Total Synthesis of (+)-Nankakurines A and B and (±)-5-epi-Nankakurine A

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Abstract

The first total syntheses of the *Lycopodium* alkaloids (+)-nankakurine A (**2**), (+)-nankakurine B (**3**) and the originally purported structure **1** of nankakurine A were accomplished. The syntheses of **2** and **3** feature a demanding intramolecular azomethine imine cycloaddition as the key step for generating the octahydro-3,5-ethanoquinoline moiety and installing the correct relative configuration at the spiro piperidine ring juncture. The cyclization precursor was prepared from octahydronaphthalene ketone **50**, which was assembled from enone (+)-**9** and diene **48** by a cationic Diels–Alder reaction. The Diels–Alder reactants were synthesized from 5-hexyn-1-ol (**16**) and (+)-pulegone (**49**), respectively. The tetracyclic ring system of **1** was generated using an unprecedented nitrogen-terminated aza-Prins cyclization cascade. The enantioselective total syntheses of (+)-nankakurine A (**2**) and (+)-nankakurine B (**3**) establish the relative and absolute configuration of these alkaloids, and are sufficiently concise that substantial quantities of **2** and **3** were prepared for biological studies. (+)-Nankakurine A and (+)-nankakurine B showed no effect on neurite outgrowth in rat hippocampal H-19 cells over a concentration range of 0.3–10 μM.

Keywords

nankakurine; *Lycopodium* alkaloids; intramolecular azomethine imine dipolar cycloaddition; nitrogen-terminated aza-Prins reaction

Introduction

Because of their diverse architectures and biological activities, *Lycopodium* alkaloids[1] have attracted significant synthetic interest for many years. In 2004, Kobayashi and co-workers reported the isolation of a structurally unique *Lycopodium* alkaloid, (+)-nankakurine A,[2] from the club moss *Lycopodium hamiltonii* collected at the southwest tip of Kyushu Island, Japan. On the basis of two-dimensional NMR data and mass spectrometric analysis, structure **1** was proposed (Figure 1).[2] The relative configuration at the spiro stereocenter of nankakurine A was assigned on the basis of ^{1}H NMR NOE experiments, and concurred with

the structure of spirolucidine (**4**), whose relative configuration had been secured earlier by single-crystal X-ray analysis of a derivative.[3]

Two years later, the Kobayashi laboratory reported that further purification of this club moss extract provided a less abundant alkaloid, (+)-nankakurine B, for which structure **3** was suggested.[4] In this case, ^{1}H NMR NOE data were interpreted to support a configuration at the spiro stereocenter opposite to that originally proposed for nankakurine A (**1**). Reductive methylation of natural nankakurine A gave nankakurine B, thus, the structure of nankakurine A was revised to **2**.[4]

Neurotrophic factors play an important role in mediating neuronal growth and can counteract neuronal atrophy and death in the adult nervous system.[5] Because of the poor pharmacokinetics documented by naturally occurring polypeptidyl-neurotrophic factors,[6] small molecules that exhibit neurotrophic effects are attracting considerable attention as potential therapeutics.[7] Thus, Kobayashi's disclosure in 2006 that nankakurine A (**2**) induced secretion of neurotrophic factors in human astrocytoma cells at a concentration of 1 μM heightened our interest in this area.[4] Similar examination of nankakurine B was not possible at the time as a result of the low abundance of these alkaloids in their natural source.[8] It was particularly provocative that nankakurines A and B bore no obvious structural relationship to other small molecule neurotrophic agents reported at that time,[7] and, moreover, that their structures were devoid of polar functional groups known to negatively affect central nervous system exposure of small-molecule drugs.[9]

Stimulated initially by the opportunity to explore a new construction of polycyclic diamines (*vide infra*) and by the prospect of obtaining sufficient quantities of nankakurines A (**2**) and B (**3**) to evaluate their potential as leads for developing new agents for combating neurodegenerative disorders, we initiated a total synthesis program in this area.[10] Herein, we report the development of the chemistry that allowed the first total syntheses of (+)-nankakurine A, (+)-nankakurine B, and the originally proposed structure of nankakurine A (**1**) to be accomplished, syntheses that confirmed the relative configuration and established the absolute configuration of these rare alkaloids.[11] Moreover, these syntheses allowed the neurotrophic activities of both **2** and **3** to be examined. In this exploration, neurotrophic activity was not observed in rat hippocampal H-19 cells over a concentration range of 0.3–10 μM.

Results and Discussion

Initial Retrosynthetic Analysis

The focus of our initial effort was the originally purported structure **1** (5-epi-nankakurine A) of nankakurine A (Scheme 1). We envisioned tetracyclic diamine **6** arising in one step from bis-homoallylic amine **8** by an amino-terminated aza-Prins cyclization of formaldiminium intermediate **7** (Scheme 1). Although carboxylate-terminated aza-Prins reactions of amino acids had been described,[12] amino-terminated aza-Prins cyclizations were unknown. This lack of precedent provided extra motivation for evaluating this approach, as we envisioned amino-terminated aza-Prins cyclizations potentially having considerable utility in heterocyclic synthesis. Cyclization of the tethered nitrogen nucleophile from the sterically less-hindered-convex face of intermediate **7** was expected to set the spiropiperidine stereocenter of **1** with high selectivity. We foresaw the central challenge in orchestrating a successful amino-terminated aza-Prins reaction as co-generating and properly matching the iminium ion electrophile and the nitrogen nucleophile. *Cis*-octahydronaphthalene amine **8** was seen deriving from the Diels–Alder reaction of (*R*)-5-methyl-2-cyclohexen-1-one (**9**) and diene **10**, a strategy that drew ample precedent from Oppolzer's pioneering early synthesis of (+)-luciduline.[13]

Synthesis of *cis*-Octahydronaphthalene Amine Intermediates

Our early exploratory studies were carried out in the racemic series, and required convenient access to 5-methyl-2-cyclohexen-1-one ((±)-**9**) and 1,3-diene **19** (Scheme 2). After examining several of the known methods for preparing cyclohexenone (±)-**9**,[14] we developed an alternate synthesis from 5-methyl-1,3-cyclohexanedione (**13**), which is commercially available or readily prepared from inexpensive orcinol (**11**) by methylation[15] followed by Birch reduction and acidic hydrolysis.[16] Reaction of dione **13** with oxalyl bromide to form β-bromoenone **14**,[17] followed by reduction with zinc in THF gave 5-methyl-2-cyclohexen-1-one ((±)-**9**) in 55% overall yield from orcinol. As noted by Cossy,[18] attempts to prepare ethylene ketal **15** from (±)-**9** by reaction with ethylene glycol in the presence of a variety of Brønsted acids under Dean–Stark conditions were complicated by migration of the double bond to provide significant amounts of 9-methyl-1,4-dioxaspiro[4.5]dec-7-ene. Although the use of the weak acid pyridinium *p*-toluenesulfonate (PPTS) allowed ketal **15** to be prepared in 29% yield (55% based on consumed (±)-**9**),[18] this ketalization was more efficient (73% yield) when carried out by reaction of (±)-**9** with 1,2-bis-(trimethylsiloxy)ethane and catalytic trimethylsilyl triflate (TMSOTf) at −78 °C.[19]

Using a Mitsunobu variant of the Gabriel amine synthesis, diene **19** was prepared in a three-step sequence from 5-hexyn-1-ol (**16**). Alcohol **16** was transformed first into amine hydrochloride salt **17**, which was protected as a sulfonamide (**18**) in 83% yield for the two step sequence.[20,21] Reaction of alkyne **18** with ethylene using Grubbs' 2nd generation catalyst[22] afforded diene **19** in 90% yield.[23] The TMSOTf-catalyzed ionic Diels–Alder reaction[24] of cyclohexenone (±)-**9** with diene **19** took place in 50–60% yield using a stoichiometric quantity of 1,2-bis-(trimethylsiloxy)ethane. During attempts to optimize this conversion, it became apparent that the moderate yield arose from reaction inhibition resulting from the buildup of (TMS)$_2$O. When ketal **15** was employed, the ionic Diels–Alder reaction proceeded in high yield with excellent *cis*-diastereoselectivity.[25] Subsequent cleavage of the ketal using FeCl$_3$ adsorbed on silica gel[26,27] provided ketone **20** in 90% yield from diene **19**.[28] Ketone **20** was quantitatively converted to *cis*-oxime **21** upon reaction at room temperature with aqueous hydroxylamine in methanol; the use of acidic or basic conditions for oxime formation resulted in significant epimerization. The robust sequence summarized in Scheme 2 reproducibly provided oxime **21** on scales of >10 g. Reduction of this intermediate with MoO$_3$ and NaBH$_4$ provided *cis*-octahydronaphthalene amine **22** in excellent yield.[29]

Exploration of Amino-Terminated aza-Prins Cyclizations and the Synthesis of (±)-5-*epi*-Nankakurine (1)

In our initial attempts to develop an amino-terminated aza-Prins cyclization, we employed a cyanomethyl amine as a formaldiminium ion precursor to allow the iminium cation to be generated under mild conditions in various solvents.[30] Cyanomethylamine derivative **23** was prepared in 78% yield by alkylation of amine **22** with chloroacetonitrile. Reaction of this formaldiminium precursor with AgO$_2$CCF$_3$ in CHCl$_3$ at room temperature gave the monocyclized product, octahydro-3,5-ethanoquinoline **24**, in nearly quantitative yield (Scheme 3). Variation of the solvent or changing the initiating reagent to Cu(O$_2$CCF$_3$) led in no case to the formation of detectable tetracyclic product. We also investigated related reactions of congeners of cyanomethylamine **23** in which the tethered nitrogen substituent was NH$_2$, NHBn, or NHC$_6$H$_4$*p*-OMe instead of NHTs; however, Ag-mediated cyclization reactions of these substrates also produced simple aza-Prins products analogous to **24**. In an attempt to see if a potential tricyclic tertiary carbenium precursor of azatricyclic **24** could be trapped by an external nitrogen nucleophile, the silver-promoted cyclization of **23** was carried out in the presence of 10 equiv of sodium azide. This reaction also led to the formation of octahydro-3,5-ethanoquinoline **24** in high yield.

Although it would be less desirable than a cascade sequence, we investigated briefly whether the spiropiperidine ring could be formed in a subsequent step from aza-Prins product **24** (Scheme 4). As intramolecular hydroamination of unsaturated *N*-tosylamines to form pyrrolidine rings in the presence of strong acids is well established,[31] tricyclic sulfonamide **24** was allowed to react with trifluoromethanesulfonic acid (TfOH) or trifluoroacetic acid (TFA, neat or in toluene, rt–80 °C). These reactions generated double bond isomers of **24**, but no trace of tetracyclic product **26**. In order to minimize protonation at N1, aza-Prins product **24** was protected as a methyl carbamate. Reaction of carbamate **25** with TfOH or TFA (neat or in $CHCl_3$, MeCN, or PhMe, rt–100 °C) resulted in the formation of multiple products, including those that resulted from loss of the carbamate and isomerization of the double bond; the desired tetracyclic product **27** was not produced. In order to further reduce the basicity of the protected amine and increase the stability of this substituent, *p*-nitrophenylsulfonyl (Ns) sulfonamide **28** was prepared. Reaction of **28** with TFA or *p*-toluenesulfonic acid (TsOH, 25–80 °C, various solvents), returned only starting material, whereas exposure of **28** to TfOH at 120 °C delivered tetralin derivative **29**. This extensive degradation presumably results from protonation of N1, followed by the cleavage of two C–N bonds to eliminate *p*-nitrophenylsulfonamide, and finally double bond isomerization to produce tetralin **29** (**30**→**31**→**32**).

A metal-catalyzed hydroamination reaction was considered as an alternative approach for preparing tetracyclic products **26** or **27** from tricyclic intermediates **24** or **25**,[32,33] however, existing literature precedent focuses largely on substrates that contain only one nitrogen substituent and typically result in the formation of pyrrolidine rings. There are only a few examples that result in the formation of piperidine rings or that utilize tri-substituted alkenes.[34] Intramolecular hydroamination of **24** and **25** utilizing $FeCl_3$ was evaluated.[35] Extended exposure of unsaturated sulfonamides **24** or **25** to $FeCl_3$ at 80 °C in 1,2-dichloroethane resulted only in slow conversion of the starting material to mixtures of alkene-migrated products.

Being sensitized at this point to the ready formation of alkene regioisomers in reactions of azatricyclic alkenes **24** and **25** with acids, we reconsidered the observation that product **24** was produced as a single double-bond isomer in the original aza-Prins cyclization. This high regioselectivity suggested the possibility that the nitrogen atom of the hydro-3,5-ethanoquinoline fragment of **23** was participating in the generation of the tricyclic aza-Prins product (Scheme 5). For stereoelectronic reasons,[36] aza-Prins cyclization of formaldiminium ion **33** should generate initially tricyclic carbenium ion **34**, which would be expected to undergo rapid nitrogen inversion[37] to isomer **35**, in which the nitrogen non-bonded electron pair would be positioned ideally to assist in deprotonation to form the conjugate acid **36** of octahydro-3,5-ethanoquinoline product **24**.[38]

To enhance the lifetime of carbenium ion intermediate **35** and potentially favor a nitrogen-terminated aza-Prins process, we investigated related reactions of *N*-acyloxy-formaldiminium ion intermediates. We initially examined initiating the cyclization from *N*-cyanomethyl and *N*-benzotriazolmethyl[39] carbamates **37** and **39** (Scheme 6). At temperatures up to 120 °C, cyanomethyl derivative **37** was unchanged when exposed to 2 equiv of AgO_2CCF_3, $AgBF_4$, or TsOH in acetonitrile or toluene. Exposure of benzotriazole derivative **39** to 0.9 equiv of $ZnBr_2$ in dichloromethane at 60 °C initiated aza-Prins cyclization to provide alkylidene decahydro-3,5-ethanoquinoline products **40** in 63% yield. Other modes of initiating the cyclization were also pursued;[39] however, in no case was any tetracyclic product detected.

We next turned to initiate the cyclization by acid-promoted reaction of carbamate **38** with formaldehyde (Scheme 7). Exposure of carbamate **38** to an excess of paraformaldehyde in

TFA/CHCl$_3$ at room temperature[12b] resulted in formation of two inseparable tetracyclic products **41** whose molecular formulas (C$_{26}$H$_{36}$N$_2$O$_4$S, MS analysis) indicated that 2 equiv of formaldehyde were involved in their genesis. As these products were also produced upon exposure of alkylidene decahydro-3,5-ethanoquinoline products **40** to identical conditions, they were assigned as the tetracyclic alkene products of aza-Prins cyclization of *N*-sulfonylformaldiminium ion intermediate **42**. Using one equiv of paraformaldehyde, the tetracyclic product **27** resulting from sulfonamide-terminated aza-Prins cyclization was formed, albeit in low yield (10–20%). In this reaction, **27** was produced in a complex mixture of products that contained the already characterized aza-Prins product **40** and tetracyclic products **41**. Much effort was expended in trying to optimize the formation of spirocyclic product **27**. Numerous variations in solvent, protic or Lewis acid, and formaldehyde precursor were surveyed, but no conditions were identified under which **27** was formed in more than 20% yield.[40,41]

Although the yield of the sulfonamide-terminated aza-Prins reaction of bicyclic precursor **38** was low, this reaction did provide sufficient quantities of tetracyclic diamine **27** to allow the originally proposed structure of nankakurine A (**1**) to be prepared in two additional steps (Scheme 8). Cleavage of the sulfonamide of **27** by reaction with Na/NH$_3$ provided amino carbamate **43** in excellent yield. Lithium aluminum hydride reduction of the methyl carbamate of this product afforded (±)-5-*epi*-nankakurine A (**1**) in 65% yield.

The NMR data for synthetic (±)-**1** did not match data reported for nankakurine A.[2,42] We considered it secure that the tethered sulfonamide would undergo C–N bond formation to the cup-shaped decahydro-3,5-ethanoquinoline intermediate (**7**, Scheme 1) from the less-hindered convex face in the sulfonamide-terminated aza-Prins reaction. With the relative configuration at the spirocyclic stereocenter of product **27** established, we hypothesized that the originally proposed structure **1** for nankakurine A was incorrect. At approximately the same time, Kobayashi and coworkers reported that the relative configuration of nankakurine A at the spiropiperidine stereocenter C5 should be reversed.[4] As discussed earlier, this conclusion was founded on ^{1}H NMR NOE studies of the conjugate acid of nankakurine B (**3**).

A serious complication in assigning the relative configuration of the spiro stereocenter of nankakurines A and B involved the existence of two conformational isomers of the spiropiperidine ring, which made NOE measurements difficult to interpret. Kobayashi and co-workers suggested that this complication was responsible for the original misassignment of the relative configuration of nankakurine A (**2**).[4] This issue was proposed to be less serious for the disalt of nankakurine B (**3**), which was suggested to exist predominantly in conformer **B** on the basis of molecular mechanics calculations (Figure 2).[4] However, molecular modeling carried out in our laboratory at the time did not support this conclusion (B3-LYP/6-311G*), nor do more recent DFT calculations using two functionals and higher-level basis sets.[43] We concluded that a definitive answer to the relative and absolute configuration of the nankakurines would require their total syntheses.

