A Pyridine Dearomatization Approach to the Matrine-type Lupin Alkaloids

Jeff K. Kerkovius,[1] Andrea Stegner,[1] Aneta Turlik,[2] Pik Hoi Lam,[1] Kendall N. Houk,[2] Sarah E. Reisman[1*]

[1]Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, CA 91125, USA. * Corresponding author. reisman@caltech.edu

[2]Departmentof Chemistry and Biochemistry University of California, Los Angeles, Los Angeles, CA 90095, USA.

Abstract:

(+)-Matrine and (+)-isomatrine are tetracyclic alkaloids isolated from the plant *Sophora flavescens,* the roots of which are used in traditional Chinese medicine. Biosynthetically, these alkaloids are proposed to derive from three molecules of (–)-lysine via the intermediacy of the unstable cyclic imine Δ^1-piperidine. Inspired by the biosynthesis, a new dearomative annulation reaction has been developed that leverages pyridine as a stable surrogate for Δ^1-piperidine. In this key transformation, two molecules of pyridine are joined with a molecule of glutaryl chloride to give the complete tetracyclic framework of the matrine alkaloids in a single step. Using this dearomative annulation, (+)-isomatrine is synthesized in four steps from inexpensive commercially available chemicals. (+)-Isomatrine then serves as the precursor to additional lupin alkaloids, including (+)-matrine, (+)-allomatrine, (+)-isosophoridine, and (–)-sophoridine.

Main text:

The lupin alkaloids are a structurally diverse class of quinolizidine-containing natural products isolated from plants in the *Lupinus* genus (Fig. 1A).[1] (+)-Matrine (**2**), the primary component of Chinese Kushen injection, inhibits proliferation in metastatic cancer cell lines and has also been investigated as a therapeutic agent against encephalomyelitis, asthma, arthritis, and osteoporosis.[2,3] (–)-Sophoridine (**4**) is an approved chemotherapeutic in China, which has also demonstrated antibiotic activity.[4] Little is known about the pharmacological properties of (+)-isomatrine (**1**) and (+)-isosophoridine (**5**), which likely reflects their limited accessibility from commercial vendors.[5]

Although the detailed enzymatic pathway has not been fully annotated, the biosynthesis of matrine is proposed to initiate with the enzymatic conversion of (–)-lysine (**6**) to Δ^1-piperidine (**7**) (Fig. 1B).[6,7] Subsequent dimerization of **7** followed by oxidation and isomerization is proposed to yield quinolizidine **8**, a shared biosynthetic precursor to several lupin alkaloids.[8,9] Mannich addition of **8** to a third equivalent of **7** and cyclization

with the pendant aldehyde is proposed to generate the oxidized tetracycle **9**, which upon reduction gives (+)-matridine (**10**). Seminal studies by Abdusalamov demonstrated that feeding ^{14}C-labeled (+)-**10** to *Goebelia Pachycarpa* resulted in the isolation of (+)-**2** with ^{14}C label at C15, suggesting that the final step in the biosynthesis of **2** is a site-selective C–H oxidation.[10, 11]

Synthetically, most of the prior work has focused on (+)-matrine (**2**), with four reported total syntheses.[12,13,14,15] Synthetic access to the minor congeners is far more limited, with a single total synthesis each of (+)-allomatrine (**3**) and (+)-isosophoridine (**5**), and no completed total syntheses of (+)-isomatrine (**1**) or (–)-sophoridine (**4**).[16,17] We sought to devise a unified synthesis that could provide access to the series of matrine-type alkaloids shown in Fig. 1A. Inspired by the proposed biosynthesis, it was envisioned that pyridine (**14**) could serve as a stable, inexpensive synthon for Δ^1-piperidine (**7**), and the remaining five carbons of the tetracyclic matrine framework could derive from glutaryl chloride (**15**, Fig. 1C). In the key step, we proposed a dearomative annulation via bis-acyl pyridinium salt **17** to form (±)-tetracycle **12**, a molecule that contains all of the carbon and nitrogen atoms of (+)-**1**. Tetracycle **12** could be elaborated to (+)-(**1**) by global reduction followed by a site-selective oxidation of (+)-isomatridine (**11**) reminiscent of the proposed biosynthesis of matrine (**2**). Isomatrine (**1**) is the least thermodynamically stable lupin alkaloid and its isomerization to both **2** and **3** has been previously reported. We therefore anticipated that access to **1** could enable the synthesis of additional lupin alkaloids.[18,19]

