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Journal
Journal of the American Chemical Society, 144(35)

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Publication Date
2022-09-07

DOI
10.1021/jacs.2c06584

Peer reviewed

HHS Public Access

Author manuscript

J Am Chem Soc. Author manuscript; available in PMC 2023 September 07.

Published in final edited form as:

J Am Chem Soc. 2022 September 07; 144(35): 15938–15943. doi:10.1021/jacs.2c06584.

A Pyridine Dearomatization Approach to the Matrine-type Lupin Alkaloids

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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.

Graphical Abstract

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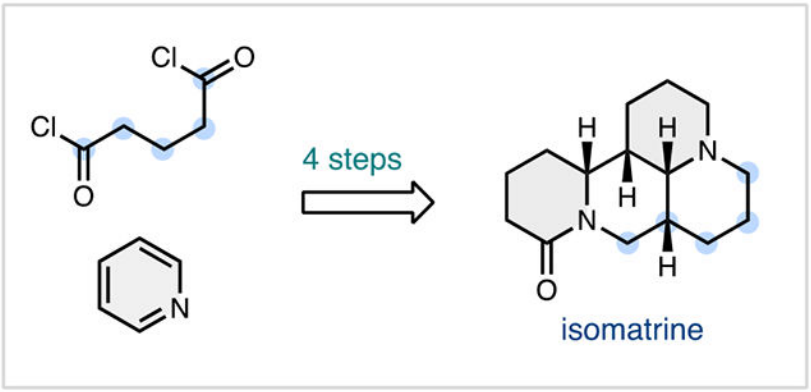
Supporting Information

The Supporting Information is available free of charge at DOI: Experimental procedures, characterization data (^{1}H and ^{13}C NMR, HRMS, FTIR) for all new compounds (PDF), coordination geometries for DFT optimized compounds. X-ray structural data are available free of charge from the Cambridge Structural Database under CCDC 2159764-2159768, 2159770-2159774, and 2163777.



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 radio-labelled (+)-**2**, suggesting that the final step in the biosynthesis of **2** is a site-selective C–H oxidation.[10,11]

Synthetically, most of the work prior to 2022 had focused on matrine (**2**), with four reported total syntheses.[12,13,14,15] Synthetic access to the minor congeners is far more limited: until a recent report by Sherburn and coworkers,[16] there was a single total synthesis each of allomatrine (**3**) and isosophoridine (**5**), and no reported total syntheses of isomatrine or sophoridine (**4**).[17,18] 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 the carbon and nitrogen atoms of **1**.[19] 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.[20]

We therefore anticipated that access to **1** could enable the synthesis of additional lupin alkaloids.[21] This type of late-stage isomerization strategy was also deployed in the 2022 Sherburn synthesis of several matrine alkaloids.[16]

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.[22] Recrystallization of (±)-**12** enabled single crystal X-ray diffraction, which confirmed the *syn-syn* relative stereochemistry.[23]

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 **Int1a** and acyl chloride **18** are in equilibrium, but the acyl chloride is the major species at 25 °C. A second, minor species assigned as the acid chloride resulting from **Int1b** (vide infra) was also observed; this species was consumed as the reaction progressed to full conversion.[23] Although deprotonation of acyl pyridinium salts or acyl chlorides can give rise to ketene intermediates,[24] 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. In order to test the importance of dispersive interactions in these TSs, the TSs were recomputed with B3LYP, a functional known to lack dispersion. Indeed, with this functional, the difference between the two transition states was only 0.1 kcal/mol. Inclusion of dispersion with Grimme's D3 correction restored the energy difference to 1.4 kcal/mol in favor of the *syn* boat transition state.

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 formation of product (±)-**12** as a single diastereomer, despite the initial mixture of monocyclization products. 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 the calculations, where the pathway initiating with a *syn* boat transition state bearing the methyl group in a pseudo-equatorial position is favored.

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. At this stage, resolution of diamine (±)-**11** can be achieved by recrystallization of the di-*p*-toluoyl tartaric acid salt to give 24% recovery (46% theoretical yield) of the desired (+)-diamine **11** in 90% ee.

Inspired by the proposed biosynthesis,[25] 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 **20** in a 54% yield. However, attempts to advance **20** via Polonovski reaction (acetic anhydride/di-*tert*-butyl-4-methyl pyridine (DTBMP)) led to formation of the undesired enamine **21**.[26] Analysis of the X-ray structure of **20** confirmed that antiperiplanar alignment of H17 with the N–O bond is ideally suited to regioselectively form the undesired elimination product **21**.

