Natural Products

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Enantioselective Total Synthesis of (−)-Hosieine A

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Dedicated to Professor Li Deng

Abstract: *The first total synthesis of (−)-hosieine A was accomplished and features an unprecedented nitroso–ene cyclization to construct the 2-azabicyclo[3.2.1]octane ring system. Phosphine-enabled stereoselective bromohydrination provided interesting mechanistic insights into the anti-Markovnikov process. Also noteworthy is the retention of stereochemistry at C9 in the facile radical debromination initiated by Et_3B/air.*

Lupin alkaloids are biosynthetically derived from L-lysine and widely distributed in the plant kingdom. More than 200 bi-, tri-, and tetracyclic, as well as dimeric structures are known and most of them have shown interesting biological activities, such as cytotoxic, oxytocic, antipyretic, antibacterial, antiviral, and hypoglycemic activities.[1] For instance, (−)-sparteine (**1**; Figure 1) has oxytocic and antiarrhythmic properties and is also utilized as a sodium channel blocker in biological studies.[2] Two α4β2 ligands, (−)-cytisine (**2**) and its analogue varenicline (**3**), are approved for medical use as smoking cessation aids.[3] The heteromeric α4β2 subclass of nicotinic acetylcholine receptors (nAChRs) is predominantly expressed in the central nervous system, and thus is pursued as a viable drug target in various therapeutic areas.[4] However, developing pharmacological ligands for these targets located behind the blood-brain barrier has been met with limited success.

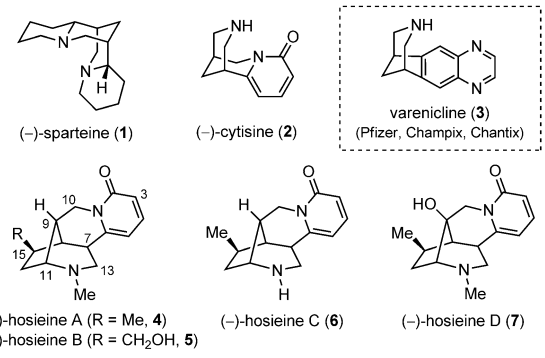
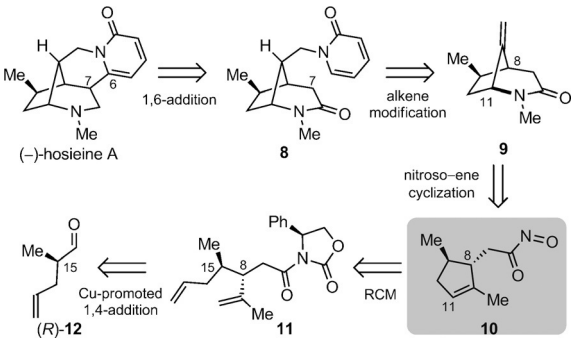


Figure 1. Selected Lupin alkaloids and varenicline.

Massiot and co-workers recently disclosed several structurally related and biogenetically intriguing cytisine-like alkaloids from the roots and stems of *Ormosia hosier* Hemsl. & E.H. Wils., which is utilized in Chinese herb medicine.[5] Among them, (−)-hosieine A (**4**) shows the highest affinity towards the α4β2 receptor with nanomolar level potency ($IC_{50} = 0.96$ nM, $K_i = 0.32$ nM), and is five times more active than nicotine. The most striking structural feature is the 2-azabicyclo[3.2.1]octane ring system, a challenging scaffold in natural product and drug design. We envisioned that it would be interesting to develop a novel approach to construct such a skeleton as well as structural analogues for future biological evaluation (Scheme 1). A disconnection between C6 and C7 is supported by the pioneering work by Gallagher and co-workers.[6] The corresponding 'open' precursor **8** can be derived from functionalization of the terminal alkene **9**. The intriguing 2-azabicyclo[3.2.1]octane skeleton can be accessed through an unprecedented nitroso–ene cyclization[7] and the stereochemistry outcome is defined by the *trans* configuration of the two substituents in **10**. Ring-closing metathesis (RCM) of **11** is expected to deliver a highly functionalized cyclopentene ring after a two-step carbon-chain elongation from the known α-methyl aldehyde (*R*)-**12**.