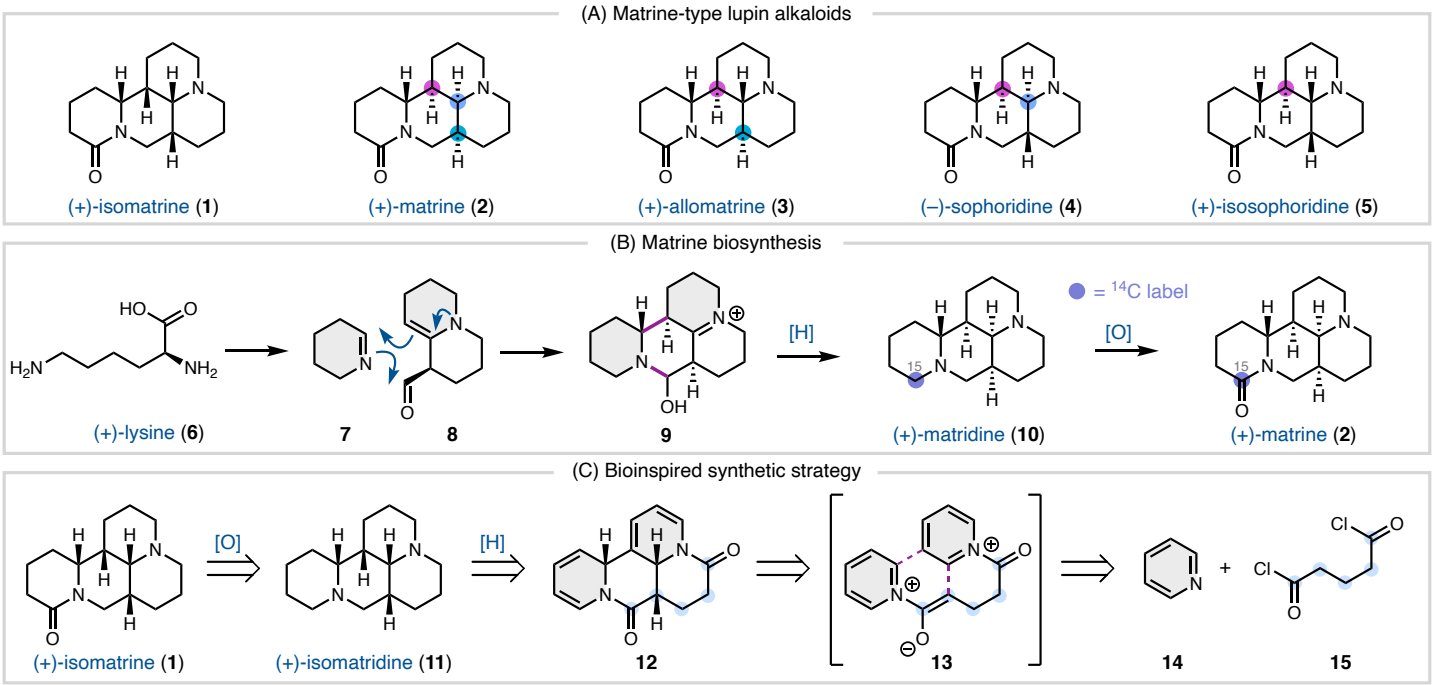

Fig. 1. (**A**) Chemical structures of matrine-type lupin alkaloids. (**B**) Proposed biosynthesis of matrine. (**C**) Retrosynthetic analysis of isomatrine.