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).[27] 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 the less sterically encumbered C15 over C17 (10:1), as determined by trapping with deuterated methanol (**22**, Fig. 3B).[28] Unfortunately, trapping of this anion with other electrophiles proved more challenging. For example, deprotonation followed by quenching with TMSCl provided silylated diamine **23** in only 35% yield, while trapping with methyl benzoate gave unstable phenyl ketone **25** 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 **24** in 55% yield. Aerobic oxidation of **24** provided isomatrine in 46% yield

(25% yield over three steps from **11**).[23, 29] 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.[30] This route provides access to (±)-isomatrine in four steps, and (+)-isomatrine can be easily accessed by incorporating the resolution of diamine **11**. To date, >1 gram of (+)-isomatrine has been prepared.

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.[20] 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.[31,32] When the reaction with PtO_2 was conducted at 80 °C for 24 hours, (–)-isomer **26** was isolated in 40% yield. To our knowledge, **26** has not yet been isolated from natural sources.

The bioinspired dearomative annulation between pyridine and glutaryl chloride developed here has enabled the first total synthesis of the lupin alkaloid (–)-sophoridine, and the shortest syntheses of (+)-isomatrine, (+)-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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

The California Institute of Technology Center for Catalysis and Chemical Synthesis is gratefully acknowledged for access to analytical equipment. We thank the Dow Next Generation Educator Funds and Instrumentation Grants for their support of the Beckman Institute X-ray Crystallography Facility at Caltech, as well as the Caltech CCE NMR facility and Multiuser Mass Spectrometry Laboratory, which is also supported by the NSF CRIF program (CHE-0541745). Dr. M. Shahgholi is acknowledged for acquisition of HRMS data. Dr. Michael Takase and Larry Henling are acknowledged for acquiring the X-ray diffraction data, and Yujia Tao is thanked for assistance in solving X-ray structures. Dr. David Miller of the Arnold lab at Caltech is acknowledged for his help in running the P450 enzyme oxidation screen. Fellowship support was provided by the Natural Sciences and Engineering Research Council (NSERC) of Canada (PGS-D fellowship to J. K. K., grant PGSD3-532535-2019), and the National Institutes of Health (NIH) (F32GM134709 to A. T.). S.E.R. acknowledges financial support from the NIH (R35GM118191), and K. N. H. acknowledges the National Science Foundation (CHE-1764328).

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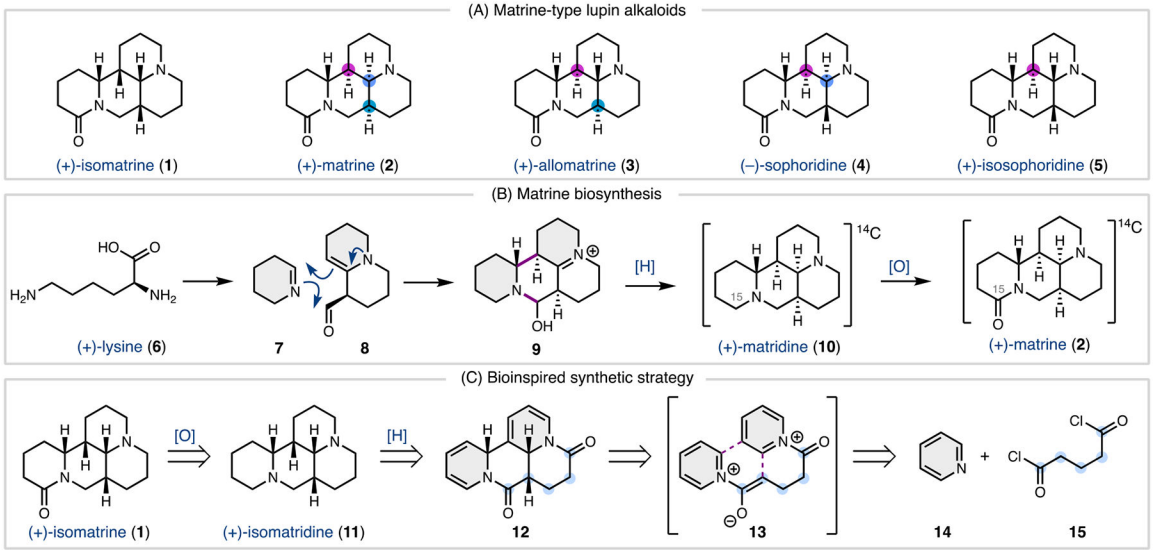


Figure 1.