Synthesis of (+)-Nankakurine A and (+)-Nankakurine B

A strategy for construction of structures (+)-**2** and (+)-**3** requires that the spiropiperidine nitrogen be located on the concave face of the tricyclic decahydro-3,5-ethanoquinoline moiety. We envisaged tetracyclic pyrazolidine **44**, which possesses the proper relative configuration at C5, as a logical precursor to nankakurines A and B (Scheme 9). Pyrazolidine **44** was seen arising by an intramolecular dipolar cycloaddition of azomethine imine **45**.[44] High regioselection in this step was anticipated based on the prospect that C–C bond-formation would be more advanced than C–N bond-formation,[44a] an expectation

bolstered by the high regioselectivity observed in Oppolzer's construction of (+)-luciduline by intramolecular cycloaddition of an analogous nitrone intermediate.[13] Hydrazine **6** would readily derive from octahydronaphthalene ketone **47**.

In a sequence analogous to that employed for the synthesis of 5-epi-nankakurine A (**1**), octahydronaphthalenone **50** was constructed in enantioenriched form by the cationic Diels–Alder reaction of (*R*)-5-methyl-2-cyclohexen-1-one ((+)-**9**) and 2-substituted-1,3-butadiene **48** (Scheme 10). Diene **48** was available in two high-yielding steps from 5-hexyn-1-ol (**16**): benzyl-protection,[45] followed by enyne cross metathesis with ethylene using Grubbs' 2nd generation catalyst.[22,23] Cyclohexenone (+)-**9** (>99% ee) was prepared from (+)-pulegone (**49**) in four steps by a known, efficient sequence.[46] Allowing diene **48**, cyclohexenone (+)-**9**, and 1,2-bis(trimethylsiloxy)ethane to react in CH_2Cl_2 at −78 °C in the presence of 10 mol % of TMSOTf,[25] followed by cleavage of the dioxolane with $FeCl_3$ adsorbed on silica gel,[26] gave *cis*-octahydroquinolone **50** in 67% yield as a single stereoisomer.[47]

Intramolecular or bimolecular dipolar cycloadditions of azomethine imines derived from formaldehyde with unactivated trisubstituted alkenes were to our knowledge unknown. As a result, we anticipated that the electron-withdrawing substituent on the dipole might need to be finely tuned for the projected cycloaddition to succeed.[44a,g] Hydrazine derivatives carrying carbomethoxy, *p*-toluenesulfonyl, and benzoyl groups were prepared in varying yields by hydrazone formation, followed by reaction with sodium cyanoborohydride, the reduction occurring exclusively from the convex β-face to deliver **51**–**53**.[48] In order to avoid partial epimerization adjacent to the ketone, it was essential that the hydrazone intermediate was prepared under neutral conditions.

The pivotal intramolecular dipolar cycloaddition was surveyed under both thermal and acidic conditions. In preliminary studies, hydrazines **51**–**53** were allowed to react with excess $(CH_2O)_n$ either in refluxing toluene in the presence of 4Å molecular sieves or at room temperature in $CHCl_3$ in the presence of 20 equiv of TFA (Table 1). With the carbamate and sulfonamide precursors, only the octahydro-3,5-ethanoquinoline aza-Prins products **55** were produced (entries 1–4). Although acidic conditions were not successful (entry 5), reaction of benzoylhydrazide **53** with $(CH_2O)_n$ and 4Å molecular sieves in refluxing toluene provided the tetracyclic pyrazolidine product **54** in 40% yield together with aza-Prins products **55** (entry 6).[49] Carrying out this reaction in the presence of basic additives provided dipolar cycloaddition product **54** in 80–85% yield, with the reaction being slightly faster in the presence of diisopropylethylamine than triethylamine (entries 7–8).

Our interpretation of the positive effect of basic additives on the efficiency of the pivotal intramolecular dipolar cycloaddition is outlined in Scheme 11. Dehydrative condensation of benzoylhydrazide **53** with paraformaldehyde generates azomethine imine **56**, which undergoes intramolecular cycloaddition to yield cycloadduct **54**. In the absence of a basic additive, the efficiency of this reaction is undermined by protonation of **56** by adventitious acid (likely formic acid) to generate *N*-benzamidoformaldiminium ion **57**, which undergoes aza-Prins cyclization to give octahydro-3,5-ethanoquinoline **55** via tertiary carbenium ion intermediate **58**. In the presence of base, iminium electrophile **57** is not generated.[50]

The total syntheses of (+)-nankakurine A (**2**) and (+)-nankakurine B (**3**) were concluded in five and six steps, respectively, from cycloadduct **54** (Scheme 12). Cleavage of the N–N bond with SmI$_2$[51] and selective reductive methylation of the secondary amine product afforded diamine **59** in 80% overall yield in this one-pot sequence. Hydrogenolytic cleavage of the *O*-benzyl protecting group, followed by reduction of the amide with aluminum hydride,[52] provided diamine alcohol **60** in 72% yield. Selective *O*-mesylation of this

intermediate at –40 °C, followed by warming the primary mesylate to ambient temperature generated the spiropiperidine ring and furnished *N*-benzylnankakurine A (**61**) in 96% yield.[53] Hydrogenolysis of this intermediate in acidic methanol then gave (+)-nankakurine A (**2**), $[\alpha]^{24}_D$ +13 (*c* 0.4, MeOH), in 99% yield. Standard reductive methylation of nankakurine A (**2**) delivered (+)-nankakurine B (**3**), $[\alpha]^{24}_D$ +12 (*c* 1.5, MeOH), in 80% yield.[54]

The ^{1}H NMR spectra of synthetic **2** and **3** did not initially match those reported for the natural products (Figure 3). Because basic nitrogen atoms readily protonate, we were able to reproducibly obtain ^{1}H and ^{13}C NMR spectra of the free base forms of nankakurines A (**2**) and B (**3**) only in CD$_3$OD containing a trace of NaOCD$_3$. These spectra were not identical to those reported for natural **2** and **3** in CD$_3$OD.[4] We surmised that the natural isolates contained unknown amounts of their conjugate acids. Thus, we examined the ^{1}H NMR spectra of synthetic (+)-nankakurine A (**2**) and (+)-nankakurine B (**3**) by titrating samples of the free bases with TFA. As reproduced in Figure 3, ^{1}H NMR spectra identical to those of the natural products were obtained. These data are consistent with the notion that the natural samples contained an undetermined amount of the conjugate acids.

Evaluation of the Neurotrophic Properties of (+)-Nankakurine A (2) and (+)-Nankakurine B (3)

The purported neurotrophic properties of (+)-nankakurine A (**2**) and (+)-nankakurine B (**3**) were investigated in the following fashion. Immortalized embryonic rat hippocampus H19-7 cells were grown in the presence of N-2 supplement medium. After 24 h, cells were treated with either **2** or **3**. After an additional 24 h, the cells were fixed, and incubated successively with an antibody against neuronal class III β-tubulin and a secondary Alexa Fluor® 546 goat anti-mouse antibody. After staining, the length of neurites and the cell count were quantified using fluorescence microscopy.[55,56] Neither (+)-nankakurine A nor (+)-nankakurine B increased neurite outgrowth over a concentration range of 0.3–10 μM (Figure 4), nor did they display any toxicity or change in cell number. Under the same conditions, a positive reference compound increased neurite outgrowth by 60% at 1.0 μM.

Conclusions

In summary, the first total syntheses of (+)-nankakurine A (**2**), (+)-nankakurine B (**3**), and the originally proposed structure of nankakurine A (**1**, 5-*epi*-nankakurine A) were accomplished. Pivotal steps in these syntheses include the first example of a dipolar cycloadditions of an azomethine imine derived from formaldehyde with an unactivated trisubstituted alkene, and a nitrogen-terminated aza-Prins cyclization. The total syntheses of (+)-**2** and (+)-**3**, together with the synthesis of the originally purported structure **1** of nankakurine A, rigorously establish the relative and absolute configuration of these *Lycopodium* alkaloids. These syntheses were sufficiently concise that substantial quantities of these alkaloids could be prepared for biological evaluation. (+)-Nankakurine A (**2**) and (+)-nankakurine B (**3**) showed no effect on neurite outgrowth in rat hippocampus H-19 cells over a concentration range of 0.3–10 μM, which stands in contrast to the report of neurotrophic activity of the former in human astrocytoma cells.[2]

Experimental Section

Materials and Methods

Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of nitrogen using anhydrous solvents. THF, DMF, CH$_2$Cl$_2$, PhMe, MeOH, MeCN, Et$_2$O, NEt$_3$ and *i*-Pr$_2$NEt were passed through activated alumina columns.[57] CHCl$_3$ was distilled from Na$_2$SO$_4$ and stored over 4 Å molecular sieves.[58] EtOH (200 proof) and

acetone (ACS grade) were purchased from commercial sources and used without further purification. $FeCl_3$/silica[26] and AlH_3[52] were prepared as previously described. SmI_2[51],[59] was freshly prepared prior to each usage. Trimethylsilyl triflate was distilled from CaH_2.[58] Methyl chloroformate was distilled from $CaCl_2$.[58] All other commercially obtained reagents were used as received. Reaction temperatures were controlled using a temperature modulator, and unless stated otherwise, reactions were performed at room temperature (rt, approximately 25 °C).

Thin-layer chromatography (TLC) was conducted with silica gel 60 F_{254} pre-coated plates, (0.25 mm) and visualized by exposure to UV light (254 nm) or stained with anisaldehyde, ceric ammonium molybdate, potassium permanganate or iodide. Flash column chromatography was performed using normal phase silica gel (60 Å, 230–240 mesh).

^{1}H NMR spectra were recorded on 500 or 600 MHz spectrometers and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. ^{13}C NMR spectra were recorded at 125 or 150 MHz. Data for ^{13}C NMR spectra are reported in terms of chemical shift (δ ppm). IR spectra were recorded on a spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Optical rotations were measured with a polarimeter. High resolution mass spectra were obtained using the electrospray ionization method.

Experimental Procedures

1,3-Dimethoxy-5-methylbenzene (12)

Orcinol (**11**, 25.0 g, 0.202 mol) was heated at reflux with MeI (62 mL, 1.0 mol) and anhydrous K_2CO_3 (140 g, 1.0 mol) in acetone (500 mL) overnight. After cooling to rt, the reaction mixture was filtered through diatomaceous earth, and the filtrate was concentrated *in vacuo.* Chromatographic purification of the residue (hexanes:EtOAc 19:1) provided **12**[60] as a clear oil (27 g, 89%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.35 (d, *J* = 2.1 Hz, 2H), 6.31 (t, *J* = 2.2 Hz, 1H), 3.80, (s, 6H), 2.32 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.9, 140.4, 107.3, 97.7, 66.1, 55.4, 22.0 ppm.

1,5-Dimethoxy-3-methylcyclohexa-1,4-diene (S1)

A solution of **12** (760 mg, 5.0 mmol) in anhydrous EtOH (5.0 mL) was added dropwise over 10 min to a solution of Li^0 (350 mg, 0.050 mol) and NH_3 (50 mL) at −50 °C. The reaction mixture was stirred at −50 °C for 1 h, then quenched by the addition of saturated aqueous NH_4Cl (10 mL) and warmed to rt. The aqueous mixture was extracted with hexanes (3 × 10 mL). The combined extracts were dried with $MgSO_4$, and concentrated in vacuo to provide **S1**[61] as a clear oil (650 mg, 85%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.58 (dt, *J* = 1.2, 3.5 Hz, 2H), 3.57 (s, 6H), 3.05 (1H, m), 2.77 (dq, *J* = 1.1, 6.7 Hz, 2H), 1.09 (d, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.4, 98.0, 54.3, 31.3, 30.9, 24.7 ppm.

5-Methylcyclohexane-1,3-dione (13)

Cyclohexadiene **S1** (650 mg, 4.2 mmol) was stirred in 1 M HCl (5 mL) and THF (50 mL) overnight at rt, and then concentrated *in vacuo*. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were dried with $MgSO_4$. The solvent was removed *in vacuo* to provide **13**[62] as a colorless solid (440 mg, 83%, a 5:1 mixture of hydroxyenone–diketone tautomers): ^{1}H NMR (500 MHz, $CDCl_3$, 3-hydroxyenone tautomer) δ 11.30, (bs, 1H), 5.47 (s, 1H), 2.43 (dd, *J* = 4.3, 17.0 Hz, 2H), 2.29–2.20 (m, 1H), 2.10 (dd, *J* = 11.1, 17.0 Hz, 2H), 1.08 (d, *J* = 6.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.2, 192.6, 104.0, 48.2, 40.7, 29.0, 21.0 ppm.

3-Bromo-5-methylcyclohex-2-enone (14)

Following a known procedure,[17] oxalyl bromide (22 mL, 240 mmol) was added dropwise over 20 min (CAUTION gas evolution) to a solution of diketone **13** (25.0 g, 198 mmol), DMF (20 mL, 260 mmol), and CH_2Cl_2 (500 mL) at 0 °C. The reaction was stirred at 0 °C for 15 min, allowed to warm to rt, and stirred for 1 h at rt, after which H_2O (500 mL) was added, and the biphasic mixture was stirred for 1 h. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (500 mL). The combined organic layers were washed with brine (500 mL), dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes:EtOAc 1:0→3:1) to provide **14**[17a] as a yellow oil (35.2 g, 94%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.46 (s, 1H), 2.86 (dd, *J* = 4.7, 18.5 Hz, 1H), 2.51 (m, 1H), 2.46 (d, *J* = 4.0 Hz, 1H), 2.37–2.30 (m, 1H), 2.10 (dd, 1H, *J* = 12.0, 16.3 Hz), 1.10 (d, 3H, *J* = 6.7 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.7, 149.6, 132.4, 44.8, 44.5, 30.8, 20.8 ppm.

5-Methylcyclohex-2-enone [(±)-9]

A 1L 3-neck round-bottom flask was charged with Zn^0 (37 g, 580 mmol, washed with AcOH and dried), 1,2-dibromoethane (6.2 mL, 72 mmol) and THF (200 mL), and the slurry was stirred and heated with a heat gun until ethylene gas evolved (CAUTION gas evolution). The slurry was allowed to cool to rt. The heating/cooling cycle was repeated two additional times. A solution of **14** (27.2 g, 144 mmol) in THF (200 mL) was added to the reaction mixture at a rate that maintained the reaction temperature <35 °C. The reaction was stirred at rt for 24 h, and then quenched by the addition of saturated aqueous NH_4Cl (300 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic extracts were dried with $MgSO_4$, and concentrated. Purification by flash chromatography (hexanes:EtOAc 0:1→1:1) provided enone **(±)-9**[63] as a pale yellow oil (14.2 g, 94%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.95 (ddd, *J* = 2.6, 5.5, 10.0 Hz, 1H), 6.01 (dd, *J* = 1.4, 10.1 Hz, 1H), 2.48 (dd, *J* = 2.6, 16.0 Hz, 1H), 2.42 (dt, *J* = 5.4, 18.6 Hz, 1H), 2.29–2.17 (m, 1H), 2.12 (dd, *J* = 12.3, 15.8 Hz, 1H), 2.04 (ddt, *J* = 2.7, 9.8, 18.5 Hz, 1H), 1.07 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.3, 150.1, 129.8, 46.5, 34.2, 30.5, 21.4 ppm; IR (thin film) 1681, 1457, 1390, 879, 734 cm^{-1}.

9-Methyl-1,4-dioxaspiro[4.5]dec-6-ene (15)

An oven-dried Schlenk tube was charged with (±)-**9** (12.1 g, 110 mmol) and 1,2-bis(trimethylsiloxy)ethane (27 mL, 0.10 mmol), evacuated, and back-filled with N_2. Dichloromethane (8.0 mL) was added, the solution was cooled to −78 °C, and TMSOTf (360 μL, 2.0 mmol) was added dropwise. The reaction vessel was sealed, and the reaction mixture was stirred at −78 °C for 23 h. The reaction mixture was quenched by the addition of NEt_3 (2 mL), warmed to rt, and filtered through a plug of basic Al_2O_3. The plug was rinsed with excess Et_2O (50 mL), and the volatiles were removed *in vacuo*. Purification of the residue by flash chromatography (hexanes:Et_2O:NEt_3 99:0:1→90:10:1) provided ketal **15**[18] as a pale yellow oil (12.3 g, 73%) along with recovered (±)-**9** (3.5 g, 30%); ketal **15**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.95 (ddd, *J* = 2.2, 5.2, 10.0 Hz, 1H), 5.60–5.57 (m, 1H), 4.07–3.83 (m, 4H), 2.14 (dt, *J* = 5.1, 17.8 Hz, 1H), 2.01–1.93 (m, 1H), 1.88–1.84 (m, 1H), 1.65 (ddt, *J* = 2.5, 10.7, 17.8 Hz, 1H), 1.48 (t, *J* = 13.0 Hz, 1H), 1.00 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.5, 127.3, 106.7, 64.8, 64.5, 42.2, 38.8, 28.1, 21.8 ppm.