Scheme 1. Synthesis plan.

The synthesis commenced from the readily available aldehyde (*R*)-**12** using a known procedure and careful distillation.[8] Subsequent Horner–Wadsworth–Emmons olefination with **13**[9] to introduce Evans' chiral auxiliary yielded the requisite *E*-isomer **14** (Scheme 2). Sodium bis(trimethylsilyl)amide (NaHMDS), the typical base used in several

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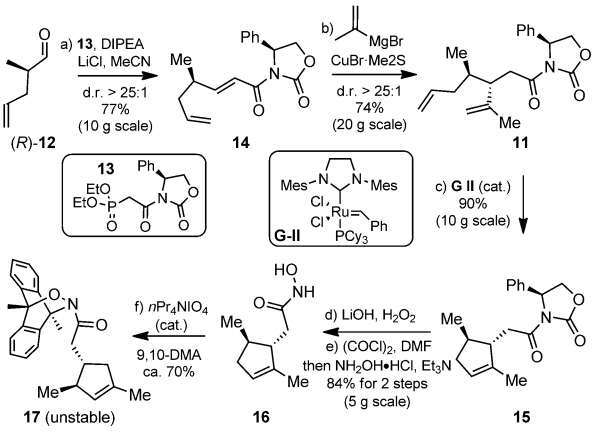
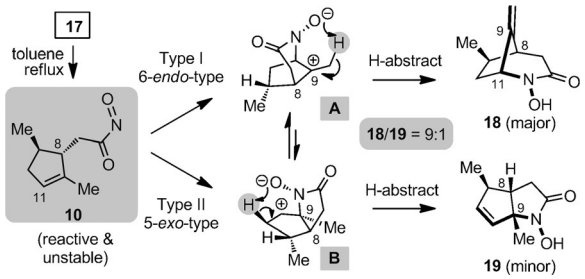


Scheme 2. Preparation of the key nitroso adduct **17**. a) **13** (1.1 equiv), DIPEA (1.0 equiv), LiCl (9.6 equiv), MeCN, RT, 20 h, 77%. b) $CuBr{\cdot}Me_2S$ (2.0 equiv), isopropenylmagnesium bromide (2.0 equiv), THF, −20°C, overnight, 74%. c) Grubbs-II (3 mol%), CH_2Cl_2, reflux, 90%. d) LiOH (3.0 equiv), H_2O_2 (aq. 30%, 5.2 equiv). e) $(COCl)_2$ (2.5 equiv), DMF (1.1 equiv), CH_2Cl_2, 0°C, 40 min; then $NH_2OH{\cdot}HCl$ (4.0 equiv), Et_3N (6.0 equiv), THF/H_2O (3:1), 30 min, 84% for 2 steps. f) nPr_4NIO_4 (0.25 equiv), 9,10-DMA (2.0 equiv), $CHCl_3$, 0°C, 30 min, ca.70%. DIPEA = *N*,*N*-diisopropylethylamine, DMA = 9,10-dimethylanthracene, DMF = *N*,*N*-dimethylformamide, THF = tetrahydrofuran.

literature precedents,[10] resulted in severe epimerization of the tertiary stereogenic center at C15. The diastereomeric ratio (d.r.) varied from 3:1 to 10:1 depending on the quality of the NaHMDS (different vendors). A mild set of reaction conditions developed by Masamune, Roush, and co-workers[10c,d] nicely solved the problem of epimerization and smoothly delivered the requisite product **14** in high diastereoselectivity (d.r. > 25:1). Copper-promoted 1,4-addition of isopropenyl magnesium bromide[11] proceeded on a 20 gram scale to deliver the corresponding adduct **11** in 74% yield with an excellent diastereoselectivity (d.r. > 25:1). The Grubbs II catalyst (**G II**)[12] was not affected by the chiral auxiliary and the corresponding RCM reaction effectively afforded a cyclopentene derivative in 90% yield (10 gram scale). Following standard procedures including hydrolytic removal of the chiral auxiliary, activation of the resulting acid with oxalyl chloride, and aminolysis with hydroxylamine, the corresponding hydroxamic acid **16** was isolated in 84% yield over two steps (5 gram scale).