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

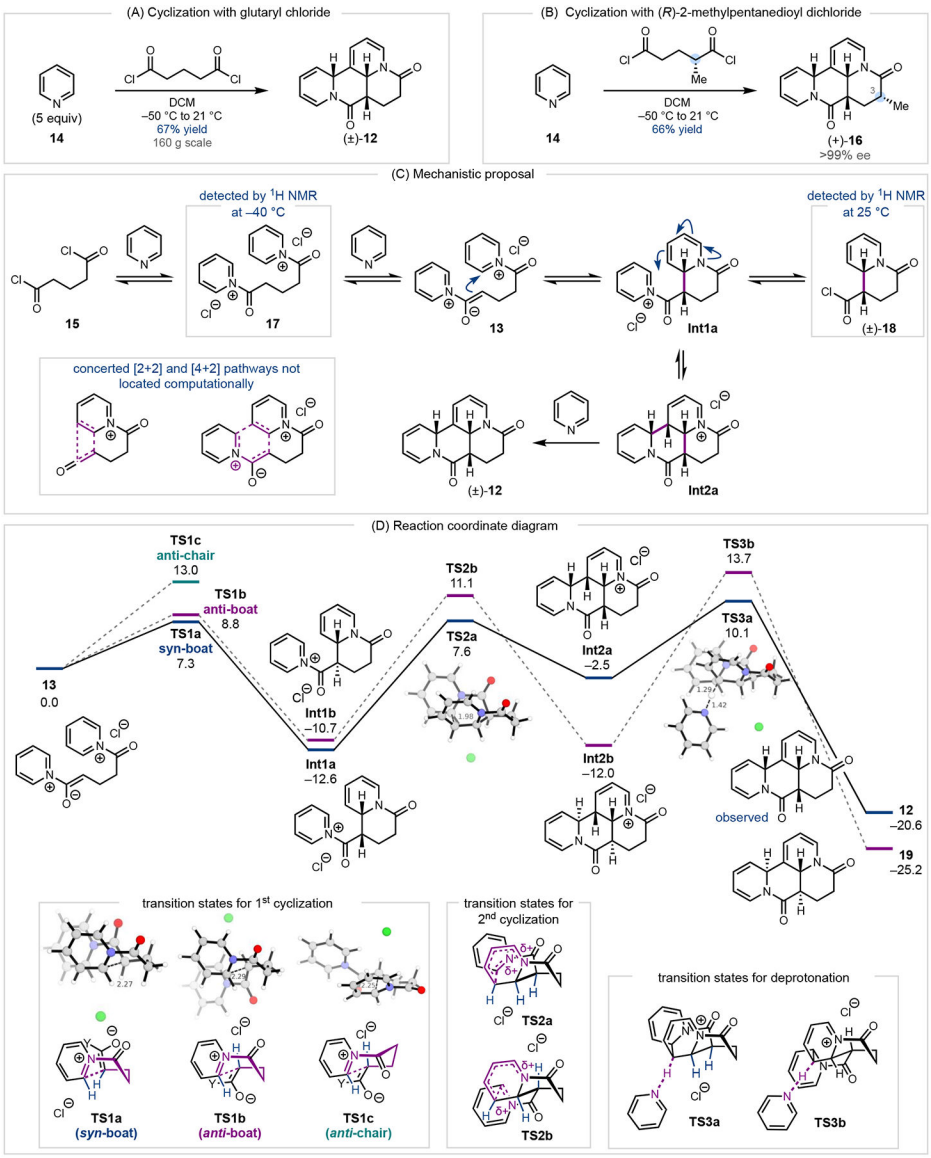


Figure 2.

(**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).

