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Total Synthesis of the Tetracyclic Lupin Alkaloid (+)-Allomatrine

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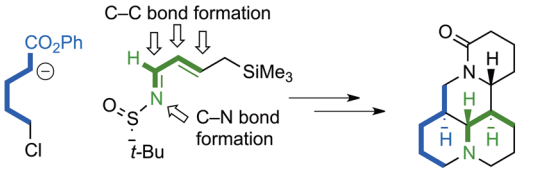
ABSTRACT



(+)-Allomatrine (1) has been synthesized using an imino-aldol reaction and *N*-acyliminium cyclization as key steps. Strategically, use of the *tert*-butylsulfinimine derivative of (*E*)-4-(trimethylsilyl)but-2-enal enabled the staged formation of three C−C bonds, a C−N bond, and the four stereogenic centers within the target.

(+)-Allomatrine (**1**) is a tetracyclic lupin alkaloid of the matrine structural class (Figure 1) first reported in 1952 as a product of chemical epimerization of (+)-matrine (**2**) at C6.[1−3] While (+)-matrine (**2**) was obtained from the root bark of *Sophora flavescens* by Nagai as early as 1889,[4] (+)-allomatrine has only recently been reported as a chemical component from the *Sophora* species.[5] Curiously, Orechoff isolated an alkaloid, (−)-leontine (**3**),[6] from *Leontice eversmanni* Bge. in the 1930s that was later shown to be the enantiomer of (+)-allomatrine (**1**).[7] Matrine (**2**) and its related alkaloids exhibit a variety of interesting biological activities such as anticancer, promotion of hair growth, and antiviral activity.[5b,8] Notably, (+)-allomatrine (**1**) mediates antinociception in mice through selective activity at the κ-opioid receptor while being structurally distinct from known pharmacological agents.[9]

Three total syntheses of racemic matrine have been accomplished with varying levels of diastereocontrol,[10−12] and a mixture enriched in (±)-allomatrine ((±)-leontine) was obtained by Mandell and co-workers from Pd-catalyzed

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(6) Orechoff, A.; Konowalowa, R. *Arch. Pharm*. **1932**, *270*, 329–334.

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(8) For examples, see: (a) Ma, L. D.; Wen, S. H.; Zhan, Y.; He, Y. J.; Uu, X. S.; Jiang, J. K. *Planta Med*. **2008**, *74*, 245–251. (b) Roh, S.-S.; Kim, C. D.; Lee, M.-H.; Hwang, S.-L.; Rang, M.-J.; Yoon, Y.-K. *Derm. Sci*. **2002**, *30*, 43–49. (c) Gao, L. M.; Han, Y. X.; Wang, Y. P.; Li, Y. H.; Shan, Y. Q.; Li, X.; Peng, Z. G.; Bi, C. W.; Zhang, T. A.; Du, N. N.; Jiang, J. D.; Song, D. Q. *J. Med. Chem*. **2011**, *54*, 869–876.

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(10) Mandell, L.; Singh, K. P.; Gresham, J. T.; Freeman, W. J. *J. Am. Chem. Soc*. **1965**, *87*, 5234–5236.

(11) Chen, J.; Browne, L. J.; Gonnela, N. C. *J. Chem. Soc., Chem. Commun*. **1986**, 905–907.

(12) Boiteau, L.; Boivin, J.; Liard, A.; Quiclet-Sire, B.; Zard, S. Z. *Angew. Chem., Int. Ed*. **1998**, *37*, 1128–1131.

