dropwise. The reaction mixture was stirred for 12 h at rt and diluted with saturated NH_4Cl(aq). The mixture was extracted with Et_2O (3 × 100 mL). The combined extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified via flash column chromatography on silica gel (gradient 8% to 10% EtOAC/hexanes) to afford allylsilane **68** (470 mg, 74%) as an inseparable ∼2.2:1 mixture of (*E*/*Z*)-olefin isomers. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21−7.35 (m, 5H), 5.25−5.54 (m, 2H), 4.79 (d, J = 14.5 Hz, 1H), 4.68 (d, J = 14.4 Hz, 1H), 4.56 (s, 2H), 4.48 (d, J = 14.4 Hz, 1H), 4.38 (d, J = 14.5 Hz, 1H), 3.58 (dd, J = 9.8, 4.1 Hz, 1H), 3.48−3.52 (m, 1H), 3.32−3.38 (m, 4H), 3.10−3.27 (m, 2H), 2.41 (dt, J = 12.8, 2.4 Hz, 1H), 2.05−2.28 (m, 2H), 1.11−1.97 (m, 16H), 0.01 (s, 9H), 0.001 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.9, 175.8, 138.3, 138.2, 129.7, 128.9, 128.9, 128.6, 128.5, 128.3, 127.5, 126.9, 126.7, 126.0, 119.8, 115.9, 55.6, 55.6, 51.3, 51.2, 48.0, 47.9, 47.8, 47.7, 44.7, 44.6, 40.8, 40.6, 36.8, 35.6, 35.4, 30.8, 29.8, 26.9, 26.8, 24.3, 24.1, 23.6, 23.3, 23.3, 21.3, 21.2, 19.8, 19.7, 18.9, −1.3, −1.4; HRMS-ES+ ($C_{28}H_{46}NO_3Si$) calcd 472.3247 (MH^+), found 472.3272.

7-((*E*/*Z*)-1-(Methoxymethoxy)-6-(trimethylsilyl)hex-4-en-2-yl)-2-tosyl-2-azaspiro[5.5]undecan-1-one (70). Anhydrous ammonia (15 mL) was condensed into a flask at −78 °C, and Na metal (158 mg, 6.9 mmol) was added portionwise until the mixture developed a dark-blue color. A solution of *N*-Bn lactam/allylsilane *E*/*Z* mixture **68** (324 mg, 0.69 mmol) in anhydrous Et_2O (15 mL) was added dropwise, and the reaction mixture was stirred at −78 °C. When the reaction was determined to be complete via TLC (about 2 h), solid NH_4Cl was added in one portion, and the mixture was warmed to rt. Additional Et_2O and brine were added, and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 50 mL), and the combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude product was purified via flash column chromatography on silica gel (10% Et_2O/CH_2Cl_2) to afford unstable NH lactam **69** (an inseparable mixture of (*E*)- and (*Z*)-olefin geometric isomers) (207 mg, 79%) as a clear colorless gum. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.84 (br s, 1H), 5.34−5.50 (m, 2H), 4.60 (s, 2H), 3.59 (dd, J = 9.7, 3.9 Hz, 1H), 3.28−3.41 (m, 5H), 2.14−2.32 (m, 3H), 0.87−1.97 (m, 16H), 0.00 (s, 9H), −0.002 (s, 9H).

To a stirred solution of NH lactam **69** (207 mg, 0.54 mmol) in dry THF (30 mL) at 0 °C was added dropwise LiHMDS (1 M in THF, 1.63 mL, 1.6 mmol), and the mixture was stirred for 30 min at that temperature. TsCl (509 mg, 2.7 mmol) and DMAP (20 mg, 0.16 mmol) were added, and the reaction mixture was stirred for 11 h at rt. The mixture was then diluted with saturated $NaHCO_3$(aq) and extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified via flash column chromatography on silica gel (gradient 10% to 20% EtOAc/hexanes) to afford *N*-tosyllactam **70** (an inseparable mixture of (*E*)- and (*Z*)-olefin geometric isomers) (251 mg, 87%) as a clear colorless gum. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, J = 10.4 Hz, 2H), 7.30 (d, J = 12.7 Hz, 2H), 5.15−5.40 (m, 1H), 4.80−4.98 (m, 1H), 4.52−4.61 (m, 2H), 4.13−4.19 (m, 1H), 3.62−3.72 (m, 1H), 3.45 (dd, J = 9.9, 4.7 Hz, 1H), 3.33−3.38 (m, 3H), 3.24 (dd, J = 8.4, 7.1 Hz, 1H), 2.37 (s, 3H), 1.93−2.11 (m, 1H), 0.75−1.94 (m, 16H), −0.02 (s, 9H), −0.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 176.5, 144.7, 144.6, 136.9, 136.7, 131.9, 130.8, 129.5, 129.0, 129.0, 128.6, 127.0, 126.2,

