Total Synthesis of Matrine Alkaloids

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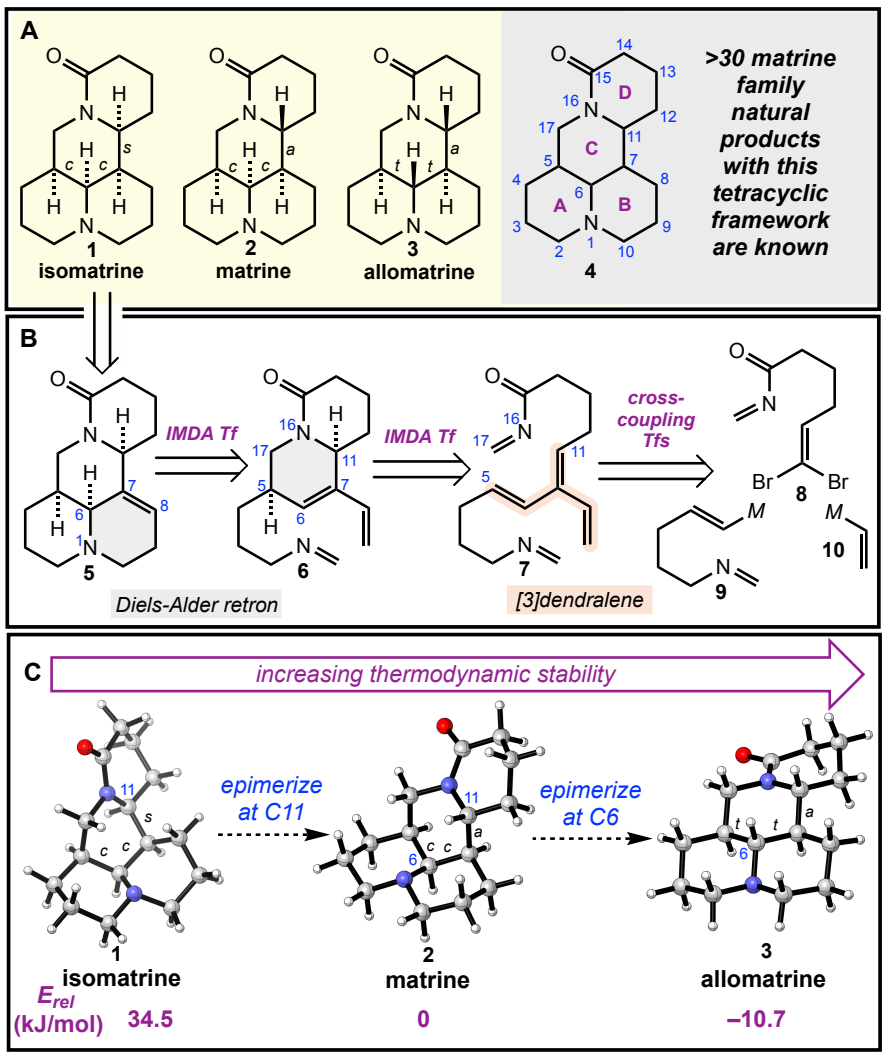
Abstract: *The total synthesis of three diastereomeric matrine natural products is reported. The eight-step synthesis commences with simple acyclic precursors, forms all four rings of the tetracyclic natural product framework and forges ten of the twenty covalent bonds of the target structure. The chemical synthesis adopts an unprecedented strategy that encompasses both transform and stereochemical attributes. A cross-conjugated triene is positioned at the core of an acyclic branched structure, which collapses to the tetracyclic natural product framework through an orchestrated sequence of two intramolecular cycloadditions. A subsequent, late-stage hydrogenation is accompanied by strain-release redox epimerizations to deliver the three natural products. Semisynthetic manipulations of matrine provide access to ten additional natural products.*