Our studies commenced with the investigation of the dearomative annulation (Fig. 2A). Addition of glutaryl chloride (**15**) to pyridine (**14**) in dichloromethane at –50 °C followed by warming to 20 °C resulted in

clean formation of (±)-tetracycle **12** in 62% yield (10 g scale). The reaction was highly robust and could be carried out on one mole scale to produce over 160 grams (67% yield) of (±)-tetracycle **12** in a single batch. The product was isolated by precipitation from the crude reaction mixture, alleviating the need for a workup or column chromatography. Given the cost of pyridine ($7/mol), glutaryl chloride ($211/mol), and all solvents ($31/mol), the raw materials cost $398/mol of product formed.[20] Recrystallization of (±)-**12** enabled single crystal X-ray diffraction, which confirmed the *syn-syn* relative stereochemistry.[21]

To elucidate the reaction pathway, mechanistic and computational studies were undertaken. Monitoring the reaction between **14** and **15** by ^{1}H NMR determined that the major species at –40 °C was bis-acyl pyridinium salt **17** (Fig. 2C). After warming to 25 °C, acid chloride **18** resulting from mono-cyclization was observed. Presumably the acyl pyridinium salt and acyl chloride **18** are in equilibrium, but the acyl chloride is the major species at 25 °C. Although deprotonation of acyl pyridinium salts or acyl chlorides can give rise to ketene intermediates,[22] no such species was detected by ^{1}H NMR or by reactIR. Attempts to calculate a pathway involving ketene intermediates failed to locate a transition state (TS) for a concerted [2+2] cycloaddition. Similarly, no TS for the concerted [4+2] cycloaddition of bis-acyl pyridinium salt **13** could be located. Investigation of a stepwise pathway determined that the lowest-energy TS for the first cyclization involves a boat-like conformation to form the *syn* product (**TS1a**, ΔG_{TS} = 7.3 kcal/mol) (Fig. 2D). Attempts to find the analogous chair-like TS were unsuccessful and led instead to conversion to the boat-like TS. The pathways leading to the *anti* mono-cyclization product (**Int1b**) are higher in energy (see **TS1b** and **TS1c**). The preference for the *syn* boat compared to the *anti* boat TS is likely due to favorable dispersive interactions between the heteroaryl ring and the oxygen-bearing carbon of the enolate, as well as minimization of the dipole moment in the *syn* TS. These TSs lead to two intermediates: *syn* intermediate **Int1a** (–12.6 kcal/mol) and *anti* intermediate **Int1b** (–10.7 kcal/mol). The TS for the second C–C bond formation (**TS2a**) is most favorable for the *syn-syn* intermediate (**Int2a**), with a barrier of 20.2 kcal/mol. The second lowest-energy pathway proceeds via **TS2b** leading to **Int2b**, which gives rise to the *anti-syn-anti* configuration at the ring fusions. The transition states leading to the other four potential diastereomers are higher in energy. Formation of **Int2a** and **Int2b** is followed by deprotonation by pyridine. While **Int2b** is lower in energy than **Int2a**, the deprotonation of **Int2a** to give *syn-syn* (±)-**12** follows the lowest-energy pathway. Thus, the selectivity-determining step is the final deprotonation (**TS3a**) and *syn-syn* (±)-**12** is favored, even though it is thermodynamically less stable than *anti-anti* **19**. These results are consistent with the experimentally observed diastereoselective formation of product (±)-**12**. When enantiopure (*R*)-2-methylpentandioyl chloride was employed, C3-methyl tetracycle (+)-**16** was obtained in 66% yield as a single diastereomer and in >99% ee (Fig. 2B). This stereochemical outcome is consistent with reaction through a boat-like transition state (**20**) with the methyl group in a pseudo-equatorial position.

