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Enantioselective Total Syntheses of Nankakurines A and B: Confirmation of Structure and Establishment of Absolute Configuration

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The *Lycopodium* alkaloids[1] have attracted synthetic interest for many years, as a result of their diverse architectures and to a lesser extent their biological activities. In 2004, Kobayashi and co-workers reported the isolation of nankakurine A,[2] a minor component of the club moss *Lycopodium hamiltonii*. Utilizing NMR and mass spectrometric analyses, 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 was in accord with the structure of spirolucidine (**4**), whose relative configuration had been secured by single-crystal X-ray analysis of a derivative.[3] Further purification of this club moss extract led to the isolation of a related, slightly less abundant, alkaloid nankakurine B, for which structure **3** was proposed.[4] In this case, ^{1}H NMR NOE data were interpreted to support a configuration at the spiro stereocenter opposite to that found in spirolucidine (**4**) and that proposed originally for nankakurine A (**1**). Since nankakurine A was converted to nankakurine B upon reductive methylation, the structure of nankakurine A was revised to **2** in 2006.[4]

Preliminary biological studies of nankakurine A (**2**) suggested its ability to induce secretion of neurotrophic factors and promote neuronal differentiation of rat adrenal PC-12 cells.[4] Neurotrophic factors play an important role in mediating neuronal growth and survival; consequently, they have long been recognized for their potential in combating neurodegenerative disorders such as Alzheimer's and Parkinson's diseases.[5] Recently, there has been interest in small molecules that exhibit neurotrophic effects[6] because of the poor pharmacokinetics of naturally occurring polypeptidyl neurotrophic factors.[7]

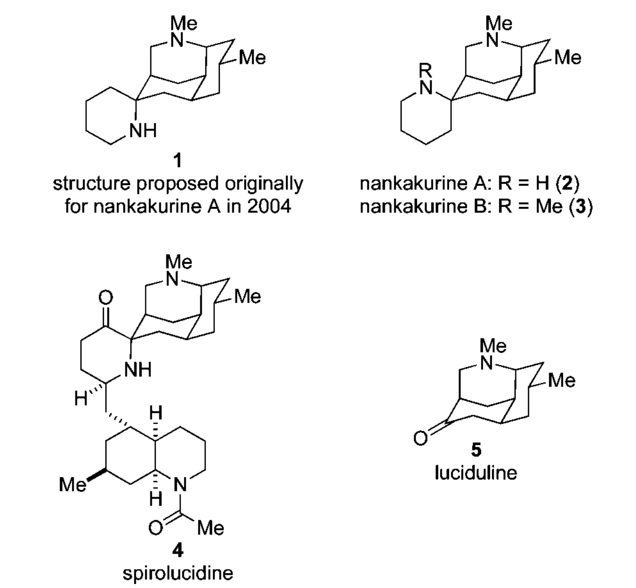
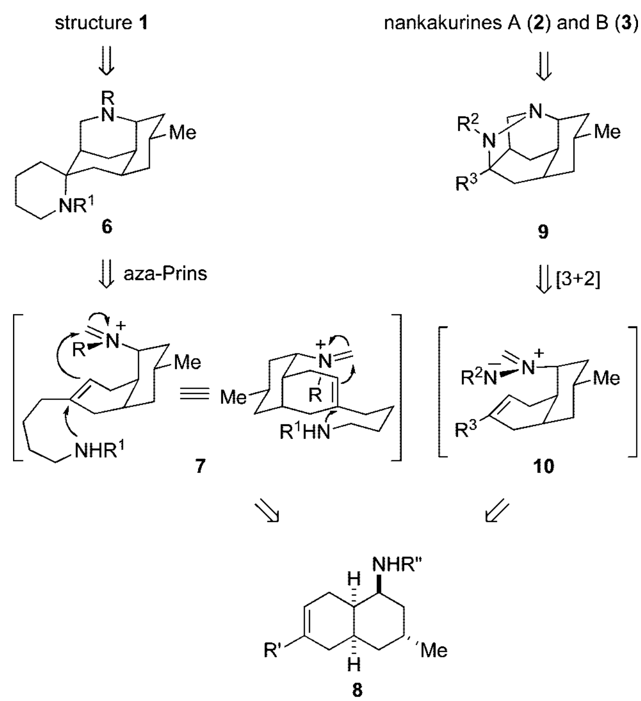


Figure 1. Nankakurines A and B and two structurally related *Lycopodium* alkaloids.