Hex-5-yn-1-amine Hydrochloride (16)

A solution of **17** (25.0 g, 255 mmol) and diisopropyl azodicarboxylate (51 mL, 260 mmol) in THF (160 mL) was added by cannula at 0 °C to a solution of PPh_3 (66.8 g, 255 mmol) and phthalimide (37.5 g, 255 mmol) in THF (330 mL) over 20 min. The clear yellow

solution was allowed to warm to rt overnight. Hydrazine hydrate (20 mL, 51% wt, 306 mmol) was added, and the resulting solution was heated at reflux for 6 h. The solution was allowed to cool to rt and concentrated HCl (50 mL) was slowly added. The solution was refluxed for 2 h, then allowed to cool to rt, and stirred overnight. The colorless precipitate (PPh$_3$O) was removed by filtration, and the eluent was removed *in vacuo*. The residual colorless solid was redissolved in H$_2$O (500 mL), and extracted with CH$_2$Cl$_2$ (3 × 500 mL). The aqueous layer was concentrated to provide **16**[64] as an off-white solid (32.8 g, 97%): ^{1}H NMR (500 MHz, CD$_3$OD) δ 2.96 (t, *J* = 7.6 Hz, 2H), 2.29–2.24 (m, 3H), 1.79 (m, 2H), 1.64–1.57 (m, 2H) ppm; ^{13}C NMR (125 MHz, CDCl$_3$) δ 84.2, 70.5, 40.5, 27.8, 26.5, 18.7 ppm. This ammonium salt was used in the subsequent step without further purification.

N-(Hex-5-ynyl)-4-methylbenzenesulfonamide (18)

p-Toluenesulfonyl chloride (12.6 g, 65.9 mmol) was added in four portions over 30 min to a solution of ammonium salt **17** (8.00 59.9 mmol), NEt$_3$ (25 mL, 180 mmol) and CH$_2$Cl$_2$ (120 mL) at 0 °C. The reaction was allowed to warm to rt and stirred overnight. The reaction was quenched with saturated aqueous NH$_4$Cl, and extracted with CH$_2$Cl$_2$ (3 × 150 mL). The combined organic layers were dried with MgSO$_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (hexanes:EtOAc 1:0→3:2) to afford sulfonamide **18**[65] as a colorless solid (12.6 g, 85%): mp 63–65 °C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.75 (d, *J* = 8.5 Hz, 2H), 7.30 (d, *J* = 8 Hz, 2H), 4.95–4.88 (m, 1H), 2.94 (q, *J* = 6.5 Hz, 2H), 2.42 (s, 3H), 2.15–2.12 (m, 2H), 1.91 (t, *J* = 2.5 Hz, 1H), 1.61–1.55 (m, 2H), 1.51–1.47 (m, 2H) ppm; ^{13}C NMR (125 MHz, CDCl$_3$) δ 143.5, 137.1, 129.9, 127.2, 83.9, 69.0, 42.8, 28.6, 25.4, 21.7, 18.0 ppm; IR (thin film) 3294, 2944, 2870, 1598, 1426, 1322, 1154, 1092 cm^{-1}; HRMS (ESI) *m/z* 274.0871 (274.0878 calcd for C$_{13}$H$_{17}$NO$_2$SNa$^+$ [MNa]$^+$).

4-Methyl-*N*-(5-methylenehept-6-enyl) Benzenesulfonamide (19)

A solution of alkyne **18** (1.5 g, 5.9 mmol) and CH$_2$Cl$_2$ (100 mL) was degassed by sparging with nitrogen for 30 min. Benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexyl-phosphine)ruthenium (0.18 g, 0.21 mmol)[22] was added to the degassed solution, and the mixture was charged to a high pressure bomb. The reaction bomb was filled with ethylene gas (300 psi), vented and re-pressurized with ethylene (300 psi). This process was repeated a total of three times. The reaction was stirred at rt under high pressure (300 psi) for 4–5 h. After venting unreacted ethylene, the reaction mixture was transferred to a round bottom flask containing silica gel and the solvent was removed *in vacuo*. The residue was purified by column chromatography (dry load, hexanes:EtOAc 4:1) to give diene **19** (1.5 g, 90%) as a tan oil: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.76 (d, *J* = 8.5 Hz, 2H), 7.28 (d, *J* = 8 Hz, 2H), 6.30 (dd, *J* = 17.5, 10.5 Hz, 1H), 5.25 (t, *J* = 6 Hz, 1H), 5.14 (d, *J* = 18 Hz, 1H), 5.00 (d, *J* = 11 Hz, 1H), 4.95 (s, 1H), 4.88 (s, 1H), 2.92 (q, *J* = 6 Hz, 2H), 2.40 (s, 3H), 2.11 (t, *J* = 7 Hz, 2H), 1.49–1.43 (m, 4H) ppm; ^{13}C NMR (125 MHz, CDCl$_3$) δ 145.8, 143.3, 138.7, 137.1, 129.7, 127.1, 115.8, 113.3, 43.1, 30.7, 29.3, 25.0, 21.5 ppm; IR (thin film) 3299, 2929, 1325, 1160, 1094 cm^{-1}; HRMS (ESI) *m/z* 302.1186 (302.1191 calcd for C$_{15}$H$_{21}$NO$_2$SNa$^+$ [MNa]$^+$).

4-Methyl-*N*-(4-(7-methyl-5-oxo-1,4,4a,5,6,7,8,8a-octahydronaphthalen-2-yl)butyl) benzenesulfonamide (20)

An oven-dried Schlenk tube was charged with **15** (5.7 g, 37 mmol) and **19** (6.9 g, 25 mmol), evacuated and back-filled with Ar. Dichloromethane (25 mL) was added, the reaction mixture was cooled to –78 °C, and TMSOTf (420 μL, 2.3 mmol) was added dropwise. The tube was sealed and stirred at –78 °C for 20 h. The reaction mixture was quenched at –78 °C by the addition of NEt$_3$ (2 mL), and warmed to rt. The mixture was diluted with 20 mL

Et$_2$O, filtered through a short silica gel column, and the eluent was concentrated *in vacuo* to afford **S2** as a yellow oil.

Ketal **S2** was dissolved in 80 mL acetone (80 mL) and stirred at rt for 4 h with FeCl$_3$/SiO$_2$ (1.3 g).[26] Silica gel (50 g) was added and the solvent was removed *in vacuo*. Purification of the residue by flash chromatography (dry packed, hexanes:Et$_2$O 9:2→1:2) provided **20** as a yellow oil (9.07 g, 93%): ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.71 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 2H), 5.19 (bs, 1H), 5.14 (t, *J* = 6.0 Hz, 1H), 2.83 (q, *J* = 6.5 Hz, 2H), 2.61 (t, *J* = 5.5 Hz, 1H), 2.44–2.39 (m, 1H), 2.37 (s, 3H), 2.34–2.29 (m, 1H), 2.16–2.12 (m, 1H), 2.09–2.04 (m, 2H), 1,97–1.90 (m, 2H), 1.87–1.74 (m, 3H), 1.68–1.59 (m, 2H), 1.40–1.35 (m, 2H), 1.34–1.26 (m, 2H), 0.97 (d, *J* = 6.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, CDCl$_3$) δ 211.9, 143.1, 137.1, 134.9, 129.6, 127.1, 118.8, 49.6, 47.0, 43.1, 38.4, 36.9, 35.6, 30.7, 29.8, 28.7, 24.2, 23.6, 22.5, 21.5 ppm; IR (thin film) 3286, 2915, 1702, 1599, 1325, 1160, 1095, 905 cm^{-1}; HRMS (ESI) *m/z* 412.1929 (412.1922 calcd for C$_{22}$H$_{31}$NO$_3$SNa$^+$ [MNa]$^+$).

(*E*)-*N*-(4-(5-(Hydroxyimino)-7-methyl-1,4,4a,5,6,7,8,8a-octahydronaphthalen-2-yl)butyl)-4-methylbenzenesulfonamide (21)

Aqueous H$_2$NOH (6.2 mL, 94 mmol, 50% wt.) was added over 5 min to a stirred solution of ketone **20** (9.07 g, 23.2 mmol) in MeOH (250 mL) at rt. The reaction was stirred for 4 h, and the solvent was removed *in vacuo*. The residue was dissolved in CH$_2$Cl$_2$ (150 mL), and saturated aqueous NH$_4$Cl (100 mL). The layers were separated, and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 × 100 mL), the combined organic layers were dried with MgSO$_4$, and concentrated to provide the *cis*-oxime as a colorless solid (9.24 g, 99%): ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.52 (bs, 1 H), 7.77 (d, *J* = 8 Hz, 2H), 7.31 (d, *J* = 7.5 Hz, 2H), 5.23 (s, 1H), 4.75 (bs, 1H), 3.21 (dd, *J* = 13, 3.5 Hz, 1H), 2.93–2.91 (m, 2H), 2.51–2.50 (m, 1H), 2.44 (s, 3H), 2.42–2.38 (m, 1H), 2.22–2.18 (m, 1H), 2.09–2.05 (m, 1H), 2.01–1.96 (m, 1H), 1.88–1.84 (m, 2H), 1.83–1.79 (m, 1H), 1.71–1.68 (m, 2H), 1.52 (dd, *J* = 13.5, 11 Hz, 1H), 1.44–1.39 (m, 2H), 1.38–1.35 (m, 3H), 1.01 (d, *J* = 6.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, CDCl$_3$) δ 160.2, 143.4, 137.4, 135.4, 129.8, 127.3, 119.2, 42.9, 39.6, 38.4, 36.9, 34.5, 32.0, 30.1, 28.9, 28.6, 25.8, 23.8, 22.3, 21.7 ppm; IR (thin film) 3286, 2907, 1597, 1458, 1446, 1323, 1156, 1092 cm^{-1}; HRMS (ESI) *m/z* 427.2025 (427.2031 calcd for C$_{22}$H$_{32}$N$_2$O$_3$SNa$^+$ [MNa]$^+$).

N-(4-(-5-Amino-7-methyl-1,4,4a,5,6,7,8,8a-octahydronaphthalen-2-yl)butyl)-4-methylbenzenesulfonamide (22)

cis-Oxime **21** (4.04 g, 10.0 mmol) was dissolved in EtOH (250 mL) and stirred at 30–35 °C. MoO$_3$ (1.9 g, 13 mmol) was added followed by NaBH$_4$ (1.9 g, 50 mmol; CAUTION, gas evolution), and the reaction was stirred for 1 h, during which the solution turned brown. A second portion of MoO$_3$ (1.9 g, 13 mmol) and NaBH$_4$ (1.9 g, 50 mmol) were added, and the reaction was stirred for an additional 1 h. A third portion of MoO$_3$ (1.9 g, 13 mmol) and NaBH$_4$ (1.9 g, 50 mmol) was added, and the reaction was stirred for an additional 1 h. The reaction mixture was cooled to rt, and a solution of KOH$_{(aq)}$ (0.2 M, 50 mL) was added. The slurry was stirred for 2 h. The brown precipitate was filtered with diatomaceous earth, and the filter cake was washed with excess methanol (300 mL). The filtrate was concentrated *in vacuo*. The residue was dissolved in saturated aqueous NH$_4$Cl (150 mL), and extracted with CH$_2$Cl$_2$ (4 × 100 mL). The combined organic layers were dried with MgSO$_4$ and concentrated to provide the amine as a colorless solid that was used without further purification (3.52 g, 90%): ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 5.23 (s, 1H), 3.61 (bs, 2H), 3.13 (bs, 1H), 2.85 (t, *J* = 6.5, Hz, 2H), 2.38 (s, 3H), 2.10–2.06 (m, 2H), 1.99–1.85 (m, 4H), 1.81 (t, *J* = 7.5 Hz, 2H), 1.58–1.29 (m, 8H), 0.96 (d, *J* = 7.5 Hz, 3H), 0.86–0.83 (m, 1H) ppm; ^{13}C NMR (125 MHz, CDCl$_3$) δ 143.1, 137.3, 135.5, 129.6, 127.1, 118.7, 49.1, 43.1, 37.7, 37.1, 35.8, 34.1, 33.0, 29.7, 29.1, 28.9,

26.6, 24.6, 21.5, 19.9 ppm; IR (thin film) 2907, 1599, 1458, 1324, 1159, 1095 cm^{-1}; HRMS (ESI) m/z 391.2417 (391.2419 calcd for $C_{22}H_{35}N_2O_2S$ [MH]$^+$).

N-(4-((4a,8a)-5-(Cyanomethylamino)-7-methyl-1,4,4a,5,6,7,8,8a-octahydronaphthalen-2-yl)butyl)-4-methylbenzenesulfonamide (23)

A mixture of amine **22** (484 mg, 1.2 mmol), chloroacetonitrile (0.16 mL, 2.5 mmol), NEt$_3$ (0.52 mL, 3.7 mmol), and tetrabutylammonium iodide (114 mg, 0.31 mmol) was stirred in THF (50 mL) at 70 °C for 30 h. The reaction was cooled to rt, and concentrated *in vacuo*. The residue was redissolved in CH$_2$Cl$_2$ (40 mL), washed with saturated aqueous NaHCO$_3$ (30 mL). The organic layer was dried with MgSO$_4$, and concentrated. The residue was purified by column chromatography (hexanes:EtOAc 4:1→3:2) to give cyanomethylamine **23** as a tan oil (418 mg, 78%): ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.76 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 5.29 (s, 1H), 4.63 (bs, 1H), 3.62–3.61 (m, 2H), 3.07–3.05 (m, 1H), 2.93 (q, J = 6.5 Hz, 2H), 2.44 (s, 3H), 2.03–2.00 (m, 2H), 1.96–1.93 (m, 3H), 1.88 (t, J = 7.5 Hz, 2H), 1.77 (bs, 1H), 1.65–1.52 (m, 3H), 1.46–1.41 (m, 2H), 1.37–1.32 (m, 3H), 1.25–1.24 (m, 1H), 1.12–1.05 (m, 1H), 0.94 (d, J = 6.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, CDCl$_3$) δ 143.3, 137.1, 129.7, 127.2, 126.5, 119.1, 118.3, 60.5, 48.0, 43.2, 37.2, 37.1, 34.9, 33.8, 29.8, 29.2, 24.6, 21.6, 21.1, 20.5, 14.2, 12.6 ppm; IR (thin film) 3267, 2917, 1600, 1466, 1459, 1380, 1328, 1161, 1095 cm^{-1}; HRMS (ESI) m/z 452.2333 (452.2348 calcd for $C_{24}H_{35}N_3O_2SNa^+$ [MNa]$^+$).

Tricyclic Amine 24

A solution of cyanomethyl amine **23** (420 mg, 0.97 mmol) in dry CHCl$_3$ (90 mL) was added to AgO$_2$CCF$_3$ (709 mg, 3.21 mmol). The suspension was stirred at rt for 2 h, after which time the reaction mixture was filtered with diatomaceous earth. The filter cake was washed with CHCl$_3$ (50 mL), and the filtrate was washed with saturated aqueous NaHCO$_3$ (50 mL), dried with MgSO$_4$, and concentrated to give **24** as a tan oil (350 mg, 90%): ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.78 (d, J = 8.5 Hz, 2H), 7.33 (d, J = 8 Hz, 2H), 5.49 (s, 1H), 2.95 (t, J = 6.5 Hz, 3H), 2.80 (dd, J = 13.5, 2 Hz, 1H), 2.67 (d, J = 13.5 Hz, 1H), 2.46 (m, 4H), 2.46 (m, 1H), 2.10 (bs, 1H) 2.01 (bs, 1H), 1.88–1.86 (m, 2H), 1.81 (bs, 2H), 1.76–1.72 (m, 2H), 1.60–1.54 (m, 1H), 1.53–1.50 (m, 1H), 1.49–1.44 (m, 3H), 1.40–1.36 (m, 1H), 1.24–1.19 (m, 1H), 1.19–1.12 (m, 1H), 0.90 (d, J = 6.0 Hz, 3H) ppm; ^{13}C NMR (125 MHz, CDCl$_3$) δ 143.3, 138.2, 137.3, 130.6, 129.8, 127.2, 55.0, 47.9, 43.2, 40.6, 40.4, 36.5, 35.0, 33.2, 33.0, 32.4, 29.5, 24.9, 22.7, 22.0, 21.7 ppm; IR (thin film) 2928, 2873, 1600, 1466, 1457, 1326, 1305, 1160, 1095 cm^{-1}; HRMS (ESI) m/z 403.2412 (403.2419 calcd for $C_{23}H_{35}N_2O_2S^+$ [MH]$^+$).

Tricyclic Carbamate 25

Triethylamine (0.10 mL, 0.75 mmol) was added to a stirred solution of amine **24** (150 mg, 0.37 mmol) and methylchloroformate (58 μL, 0.75 mmol) in CH$_2$Cl$_2$ (4.2 mL), and the reaction was stirred at rt for 12 h. The reaction mixture was concentrated, and the residue was purified by chromatography (hexanes:EtOAc 4:1→3:2) to give carbamate **25** as a colorless oil (114 mg, 67%): ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.79 (d, J = 8.5 Hz, 2H), 7.33 (d, J = 8 Hz, 2H), 5.22 (s, 1H), 5.14 (t, J = 6 Hz, 1H), 3.89–3.86 (m, 1H), 3.63 (s, 3H), 3.55 (q, J = 3 Hz, 1H), 3.03–3.00 (m, 1H), 2.94 (q, J = 6.5 Hz, 2H), 2.91 (dd, J = 12.5, 3.5 Hz, 1H), 2.45 (m, 4H), 2.10 (bs, 1H), 1.94–1.92 (m, 2H), 1.83–1.77 (m, 2H), 1.73–1.70 (m, 1H), 1.68–1.65 (m, 1H), 1.53–1.49 (m, 3H), 1.41–1.36 (m, 2H), 1.26–1.20 (m, 1H), 0.98–0.92 (m, 1H), 0.85 (d, J = 6.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, CDCl$_3$) δ 158.7, 143.3, 137.4, 137.2, 129.7, 128.9, 127.2, 55.9, 52.2, 49.6, 43.2, 41.0, 39.4, 36.9, 34.7, 33.7, 31.9, 31.8, 29.2, 24.7, 22.3, 22.0, 21.6 ppm; IR (thin film) 3269, 2945, 2917, 2850, 1702, 1685, 1442,

1326, 1307, 1294, 1268, 1243, 1230, 1201, 1157, 1094 cm^{-1}; HRMS (ESI) *m/z* 483.2290 (483.2293 calcd for $C_{25}H_{36}N_2O_4SNa^+$ [MNa]$^+$).