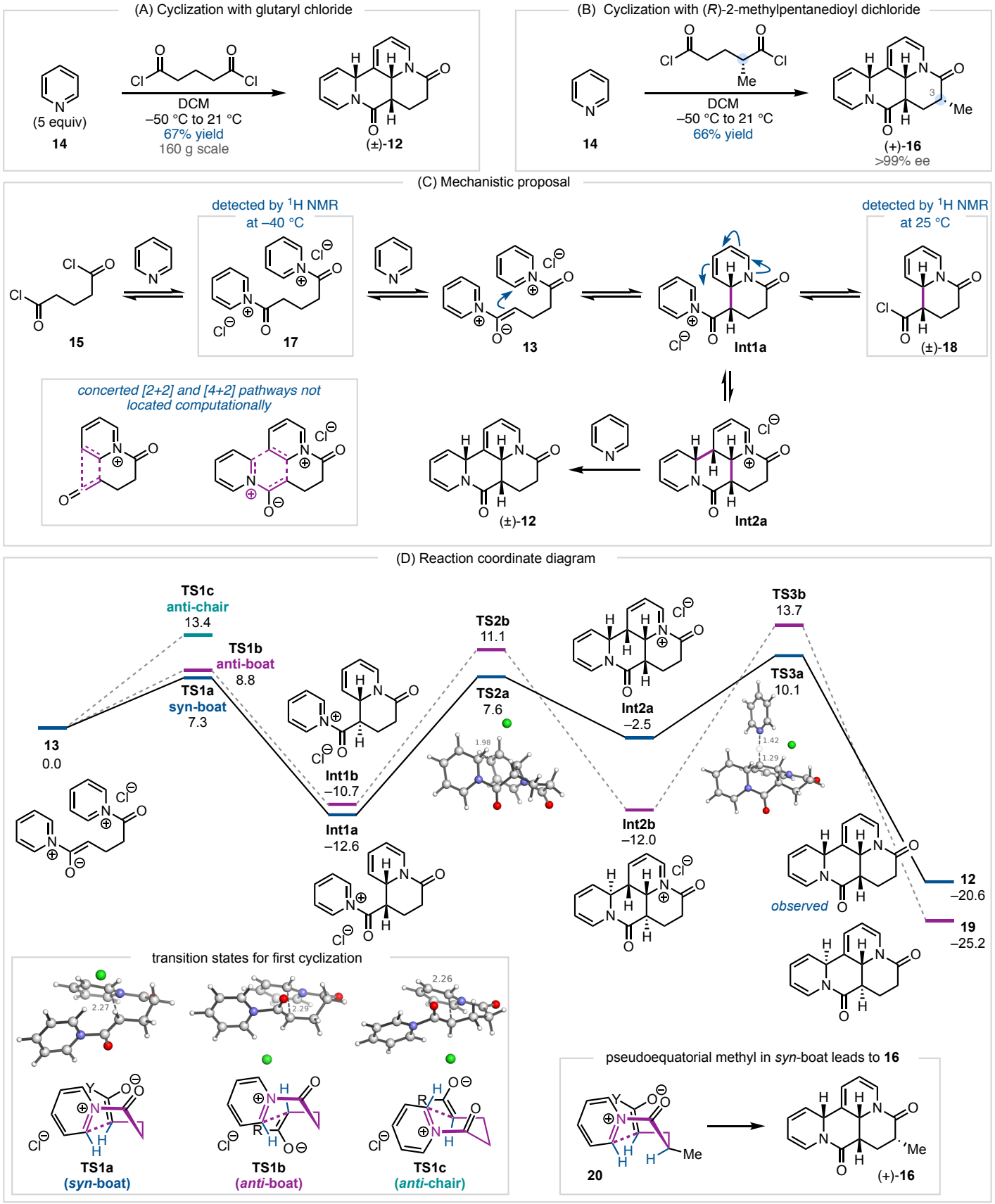

Fig. 2. (**A**) Diastereoselective cyclization of pyridine and glutaryl chloride. (**B**) Diastereoselective cyclization of (*R*)-2-methylpentandioyl chloride. (**C**) Proposed mechanism for the diastereoselective cyclization. (**D**) Reaction coordinate diagram – performed with Gaussian using ωB97XD/def2-TZVP/SMD(DCM).