Scheme 1



The scarcity of the nankakurines (**2** and **3** were isolated in 0.0003 and 0.0002%, respectively),[4] contributed to the uncertainty regarding their relative configuration, and has prevented further evaluation of the purported neurotrophic properties of nankakurine A. We report herein total syntheses of (+)-nankakurine A, (+)-nankakurine B, and the originally purported structure **1** of nankakurine A, which rigorously establish the relative and absolute configuration of these rare alkaloids as **2** and **3**, respectively.

Although nankakurines A and B might well be assembled from luciduline (**5**), we were intrigued by the opportunity to evaluate an amino-terminated aza-Prins cyclization for directly assembling the diazatetracyclic ring system of structure **1** (Scheme 1, **7** → **6**). Although aza-Prins cyclizations are often used to assemble azacyclic ring systems,[8] few examples of terminating such cyclizations by tethered heteroatom nucleophiles have been described and none to our knowledge wherein this nucleophile is nitrogen.[9] *cis*-Decalin amine **8**, the precursor of formaldiminium ion **7**, would be available by a Diels−Alder construction that draws direct precedent from the first total synthesis of (+)-luciduline (**5**) by Oppolzer and Petrzilka.[10]

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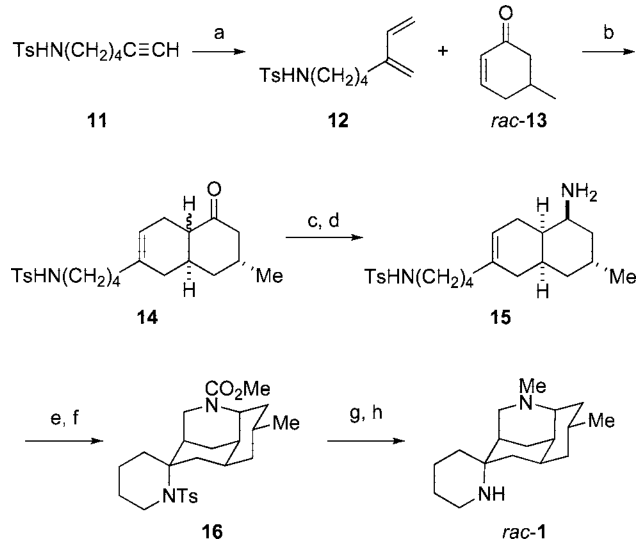
Scheme 2



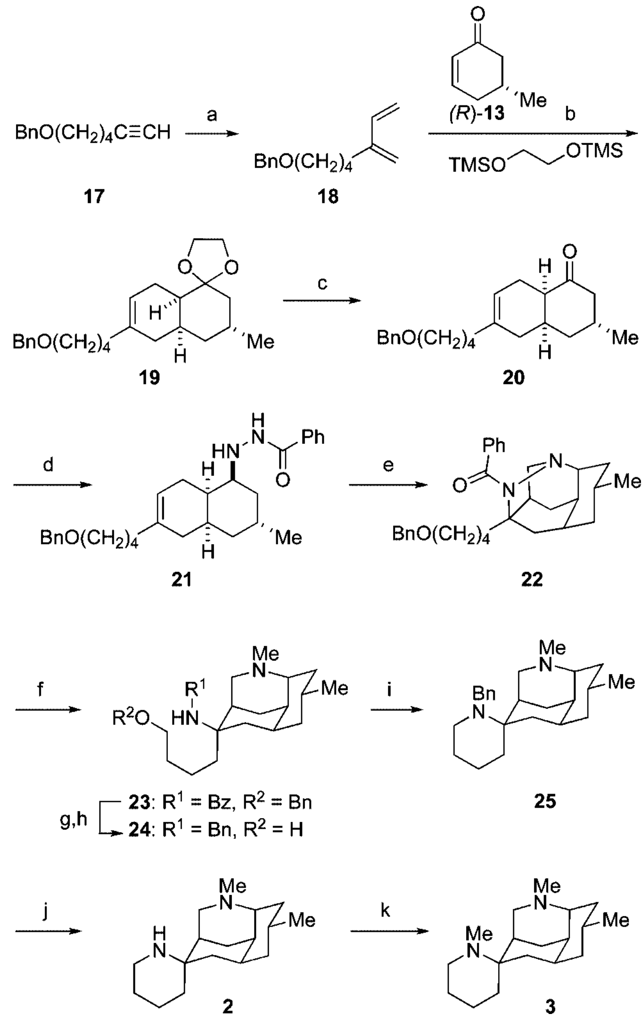
^{a} Reagents: (a) 2.5 mol % Grubbs' second-generation catalyst, ethylene (300 psi), CH_2Cl_2, 25 °C (90%); (b) 50 mol % of $EtAlCl_2$, CH_2Cl_2, PhMe, 25 °C (74%, 1:1−1:3 *cis*:*trans*); (c) $HONH_2 \cdot HCl$, MeOH, KOH, 25 °C (56%); (d) MoO_3, $NaBH_4$, MeOH, 25 °C (98%); (e) $ClCO_2Me$, Et_3N, CH_2Cl_2, 25 °C (56%); (f) $(CH_2O)_n$, TFA, $CHCl_3$, 25 °C (20%); (g) Na, NH_3, THF, −78 °C (98%); (h) $LiAlH_4$, THF, 25 °C (65%).