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125.3, 96.9, 96.9, 68.8, 68.3, 55.7, 55.7, 50.6, 50.2, 47.5, 47.5, 45.1, 44.6, 40.7, 40.6, 36.2, 35.6, 35.6, 30.7, 30.5, 30.1, 29.6, 26.5, 26.4, 24.0, 23.7, 23.2, 23.1, 22.1, 22.0, 21.1, 21.1, 20.6, 20.5, 18.7, −1.4, −1.5; HRMS-ES+ ($C_{28}H_{46}NO_5SiS$) calcd 536.2866 (MH^+), found 536.2877.

9-((Methoxymethoxy)methyl)-1-tosyl-11-vinyldodecahydro-1*H*-benzo[*e*]quinoline (73). To a stirred solution of *N*-tosyllactam **70** (50 mg, 0.095 mmol) in dry CH_2Cl_2 (20 mL) at −78 °C was added dropwise DIBAL-H (1 M in PhMe, 1.4 mL, 1.4 mmol). After the reaction mixture was stirred for 45 min, anhydrous $FeCl_3$ (150 mg, 0.95 mmol) was added in one portion, and the mixture was warmed to 5 °C over 1.5 h (the formation of a slightly turbid green solution indicated that the reaction had gone to completion). An equal volume of saturated aqueous potassium sodium tartrate solution was added, and the resulting biphasic mixture was stirred for 2 h at rt. The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified via flash column chromatography on silica gel (8:1:1 hexanes/CH_2Cl_2/Et_2O) to afford tricycle **73** (33 mg, 78%) as a clear colorless gum. ^{1}H NMR (850 MHz, $CDCl_3$) δ 7.68 (d, J = 8.2 Hz, 2H), 7.23 (d, J = 8.1 Hz, 2H), 5.50−5.55 (m, 1H), 4.86 (dd, J = 17.0, 1.1 Hz, 1H), 4.63 (dd, J = 10.1, 1.6 Hz, 1H), 4.60 (d, J = 6.5 Hz, 1H), 4.58 (d, J = 6.5 Hz, 1H), 3.60 (dd, J = 13.8, 5.3 Hz, 1H), 3.48−3.50 (m, 2H), 3.35−3.38 (m, 4H), 2.91 (td, J = 13.5, 3.4 Hz, 1H), 2.75−2.79 (m, 1H), 2.42−2.47 (m, 1H), 2.41 (s, 3H), 2.18 (br d, J = 13.9 Hz, 1H), 1.85 (dt, J = 13.2, 3.7 Hz, 1H), 1.74 (br d, J = 13.9 Hz, 2H), 1.66−1.70 (m, 2H), 1.54−1.61 (m, 2H), 1.49 (br d, J = 13.3 Hz, 1H), 1.41 (br d, J = 13.9 Hz, 1H), 1.22−1.33 (m, 3H), 1.14 (qd, J = 12.9, 3.9 Hz, 1H), 0.97 (td, J = 13.3, 3.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.7, 141.6, 139.4, 129.4, 127.3, 115.2, 97.0, 70.6, 66.4, 55.6, 47.8, 40.5, 39.9, 37.5, 36.9, 35.7, 34.4, 26.7, 23.5, 21.9, 21.1, 20.3, 20.1; HRMS-ES+ ($C_{25}H_{38}NO_4S$) calcd 448.2522 (MH^+), found 448.2536.