Members of the *Sophora* genus of plants are used in traditional medicine in Asia,[1,2] South America[3] and Australasia.[4] The majority of the known biologically active constituents belong to the matrine family of alkaloids (**4**, **Scheme 1A**).[1,5] These tetracyclic natural products comprise an **AB** quinolizidine bicycle linked to a **D** ring piperidone through fusion of a **C** ring piperidine. Six natural diastereomeric forms are known,[6–11] of which (*cis, cis, anti*)-matrine (**2**) is the most abundant, with (*trans, trans, anti*)-allomatrine (**3**) and (*cis, cis, syn*)-isomatrine (**1**) being 16 and 286 times less abundant, respectively.[12] Matrine (**2**) has anticancer activity[13] through proliferation inhibition and apoptosis induction of various cancer cell lines.[14] It has also been used for the clinical treatment of hepatitis B,[15] and has antiviral activity,[16,17] being identified as a candidate for COVID-19 treatment.[18] Information on the biological activity of isomatrine (**1**), allomatrine (**3**) and their derivatives is scarce, because of their low natural abundance.

There are three reported total syntheses of (±)-matrine (**2**),[19] one synthesis of (+)-allomatrine (**3**)[20] and several other syntheses and semi-syntheses of related molecules bearing the matrine tetracyclic core.[21] A preprint has also recently appeared.[22] Herein we disclose a conceptually novel and step economic synthetic approach to matrine alkaloids.[23] The approach leverages both: (a) the ability of dendralenes to rapidly generate target-relevant structural complexity (**Scheme 1B**),[24] and (b) redox isomerization of amides and amines to drive successive strain-release epimerizations in a tetracyclic framework (**Scheme 1C**).

The strategy is explained in **Scheme 1B**. The retrosynthetic introduction of unsaturation at C7=C8 of the least thermodynamically stable diastereomer (i.e. **1** ⇒ **5**) completes a B-ring hetero-Diels-Alder (HDA) retron. Next, application of a HDA transform simultaneously disconnects the C9–C10 and C6–N1 bonds, hence the A and B rings, revealing bicycle **6**. This maneuver also unveils a new C-ring hetero-Diels-Alder (HDA) retron, in which unsaturation has been transmitted to C6=C7. A second HDA transform can now be employed, disconnecting the C5–C17 and C11–N16 bonds, hence the C and D rings, deriving disubstituted [3]dendralene **7** as a synthetic precursor. Twofold C–C disconnection of the dendralene[25] unearths cross-coupling synthons **8**, **9** and **10**.



Scheme 1. (**A**) Chemical structures and ring system assignment of matrine alkaloids. (**B**) Retrosynthetic analysis of (*cis, cis, syn*)-tetracycle (**1**) for a strain release divergent synthesis of matrine type alkaloids. (**C**) Calculated (M06-2X/6-311+G(d,p)) relative energies of isomatrine (**1**), matrine (**2**) and allomatrine (**3**) in kJ/mol.

In the synthetic direction, a kinetically controlled catalytic hydrogenation would deliver elemental hydrogen to the more accessible convex face of tetracyclic alkene **5**, hence resulting in naturally occurring (*cis, cis, syn*)-isomatrine **1**, which is calculated[26] (**Scheme 1C**) to be the least thermodynamically stable matrine diastereomer. Access to (*cis, cis, anti*)-matrine **2** and (*trans, trans, anti*)-allomatrine **3**, progressively more thermodynamically stable (**Scheme 1C**) natural diastereomers, could then be envisaged by exploiting first amide then amine epimerization chemistry at C11 and C6, through reversible iminium formation.[27] Experimental evidence for such epimerizations in the matrine series can be inferred from Mandell's work[19a] and are directly evidenced by precedent from Ueno.[12] Galasso and co-workers previously identified the order of thermodynamic stability of matrine diastereomers by

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calculations at the B3LYP/(6-31G(d,p)) level of theory.[26] Our M06-2X/(6-311+G(d,p)) calculations confirm these earlier findings, hence setting the scene for late stage divergent synthesis through epimerization-induced strain release.