An unoptimized sequence that led to diazatetracycle **1**, the structure proposed originally for nankakurine A, is summarized in Scheme 2. Enyne metathesis of *N*-tosylaminoalkyne **11**[11] and ethylene in the presence of 2.5 mol % of Grubbs' second-generation catalyst[12] provided 1,3-diene **12** in 90% yield.[13] The Diels−Alder reaction of diene **12** and racemic cyclohexenone *rac*-**13** took place at room temperature in the presence of 50 mol % of $EtAlCl_2$ to generate decalone **14** in 74% yield as a mixture of *cis* and *trans* epimers. Conversion of the *cis* epimer to the oxime under conditions designed to equilibrate the decalone epimers,[10] and subsequent reduction with $NaBH_4$ and MoO_3[14] provided *cis*-decalin amine **15** in 55% yield. Attempts to cyclize formaldiminium ions derived from **15**, or its *N*-Me congener, yielded only tricyclic aza-Prins products. However, the desired nitrogen-terminated aza-Prins biscyclization could be realized by reaction of the methyl carbamate derived from amine **15** with 1 equiv of paraformaldehyde and 20 equiv of TFA at room temperature in $CHCl_3$. Although the yield of this conversion was low, it did provide sufficient amounts of tetracyclic diamine **16** to allow *rac*-**1** to be accessed in two additional reductive steps. ^1H and ^{13}C NMR spectra of this product are quite different from those reported for nankakurine A,[2] confirming that the initial structural assignment for this alkaloid was incorrect.

At this point, it seemed likely that nankakurine A was indeed structure **2**[4] having the relative configuration of the spiropiperidine unit that orients both nitrogen atoms on the concave face of the bridged tricyclic moiety. Connecting these atoms provides potential precursor **9**, which we hoped could be accessed by intramolecular dipolar cycloaddition of azomethine imine intermediate **10** (Scheme 1).[15]

The successful asymmetric total syntheses of (+)-nankakurines A (**2**) and B (**3**) commenced with the preparation of diene **18** in 90% yield by ruthenium-catalyzed cross metathesis of benzyloxyalkyne **17**[16] and ethylene (Scheme 3).[12,13] To circumvent epimerization of the *cis*-decalone product during the Diels−Alder reaction, the cycloaddition of diene **18** and (*R*)-5-methylcyclohex-2-en-1-one [(*R*)-**13**][17] was carried out at low temperature on multigram

Scheme 3



^{a} Reagents: (a) 5 mol % of Grubbs' second-generation catalyst, ethylene (300 psi), CH_2Cl_2, 25 °C (90%); (b) 10 mol % of TMSOTf, CH_2Cl_2, −78 °C (64%); (c) $FeCl_3/SiO_2$, acetone, 25 °C (99%); (d) i. $H_2NNHCOPh$, MeOH, ii. $NaCNBH_3$, MeOH, HCl, 25 °C (80%); (e) $(CH_2O)_n$, 4 Å molecular sieves powder, (*i*-Pr)$_2$NEt, PhMe, 115 °C (82%); (f) i. SmI_2, 9:1 THF−MeOH, ii. 37% aq formaldehyde, $NaCNBH_3$, MeOH, HCl, 25 °C (80%); (g) H_2, 10 mol % of $Pd(OH)_2$, HCl, MeOH, 25 °C (97%); (h) AlH_3, THF, 25 °C (74%); (i) MsCl, Et_3N, CH_2Cl_2, −40 °C (96%); (j) H_2, 10 mol % of Pd/C, HCl, MeOH, 25 °C (99%); (k) 37% aq formaldehyde, $NaCNBH_3$, MeOH, HCl, 25 °C (80%).