Tricyclic Sulfonamide 28

p-Nitrophenylsulfonyl chloride (96 mg, 0.43 mmol) was added to a stirred solution of amine **24** (175 mg, 0.434 mmol) and NEt$_3$ (90 μL, 0.65 mmol) in CH$_2$Cl$_2$ (20 mL), and the yellow solution was stirred overnight at rt. The reaction was quenched with 2 M HCl (10 mL), the layers were separated, and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 × 10 mL). The combined organic layers were washed with brine (20 mL), dried with MgSO$_4$, and concentrated. The resulting residue was purified by chromatography (hexanes:EtOAc, 1:1) to give sulfonamide **28** as yellow foam/oil (216 mg, 88%): ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.00 (m, 1H), 7.77–7.67 (m, 5H), 7.32 (d, *J* =8.0 Hz, 2H), 5.22 (s, 1H), 4.62 (t, *J* = 6.0 Hz, 1H), 3.72 (d, *J* = 11.2 Hz, 1H), 3.57 (d, *J* = 2.9 Hz, 1H), 3.00–2.93 (m, 3H), 2.43 (s, 3H), 2.21–2.10 (m, 3H), 1.96 (m, 1H), 1.81 (m, 2H), 1.76–1.36 (m, 6H), 1.22–1.07 (m, 3H), 0.90 (dt, *J* = 14.3, 2.3 Hz, 1H), 0.28 (d, *J* = 6.1 Hz, 3H) ppm; ^{13}C NMR (125 MHz, CDCl$_3$) δ 147.7, 143.2, 136.9, 135.0, 133.4, 132.1, 130.9, 129.6, 128.4, 127.0, 124.9, 60.3, 58.0, 50.6, 42.9, 40.2, 38.5, 36.6, 34.8, 34.2, 31.9, 29.1, 23.9, 21.6, 21.4, 21.0, 14.1 ppm.

N-(4-(3,7-Dimethyl-5,6,7,8-tetrahydronaphthalen-2-yl)butyl)-4-methylbenzenesulfonamide (29)

Trifluoromethanesulfonic acid (13 mg, 0.085 mmol) was added to a solution of **28** (50 mg, 0.085 mmol) in toluene (5.0 mL). The reaction mixture was heated to reflux for 2 h, and then cooled to rt, and quenched with saturated aqueous NaHCO$_3$ (10 mL). The layers were separated, and the organic layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried with MgSO$_4$, concentrated *in vacuo*, and the resulting residue was purified by column chromatography (hexanes:EtOAc 4:1) to give **29** in low yield: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 6.84 (s, 1H), 6.74 (s, 1H), 4.26 (t, *J* = 6.1 Hz, 1H), 2.86 (q, *J* = 14.5, 7.9 Hz, 2H), 2.73–2.70 (m, 2H), 2.48–2.39 (m, 2H), 2.42 (s, 3H), 2.33–2.28 (m, 2H), 2.17 (s, 3H), 1.86–1.80 (m, 2H), 1.55–1.50 (m, 3H), 1.36–1.25 (m, 2H), 1.04 (d, *J* = 6.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, CDCl$_3$) δ 143.4, 137.1, 136.9, 134.3, 134.2, 132.8, 130.5, 129.7, 129.3, 127.1, 43.2, 37.7, 32.3, 31.6, 29.5, 29.4, 28.7, 27.3, 22.0, 21.5, 18.8 ppm; IR (thin film) 3282, 2932, 1455, 1326, 1158, 1094, 814 cm^{-1}; HRMS (ESI) *m/z* 408.1964 (408.1973 calcd for $C_{23}H_{31}NO_2SNa$ [(MNa)$^+$]).

Methyl Cyanomethyl(3-methyl-6-(4-(4-methylphenylsulfonamido)butyl)-1,2,3,4,4a,5,8,8a-octahydronaphthalen-1-yl)carbamate (37)

Methyl chloroformate (26 μL, 0.340 mmol) was added to a mixture of **23** (73 mg, 0.017 mmol) and K$_2$CO$_3$ (0.14 g, 1.0 mmol) in THF (3.0 mL), and the yellow mixture was stirred overnight at rt. The reaction mixture was directly purified by column chromatography (hexanes/EtOAc 4:1→3:2) to provide carbamate **37** as yellow oil (43 mg, 52%): ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.24 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 5.24 (s, 1H), 4.35 (t, *J* = 6.1 Hz, 1H), 4.26 (bs, 1H), 3.92 (d, *J* = 17.7 Hz, 1H), 3.79 (s, 3H), 2.92 (q, *J* = 13.3, 6.6 Hz, 2H), 2.43 (s, 3H), 2.26–2.08 (m, 4H), 1.97 (ddd, *J* = 12.9, 12.9, 5.5 Hz, 1H), 1.85 (t, *J* = 7.1 Hz, 2H), 1.71 (d, *J* = 15.7 Hz, 1H), 1.52–1.45 (m, 5H), 1.36 (m, 2H), 1.28 (m, 2H), 1.07 (dd, *J* = 7.3 Hz, 3H), 0.98 (m, 1H) ppm; ^{13}C NMR (125 MHz, CDCl$_3$) δ 143.42, 136.9, 135.2, 129.7, 127.1, 117.7, 116.9, 53.8, 53.4, 43.1 36.9, 34.0, 32.4, 31.4, 29.3, 29.1, 28.4, 27.8, 24.4, 21.5, 20.3, 18.9, 14.6 ppm.[66]

Methyl 3-Methyl-6-(4-(4-methylphenylsulfonamido)butyl)-1,2,3,4,4a,5,8,8a-octahydro-naphthalen-1-yl carbamate (38)

Methyl chloroformate (81 μL, 1.0 mmol) was added dropwise over 5 min to a stirred mixture of amine **22** (340 mg, 0.87 mmol) and Na_2CO_3 (120 mg, 1.1 mmol) in H_2O–CH_2Cl_2 (1:1, 2 mL) at rt. The reaction was stirred vigorously for 3 h, after which time the layers were separated. The organic layer was dried with $MgSO_4$, and the solvent was removed *in vacuo*. The resulting residue was purified by column chromatography (hexanes:EtOAc 1:0→1:1) to provide carbamate **38** as a colorless solid (310 mg, 80%): ^{1}H NMR (500 MHz, DMSO-d_6, 298.0 K, peak broadening caused by dynamic NMR processes) δ 7.65 (d, *J* = 7.8 Hz, 2H), 7.45 (t, *J* = 4.9 Hz, 1H), 7.37 (d, *J* = 7.8 Hz, 2H), 6.98 (bs, 1H), 5.21 (bs, 1H), 3.71 (bs, 1H), 3.49 (s, 3H), 2.69 (bs, 2H), 2.37 (s, 3H), 2.10 (d, *J* = 17.0 Hz, 1H), 2.05–1.86 (m, 4H), 1.85–1.57 (m, 4H), 1.48 (m, 1H), 1.40 (t, *J* = 9.6 Hz, 1H), 1.36–1.19 (m, 5H), 1.00 (d, *J* = 7.0 Hz, 3H), 0.93 (d, *J* = 12.7 Hz, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6, 323.0 K, peak broadening caused by dynamic NMR processes) δ 155.7, 144.2, 137.9, 134.5, 129.3, 126.3, 118.3, 50.8, 48.0, 42.3, 39.9, 36.4, 35.3, 33.6, 31.6, 28.3, 27.6, 26.3, 23.9, 20.7, 19.8, 19.0 ppm; IR (thin film) 3267, 2908, 1698, 1528, 1158 cm^{-1}; HRMS (ESI) *m/z* 471.2282 (471.2293 calcd for $C_{24}H_{36}N_2O_4SNa$ [MNa]$^+$).

Methyl (1*H*-Benzo[*d*][1,2,3]triazol-1-yl)methyl(3-methyl-6-(4-(4-methylphenylsulfonamido)-butyl)-1,2,3,4,4a,5,8,8a-octahydronaphthalen-1-yl)carbamate (39)

Trifluoroacetic acid (4–5 drops) was added to a solution of **38** (50 mg, 0.11 mmol) and (1*H*-benzo[*d*][1,2,3]triazol-1-yl)methanol (0.050 mL, 0.33 mmol) in dry acetonitrile (2.5 mL). The resulting solution was stirred at rt overnight, and the solvent was removed *in vacuo*. The residue was dissolved in Et_2O and unreacted benzotriazole was removed by filtration. The remaining material was purified by column chromatography (hexanes:EtOAc 4:1→1:1) to afford benzotriazole **39** (45 mg, 70%). An analytical sample was further purified using preparatory HPLC (hexanes:EtOAc 19:1→3:2) ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.05 (d, *J* = 8.3 Hz, 1H), 8.01 (d, *J* = 8.2 Hz, 1H), 7.57–7.54 (m, 3H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 2H), 6.12 (s, 2H), 5.23 (s, 1H), 4.70 (bs, 1H), 3.88 (bs, 1H), 3.63 (s, 3H), 3.25 (t, *J* = 7.5 Hz, 2H), 2.39 (s, 3H), 2.05–1.93 (m, 6H), 1.78 (t, *J* = 7.2 Hz, 2H), 1.71–1.26 (m, 8H), 1.15 (m, 1H), 1.03 (d, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (125 MHz, CDCl$_3$) δ 156.7, 146.3, 144.2, 136.5, 135.7, 132.8, 130.0, 128.4, 127.1, 124.7, 120.0, 119.4, 111.0, 66.1, 59.3, 52.0, 50.0, 47.7, 37.2, 36.8, 35.2, 33.6, 29.9, 28.9, 27.5, 24.6, 21.7, 20.3, 15.5 ppm; IR (thin film) 3386, 3332, 1712, 1520, 1454, 1342, 1261, 1234, 1157, 1115, 1034, 933, 748 cm^{-1}; HRMS (ESI) *m/z* 602.2777 (602.2776 calcd for $C_{31}H_{41}N_5O_4SNa$ [MNa]$^+$).

Sulfonamide-Terminated Aza-Prins Cyclization to Form Tetracyclic Sulfonamide 27

A stock solution of paraformaldehyde (20 mg), TFA (1 mL) and CHCl$_3$ (10 mL) was prepared in a flame-dried round-bottom flask under nitrogen. An aliquot of the stock formaldehyde solution (0.30 mL, ~1 equiv of paraformaldehyde and 20 equiv of TFA) was added to a solution of amide **38** (0.10 g, 0.022 mmol) in CHCl$_3$ (1 mL), and the resulting mixture was stirred at rt until complete consumption of the starting material was observed by electrospray MS analysis (~3 h). The reaction was quenched with saturated aqueous NaHCO$_3$ (3 mL) and extracted with CHCl$_3$ (3 × 3 mL). The combined organic layers were dried with $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by preparative HPLC (Alltima silica 5 micron, length 250 mm, ID 22 mm; hexanes:EtOAc 7:3; 16 mL/min; retention time 9.8–11 min) to give tetracyclic product **27** (20 mg, 20%) as a colorless solid: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.66 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 3.72 (m, 1H), 3.62 (s, 3H), 3.48 (ddd, *J* = 14.6, 4.0, 4.0 Hz, 1H), 3.32 (t, *J* = 12.7 Hz, 1H), 2.74 (m, 1H), 2.50 (dd, *J* = 13.2, 5.0 Hz, 1H), 2.42 (s, 3H), 2.40–2.39 (m, 1H), 2.18–2.12 (m, 2H), 1.95–1.91 (m, 3H), 1.82 (ddd, *J* = 13.5, 10.8, 2.7 Hz, 1H), 1.85–1.73 (m, 2H),

1.63–1.45 (m, 4H), 1.01 (ddd, J = 12.8, 12.8, 3.0 Hz, 1H), 0.97 (ddd, J = 13.9, 3.5, 3.5 Hz, 1H), 0.88 (dd, J = 6.5 Hz, 3H), 0.83 (ddd, J = 14.4, 14.4, 3.0 Hz, 1H) ppm; ^{13}C NMR (125 MHz, CDCl$_3$) δ 156.2, 143.3, 135.2, 129.8, 127.4, 59.4, 56.7, 54.3, 51.9, 49.3, 40.1, 38.9, 36.1, 36.0, 35.1, 34.1, 32.1, 30.9, 29.3, 24.9, 22.0, 21.7, 21.4 ppm; IR (thin film) 1713 cm^{-1}; HRMS (ESI) m/z 483.2284 (483.2293 calcd for C$_{25}$H$_{36}$N$_2$O$_4$SNa [MNa]$^+$).

Tetracyclic Carbamate 43

A flame dried three-neck flask was equipped with a stir bar, two rubber septa, and a cold-finger condenser under nitrogen. The condenser and the round bottom flask were cooled to −78 °C and ammonia gas was condensed into the three-neck round bottom flask (~10 mL). To this solution at −78 °C was added Na^0 (0.010 g, 0.46 mmol, washed with HPLC grade pentane three times). The resulting deep blue reaction was stirred at −78 °C for 5 min, and then a solution of tetracyclic aza-Prins product **27** (7.0 mg, 0.015 mmol) in THF (3 mL) was added dropwise. The reaction was stirred at −78 °C for 15 min and quenched by the slow addition of methanol (MeOH added dropwise until reaction becomes clear, ~2 mL) followed by the addition of saturated aqueous NH$_4$Cl (3 mL). The resulting mixture was allowed to warm to rt overnight open to the atmosphere. The aqueous solution was extracted with CH$_2$Cl$_2$ (3 × 10 mL), and the combined organic solutions were dried with MgSO$_4$, and concentrated *in vacuo* to provide an orange oil. This residue was purified by column chromatography (MeOH:CHCl$_3$:NH$_4$OH 10:90:1) to afford carbamate **43** (5.0 mg, 98%) as a colorless oil. NMR spectra are reported as the free base generated by the addition of NaOCD$_3$ to the NMR sample: ^{1}H NMR (500 MHz, CD$_3$OD) δ 3.74 (bs, 1H), 3.60 (s, 3H), 2.88 (m, 1H), 2.76–2.66 (m, 2H), 2.57 (dd, J = 11.0, 3.6 Hz, 1H), 2.33 (m, 1H), 2.12 (d, J = 14.0 Hz, 1H), 1.99 (dd, J = 11.6, 2.8 Hz, 1H), 1.92 (ddd, J = 13.8, 11.1, 3.2 Hz, 1H), 1.88–1.71 (m, 3H), 1.70–1.50 (m, 4H), 1.48–1.42 (m, 2H), 1.40–1.29 (m, 2H), 1.06 (ddd, J = 12.8, 12.8, 3.1 Hz, 1H), 0.96 (ddd, J = 16.6, 4.6, 4.6 Hz, 1H), 0.87 (d, J = 6.5 Hz, 3H), 0.86 (m, 1H) ppm; ^{13}C NMR (125 MHz, CD$_3$OD) δ 158.1, 60.9, 57.8, 56.6, 52.5, 41.5, 40.0, 38.4, 37.8, 37.1, 35.5, 34.1, 32.2, 31.3, 24.8, 22.6, 22.5 ppm;[66] IR (thin film) 3363, 1706 cm^{-1}; HRMS (ESI) m/z 307.2386 (307.2393 calcd for C$_{18}$H$_{31}$N$_2$O$_2$ [MH]$^+$).

5-epi-Nankakurine A (1)

An Et$_2$O solution of LiAlH$_4$ (0.30 mL, 0.29 mmol, 1.0 M) was added dropwise to a solution of *N*-methyl carbamate **43** (9.0 mg, 0.029 mmol) in THF (3.0 mL) at 0 °C. The reaction mixture was allowed to warm to rt, stirred overnight at rt, quenched with H$_2$O (2.0 mL), and Rochelle salt (20 mL), and stirred for an additional 2 h. The mixture was transferred to a separatory funnel, diluted with Et$_2$O (20 mL), agitated and the two solutions were separated. The aqueous solution was extracted with CH$_2$Cl$_2$ (5 × 20 mL), the combined organic solutions were dried over MgSO$_4$, filtered and then concentrated *in vacuo* to yield orange oil residue. The residue was purified by column chromatography (MeOH:CHCl$_3$:NH$_4$OH 10:90:1) to afford diamine **(±)-1** (5.0 mg, 65%) as a yellow oil: IR (thin film) 3458, 1679 cm^{-1}; HRMS (ESI) m/z 263.2490 (263.2487 calcd for C$_{17}$H$_{31}$N$_2$$^+$ [MH]$^+$).