At this stage, attention turned to elaborating (±)-**12** to (+)-isomatrine (**1**) (Fig. 3A). Hydrogenation of (±)-tetraene **12** proceeded smoothly followed by reduction with alane to give (±)-isomatridine (**11**) in 60% yield over two steps. Purification was readily accomplished by generating the hydrogen oxalate salt followed by trituration in acetone, obviating the need for column chromatography. Resolution of diamine (±)-**11** by recrystallization of the di-*p*-toluoyl tartaric acid salt gave 24% recovery (46% theoretical yield) of the desired (+)-diamine **11** in 90% ee.

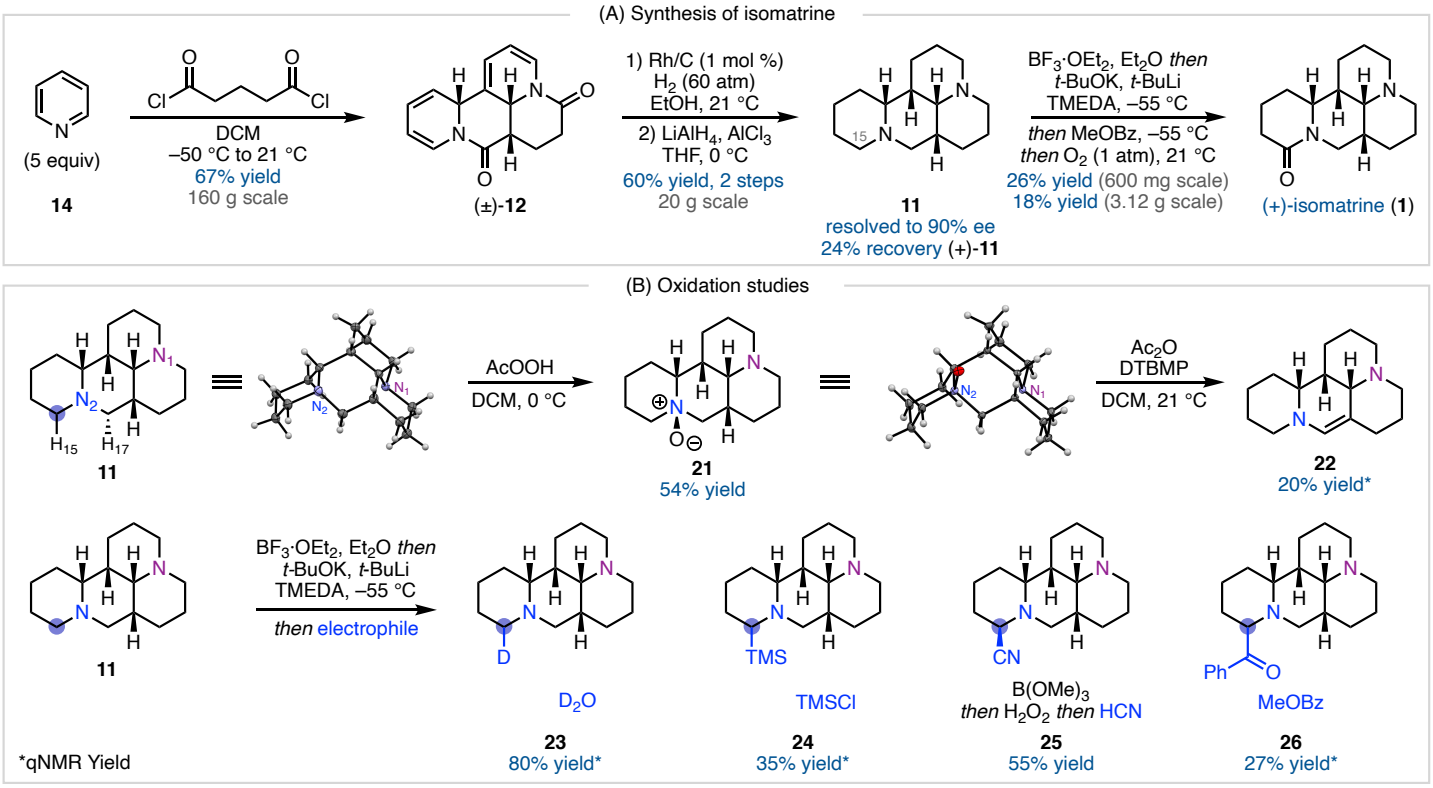

Fig. 3. (**A**) Completed total synthesis of isomatrine. (**B**) Attempted oxidation reactions.

Inspired by the proposed biosynthesis,[23] we initially investigated the enzymatic oxidation of (+)-**11** to give (+)-**1**. Unfortunately, a screen of >180 bacterially derived P450 enzymes (both wild type and mutants) failed to produce any promising leads. As a result, our focus turned towards non-enzymatic methods for the selective oxidation of C15. Analysis of the X-ray structure of diamine **11** revealed that N1 points into the cavity of the molecule while the N2 lone pair points outwards. Selective oxidation of N2 was achieved by treatment of diamine **11** with peracetic acid to yield the expected *N*-oxide **21** in a 54% yield. However, attempts to advance **21** via Polonovski reaction (acetic anhydride/di-*tert*-butyl-4-methyl pyridine (DTBMP)) led to formation of the undesired enamine **22**.[24] Analysis of the X-ray structure of **21** confirmed that antiperiplanar alignment of H17 with the N–O bond is ideally suited to regioselectively form the undesired elimination product **22**.