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isomerization of synthetic (±)-matrine.[10] Okuda et al. also reported a semisynthesis of (+)-allomatrine from octadehydromatrine,[13] which required optical resolution of an intermediate. We are not aware of any stereocontrolled total syntheses of allomatrine, although Zard and co-workers obtained a tetracyclic intermediate with the required relative stereochemistry as a minor diastereoisomer during their total synthesis of (±)-matrine using a xanthate-mediated radical cascade approach.[12]

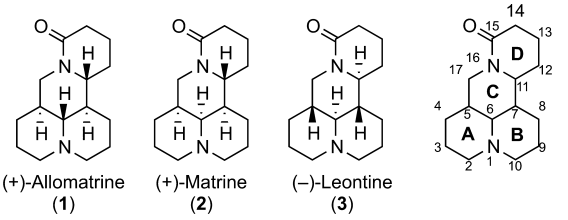
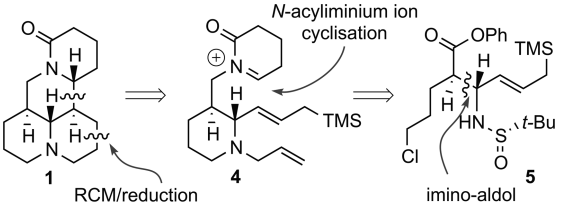


Figure 1. Tetracyclic alkaloids of the matrine family.

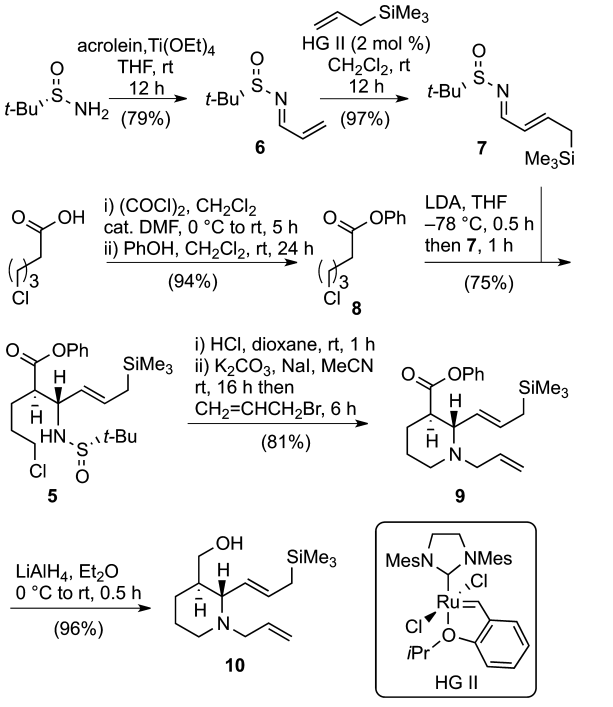
As a prelude to the enantiocontrolled synthesis of tetracyclic lupin alkaloids containing a quinolizidine core, we recently described a short stereoselective synthesis of epilupinine[14] using an imino-aldol reaction of a *tert*-butylsulfinimine as the key step.[15,16] The high level of *syn* diastereoselectivity attained by using the imino-aldol was considered to provide an excellent platform for a stereocontrolled synthesis of other quinolizidine-containing lupin alkaloids.[3] Here we describe a stereocontrolled synthesis of (+)-allomatrine (**1**) using an imino-aldol reaction and *N*-acyliminium ion cyclization as key steps.

Scheme 1. Synthetic Plan for (+)-Allomatrine (**1**)



Analysis of the tetracyclic framework of allomatrine (**1**) suggested that the C7–C11 bond could be formed through addition of an *N*-acyliminium ion to a sufficiently reactive pendant alkene, such as an allylsilane (Scheme 1).[17,18] Closure of the final B ring of the tetracycle would then proceed by using RCM.[19] The key allylsilane functionality could be introduced through an imino-aldol reaction of the enolate obtained from phenyl 5-chloropentanoate and the *tert*-butylsulfinimine of (*E*)-4-(trimethylsilyl)but-2-enal,[14] where the ester group would later provide suitable functionality to append the C/D ring precursor to the *N*-acyliminium ion.

Scheme 2. Imino-aldol Reaction and Subsequent Synthesis of *N*-Allylated Piperidine **10**



First, a convenient access to sulfinimine **7** was achieved in 77% yield over two steps through formation of the *tert*-butylsufinimine **6** of acrolein followed by cross-metathesis with allyltrimethylsilane (Scheme 2).[20] The alternative order of steps gave inferior yields and the inconvenience of a rather volatile and sensitive aldehyde intermediate. The lithium enolate of phenyl 5-chlorovalerate (**8**) underwent

(13) Okuda, S.; Yoshimoto, M.; Tsuda, K. *Chem. Pharm. Bull.* **1966**, *14*, 275–279.