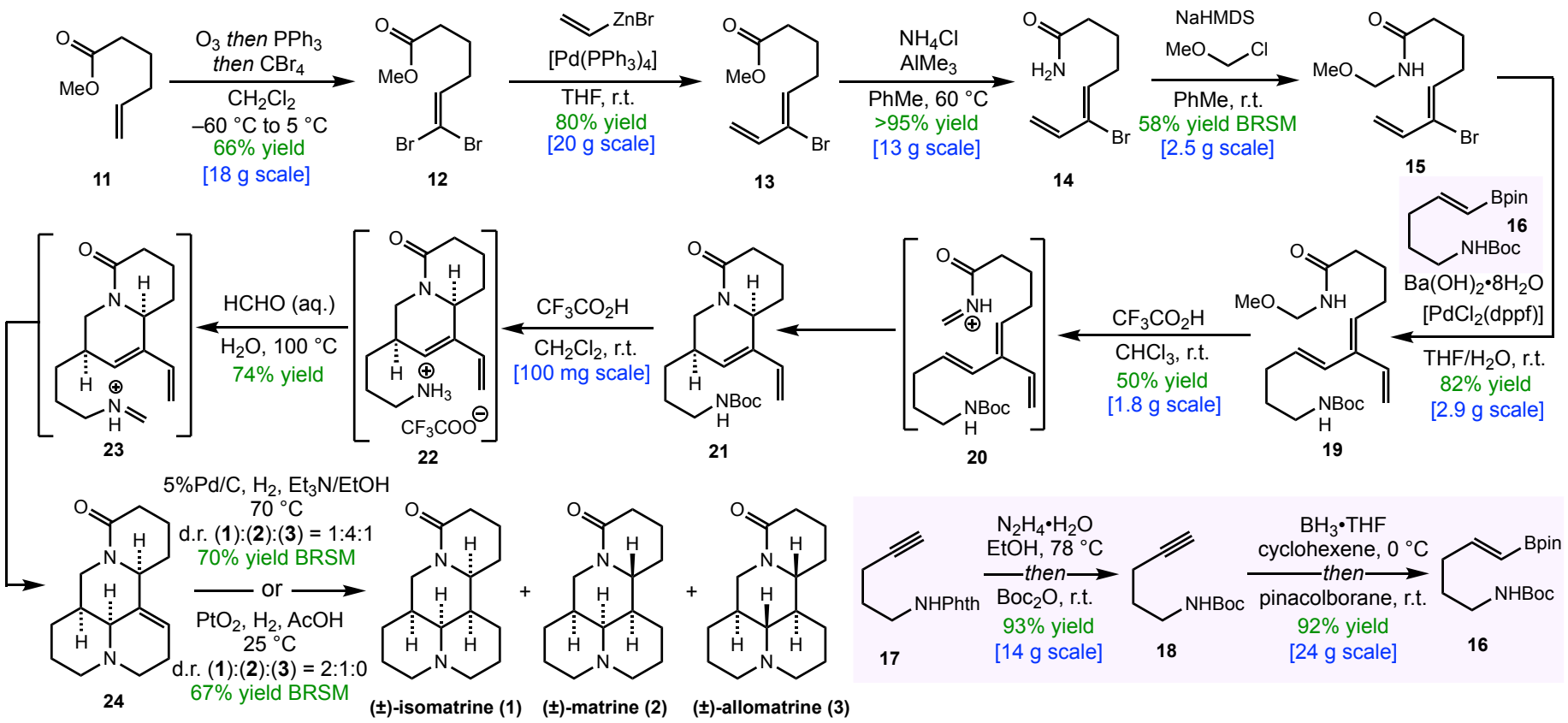
The successful implementation of this synthetic strategy in the laboratory is summarized in **Scheme 2**. The chemical synthesis required the development of new methods that are likely to be of broader significance. These innovations are described in more detail in the SI. The translation of strategy (**Scheme 1B**) into synthetic reality (**Scheme 2**) required iminium functionalities as dienophiles, the lability of which mandated their *in situ* generation.

