ORGANIC LETTERS

2013
Vol. 15, No. 17
4596–4599

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

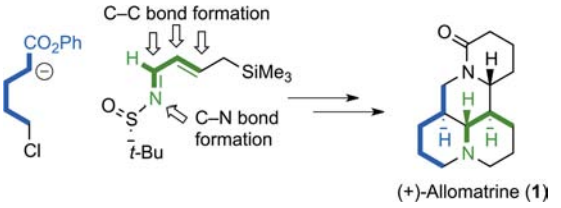
Samuel V. Watkin,[†] Nicholas P. Camp,[‡] and Richard C. D. Brown*,[†]

Department of Chemistry, The University of Southampton, Highfield, Southampton SO17 1BJ, U.K., and Eli Lilly Research Centre U.K., Erl Wood Manor, Windlesham GU20 6PH, U.K.

rcb1@soton.ac.uk

Received August 2, 2013

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

[†] The University of Southampton.
[‡] Eli Lilly Research Centre U.K.

(1) Isomerization of (+)-matrine to (+)-allomatrine: Ochiai, E.; Okuda, S.; Minato, H. *Yakugaku Zasshi*. **1952**, *72*, 781–784.

(2) Structural and stereochemical elucidation: (a) Bohlmann, F.; Weise, W.; Rahtz, D.; Arndt, C. *Chem. Ber*. **1958**, *91*, 2176–2189. (b) Tsuda, K.; Mishima, H. *J. Org. Chem*. **1958**, *23*, 1179–1183. X-ray structure: (c) Ibragimov, B. T.; Tishenko, G. N.; Kushmuradov, Y. K.; Aripov, T. F.; Sadikov, A. S. *Khim. Prir. Soedin*. **1979**, 416–417. Absolute stereochemistry (inferred from 11*R* configuration in (+)-matrine): (d) Okuda, S.; Yoshimoto, M.; Tsuda, K.; Utzugi, N. *Chem. Pharm. Bull*. **1966**, *14*, 314–318.

(3) For a review of lupin alkaloids, see: (a) Ohmiya, S.; Saito, K.; Murakoshi, I. In *The Alkaloids: Chemistry and Pharmacology*; Cordell, G. A., Ed.; Academic Press: New York, 1995; Vol. 47, pp 1−114. For the most recent in a series of reviews of quinolizidine alkaloids, see: (b) Michael, J. P. *Nat. Prod. Rep*. **2008**, *25*, 139–165.

(4) Nagai, N. *Yakugaku Zasshi* **1889**, *9*, 54–87.

(5) Allomatrine is described as a natural product in previous publications; however, these papers give reference to isomerized matrine or personal communications. For isolation of (+)-allomatrine *Sophora* species, see: (a) Xiao, P.; Li, J.; Kubo, H.; Saito, K.; Murakoshi, I.; Ohmiya, S. *Chem. Pharm. Bull*. **1996**, *44*, 1951–1953. (b) Ding, P.-L.; Liao, Z.-X.; Huang, H.; Zhou, P.; Chen, D.-F. *Bioorg. Med. Chem. Lett*. **2006**, *16*, 1231–1235. (c) Liu, X.-J.; Cao, M.-A.; Li, W.-H.; Shen, C.-S.; Yan, S.-Q.; Yuan, C.-S. *Fitoterapia* **2010**, *81*, 524–527.

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

(7) Rulko, F.; Proskurnina, N. F. *Zh. Obshch. Khim*. **1961**, *31*, 308–313.

(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.

(9) Higashiyama, K.; Takeuchi, Y.; Yamauchi, T.; Imai, S.; Kamei, J.; Yajima, Y.; Narita, M.; Suzuki, T. *Biol. Pharm. Bull*. **2005**, *28*, 845–848.

(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.

10.1021/ol402198n
Published on Web 08/27/2013

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]

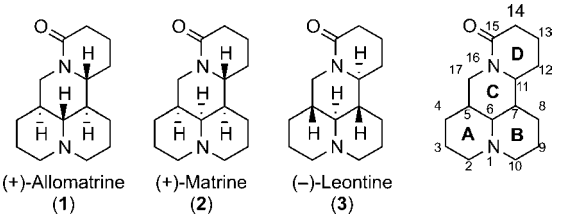
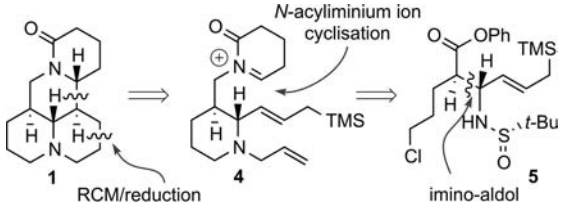


Figure 1. Tetracyclic alkaloids of the matrine family.