Direct oxidation of the hydroxamic acid to a nitroso and subsequent ene reaction under several oxidative conditions were not successful since the resulting nitroso compound is highly reactive and severe decomposition occurred. Therefore, the programmed nitroso–ene cyclization through a modified Keck protocol was adopted (Scheme 2). Oxidation of the hydroxamic acid with a catalytic amount of nPr_4NIO_4 in the presence of 9,10-dimethylanthracene (9,10-DMA) afforded the unstable adduct **17**, which was immediately subjected to the thermal retro-Diels–Alder reaction to reveal the very reactive acylnitroso intermediate **10** (Scheme 3).[13] The intramolecular ene reaction simultaneously occurred to deliver the requisite 2-aza-bicyclo[3.2.1]octane **18** along with the 2-azabicyclo[3.3.0]octane **19** in a 9:1 ratio and a combined

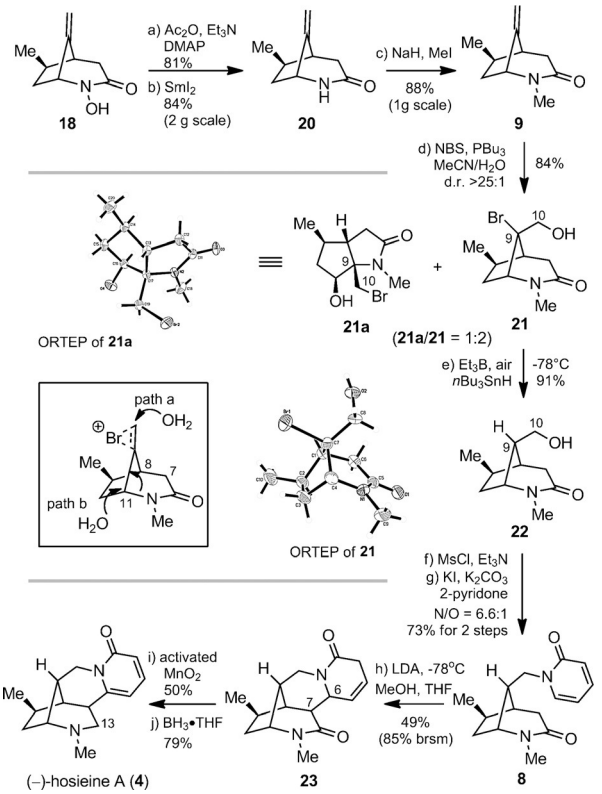


Scheme 3. A proposed polar nitroso–ene cyclization.

yield of 65% from **16**.[14] The high electrophilicity of the acylnitroso group in **10** led us to interpret the regioselectivity by a polar ene mechanism.[15] Under the thermodynamic conditions, the first C–N bond formation may be derived from either a 6-*endo*-type (Type I) or 5-*exo*-type (Type II) reaction to reach the resting state **A** or **B**, respectively. The more stable tertiary carbocation in **A** would favorably drive the reaction pathway towards the formation of **18**. Although a diradical pathway is also possible,[16] the zwitterionic 6-*endo*-type cyclization (Type I) is likely to be dominant and deliver the bridged ring system as in **18**.