We became interested in a report by Kessar and coworkers demonstrating that amine–BF_3 adducts could undergo deprotonation using mixtures of *tert*-butyl lithium (*t*-BuLi) and potassium *tert*-butoxide (*t*-BuOK).[25] Consistent with the selectivity in the *N*-oxide formation, treatment of diamine (+)-**11** with $BF_3 \cdot OEt_2$ quantitatively formed the Lewis acid-base complex. Deprotonation of the BF_3 complex of (+)-**11** with a mixture of *t*-BuLi and *t*-BuOK in *N,N,N,N*-tetramethylethylenediamine (TMEDA) occurred with good selectivity for C15, as determined by trapping with deuterated methanol (**23**, Fig. 3B).[26] Unfortunately, trapping of this anion with other electrophiles proved more challenging. For example, deprotonation followed by quenching with TMSCl provided silylated diamine **24** in only 35% yield, while trapping with methyl benzoate gave unstable phenyl ketone **26** in 27% yield. The best yield of C15-functionalized product was obtained when **11** was deprotonated and then trapped with trimethyl borate; oxidation with hydrogen peroxide and trapping of the resultant enamine with HCN gave aminonitrile **25** in 55% yield. Aerobic oxidation of **25** provided isomatrine in 46% yield (25% yield over three steps from **11**).[27] Alternatively, deprotonation of (+)-**11**, trapping with methyl benzoate, and aerobic oxidation could be carried out in a single reaction flask to give (+)-**1** directly in 18–26% yield, depending on the scale.[28] To date, >1 gram of (+)-isomatrine has been prepared in 10% overall yield by this four-step route.