A portion of this sample was dissolved in 0.60 mL of CD$_3$OD for NMR analysis and 150 μL of NaOCD$_3$ (~0.1 M in CD$_3$OD) was added to assure that only the free base was present. Aliquots of a solution of TFA in CD$_3$OD (15–25 μL portions of a 0.15 M solution) were added to this sample and ^{1}H NMR spectra were obtained after each addition (Figure S1). Under no conditions were spectra obtained that matched the ^{1}H NMR data reported for nankakurine A.[2] ^{1}H NMR (500 MHz, CD$_3$OD/CD$_3$ONa) δ 2.80 (m, 1H), 2.73 (dd, J = 14.6, 3.6 Hz, 1H), 2.54 (dd, J = 14.5, 10.9 Hz, 1H), 2.36 (bs, 1H), 2.28 (s, 3H), 2.28 (m, 1H), 2.02 (m, 1H), 1.95–1.82 (m, 3H), 1.75–1.66 (m, 4H), 1.54–1.43 (m, 4H), 1.19 (t, J = 2.9 Hz, 1H), 1.06 (m, 1H), 1.00 (ddd, J = 12.8, 12.8, 3.2 Hz, 1H), 0.86 (m, 1H), 0.86 (dd, J = 6.7 Hz,

3H), 0.74 (t, J = 12.8 Hz, 1H) ppm; ^{13}C NMR (125 MHz, CD$_3$OD) δ 63.3, 56.5, 56.1, 42.0, 40.7, 39.0, 37.8, 35.4, 34.4, 32.5, 32.2, 30.9, 23.0, 22.9, 22.6 ppm.[67]

((Hex-5-ynyloxy)methyl)benzene (S3)[45]

A slurry of KH (35 g, 260 mmol) in THF (100 mL) was added to a mixture of alcohol **16** (28 mL, 250 mmol), tetra-*n*-butylammonium iodide (470 mg, 1.3 mmol) and benzyl bromide (33 mL, 280 mmol) in THF (500 mL) at 0 °C. The suspension was warmed to rt, and stirred overnight. The reaction was quenched by the addition of H$_2$O (400 mL), and the layers were separated. The aqueous layer was extracted with Et$_2$O (2 × 200 mL). The combined organic extracts were dried with MgSO$_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (hexanes:EtOAc 99:1) to give benzyl ether **S3** as a yellow oil (46.5 g, 97%): ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.43–7.33 (m, 4H), 7.31 (m, 1H), 4.53 (s, 2H), 3.52 (t, J = 6.3 Hz, 2H), 2.24 (ddd, J = 7.0, 7.0, 2.5 Hz, 2H), 1.97 (t, J = 2.5 Hz, 1H), 1.84–1.72 (m, 2H), 1.71–1.60 (m, 2H) ppm; ^{13}C NMR (125 MHz, CDCl$_3$) δ 138.7, 128.5, 127.7, 127.6, 84.5, 73.0, 69.8, 68.6, 28.9, 25.4, 18.4 ppm; IR (thin film) 3298, 2941, 2860, 1455, 1362, 1206, 1106 cm^{-1}; HRMS (ESI) *m/z* 211.1100 (211.1099 calcd for C$_{13}$H$_{16}$ONa$^+$ [MNa]$^+$).

((5-Methylenehept-6-enyloxy)methyl)benzene (48)

Benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine)ruthenium[22] (1.12 g, 1.33 mmol) was added to a solution of alkyne **S3** (5.0 g, 27 mmol) and CH$_2$Cl$_2$ (400 mL), which was degassed with nitrogen for 60 min. The solution was charged to a high-pressure bomb. The reaction bomb was filled with ethylene gas (300 psi), vented and re-pressurized with ethylene (300 psi). This process was repeated a total of three times. The reaction was stirred under pressure (300 psi) for 4–5 h. After venting unreacted ethylene, the reaction mixture was transferred to a round bottom flask containing silica gel and the solvent was removed *in vacuo*. The residue was dry loaded and purified by column chromatography (hexanes:EtOAc, 19:1) to give diene **48** (5.2 g, 90%) as a tan oil: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.39 (d, J = 4.5 Hz, 4H), 7.35–7.28 (m, 1H), 6.42 (dd, J = 17.6, 10.8 Hz, 1H), 5.27 (d, J = 17.6 Hz, 1H), 5.10 (d, J = 10.9 Hz, 1H), 5.05 (d, J = 11.5 Hz, 2H), 4.55 (s, 2H), 3.54 (t, J = 6.4 Hz, 2H), 2.27 (t, J = 7.6 Hz, 2H), 1.80–1.68 (m, 2H), 1.67–1.59 (m, 2H) ppm; ^{13}C NMR (125 MHz, CDCl$_3$) δ 146.3, 139.1, 138.8, 128.5, 127.8, 127.6, 115.9, 113.3, 73.1, 70.4, 31.3, 29.8, 24.9 ppm; IR (thin film) 2939, 2858, 1596, 1455, 1362, 1104, 895 cm^{-1}; HRMS (ESI) *m/z* 217.1600 (217.1592 calcd for C$_{15}$H$_{20}$O$^+$ [MH]$^+$).

(3′*R*,4a′*S*,8a′*R*)-6′-(4-(Benzyloxy)butyl)-3′-methyl-3′,4′,4a′,5′,8′,8a′-hexahydro-2′*H*-spiro[[1,3]dioxolane-2,1′-naphthalene] (S4)

Trimethylsilyl trifluoromethanesulfonate (0.20 mL, 1.1 mmol) was added dropwise to a solution of enone (+)-**9**[46] (1.31 g, 11.9 mmol, >99% ee as determined by chiral HPLC) in CH$_2$Cl$_2$ (0.75 mL) at −78 °C. 1,2-Bis(trimethylsiloxy)ethane (2.93 mL, 11.9 mmol) was added, and the resulting solution was stirred at −78 °C for 5 min. Diene **48** (2.35 g, 10.9 mmol) was added, and the reaction was stirred at −78 °C for 22 h. The reaction was then quenched with NEt$_3$ (0.25 mL), and the reaction was warmed to rt. The solution was passed through a small plug of neutral alumina and eluted with 50 mL of CH$_2$Cl$_2$, and the eluent was concentrated *in vacuo*. The residue was purified by column chromatography (hexanes:Et$_2$O 49:1) to give ketal **S4** (2.53 g, 64%) as a clear oil: [α]$^D_{23}$ − 1.7 (*c* = 1.25, CH$_3$Cl); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.35 (d, J = 4.4 Hz, 4H), 7.29 (m, 1H), 5.27 (s, 1H), 4.52 (s, 2H), 3.95–3.82 (m, 4H), 3.48 (t, J = 6.6 Hz, 2H), 2.18–2.02 (m, 4H), 1.97 (t, J = 7.3 Hz, 2H), 1.97 (m, 1H), 1.93–1.86 (m, 1H), 1.80 (dd, J = 13.7, 3.9 Hz, 2H), 1.66–1.55 (m, 3H), 1.53–1.40 (m, 2H), 1.22–1.12 (m, 2H), 0.98 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (125

MHz, CDCl$_3$) δ 138.9, 136.7, 128.5, 127.7, 127.5, 118.8, 111.7, 73.0, 70.6, 65.2, 64.4, 41.6, 39.7, 37.8, 37.2, 32.0, 31.1, 29.3, 26.2, 24.2, 24.2, 21.8 ppm; IR (thin film) 2916, 2871, 1455, 1102, 1048, 949 cm^{-1}; HRMS (ESI) *m/z* 388.2852 (388.2852 calcd for C$_{24}$H$_{34}$O$_3$NH$_4^+$ [MNH$_4$]$^+$).

(3*R*,4a*S*,8a*R*)-6-(4-(Benzyloxy)butyl)-3-methyl-3,4,4a,5,8,8a-hexahydronaphthalen-1(2*H*)-one (50)

A preformed mixture of FeCl$_3$/SiO$_2$[26] (0.375 g) was added to a solution of ketal **S4** (2.0 g, 5.4 mmol) in acetone (50 mL, ACS grade), and the resulting suspension was stirred at rt for 2 h. The solvent was removed *in vacuo*, and the residue was purified by column chromatography (hexanes:Et$_2$O, 19:1) to provide the ketone **50** (1.75 g, 99%) as a colorless oil: [α]$^D_{23}$ + 55 (*c* = 2.5, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.31 (d, *J* = 4.4 Hz, 4H), 7.28–7.19 (m, 1H), 5.31 (s, 1H), 4.47 (s, 2H), 3.43 (t, *J* = 6.5 Hz, 2H), 2.64 (t, *J* = 5.8 Hz, 1H), 2.54 (dd, *J* = 17.5, 2.9 Hz, 1H), 2.46–2.38 (m, 1H), 2.35 (dd, *J* = 13.1, 4.3 Hz, 1H), 2.24–2.10 (m, 1H), 1.96 (t, *J* = 12.6 Hz, 2H), 1.89 (td, *J* = 13.2, 6.4 Hz, 2H), 1.88–1.78 (m, 3H), 1.63 (ddd, *J* = 16, 11.9, 4.3 Hz, 1H), 1.54 (dd, *J* = 14.1, 6.9 Hz, 2H), 1.48–1.36 (m, 2H), 1.00 (d, *J* = 6.4 Hz, 3H) ppm; ^{13}C NMR (125 MHz, CDCl$_3$) δ 211.6, 138.9, 135.6, 128.5, 127.7, 127.6, 118.6, 72.9, 70.4, 49.7, 47.2, 38.7, 37.6, 35.7, 30.8, 30.1, 29.5, 24.2, 23.8, 22.6 ppm; IR (thin film) 3397, 2913, 2868, 1708, 1454, 1104 cm^{-1}; HRMS (ESI) *m/z* 349.2143 (349.2144 calcd for C$_{22}$H$_{30}$O$_2$Na$^+$ [MNa]$^+$).

Methyl *N'*-6-(4-(Benzyloxy)butyl)-3-methyl-1,2,3,4,4a,5,8,8a-octahydronaphthalen-1-ylmethanehydrazonoperoxoate (51)

A solution of methyl hydrazidocarbamate (0.010 g, 0.11 mmol) and decalone **50** (33 g, 0.010 mmol) was stirred at rt for 3 days in MeOH (1.0 mL), and NaCNBH$_3$ (6.9 mg, 0.11 mmol) and bromocresol green indicator (~1 mg) were added to the solution. A MeOH/HCl solution then was added dropwise over 30 min at a rate to maintain the pH ~3–5. (A green/blue color was maintained for 30 minutes and the reaction was complete when a yellow color persisted.) The reaction mixture was quenched with 6 N KOH (1.0 mL), and stirred for 1 h. This mixture was diluted with saturated aqueous NH$_4$Cl (5 mL), and extracted with CH$_2$Cl$_2$ (5 × mL). The combined organic layers were dried with MgSO$_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (hexanes:EtOAc 4:1) to give hydrazide **51** (4.8 mg, 12%) as a colorless solid: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.36–7.26 (m, 5H), 6.04 (bs, 1H), 5.41 (s, 1H), 4.51 (s, 2H), 3.71 (s, 3H), 3.48 (t, *J* = 6.2 Hz, 2H), 3.15 (bs, 1H), 2.18–1.84 (m, 8H), 1.67–1.41 (m, 9H), 1.16 (m, 1H), 0.95 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (125 MHz, CDCl$_3$) δ 158.1, 138.9, 128.6, 127.8, 127.7, 126.7, 119.1, 73.1, 70.6, 52.5, 37.81, 34.6, 33.9, 32.2, 30.4, 29.9, 29.6, 24.4, 22.9, 20.7, 14.4 ppm;[67] IR (thin film) 3324, 1726, 1455,, 1365, 1261, 1101 cm^{-1}; HRMS (ESI) *m/z* 423.2618 (423.2624 calcd for C$_{24}$H$_{36}$N$_2$O$_3$Na$^+$ [MNa]$^+$).

N'-(6-(4-(Benzyloxy)butyl)-3-methyl-1,2,3,4,4a,5,8,8a-octahydronaphthalen-1-yl)-4-methylbenzenesulfonohydrazide (52)

A solution of tosylhydrazide (0.24 g, 1.3 mmol) in MeOH (15 mL), was added over 30 h by syringe pump to a solution of **50** (0.400 g, 1.23 mmol) and KOH (1.65 g, 29.5 mmol) in MeOH (15 mL) at rt. The reaction was quenched with saturated aqueous NH$_4$Cl (30 mL), and extracted with CH$_2$Cl$_2$ (3×20 mL). The combined organic extracts were dried with MgSO$_4$ and concentrated. The residue was purified by column chromatography (hexanes:EtOAc 9:1→3:1) to provide the corresponding hydrazone (0.070 g) as a colorless solid. A mixture of MeOH and concentrated HCl (9:1) was added dropwise at rt over 1 h to a stirred mixture of hydrazone (0.70 g, 0.14 mmol), NaBH$_3$CN (0.010 g, 0.15 mmol) and a trace (~ 0.2 mg) of methyl orange in MeOH (3 mL). The rate of addition was controlled so

that the color of the reaction mixture remained orange-red (pH = 3–4) over 1 h. The reaction was quenched with aqueous 6 N KOH (10 mL). The aqueous layer was extracted with Et_2O (5 × 10 mL). The combined organic layers were washed with water (30 mL) and brine (30 mL), dried with $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (hexanes:EtOAc 9:1→3:1) provided **52** as a colorless solid (45 mg, 7%, 2 steps): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83–7.78 (m, 3H), 7.36–7.32 (m, 4H), 7.30–7.28 (m, 3H), 5.78 (s, 1H), 5.23 (s, 1H), 4.51 (s, 2H), 3.49–3.44 (m, 2H), 3.32 (m, 1H), 2.44 (s, 3H), 2.01–1.73 (m, 6H), 1.60–1.38 (m, 8H), 1.03–0.86 (m, 5H), 0.82 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.1, 138.9, 135.7, 129.8, 128.6, 128.4, 127.9, 127.8, 127.7, 118.6, 73.1, 70.6, 41.7, 37.8, 37.6, 37.5, 34.4, 33.5, 30.4, 29.9, 29.6, 29.5, 25.5, 24.4, 21.8 ppm; IR (thin film) 1454, 1362, 1207, 1103, 1034, 1011, 814 cm^{-1}.

N'-((1*S*,3*R*,4a*S*,8a*R*)-6-(4-(Benzyloxy)butyl)-3-methyl-1,2,3,4,4a,5,8,8a-octahydronaphthalen-1-yl)benzohydrazide (53)

A solution of benzoic hydrazide (0.38 g, 2.8 mmol) and **50** (0.90 g, 2.8 mmol) was stirred at rt for 3 days in MeOH (20 mL), and $NaCNBH_3$ (0.190 g, 3.03 mmol) and bromocresol green indicator (~1 mg) were added to the solution. A MeOH/HCl solution then was added dropwise over 30 min at a rate to maintain a pH ~3–5. (A green/blue color was maintained for 30 minutes and the reaction was complete when a yellow color persisted.) The reaction mixture was quenched with 6 N KOH (2 mL), and stirred for 1 h. This mixture was diluted with saturated aqueous NH_4Cl, and extracted with CH_2Cl_2 (5 × 20 mL). The combined organic layers were dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (hexanes:EtOAc 4:1) to give **53** (0.98 g, 80%) as a colorless solid: mp 98–101 °C; $[\alpha]^D_{24}$ −21 (*c* = 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, DMSO–*d_6*, 323 K, peak broadening caused by dynamic NMR processes) δ 9.90 (bs, 1H), 7.81 (d, *J* = 6.5 Hz, 2H), 7.51 (t, *J* = 7.3 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.33–7.24 (m, 5H), 5.35 (bs, 1H), 4.88 (bs, 1H), 4.42 (s, 3H), 3.40 (t, *J* = 6.3 Hz, 2H), 3.11 (bs, 1H), 2.25–1.93 (m, 5H), 1.90–1.87 (m, 3H), 1.64 (m, 1H), 1.54–1.46 (m, 3H), 1.42–1.38 (m, 2H), 1.24 (m, 1H), 1.03 (m, 1H), 0.97 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO–*d_6*, 340 K) δ 149.5, 138.5, 130.6, 127.8, 127.7, 126.9, 126.8, 126.7, 118.6, 71.5, 69.3, 36.6, 34.1, 33.4, 28.5, 28.3, 23.5, 19.8 ppm; IR (thin film) 3291, 2915, 2862, 1630, 1457, 1315, 1103 cm^{-1};[68] HRMS (ESI) *m/z* 469.2823 (469.2831 calcd for $C_{29}H_{38}N_2O_2Na^+$ [MNa]$^+$).