Although the intriguing mechanism of the nitroso–ene cyclization remains under further investigation, a gram-scale reaction provides a sufficient amount of **18** for the next transformation. Thus, removal of the N-hydroxy group was initially carried out with a low-valent titanium complex ($TiCl_3$),[17] however, the reaction resulted in a complex mixture and only 10% of the expected product **20** was isolated (Scheme 4). An alternative protocol was undertaken with the application of SmI_2 to cleave the N–O bond after acetyl activation.[18] The clean transformation allowed us to smoothly perform the methylation with methyl iodide on the amide to give the N-methylated product **9** in 88% yield.

The subsequent alkene functionalization turns out to be very challenging. Our initial proposal to perform a hydroboration under numerous reaction conditions were discouraging (Table 1, entries 1–3).[14] Radical bromination conditions adopted from the literature only gave dibromo adducts (entry 4),[19] which were inert to any attempts at pyridone installation. Although epoxidation with in situ generated DMDO could afford two inseparable stereoisomers (d.r. 3:2; entry 5), the subsequent ring-opening with 2-pyridone was still not effective. We reasoned that the heteroatom at C9 might suppress the substitution at C10 as a result of a possible electronic repulsion, thus the halogen at C9 should be removed prior to the installation of pyridone. With this assumption in mind, bromohydrination of the alkene was executed to subsequently reveal the tertiary carbon center at C9 in hosieines A–C (**4**–**6**). Inspired by seminal work by Ishihara and co-workers on bromonium-ion-intiated polyene cyclization,[20] a novel bromohydrination was realized with NBS and phosphine (entry 6). After numerous experiments, NBS/PBu_3 in MeCN/H_2O proved to be an excellent system to cleanly convert **9** into **21** and a rearranged minor product (**21a**) with a combined yield of 84% (entry 7; for structures see Scheme 4). The exclusive stereoselectivity for both **21** and **21a** implies a possible hyperconjugation between the σ* orbi-

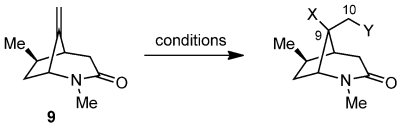


Scheme 4. Complete synthesis of (−)-hosieine A (**4**). a) Ac_2O (1.2 equiv), Et_3N (1.3 equiv), DMAP (cat.), RT, 45 min, 81%. b) SmI_2 (2.4 equiv), THF, RT, 20 min, 84%. c) NaH (1.2 equiv), MeI (1.5 equiv), THF/DMF (2:1), RT, 1 h, 88%. d) NBS (1.5 equiv), PBu_3 (0.4 equiv), $MeCN/H_2O$ (5:3), 0°C, 84% (**21**/**21a** = 2/1). e) Et_3B (0.4 equiv), air, nBu_3SnH (3.5 equiv), toluene, −78°C, 1 h, 91%. f) MsCl (1.2 equiv), Et_3N (1.4 equiv), CH_2Cl_2, 0°C, 15 min. g) K_2CO_3 (2.0 equiv), KI (0.1 equiv), 2-pyridone (1.1 equiv), toluene, reflux, 5 h, 73% for 2 steps. h) LDA (2.0 equiv), THF, −78°C, 30 min; MeOH, 49% (85% brsm). i) activated MnO_2 (36 equiv), CH_2Cl_2, RT, 30 min, 50%. j) BH_3·THF (26 equiv), THF, 0°C, 1 h, 79%. Thermal ellipsoids in ORTEP shown at 30% probability. brsm = based on the recovered starting material, DMAP = 4-dimethylaminopyridine, LDA = lithium diisopropylamide, MsCl = methyl sulfonyl chloride, NBS = *N*-bromosuccinimide.

tal of C9−Br and two filled σ orbitals of C11−N and C8−C7 as a result of the antiperiplanar alignment which is exemplified in le Noble's model.[21] The incoming H_2O favorably attacks the less substituted site (C10) to yield an anti-Markovnikov product (see path a of the insert in Scheme 4) while the C11−N bond migration results in the fused-ring structure **21a** (see path b of the insert in Scheme 4). Further X-ray analysis unambiguously confirmed the structural features of the bromohydrins **21** and **21a**.[22]

With enough of the key primary alcohol **21** in hand, we then investigated the radical debromination. The following step was anticipated to be challenging since the radical-initiated transformation might result in two stereoisomers. The initial attempt with AIBN/Bu_3SnH in refluxing toluene only resulted in a complex mixture. After screening several reaction conditions, to our delight, the stereochemistry at C9 was exclusively retained during the Et_3B/air-induced facial

Table 1: Functionalization of alkene **9**.