Initial attempts to reproduce Okuda's Pt-catalyzed isomerization of (+)-isomatrine failed to provide the reported yields of (+)-matrine (**2**) and (+)-allomatrine (**3**), and instead produced a mixture of five compounds.[18] To improve the yield of **2** and **3**, while also broadening the synthetic access to other congeners, an investigation of several isomerization catalysts was carried out. Use of Rh/C provided the best yields of (+)-**2** (32% yield, Fig. 4), while (+)-**3** could be obtained in 83% yield when Pd/C was used. Isomerization with Pt/C provided (+)-isosophoridine (**5**) in 55% yield. Finally, use of PtO_2 at 98 °C for 15 minutes furnished (–)-sophoridine (**4**) in 10% yield, together with the other isomers.[29,30] When the reaction with PtO_2 was conducted at 80 °C for 24 hours, (–)-isomer **27** was isolated in 40% yield. To our knowledge, **27** has not yet been isolated from natural sources.

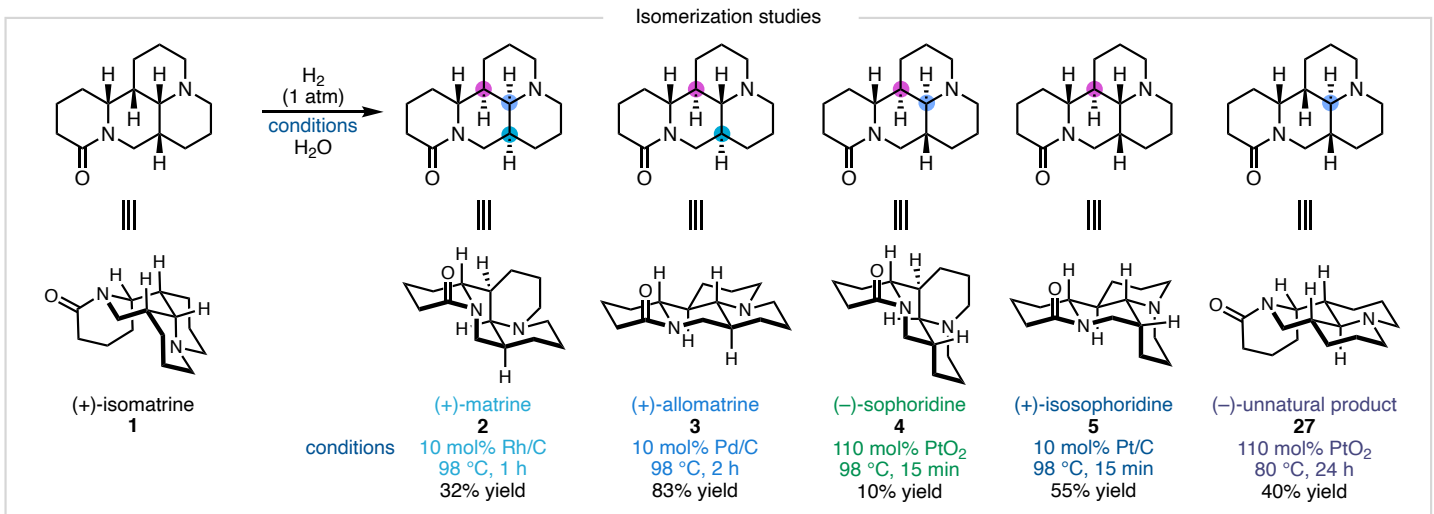

Fig. 4. Isomerization of (+)-isomatrine to additional matrine-type lupin alkaloids.

The bioinspired dearomative annulation between pyridine and glutaryl chloride developed here has enabled the first total synthesis of the lupin alkaloids (+)-isomatrine and (–)-sophoridine, and the shortest syntheses of (+)-matrine, (+)-allomatrine, and (+)-isosophoridine reported to date. The brevity of this route results from the ability to construct the entire carbon framework of the matrine-type alkaloids in a single step. The diversity of matrine-type alkaloids prepared from commodity chemicals is anticipated to support future pharmacological investigations.

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Supplementary Materials:

Materials and Methods
Table S1 – S23
Fig S1 – S7
Scheme S1 – S6
NMR Spectra
Full Reference List

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