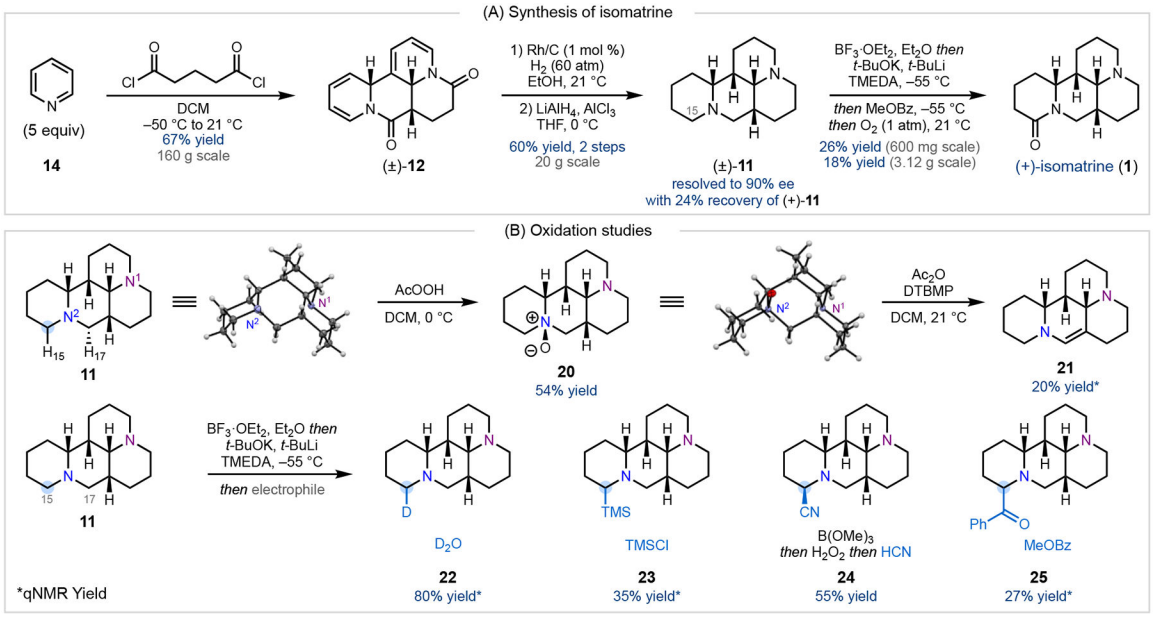
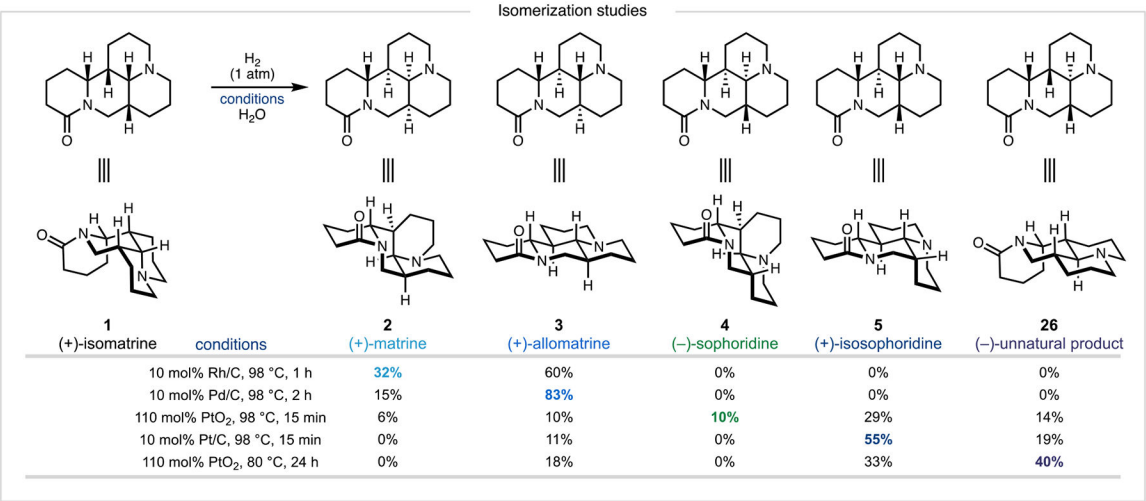


Figure 3.

(**A**) Complete total synthesis of isomatrine. (**B**) Attempted oxidation reactions.



conditions	2 (+)-matrine	3 (+)-allomatrine	4 (–)-sophoridine	5 (+)-isosophoridine	26 (–)-unnatural product
10 mol% Rh/C, 98 °C, 1 h	**32%**	60%	0%	0%	0%
10 mol% Pd/C, 98 °C, 2 h	15%	**83%**	0%	0%	0%
110 mol% PtO_2, 98 °C, 15 min	6%	10%	**10%**	29%	14%
10 mol% Pt/C, 98 °C, 15 min	0%	11%	0%	**55%**	19%
110 mol% PtO_2, 80 °C, 24 h	0%	18%	0%	33%	**40%**

Figure 4.

Isomerization of (+)-isomatrine to additional matrine-type lupin alkaloids. Highlighted values are the isolated yields of the indicated products.