9-((Methoxymethoxy)methyl)-1-tosyldodecahydro-1*H*-benzo[*e*]quinolin-11-yl)methanol (74). Ozone gas was bubbled through a stirred solution of tricyclic alkene **73** (33 mg, 0.074 mmol) in dry CH_2Cl_2 (10 mL) at −78 °C for 5 min until a blue color was observed. PPh_3 (58 mg, 0.22 mmol) was added to the reaction mixture, which was subsequently warmed to rt over 10 h. The mixture was diluted with MeOH (4 mL) and cooled to 0 °C, and $NaBH_4$ (20 mg, 0.53 mmol) was added in one portion. The reaction mixture was stirred for 5 min and then diluted with an equal volume of saturated NH_4Cl(aq) solution, causing two layers to form. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified via flash column chromatography on silica gel (gradient 25% to 35% EtOAc/hexanes) to afford tricyclic alcohol **74** (30 mg, 91%) as a clear colorless gum. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 7.9 Hz, 2H), 4.60 (q, J = 6.6 Hz, 2H), 3.90 (dd, J = 12.1, 2.8 Hz, 1H), 3.70 (br d, J = 14.4 Hz, 1H), 3.34−3.52 (m, 7H), 2.98−3.12 (m, 1H), 2.44 (s, 3H), 2.15 (br t, J = 10.0 Hz, 1H), 1.91 (dd, J = 9.8, 3.9 Hz, 1H), 0.52−1.69 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4, 138.7, 129.9, 127.3, 97.1, 70.8, 63.4, 55.7, 47.8, 40.9, 37.6, 35.9, 35.8, 35.1, 32.9, 30.1, 26.5, 23.5, 21.9, 21.0, 19.9, 19.9; HRMS-ES+ ($C_{24}H_{38}NO_5S$) calcd 452.2471 (MH^+), found 452.2445.

9,11-Bis((methoxymethoxy)methyl)-1-tosyldodecahydro-1*H*-benzo[*e*]quinoline (75). To a stirred solution of alcohol **74** (24.3 mg, 0.053 mmol) in dry CH_2Cl_2 (2 mL) at 0 °C were added MOMCl (20 μL, 0.22 mmol) and DIEA (70 μL, 0.44 mmol). The reaction mixture was stirred overnight at rt then diluted with saturated $NaHCO_3$(aq) solution. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified via flash column chromatography on silica gel (15% EtOAc/hexanes) to afford bis-MOM ether **75** (22 mg, 80%) as a clear colorless gum. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J = 8.3 Hz, 2H), 7.28 (d, J = 6.9 Hz, 2H), 4.60 (q, J = 6.6 Hz, 2H), 4.47 (q, J = 6.4 Hz, 2H), 3.69 (dd, J = 13.5, 3.6 Hz, 1H), 3.38−3.53 (m, 3H), 3.37 (s, 3H), 3.30 (s, 3H), 3.15 (t, J = 9.4 Hz, 1H), 2.97 (td, J = 11.9, 3.5 Hz, 1H), 2.30−2.43 (m, 4H), 2.05−2.18 (m, 2H), 0.86−1.76 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.9, 139.2, 129.7, 127.3, 97.0, 97.0, 70.7, 70.5, 63.9, 55.6, 55.5, 47.9, 40.6, 37.6, 35.6, 34.6, 34.3, 34.1, 30.7, 30.1, 26.7, 23.6, 21.8, 21.1, 20.3, 20.1; HRMS-ES+ ($C_{26}H_{45}N_2O_6S$) calcd 513.2998 (MNH_4^+), found 513.3034.