The total synthesis commenced with methyl hex-5-enoate **11**, which was converted into its 1,1-dibromoalkene derivative **12** through a scalable, one step ozonolysis/olefination transformation. Following the breakdown of the ozonide with excess PPh_3, addition of CBr_4 brings about a Ramirez dibromolefination.[28] The solvent and reagent compatibility of the two reactions makes for an uncommonly smooth telescoped procedure. The next four steps address the stereoselective construction of the substituted [3]dendralene core. This sequence is punctuated by elaboration of the ester into the functionality needed for *N*-acyliminium generation. First, a selective, $[Pd(PPh_3)_4]$-catalyzed single Negishi cross-coupling[25,29] of dibromoalkene **12** with vinylzinc bromide gave *Z*-bromodiene **13**. (Suzuki-Miyaura and Stille cross-couplings were inferior.[30]) Switching to the other end of the chain, the methyl ester **13** was elaborated into the corresponding *N*-methoxymethylamide **15** over two steps via the primary amide **14**. (Incorporation of the MOM group is best achieved through incomplete conversion, otherwise significant quantities of the dialkylation product are formed.) Next, a Suzuki-Miyaura sp^2–sp^2 cross-coupling of *Z*-bromodiene **15** with *E*-alkenylboronic ester **16** (generated on scale through a convenient 2 step synthesis[31-32] from **17**, via **18**) gave the desired [3]dendralene **19**, in which the C=C geometry of the nucleophilic partner has been retained but that of the electrophilic partner has been inverted (dr = 6:1). This process, which was guided by our experience with related Negishi methodology,[25,33] is to our knowledge the first example of a stereoinvertive Suzuki-Miyaura cross-coupling.

With the acyclic dendralenic precursor in hand, the two-step assembly of the tetracyclic framework could commence. The first of the two intramolecular HDA reactions was triggered by exposure of MOM-amide **19** to dilute TFA, generating putative *N*-acyliminum species **20**,[34] which cyclized rapidly at ambient temperature to *cis*-bicycle **21**. Reported intramolecular cycloadditions of this type deploy pyrolytic methods for *N*-acylimine generation[35] which required long reaction times and gave lower yields of adduct **21**. We therefore invented a milder and operationally simpler approach, which leverages the enhanced reactivity of the LUMO-lowered *N*-acyliminum dienophile.

Removal of the *N*-Boc protecting group from the side chain of bicycle **21** by exposure to TFA gave ammonium salt **22**, which was heated in a sealed tube with degassed aqueous formaldehyde to deliver tetracycle **24** as a single diastereomer. This second intramolecular HDA reaction is inspired by work from Grieco,[36] and presumably involves *in situ* generation of iminium dienophile **23**, which is constrained to engage with the top face of the pendant semicyclic diene.

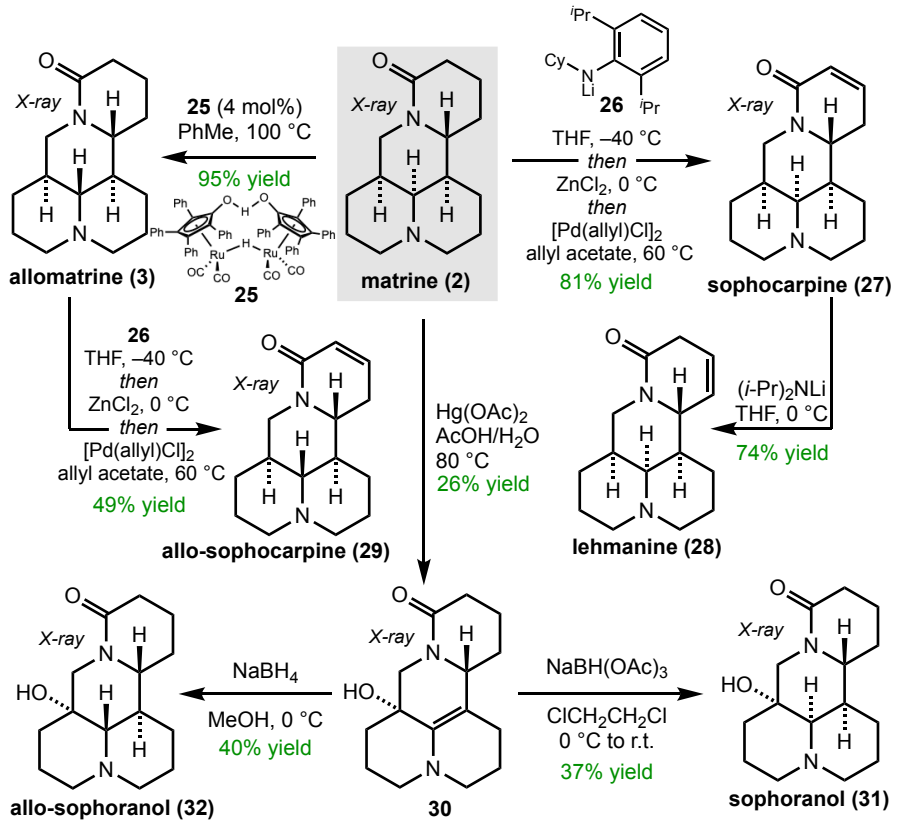
Catalytic hydrogenation of the sensitive, trisubstituted allylic amine **24** gave mixtures of natural products. With 5% Pd/C, a mixture of isomatrine (**1**), matrine (**2**) and allomatrine (**3**) was obtained. Matrine was isolated as the dominant product under the conditions given in **Scheme 2** but the product ratio varies with reaction conditions. With PtO_2 as pre-catalyst, a 2:1 mixture of isomatine and matrine is generated. As explained above, isomatrine (**1**) is the likely kinetic product of hydrogenation. Subsequent Pd/Pt-catalyzed isomerizations then proceed at the two epimerizable positions through dehydrogenation/hydrogenation sequences involving (*N*-acyl) iminium intermediates.[37]