(14) Cutter, A. C.; Miller, I. R.; Keily, J. F.; Bellingham, R. K.; Light, M. E.; Brown, R. C. D. *Org. Lett.* **2011**, *13*, 3988–3991.

(15) For examples of imino-aldol reactions of sulfinimines, see: (a) Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **2002**, *67*, 7819–7832. (b) Davis, F. A.; Reddy, R. T.; Reddy, R. E. *J. Org. Chem.* **1992**, *57*, 6387–6389. (c) Davis, F. A.; Song, M. *Org. Lett.* **2007**, *9*, 2413–2416.

(16) For reviews of sulfinimines in synthesis, see: (a) Zhou, P.; Chen, B.-C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003–8030. (b) Morton, D.; Stockman, R. A. *Tetrahedron* **2006**, *62*, 8869–8905. (c) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600–3740.

(17) For reviews of *N*-acyliminium ion chemistry, see: (a) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817–3856. (b) Marson, C. M. *ARKIVOC* **2001**, *(i)*, 1–16. (c) Maryanoff, B. E.; Zhang, H. C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431–1628. (d) Gonzalez-Lopez, M.; Shaw, J. T. *Chem. Rev.* **2009**, *109*, 164–189. (e) Yazici, A.; Pyne, S. G. *Synthesis* **2009**, 513–541.

(18) For early examples of allylsilane addition to *N*-acyliminium ions. Intermolecular: (a) Hart, D. J.; Tsai, Y. M. *Tetrahedron Lett.* **1981**, *22*, 1567–1570. (b) Kraus, G. A.; Neuenschwander, K. *J. Chem. Soc., Chem. Commun.* **1982**, 134–135. (c) Aratani, M.; Sawada, K.; Hashimoto, M. *Tetrahedron Lett.* **1982**, *23*, 3921–3924. Intramolecular: (d) Hiemstra, H.; Sno, M. H. A. M.; Vijin, R. J.; Speckamp, W. N. *J. Org. Chem.* **1985**, *50*, 4014–4020. For further examples, see ref 17.

(19) van den Broek, S. A. M. W.; Meeuwissen, S. A.; van Delft, F. L.; Rutjes, F. P. J. T. In *Metathesis in Natural Product Synthesis: Strategies, Substrates and Catalysts*; Cossy, J., Arseniyadis, S., Meyer, C., Eds.; Wiley–VCH Verlag: Weinheim, 2010; pp 45–85.

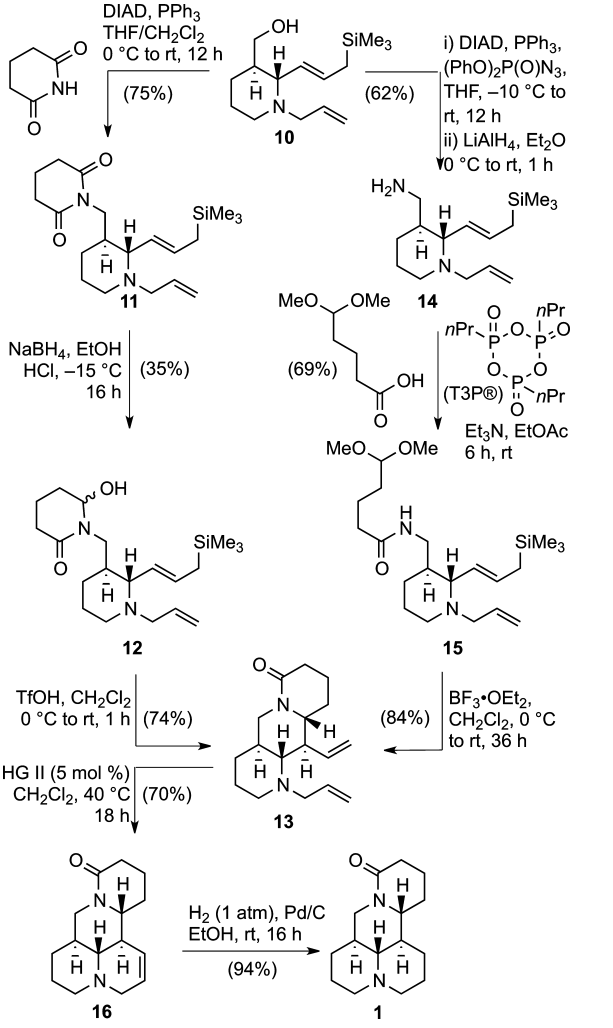
(20) (a) Raghavan, S.; Krishnaiah, V.; Sridhar, B. *J. Org. Chem.* **2010**, *75*, 498–501. (b) BouzBouz, S.; De Lemos, E.; Cossy, J. *Adv. Synth. Catal.* **2002**, *344*, 627–630.