Intramolecular Azomethine Imine Cycloaddition to Form Tetracyclic Pyrazolidine 54

Benzoyl hydrazide **53** (250 mg, 0.56 mmol) was added to a sealable tube containing paraformaldehyde (84 mg, 2.8 mmol), 4 Å molecular sieves powder (1.7 g, activated by flame drying under vacuum), diisopropylethylamine (93 μL, 0.56 mmol) and toluene (12 mL). The resulting suspension was placed in an oil bath pre-heated to 115 °C and stirred at 115 °C until the starting material was completely consumed (~20 h) as monitored by electrospray MS analysis or TLC (hexanes:EtOAc 4:1). The reaction mixture was allowed to cool to rt, and the molecular sieves were removed by filtration through a plug of neutral alumina, eluting with Et_2O (50 mL). The solution was concentrated *in vacuo*, and the residue was purified by column chromatography (hexanes:EtOAc 4:1) to give the tetracyclic product **54** (218 mg, 85%) as a colorless solid: mp 123–126 °C; $[\alpha]^D_{23}$ −16 (*c* = 1.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52–7.50 (m, 2H), 7.38–7.25 (m, 8H), 4.47 (s, 2H), 3.47 (ddd, *J* = 21.7, 9.3, 6.2 Hz, 2H), 3.19 (m, 1H), 2.90 (t, *J* = 4.3 Hz, 1H), 2.73 (d, *J* = 10.8 Hz, 1H), 2.57 (ddd, *J* = 13.2, 13.2, 3.9 Hz, 1H), 2.40 (t, *J* = 4.8 Hz, 1H), 2.24 (d, *J* = 14.8 Hz, 1H), 2.07 (m, 1H), 1.89 (dd, *J* = 14.7, 11.1 Hz, 1H), 1.82–1.67 (m, 4H), 1.67–1.48 (m, 6H), 1.35–1.26 (m, 1H), 1.16 (ddd, *J* = 12.4, 1.9, 1.9 Hz, 1H), 1.04 (ddd, *J* = 12.9, 12.9, 4.9 Hz, 1H), 0.81 (ddd, *J* = 13.5, 13.3, 5.7 Hz, 1H) 0.73 (d, *J* = 6.3 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 138.9, 138.2, 129.7, 128.5, 128.1, 127.9, 127.6, 127.6, 73.0, 70.3, 69.9, 62.8, 62.4, 42.2, 40.2, 38.1, 36.3, 34.5, 34.2, 33.7, 33.4, 30.1, 23.5, 22.5, 21.1

ppm; IR (thin film) 1624 cm^{-1}; HRMS (ESI) *m/z* 459.3009 (459.3011 calcd for C$_{30}$H$_{39}$N$_2$O$_2^+$ [MH]$^+$).

Tricyclic Amino Amide (59)

A solution of SmI$_2$ (9 mL, ~1 M in THF)[51,59] was added at a rapid rate to a stirring solution of tetracyclic pyrazolidine **54** (120 mg, 0.26 mmol) in MeOH (1.0 mL), which had been sparged with argon for 30 min. The deep blue reaction mixture was stirred at rt under argon for 30 min, and then quenched with 37% aqueous formaldehyde (2 mL). Bromocresol green indicator (~1 mg) and NaCNBH$_3$ (50 mg, 0.78 mmol) were added, and a solution of MeOH/HCl was then added dropwise over 30 min at a rate to maintain a pH ~3–5. (A green/blue color was maintained for 30 minutes and the reaction complete when a yellow color persisted.) The reaction mixture was then quenched with aqueous 6 N KOH (2 mL) and stirred for 1 h. The mixture was diluted with saturated aqueous NH$_4$Cl, and extracted with CH$_2$Cl$_2$ (5 × 10 mL). The combined organic layers were dried with MgSO$_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (hexanes:acetone 7:3) to give tricyclic amino amide **59** (100 mg, 80%) as a yellow oil: [α]$^D_{24}$ +10 (*c* = 0.8, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.71 (d, *J* = 7.4 Hz, 2H), 7.47 (t, *J* = 7.2 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.36–7.19 (m, 5H), 5.74 (s, 1H), 4.44 (s, 2H), 3.43 (dddd, *J* = 21.8, 9.0, 6.5, 6.5 Hz, 2H), 2.93 (d, *J* = 11.8, 1H), 2.60 (bs, 1H), 2.42 (t, *J* = 12.2, 1H), 2.26 (ddd, *J* = 13.0, 13.0, 4.2 Hz, 1H), 2.14 (dd, *J* = 11.8, 2.5 Hz, 1H), 2.03 (s, 3H), 1.97–1.87 (m, 4H), 1.81–1.79 (m, 2H), 1.71 (dd, *J* = 11.8, 5.7 Hz, 1H), 1.59 (ddd, *J* = 14.5, 14.5, 6.8 Hz, 2H), 1.52–1.37 (m, 4H), 1.29–1.24 (m, 1H), 1.18 (ddd, *J* = 12.4, 12.8, 4.9 Hz, 1H), 0.89 (m, 1H), 0.84 (d, *J* = 6.4, 3H) ppm; ^{13}C NMR (125 MHz, CDCl$_3$) δ 166.8, 138.9, 136.1, 131.3, 128.7, 128.5, 127.8, 127.6, 126.9, 73.0, 70.6, 63.7, 60.4, 59.3, 43.4, 40.6, 39.0, 37.7, 36.2, 35.4, 34.2, 32.9, 31.1, 30.2, 22.8, 21.2, 20.8 ppm; IR (thin film) 2921, 2852, 2771, 1644, 1528, 1488, 1455, 1102 cm^{-1}; HRMS (ESI) *m/z* 475.3329 (475.3325 calcd for C$_{31}$H$_{43}$N$_2$O$_2^+$ [MH]$^+$).

Diamino Alcohol (S5)

A round bottom flask containing diamine **59** (140 mg, 0.29 mmol), Pearlman's catalyst (20 wt.% Pd(OH)$_2$/C, 41 mg, 0.030 mmol), concentrated HCl (1 drop) and MeOH (10 mL) was fitted with a septa and a balloon of hydrogen gas. The reaction vessel was evacuated and backfilled with hydrogen 5 times. The reaction mixture was stirred at rt for 1 h, and filtered through a syringe filter (25 mm, 0.45 μm pore size), and the filtrate concentrated *in vacuo*. The residue was purified by column chromatography (MeOH:CHCl$_3$:NH$_4$OH (5:95:1)) to give diamino alcohol **S5** (110 mg, 97%) as a colorless solid: mp 60–63 °C; [α]$^D_{24}$ + 14 (*c* = 1.15, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.73 (d, *J* = 7.3 Hz, 2H), 7.48 (t, *J* = 7.3 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 2H), 5.82 (s, 1H), 3.67–3.59 (m, 2H), 2.94 (d, *J* = 11.8 Hz, 1H), 2.57 (bs, 1H), 2.43 (t, *J* = 12.4 Hz, 1H), 2.33 (ddd, *J* = 12.8, 12.8, 4.2 Hz, 1H), 2.15 (dd, *J* = 11.8, 2.9 Hz, 1H), 2.05 (s, 3H), 1.99–1.82, (m, 7H), 1.72 (dd, *J* = 11.9, 5.8 Hz, 1H), 1.63–1.47 (m, 5H), 1.40 (m, 1H), 1.30 (m, 1H), 1.19 (ddd, *J* = 12.7, 12.4 4.9 Hz, 1H), 0.91 (m, 1H), 0.86 (d, *J* = 6.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, CDCl$_3$) δ 167.1, 135.9, 131.4, 128.8, 126.9, 63.7, 62.6, 60.5, 59.3, 43.4, 40.6, 39.0, 37.8, 36.4, 35.3, 33.8, 32.9, 32.8, 31.1, 22.8, 21.2, 20.0 ppm; IR (thin film) 3343, 2944, 2921, 2865, 2771, 1644, 1530, 1457 cm^{-1}; HRMS (ESI) *m/z* 385.2838 (385.2885 calcd for C$_{24}$H$_{37}$N$_2$O$_2^+$ [MH]$^+$).

Diamino Alcohol (60)

A THF solution of AlH$_3$[52] (3.6 mL, 1.8 mmol, ~0.5 M) was added to a solution of amide **S5** (70 mg, 0.18 mmol) in THF (4 mL). The reaction mixture was stirred at rt for 3 h, and then quenched with Rochelle salt. The resulting mixture was stirred overnight and then extracted with CH$_2$Cl$_2$ (10 × 10 mL). The combined organic extracts were dried over MgSO$_4$ filtered

and concentrated *in vacuo*. Purification of the residue by column chromatography (MeOH:CHCl$_3$:NH$_4$OH 0:99:1→10:90:1) afforded diamino alcohol **60** (50 mg, 74%) as a colorless oil: $[\alpha]^D_{23}$ + 4.3 (*c* = 0.7, MeOH); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.38 (d, *J* = 7.3 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 1H), 7.23 (t, *J* = 7.3 Hz, 1H), 3.67 (t, *J* = 6.6 Hz, 2H), 3.62 (d, *J* = 3.6 Hz, 1H), 3.60 (m, 1H), 3.07 (d, *J* = 11.6 Hz, 1H), 2.19 (t, *J* = 12.8 Hz, 1H), 2.13 (dd, *J* = 11.6, 2.9 Hz, 1H), 2.08 (s, 3H), 2.01–1.84 (m, 4H), 1.83–1.62 (m, 5H), 1.55–1.34 (m, 10H), 1.16 (ddd, *J* = 12.6, 12.4, 4.9 Hz, 1H), 0.87 (m, 1H), 0.83 (d, *J* = 6.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, CDCl$_3$) δ 141.9, 128.6, 128.5, 126.9, 63.8, 63.4, 58.6, 57.4, 45.4, 43.6, 41.0, 39.5, 39.2, 36.6, 36.1, 33.9, 33.8, 33.5, 32.0, 22.9, 21.1, 19.4 ppm; IR (thin film) 3342, 2921, 2865, 2769, 1455, 1061 cm^{-1}; HRMS (ESI) *m/z* 371.3062 (371.3062 calcd for C$_{24}$H$_{39}$N$_2$O$_2$$^+$ [MH]$^+$).

N-Benzyl Nankakurine A (61)

Methanesulfonyl chloride (25 µL, 0.32 mmol) was added dropwise to a solution of diamino alcohol **60** (110 mg, 0.29 mmol) and NEt$_3$ (54 µL, 0.38 mmol) in CH$_2$Cl$_2$ (5.0 mL) at −40 °C. The reaction was stirred at −40 °C for 30 min and then the reaction was quenched at −40 °C with MeOH (0.6 mL) and NEt$_3$ (0.2 mL). The resulting solution was allowed to warm to rt and stirred for 3 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography (MeOH:CHCl$_3$:NH$_4$OH 0:99:1→10:90:1) to afford diamine **61** (100 mg, 96%) as a colorless oil: $[\alpha]^D_{24}$ + 4.6 (*c* = 1.0, CHCl$_3$); ^{1}H NMR (500 MHz, CD$_3$OD) δ 7.35 (d, *J* = 7.4 Hz, 2H), 7.24 (t, *J* = 7.4 Hz, 2H), 7.14 (t, *J* = 7.4 Hz, 1H), 3.88 (s, 2H), 3.35 (ddd, *J* = 10.9, 2.3, 2.3 Hz, 1H), 2.80 (m, 1H), 2.72 (t, *J* = 12.5 Hz, 1H), 2.49 (d, *J* = 13.8 Hz, 1H), 2.34 (bs, 1H), 2.14 (s, 3H), 2.10–1.93 (m, 5H), 1.85 (m, 1H), 1.75 (m, 1H), 1.65–1.33 (m, 19H), 1.14 (ddd, *J* = 12.7, 12.7, 4.9 Hz, 1H), 0.88 (m, 1H), 0.82 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (125 MHz, CD$_3$OD) δ 144.6, 129.3, 129.0, 127.3, 64.9, 59.3, 59.1, 50.8, 44.8, 43.5, 42.5, 42.1, 40.5, 37.6, 34.8, 33.3, 32.9, 31.1, 23.2, 22.2, 21.4, 21.2 ppm; IR (thin film) 2944, 2921, 2863, 2769, 1621, 1453, 1104 cm^{-1}; HRMS (ESI) *m/z* 353.2953 (353.2957 calcd for C$_{24}$H$_{37}$N$_2$$^+$ [MH]$^+$).

(+)-Nankakurine A (2)

A round bottom flask containing *N*-benzylnankakurine A (**61**) (90 mg, 0.26 mmol), palladium on carbon catalyst (10 wt % Pd/C, 27 mg, 0.03 mmol), concentrated HCl (1 drop) and MeOH (4.0 mL) was fitted with a septa and a balloon of hydrogen gas. The reaction vessel was evacuated and backfilled with hydrogen 5 times. The reaction mixture was stirred at rt for 1 h, and then filtered through a syringe filter (25 mm, 0.45 µm pore size), and the filtrate concentrated *in vacuo*. The residue was purified by column chromatography (MeOH:CHCl$_3$:NH$_4$OH 5:95:1) to give (+)-nankakurine A (66 mg, 99%) as a colorless solid: $[\alpha]^D_{24}$ + 13 (*c* = 0.4, MeOH); IR (thin film) 3397, 1671 cm^{-1}; HRMS (ESI) *m/z* 263.2484 (263.2487 calcd for C$_{17}$H$_{31}$N$_2$$^+$ [MH]$^+$).

A portion of this sample was dissolved in 0.60 mL of CD$_3$OD and 150 µL of NaOCD$_3$ (~0.1 M in CD$_3$OD) was added to assure that only the free base was present. Aliquots of a solution of TFA in CD$_3$OD (15–25 µL portions of a 0.15 M solution) were successively added to the sample, and ^{1}H NMR spectra were obtained after each addition (Figure S2). Spectra matching the reported spectrum of (+)-nankakurine A[2] were obtained upon addition of several portions of TFA•CD$_3$OD (Figure 3 and S3). NMR spectra of the free base: ^{1}H NMR (500 MHz, CD$_3$OD/CD$_3$ONa) δ 3.00 (ddd, *J* = 11.9, 5.1, 2.7 Hz, 1H), 2.80 (t, *J* = 4.5 Hz, 2H), 2.28 (t, *J* = 12.7 Hz, 1H), 2.13 (dd, *J* = 12.7, 2.8 Hz, 1H), 2.11 (s, 3H), 2.05–2.02 (m, 2H), 2.01–1.90 (m, 1H), 1.89–1.76 (m, 3H), 1.69–1.67 (m, 3H), 1.66–1.44 (m, 7H), 1.20 (ddd, *J* = 12.7, 12.7, 5.1 Hz, 1H), 0.89 (m, 1H), 0.84 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (125 MHz, CD$_3$OD) δ 65.2, 58.7, 56.0, 43.6, 42.0, 41.4, 40.1, 37.6, 34.8, 34.6, 32.7, 26.5, 23.2, 22.2, 21.1 ppm.[2,66]

(+)-Nankakurine B (3)

To a solution of synthetic (+)-nankakurine A (24 mg, 0.9 mmol) in MeOH (3 mL) was added NaCNBH$_3$ (17 mg, 0.28 mmol). To the resulting solution was added a MeOH/HCl solution dropwise over 30 min at a rate to maintain a pH of ~3–5 (no indicator was used because it was difficult to separate from nankakurine B). The reaction mixture was quenched with aqueous 6 N KOH and stirred for 1 h, saturated aqueous NH$_4$Cl was added, and the mixture was extracted with CH$_2$Cl$_2$ (5 × 20 mL). The combined organic layers were dried over MgSO$_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (MeOH:CHCl$_3$:NH$_4$OH (10:90:1)) to give (+)-nankakurine B (20 mg, 80%) as a colorless solid: $[\alpha]^D_{24}$ + 12 (*c* = 1.5, MeOH); IR (thin film) 3449, 1680 cm^{-1}; HRMS (ESI) *m/z* 276.2635 (276.2644 calcd for C$_{18}$H$_{33}$N$_2^+$ [MH]$^+$)

A portion of this sample was dissolved in 0.60 mL of CD$_3$OD and 150 µL of NaOCD$_3$ (~0.1 M in CD$_3$OD) was added. ^{1}H and ^{13}C NMR spectra of the free base were obtained, and aliquots of a solution of TFA in CD$_3$OD (15–25 µL portions of a 0.15 M solution) were successively added to the sample (Figure 1 and S4). Spectra matching the reported spectrum of (+)-nankakurine B[4] were obtained after the addition of TFA•CD$_3$OD (Figure 1 and S5). NMR spectra of the free base: ^{1}H NMR (500 MHz, CD$_3$OD/CD$_3$ONa) δ 3.09 (ddd, *J* = 11.4, 5.1, 2.7 Hz, 1H), 3.0 (bs, 1H), 2.80 (bs, 1H), 2.49 (t, *J* = 12.6 Hz, 1H), 2.41 (s, 3H), 2.10 (s, 3H), 2.08 (dd, *J* = 11.9, 3.0 Hz, 1H), 2.05–1.93 (m, 3H), 1.92–1.77 (m, 4H), 1.76–1.54 (m, 5H), 1.53–1.38 (m, 4H), 1.22 (ddd, *J* = 12.7, 12.7, 4.6 Hz, 1H), 0.90 (m, 1H), 0.85 (d, *J* = 6.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, CD$_3$OD) δ 64.9, 60.4, 58.6, 43.4, 42.2, 40.3, 36.9, 35.2, 34.5, 32.7, 25.9, 23.2, 22.3, 20.6, 19.1 ppm.[69]

Neurite Growth Assay

H19-7 cells (ATCC) were derived from hippocampi from E17 rat embryos and immortalized by retroviral transduction of SV40 large T antigen. The H19-7 cells were plated at low density (20 000 cell/well) in 48-well cell culture plates in N2-supplemented DMEM. After 24 h in culture, cells were treated with 0.3–10 µM concentrations of either nankakurine A (**2**) or nankakurine B (**3**) or with 1 µM of a reference compound in culture medium. After treatment for 24 h, cells were fixed with 4% paraformaldehyde for 20 min, permeabilized with triton X100 and incubated with an antibody against neuronal class b-III tubulin (Tuj1, Covance) overnight at 4 °C. Cells were incubated with a secondary Alexa Fluor® 546 goat anti-mouse antibody for 30 min at room temperature. Both length of neurites stained by Tuj1 and cell counting were quantified using a fluorescence microscope (Zeiss) coupled to an automated image analysis system (ExploraNova). The ratio between these two endpoints (total length of neurites per cell in µm) allowed us to evaluate the activity of nankakurines on neurite outgrowth of H19-7 cells. Data are expressed as percent of neurite length in treated-cells compared to non-treated cells (control).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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27. These mild conditions were important for conserving the configurational integrity of the *cis*-octahydronaphthalene ketone product.