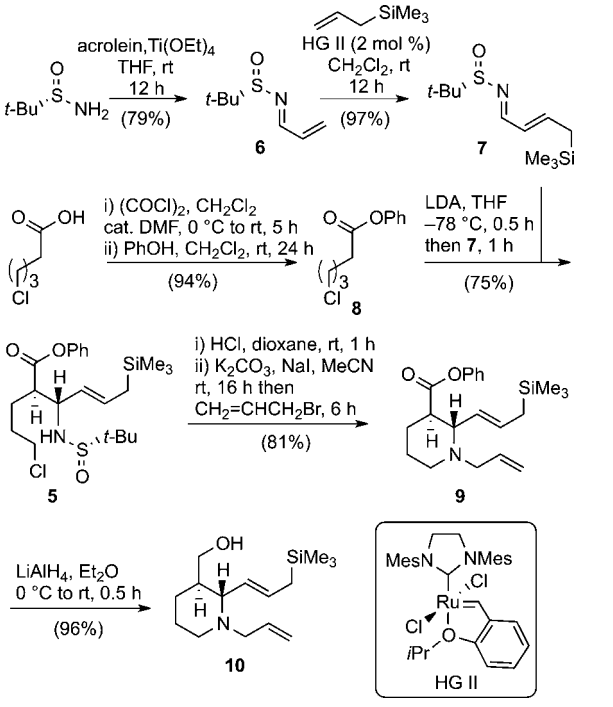
As a prelude to the enantiocontrolled synthesis of tetracyclic lupin alkaloids containing a quinolizidine core, we recently described a short stereoselective synthesis of epilupinine[14] using an imino-aldol reaction of a *tert*-butylsulfinimine as the key step.[15,16] The high level of *syn* diastereoselectivity 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.

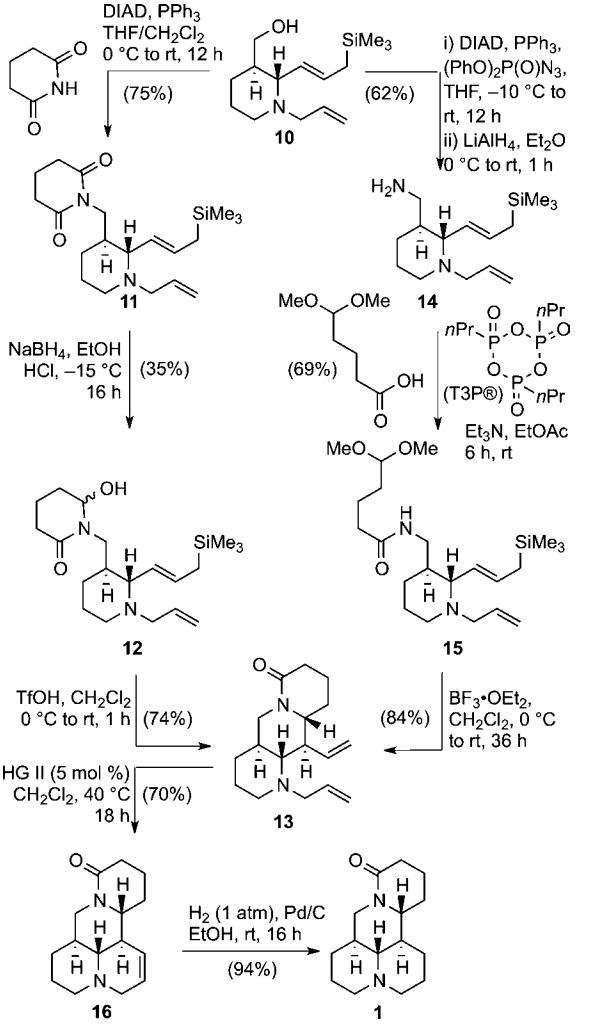
(20) (a) Raghavan, S.; Krishnaiah, V.; Sridhar, B. *J. Org. Chem.* **2010**, *75*, 498–501. (b) BouzBouz, S.; De Lemos, E.; Cossy, J. *Adv. Synth. Catal.* **2002**, *344*, 627–630.

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**)



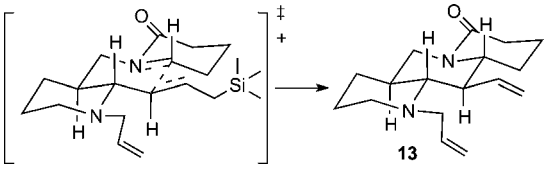


Figure 2. Proposed chairlike TS arrangement in the *N*-acyliminium cyclization reaction.

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.

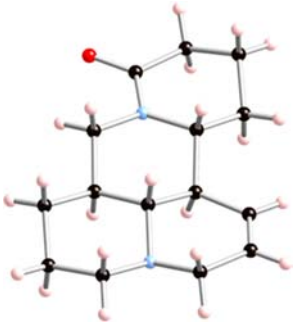


Figure 3. X-ray structure of 8,9-dehydroallomatrine (**16**).

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.

Acknowledgment. We acknowledge Eli Lilly, EPSRC, and the European Regional Development Fund (ERDF, ISCE-Chem, INTERREG IVa program 4061) for support.

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.