Entry	Reagents and conditions	X, Y	Yield [%][a]
1	9-BBN; H_2O_2	X = H, Y = OH	n.r.
2	HBpin, $[RhCl(PPh_3)_3]$; H_2O_2	X = H, Y = OH	n.r.
3	BH_3·py/I_2; H_2O_2	X = H, Y = OH	n.r.
4[b,c]	*m*CPBA/HBr (1:3)	X = Br, Y = Br	96
5[b,c]	oxone/acetone	X, Y = O	99 (d.r. 3:2)
6[d]	NBS, PPh_3, $MeCN/H_2O$, 60°C	X = Br, Y = OH (**21** and **21a**)	85 (ratio 1:1)
7[d,e]	NBS, PBu_3, $MeCN/H_2O$, 0°C	X = Br, Y = OH (**21** and **21a**)	84 (ratio 2:1; d.r. > 25:1)

[a] Yield of isolated product. [b] Stereochemistry was not assigned. [c] Yield was estimated by ^{1}H NMR ($CDCl_3$) spectroscopy. [d] The ratio of **21**/**21a** was determined by ^{1}H NMR ($CDCl_3$) spectroscopy. The structure of **21a** was identified as a rearranged product. [e] The d.r. value is that for both **21** and **21a**. 9-BBN = 9-Borabicyclo[3.3.1]nonane, HBpin = pinacolborane, n.r. = no reaction, py = pyridine, *m*CPBA = *meta*-chloroperoxybenzoic acid.

radical debromination in the presence of Bu_3SnH (Scheme 4).[23] The retention of chirality may be attributed to a similar hyperconjugation proposed in the bromohydrination step.[21] After activation of the primary alcohol in **22**, 2-pyridone was introduced smoothly to yield the requisite compound **8** in favor of N-alkylation (N/O: 6.6:1). During the subsequent kinetically controlled 1,6-conjugate addition, developed by Gray and Gallagher,[6] it was essential to use LDA and subsequent protonation at −78°C with MeOH, instead of a regular aqueous solution of NH_4Cl. Activated MnO_2 effectively effected dehydrogenation and subsequent borane reduction of the amide (C13) completed the total synthesis of (−)-hosieine A (**4**). The data for the synthetic sample is identical[14] with the reported data (synthetic: $[\alpha]_D^{27} = -144$ ($c = 0.17$, MeOH); natural:[4] $[\alpha]_D^{20} = -122$ ($c = 0.11$, MeOH)).

In summary, the first total synthesis of (−)-hosieine A (**4**) was accomplished through an unprecedented nitroso–ene cyclization to furnish the 2-azabicyclo[3.2.1]octane ring system. Moreover, phosphine-enabled stereoselective bromohydration of the alkene provides an interesting mechanistic application of hyperconjugation into the anti-Markovnikov process. The retention of stereochemistry during the radical debromination by Et_3B-air/Bu_3SnH is also noteworthy. The rapid access to 2-azabicyclo[3.2.1]octane would facilitate future structural derivatization for pursuing potential nAChRs. The novel ring construction strategy of the nitroso–ene cyclization clearly paves a way towards other bridged systems in complex natural products (e.g. aconitine). Investigations along these lines are currently underway.

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Keywords: ene reaction · hyperconjugation · receptors · ring-closing metathesis · total synthesis

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[14] See the Supporting Information for details.

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[22] CCDC 1400914 (**21**) and 1400781 (**21a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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