scale by a modification of the method of Gassman.[18] Allowing diene **18**, cyclohexenone (*R*)-**13**, and 1,2-bis(trimethylsiloxy)ethane to react in CH_2Cl_2 at −78 °C in the presence of 10 mol % of TMSOTf provided *cis*-decalone acetal **19** in 64% yield, as a single stereoisomer. Cleavage of the dioxolane with $FeCl_3$ adsorbed on silica gel[19] gave *cis*-decalone **20** in 99% yield. Condensation of this product with benzoic hydrazide, followed by a stereoselective reduction of the hydrazone intermediate with $NaCNBH_3$ delivered benzoic hydrazide **21** in 80% yield.

With hydrazide **21** in hand, we turned to the pivotal intramolecular azomethine imine cycloaddition reaction. Early survey experiments revealed that addition of base was required in order to obtain tetracyclic pyrazolidine **22** in high yield; in the absence of base, tricyclic aza-Prins products predominated.[20,21] Under optimized conditions, pyrazolidine **22** was isolated in 82% yield when hydrazide **21** was heated with excess paraformaldehyde, 1 equiv of *N*,*N*-diisopropylethylamine, and powdered 4 Å molecular sieves in toluene at 115 °C. Single-crystal X-ray analysis of product

22[22] confirmed that the dipolar cycloaddition had taken place with the expected regioselectivity.[10,15]

The conversion of tetracyclic pyrazolidine **22** to (+)-nankakurines A (**2**) and B (**3**) commenced with cleavage of the N−N bond with SmI_2[23] and selective in situ reductive methylation of the secondary amine to generate diamine **23** in 80% yield. Hydrogenolytic cleavage of the *O*-benzyl protecting group, followed by reduction of the amide with AlH_3,[24] gave diamine alcohol **24** in 72% yield.[25] Selective O-mesylation of this intermediate at −40 °C, followed by warming the primary mesylate to ambient temperature to form the spiropiperidine ring, provided *N*-benzylnankakurine A (**25**) in 96% yield. Hydrogenolysis of this intermediate in acidic methanol gave (+)-nankakurine A (**2**), $[\alpha]^{24}_{D}$ +13 (*c* 0.4, MeOH),[26a] in 99% yield. Standard reductive methylation of nankakurine A (**2**) delivered (+)-nankakurine B (**3**), $[\alpha]^{24}_{D}$ +12 (*c* 1.5, MeOH),[26b] in 80% yield.[27]

In summary, the first total syntheses of (+)-nankakurine A (**2**) and (+)-nankakurine B (**3**) were accomplished, respectively, in 13 steps and 20% overall yield and 14 steps and 16% overall yield. These syntheses, together with the synthesis of the originally purported structure **1** of nankakurine A, rigorously establish the relative and absolute configuration of (+)-nankakurines A (**2**) and B (**3**). These enantioselective total syntheses are sufficiently concise that gram quantities of (+)-nankakurine A (**2**) and (+)-nankakurine B (**3**) will be available for further biological studies.

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Supporting Information Available: Experimental details and copies of ^{1}H and ^{13}C NMR spectra of new compounds; CIF file for compound **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) 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]

(27) Because they are strong bases and readily pick up protons (and potentially also CO_2), we could reproducibly obtain ^{1}H and ^{13}C NMR spectra of the free-base forms of nankakurines A (**2**) and B (**3**) only in CD_3OD containing a trace amount of $NaOCD_3$. These spectra were not identical to those reported for natural **2** and **3** in CD_3OD.[2,4] However, by adding successive amounts of CF_3CO_2H to samples of synthetic **2** and **3**, ^{1}H and ^{13}C NMR spectra identical to those of the natural products were obtained, consistent with the notion that the natural samples contained an undetermined amount of the conjugate acids. See the Supporting Information for details.

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