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33. Most late transition metals effect hydroamination by initial activation of the olefin, followed by attack of the amine nucleophile onto the alkene from the face trans to the coordinated metal.[32] For the metal-catalyzed hydroamination of **24** or **25**, the most sterically accessible face of the olefin for metal coordination resides on the convex face of the tricycle, which would require cyclization of the amine to occur from the concave face, and would deliver the incorrect stereochemistry of the piperidine spirocycle. The steric effect of the tricycle could inhibit this cyclization. Metals that promote hydroamination by amine activation represent the most attractive catalysts to prepare *epi*-nankakurine A (**1**).

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40. The yield was similar in CHCl$_3$ alone. Although AcOH promoted the desired reaction in 12% yield, reactions employing other acids such as camphorsulfonic acid, methanesulfonic acid, and formic acid did not afford any of the tetracyclic product **27**. Moreover the desired spirotetracyclic product was not detected when TFA was employed neat or as a solution in THF, MeOH, DMF, PhMe, or H$_2$O. The use of Lewis acids, such as BF$_3$•OEt, TiCl$_4$, SnCl$_4$, AlCl$_3$, FeCl$_3$, CeCl$_3$ or TMSOTf at −65 °C to room temperature in CH$_2$Cl$_2$ did not provide any detectable **27**. The use of formalin or 1,3,5-trioxane instead of formaldehyde under various conditions also did not lead to **27**.

41. We do not attribute the low yield of **27**, in an appreciable extent, to its instability under acidic conditions. Although **27** fragments slowly to a mixture of tricyclic alkenes **40** in the presence of 10 equiv of TFA in CDCl$_3$, its half-life under these conditions was ~ 5 h.

42. After eventually completing the synthesis of authentic nankakurine A (**2**), we became convinced that the spectra in the original report were obtained from a natural sample that contained a mixture of the free base and its conjugate acid (vide infra). As a result, ^{1}H NMR spectra of various mixtures of synthetic (±)-**1** and its trifluoroacetate salt were measured. None of these spectra

matched the ^{1}H NMR data reported for natural nankakurine A (see data in the Supporting Information).[2]

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47. The Diels–Alder reaction of enone (+)-**9** and diene **48**, and subsequent deprotection to prepare **50** was performed prior to the finding that the Diels–Alder reaction of (±)-**15** with **19**, followed by deprotection provided a higher yield of the *cis*-octahydronaphthalene ketone. It would be expected that the Diels–Alder reaction of (+)-**15** with **48** would increase the yield of **50** obtained after deprotection.

48. Hydrazines **51** and **52** were prepared only once; no attempt was made to optimize their syntheses.

49. The structure of **54** was confirmed by single-crystal X-ray analysis: CCDC 690534. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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53. To facilitate monitoring reactions and purifying intermediates, the *N*-benzyl protecting group was retained until the last step.

54. Reported optical rotations for the natural products are: (a) nankakurine A: $[\alpha]^{21}_D$ +16 (*c* 0.4, MeOH),[2] (b) nankakurine B: $[\alpha]^{19}_D$ +12 (*c* 1.0, MeOH).[4]

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66. One ^{13}C NMR signal was not observed.

67. Two ^{13}C NMR signals were not observed.

68. Several ^{13}C NMR signals were not observed, because of peak broadening caused by dynamic NMR processes.

69. Three ^{13}C NMR signals were not observed.
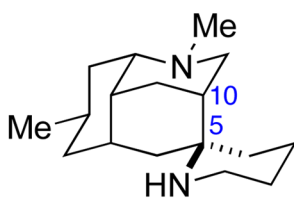
1

structure proposed originally
for nankakurine A in 2004
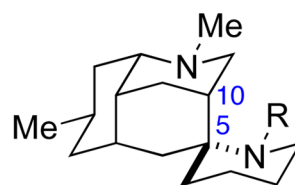
nankakurine A: R = H (**2**)
nankakurine B: R = Me (**3**)
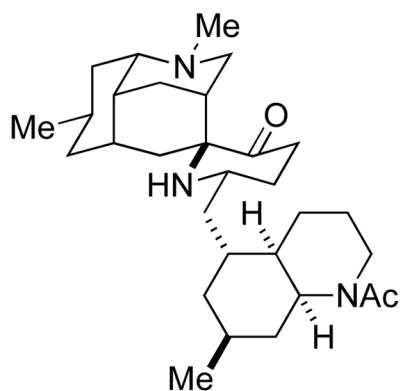
spirolucidine (**4**)
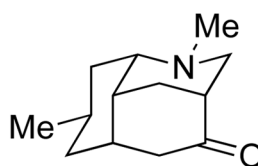
luciduline (**5**)

FIGURE 1.
Nankakurines A and B and two structurally related *Lycopodium* alkaloids.

conformer **A**   conformer **B**
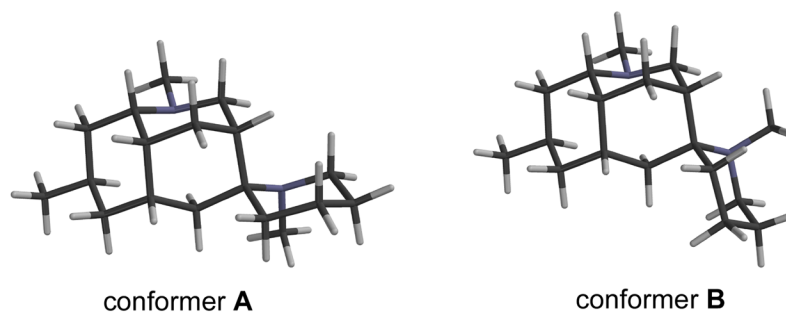
calculation	ΔE, kcal/mol
B3-LYP/6-311G*	−0.37
B3-LYP/def2-TZVP	−0.13
B3-LYP/def2-TZVP	−0.03*
PBEO/def2-TZVP	−0.18
PBEO/def2-TZVP	−0.08*