9,11-Bis((methoxymethoxy)methyl)dodecahydro-1*H*-benzo-[*e*]quinoline (76). Anhydrous ammonia (ca. 7.5 mL) was condensed into a flask at −78 °C, and Li metal (25 mg, 3.5 mmol) was added until a blue color persisted. A solution of bis-MOM ether **75** (68 mg, 0.136 mmol) in dry Et_2O (8 mL) was added dropwise, and the mixture was stirred for 1 min at −78 °C and then quenched with NH_4Cl(s). The reaction mixture was warmed to rt, diluted with CH_2Cl_2, filtered through a sintered glass frit, and concentrated in vacuo. The crude product was purified via flash column chromatography on silica gel (gradient 1:1 Et_2O/CH_2Cl_2 to 1:1:0.1:0.01 Et_2O/CH_2Cl_2/MeOH/TEA) to afford tricyclic amine **76** (37 mg, 81%) as a clear colorless gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.64 (q, J = 6.4 Hz, 2H), 4.58 (q, J = 6.6 Hz, 2H), 3.68 (dd, J = 9.8, 4.4 Hz, 1H), 3.57 (dd, J = 9.7, 6.8 Hz, 1H), 3.48 (dd, J = 9.5, 3.5 Hz, 1H), 3.38 (s, 3H), 3.34 (s, 3H), 3.18 (br d, J = 12.2 Hz, 1H), 2.92−2.97 (m, 1H), 2.75 (br d, J = 13.2 Hz, 1H), 2.70 (br d, J = 11.6 Hz, 1H), 2.43−2.55 (m, 1H), 1.87−1.98 (m, 2H), 0.81−1.86 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 97.1, 97.0, 72.7, 69.8, 65.8, 56.4, 55.8, 46.7, 39.5, 35.1, 34.2, 32.3, 32.1, 30.1, 26.2, 23.1, 20.4, 18.2, 17.7; HRMS-ES+ ($C_{19}H_{36}NO_4$) calcd 342.2644 (MH^+), found 342.2649.

Racemic Myrioneurinol ((±)-7). To a stirred solution of tricyclic amine **76** (36.9 mg, 0.11 mmol) in THF (25 mL) was added 6 N HCl(aq) (14 mL). The reaction mixture was heated at 50 °C for 90 min and then cooled to rt. The mixture was basicified with Na_2CO_3(aq) to a pH of >10. The mixture was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were washed with a small amount of brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified via flash column chromatography on silica gel (gradient 66% to 100% Et_2O/CH_2Cl_2) to afford racemic myrioneurinol ((±)-7) (22 mg, 75%) as a clear colorless gum. ^{1}H NMR (850 MHz, $CDCl_3$) δ 4.47 (d, J = 10.2 Hz, 1H), 4.42 (d, J = 10.2 Hz, 1H), 3.91 (dd, J = 11.1, 4.3 Hz, 1H), 3.64 (dd, J = 11.1, 4.3 Hz, 1H), 3.48 (dd, J = 10.2, 6.0 Hz, 1H), 3.28 (td, J = 13.6, 4.3 Hz, 1H), 3.21 (t, J = 11.1 Hz, 1H), 2.67 (dd, J = 11.9, 5.1 Hz, 1H), 2.49 (br d, J = 12.8 Hz, 1H), 2.46 (qt, J = 12.8, 4.3 Hz, 1H), 2.28 (d, J = 11.1 Hz, 1H), 1.74−1.80 (m, 2H), 1.68 (br d, J = 13.6 Hz, 1H), 1.59 (dd, J = 12.8, 2.6 Hz, 1H), 1.56 (dt, J = 12.8, 3.4 Hz, 2H), 1.48−1.53 (m, 2H), 1.35−1.45 (m, 2H), 1.24−1.30 (m, 2H), 1.20 (qd, J = 12.8, 3.4 Hz, 1H), 1.14 (td, J = 11.1, 2.6 Hz, 1H), 0.87 (td, J = 14.5, 3.4 Hz, 1H), 0.80 (q, J = 11.9 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$, APT) δ 86.8 (CH_2), 73.6 (CH_2), 69.6 (CH), 65.4 (CH_2), 47.7 (CH), 45.0 (CH_2), 37.1 (CH), 36.3 (C), 34.4 (CH_2), 31.1 (CH_2), 27.2 (CH), 26.7 (CH_2), 23.1 (CH_2), 20.5 (CH_2), 20.5 (CH_2), 19.8 (CH_2); IR (neat) 3399, 1028 cm^{-1}; HRMS-ES+ ($C_{16}H_{28}NO_2$) calcd 266.2120 (MH^+), found 266.2132.

■ ASSOCIATED CONTENT

Supporting Information

Proton and carbon NMR spectra of new compounds and X-ray data (CIF) for compounds **32**, **37**, **44a**, and **44b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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