Scheme 2. Total synthesis of isomatrine (**1**), matrine (**2**) and allomatrine (**3**).

In support of the original hypothesis (**Scheme 1C**), exposure of isolated synthetic isomatrine to the hydrogenation reaction conditions gave mixtures of matrine and allomatrine. Similarly, matrine was isomerized to allomatrine.

Extensive manipulations of (commercially available) matrine are provided in the SI: these transformations can, in principle, be applied to material accessed through total synthesis. Selected, original conversions are depicted in **Scheme 3**, with others provided in the SI. Shvo's catalyst **25**[38] is the preferred method to bring about the isomerization of matrine (**2**) into allomatrine (**3**), since it does so cleanly and reproducibly, presumably through a similar mechanism to Pd or Pt hydrogenation catalysts.[39] Newhouse dehydrogenation[40] of the 2-piperidone rings of both matrine and allomatrine furnish sophocarpine **27**[41] and its *allo*-diastereomer **29** respectively. Kinetic α-protonation of the lithium dienolate derived from sophocarpine yields lehmanine **28**. The known oxidation of matrine **2** to 5-hydroxy-enamine **30**[42] provides an opportunity to access sophoranol **31** and its *allo*-congener **32** by exploiting substrate-directed diastereoselective hydride transfers, either with or without reactant-reagent hydroxyl coordination.



Scheme 3. Conversion of matrine into six other alkaloids.

In summary, a step economic total synthesis of matrine alkaloids has been devised. This new approach forms all four rings of the natural product commencing from simple acyclic feedstocks. Only two reactions are deployed for the synthesis of the tetracycle, with each intramolecular Diels-Alder reaction generating two rings and two covalent bonds of the target structure. The least thermodynamically stable of three diastereomeric natural products is first formed, then redox epimerizations of amidomethine and aminomethine stereocenters grants access to two more thermodynamically stable targets.

The two core strategic contributions of this work are the diene-transmissive twofold intramolecular Diels-Alder sequence and the redox epimerization-driven late-stage target diversification. Both represent powerful innovations that will see wider application. This work also introduces several new synthetic technologies, including: (a) the telescoped ozonolysis/ Ramirez sequence as an olefin cross metathesis equivalent; (b) the stereoinvertive Suzuki-Miyaura coupling for diastereoselective [3]dendralene synthesis; and (c) *N*-methoxymethylamides for *N*-acyliminium generation and reaction as a Diels-Alder dienophile. This work also describes the first twofold intramolecular Diels-Alder sequence of a dendralene, and the first Diels-Alder reactions of dendralenes with imine dienophiles.

Medicinal chemistry investigations into matrine alkaloids will be advanced by access to compounds with the widest possible structural variation. Some analogues are best prepared starting from the isolated natural product (**Scheme 3**) whereas for others, "ground up" construction through total synthesis (**Scheme 2**) will be the better choice. Within the latter domain, total syntheses that combine step economy with structural diversity are particularly prominent. Drawing upon the vast literature of the Diels-Alder reaction, work is underway to build upon these findings to access matrine analogues with the widest possible structural variety.

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Keywords: synthesis design • total synthesis • dendralene • diastereoselectivity • Diels-Alder

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