FIGURE 2.
Molecular models of low-energy conformations of the most stable disalts of nankakurine B
(**2**); ΔE = E(conf B) – E(conf A) in kcal/mol; energies marked with an asterisk refer to DFT
calculations using the COSMO model for methanol solvent.
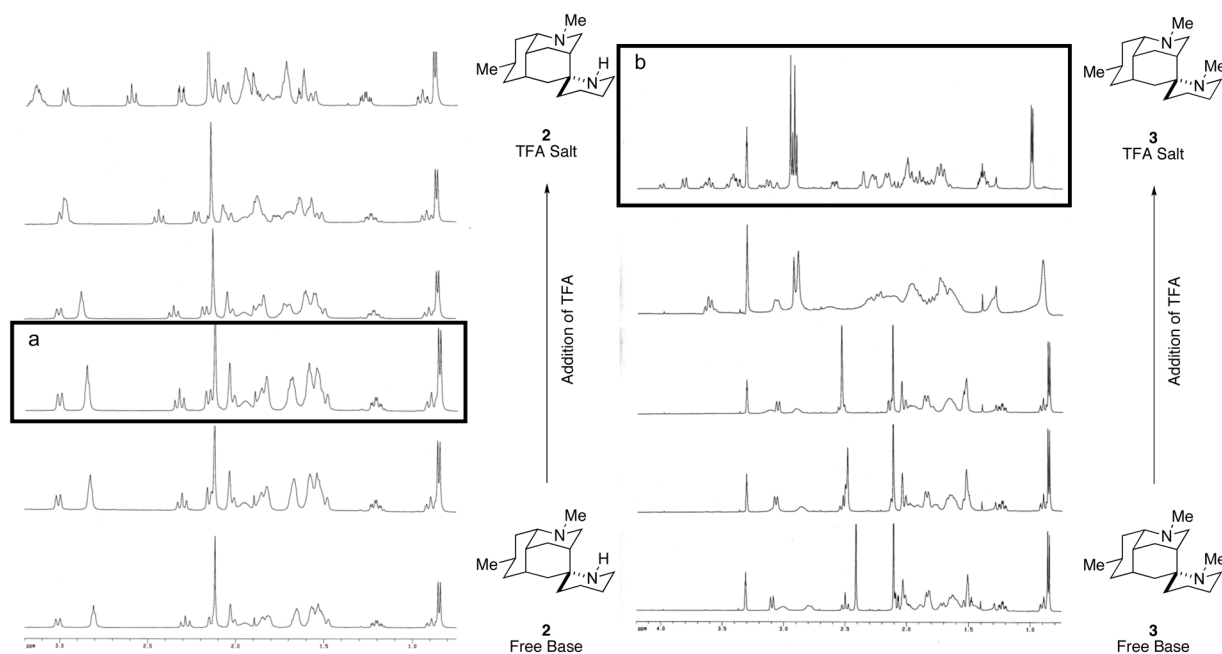
FIGURE 3.
^{1}H NMR Spectra of the Titration of Synthetic (+)-**2** and (+)-**3** with TFA. ^{a} Matches ^{1}H NMR of **2** reported in 2004.[2] ^{b} Matches ^{1}H NMR of **3** reported in 2006.[4]
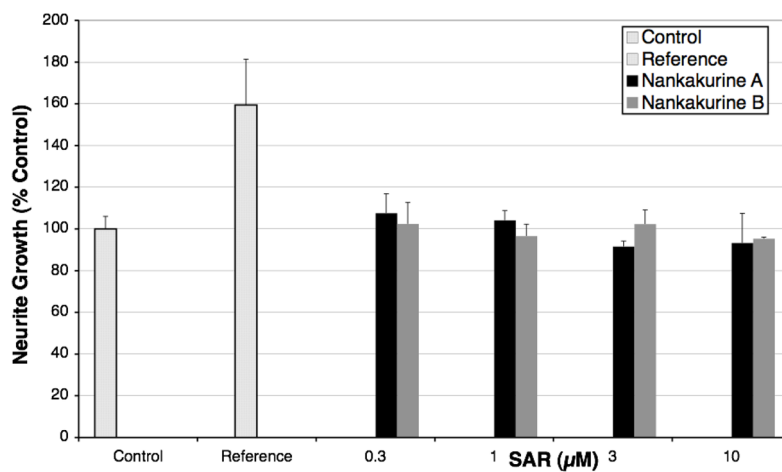
FIGURE 4.
Absence of neurotrophic properties of (+)-nankakurine A (**2**) and (+)-nankakurine B (**3**) in rat hippocampus cells; data are expressed as the mean of two separate experiments; control = DMSO; reference = positive reference compound.
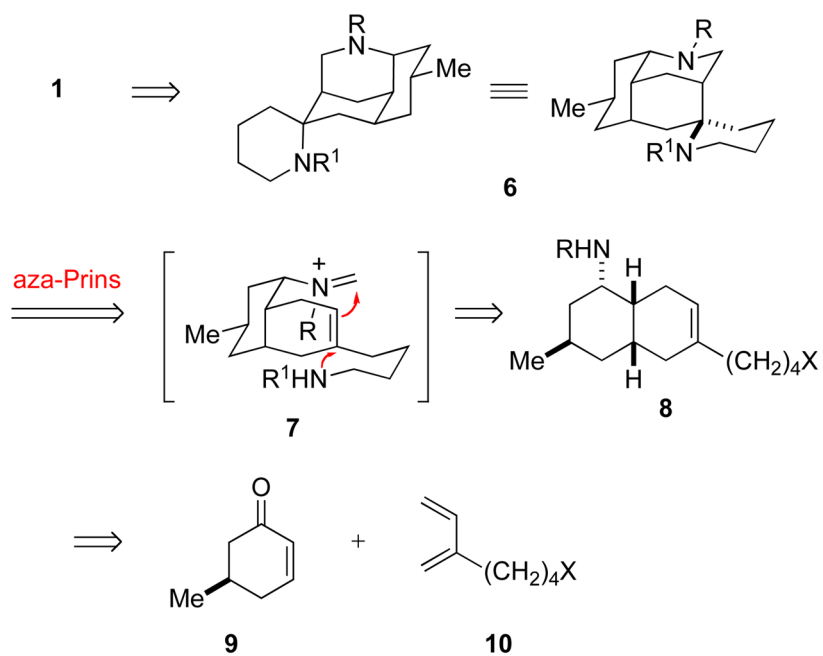
SCHEME 1.
Retrosynthetic Analysis of 5-epi-Nankakurine (**1**)
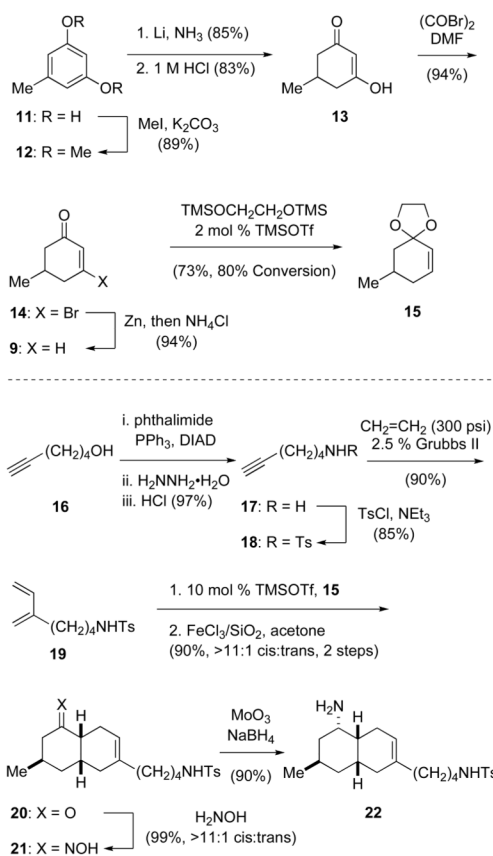
SCHEME 2.
Synthesis of *cis*-Octahydronaphthalene Amine **22**.
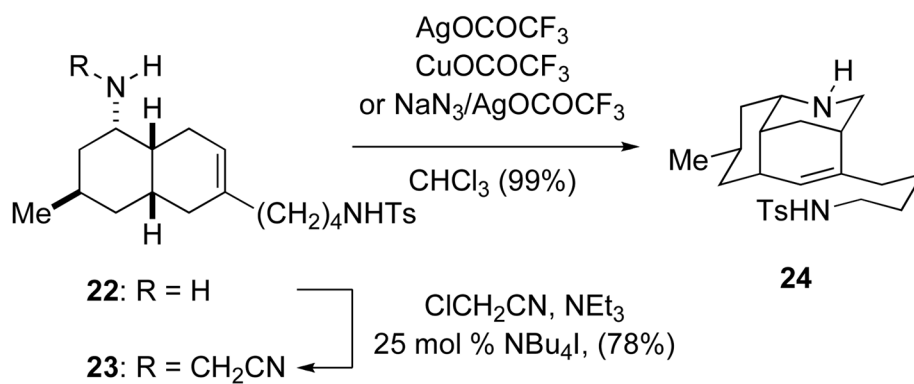
SCHEME 3.
Attempted Nitrogen-Terminated Aza-Prins Reaction of Cyanomethyl Amine **23**.
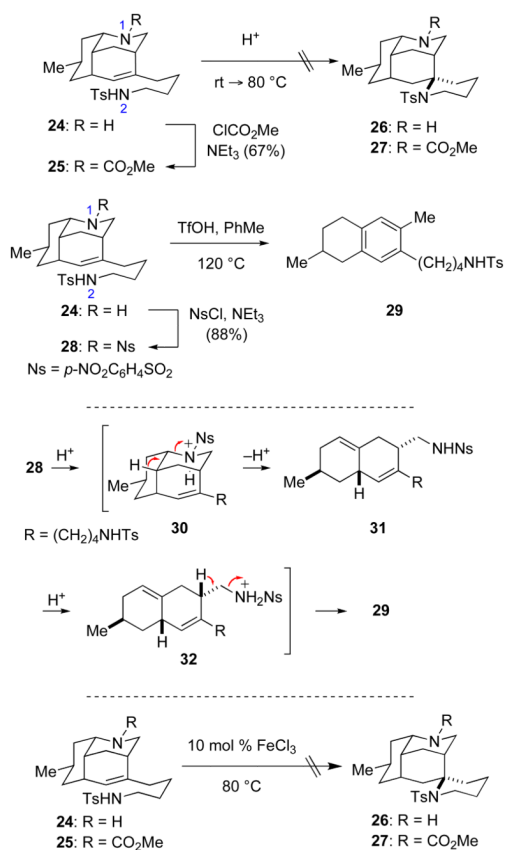
SCHEME 4.
Attempted Hydroamination of Tricyclic Unsaturated Sulfonamides **24**, **25**, and **28**.
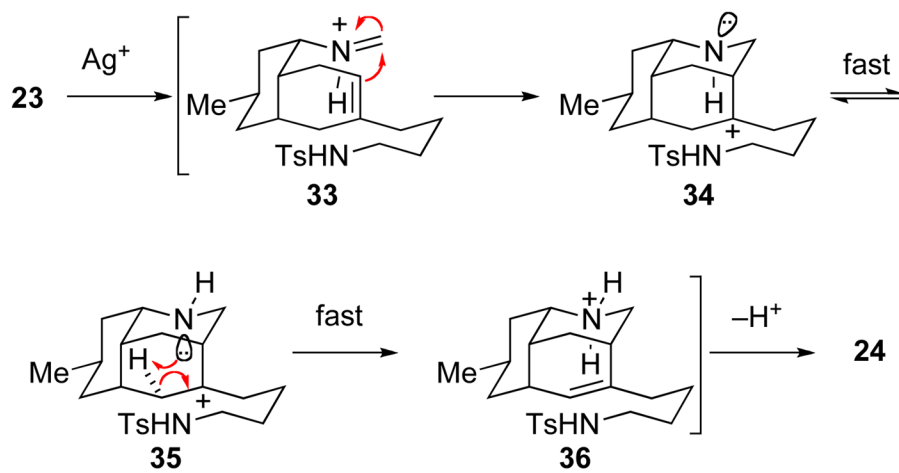
SCHEME 5.
Potential Nitrogen Participation in the Aza-Prins Cyclization to form Octahydro-3,5-ethanoquinoline **24**.
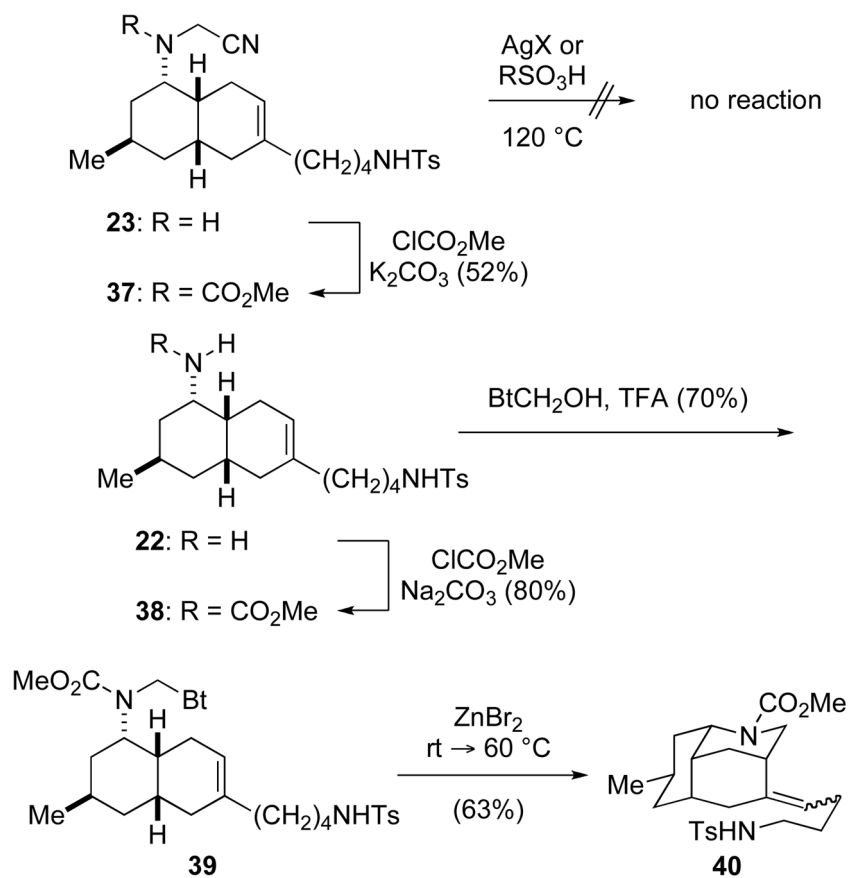
SCHEME 6.
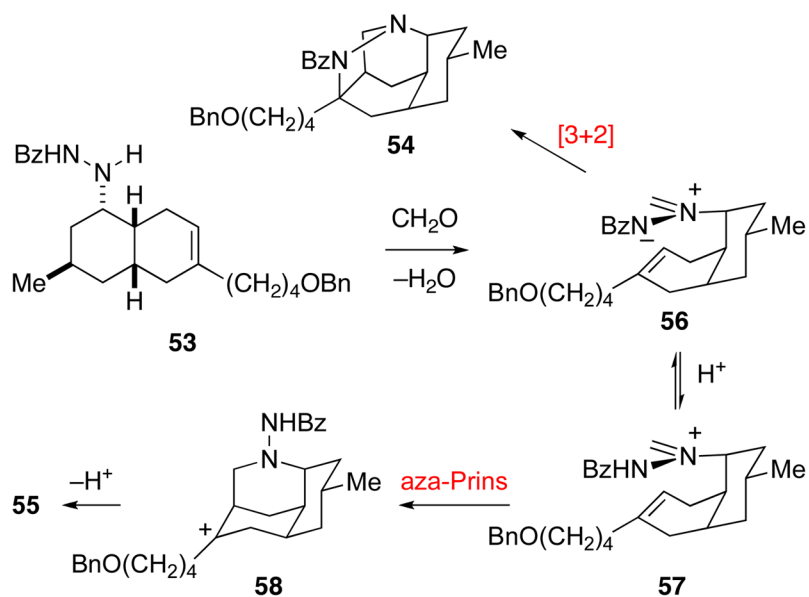Attempted Sulfonamide-Terminated Aza-Prins Reaction of Carbamates **37** and **39**.
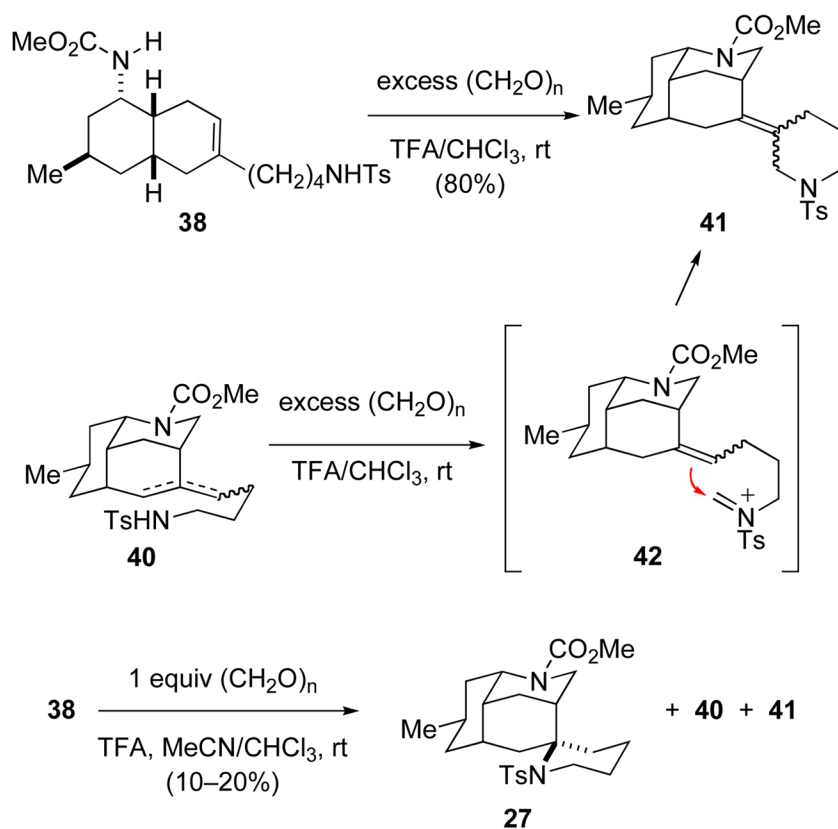
SCHEME 7.
Sufonamide-terminated Aza-Prins Cyclization to Form Spirotetracyclic Product **27**.
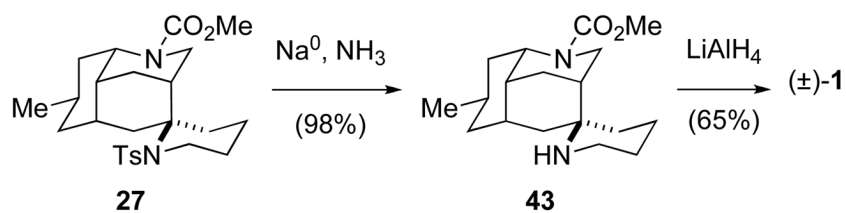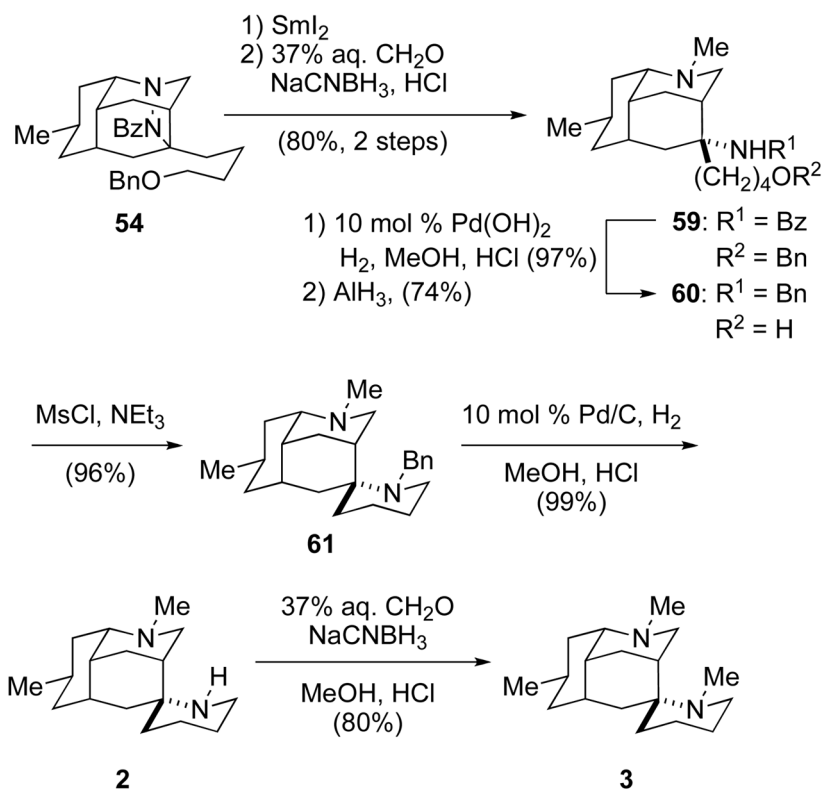
SCHEME 8.
Elaboration of **27** to (±)-5-*epi*-Nankakurine A (**1**).
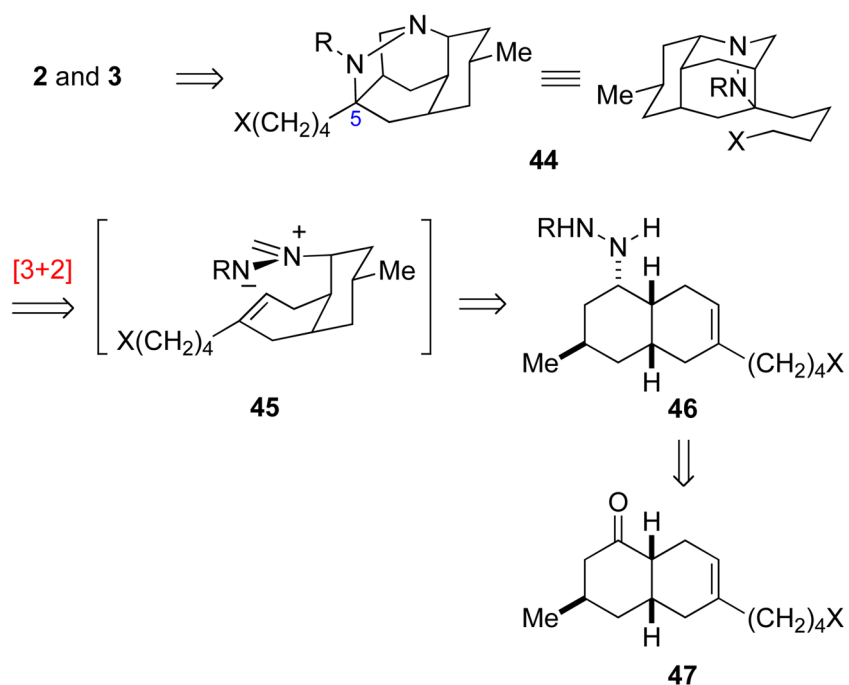
SCHEME 9.
Retrosynthetic Analysis of (+)-Nankakurines A (**2**) and B (**3**)
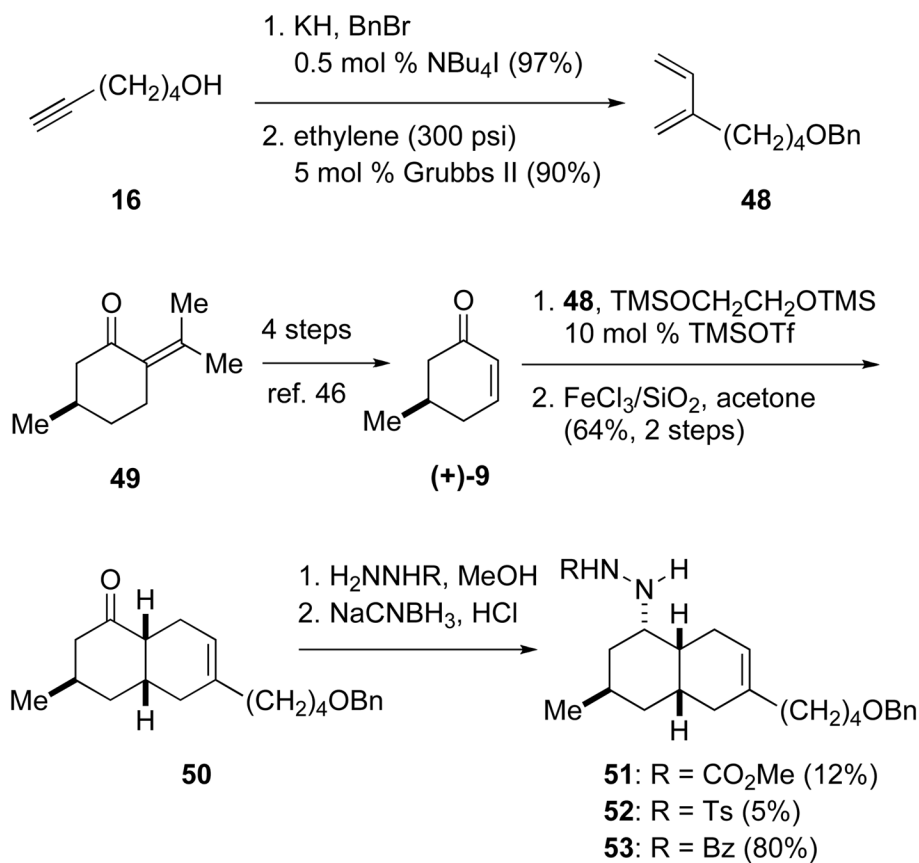
SCHEME 10.
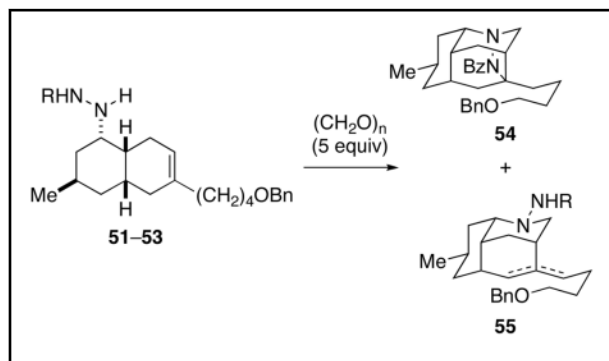Synthesis of *cis*-Octahydronaphthalene Hydrazine Derivatives **51–53**.

SCHEME 11.
Competition Between Intramolecular Azomethine Imine Dipolar Cycloaddition and Aza-Prins Cyclization.

SCHEME 12.
Completion of the Enantioselective Total Syntheses of (+)-Nankakurine A (**2**) and (+)-Nankakurine B (**3**)

TABLE 1

Dipolar Cycloaddition of Unsaturated Hydrazine Derivatives **51**–**53**.

entry	R	solvent^a	additive	yield 54
1	CO$_2$Me	CHCl$_3$	TFA (20 equiv)	0%
2	CO$_2$Me	PhMe	4Å mol. sieves	0%
3	Ts	CHCl$_3$	TFA (20 equiv)	0%
4	Ts	PhMe	4Å mol. sieves	0%
5	Bz	CHCl$_3$	TFA (20 equiv)	0%
6	Bz	PhMe	4Å mol. sieves	40%
7	Bz	PhMe	Et$_3$N 4Å mol. sieves	80%^{b}
8	Bz	PhMe	i-Pr$_2$NEt 4Å mol. sieves	85%^{c}

^{a}Reactions run in CHCl$_3$ at rt or PhMe at 120 °C.

^{b}24 h.

^{c}5 h.