addition to sulfinimine **7** with near-perfect diastereoselectivity (only one diastereoisomer was observed by ^{1}H NMR); a single *syn* adduct **5** was isolated in 75% yield.[21] The stereochemical assignment was confirmed in subsequent derivatives (see below) and is consistent with a cyclic chairlike transition-state model previously described.[14,15] This highly functionalized imino-aldol **5** was subjected to a one-pot deprotection, cyclization, and allylation sequence furnishing the alkylated piperidine **9** in 81% yield over the three steps. A single equivalent of HCl in dioxane was employed in the deprotection of the sulfinyl group, with preservation of the allylsilane functionality. Subsequent $LiAlH_4$ reduction of the phenyl ester yielded primary alcohol **10**, in preparation for attachment of the C/D-ring precursor.

In the first approach to closing the C-ring, the primary alcohol **10** was coupled with glutarimide under Mitsunobu conditions to secure the bicyclic derivative **11** in 75% yield (Scheme 3). The *N*-acyliminium precursor, aminal **12**, was accessed by reduction of glutarimide **11** with $NaBH_4$/HCl at −15 °C.[22] Although this reduction proved to be capricious, it allowed the cyclization to be explored. Pleasingly, treatment of **12** with TfOH afforded the desired tricyclic diene **13** in 74% yield as a predominant diastereoisomer. The stereochemical course of the cyclization can be accounted for by a kinetically controlled reaction proceeding through a *trans*-decalin chairlike arrangement in the transition state (Figure 2).[18d] Spectroscopic evidence to support the stereochemical assignment of tricyclic diene **13** came from ^{1}H NMR analysis and was later corroborated with X-ray structural data for the tetracycle **16** formed after successful RCM (see below).

Attempts to improve the efficiency of the reduction of glutarimide **11** under a variety of conditions met with limited success, typically yielding *N*-acyliminium precursor **12** with low conversion or as a complex mixture.[23] Therefore, 5,5-dimethoxypentanamide derivative **15** was targeted as an alternative cyclization precursor (Scheme 3).[24] The required primary amine **14** was obtained by conversion of the alcohol **10** to the azide followed by azide reduction using $LiAlH_4$. 5,5-Dimethoxypentanoic acid[25] was then coupled with primary amine **14** in 69% yield using the cyclic triphosphate coupling reagent T3P (propylphosphonic anhydride). Treatment of acetal **15** with an excess of $BF_3 \cdot OEt_2$ initiated a sequence of reactions culminating in *N*-acyliminium ion formation and ring-closure to produce tricyclic diene **13** in 84% yield, effectively doubling the overall yield for the transformation of **10** to diene **13**.

Scheme 3. *N*-Acyliminium Cyclization and Total Synthesis of (+)-Allomatrine (**1**)



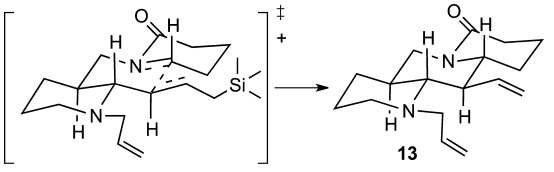


Figure 2. Proposed chairlike TS arrangement in the *N*-acyliminium cyclization reaction.

The total synthesis of (+)-allomatrine (**1**) was completed by inducing RCM of the diene **13** by exposure to the Hoveyda−Grubbs II (HG II) catalyst in CH_2Cl_2, followed by hydrogenation of 8,9-dehydroallomatrine (**16**) over Pd/C. Gratifyingly, 8,9-dehydroallomatrine (**16**) afforded crystals suitable for structural determination by X-ray

(21) We have observed improved diastereoselectivities for phenyl esters compared to the corresponding methyl esters in imino-aldol reactions with *tert*-butylsulfinimines (see ref 14).

(22) Hubert, J. C.; Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437–1441.

(23) (a) Judd, W. R.; Ban, S.; Aubé, J. *J. Am. Chem. Soc.* **2006**, *128*, 13736–13741. (b) Hande, S. M.; Nakajima, M.; Kamisaki, H.; Tsukano, C.; Takemoto, Y. *Org. Lett.* **2011**, *13*, 1828–1831.

(24) (a) Hart, D. J.; Hong, W. P.; Hsu, L. Y. *J. Org. Chem.* **1987**, *52*, 4665–4673. (b) Hart, D. J.; Leroy, V. *Tetrahedron* **1995**, *51*, 5757–5770. (c) Ikeda, S.; Shibuya, M.; Kanoh, N.; Iwabuchi, Y. *Org. Lett.* **2009**, *11*, 1833–1836.

(25) (a) Nakamura, Y.; Shin, C. *Chem. Lett.* **1991**, *20*, 1953–1956. (b) Chen, J.; Chen, J.; Xie, Y.; Zhang, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 1024–1027.

(26) Light, M. E.; Watkin, S. V.; Brown, R. C. D. Private communication to C.S.D. 2013, CCDC 948924.

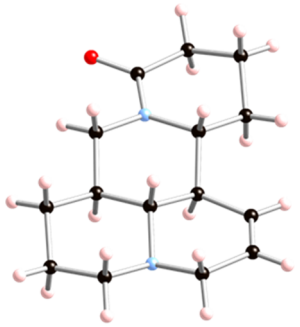


Figure 3. X-ray structure of 8,9-dehydroallomatrine (**16**).

diffraction (Figure 3),[26] thus confirming the stereochemical assignment of the product **13** from the *N*-acyliminium cyclization. In addition, spectroscopic and physical data for synthetic (+)-allomatrine (**1**) were consistent with those previously reported.[1,27]

(27) (a) Bohlmann, F.; Zeisberg, R. *Chem. Ber*. **1975**, *108*, 1043–1051. (b) Galasso, V.; Asaro, F.; Berti, F.; Pergolese, B.; Kovac, B.; Pichierri, F. *Chem. Phys*. **2006**, *330*, 457–468. (c) Okuda, S.; Yoshimoto, M.; Tsuda, K. *Chem. Pharm. Bull*. **1966**, *14*, 275–279. (d) Bohlmann, F.; Schumann, D. *Tetrahedron Lett*. **1965**, 2435–2440.

In conclusion, a highly diastereoselective synthesis of (+)-allomatrine has been described (13% overall yield, 13 steps) involving an imino-aldol reaction and an intramolecular addition of an allylsilane to an *N*-acyliminium as key steps. The introduction of the *tert*-butylsulfinimine derivative of (*E*)-4-(trimethylsilyl)but-2-enal (**7**) is noteworthy as this functional group-rich fragment is ultimately responsible for the staged formation of 3 C−C bonds, a C−N bond, and the four stereogenic centers within the natural product and may be applied in the synthesis of other polycyclic amines.

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Supporting Information Available. Experimental procedures, characterization data, and copies of ^{1}H NMR and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.