Aloperine: Stereocontrolled Synthesis of Two Stereoisomers and Determination of Absolute Configuration

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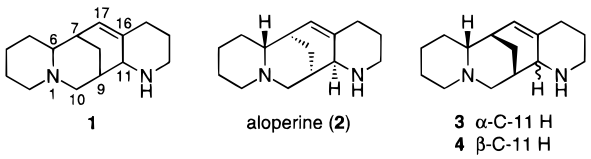
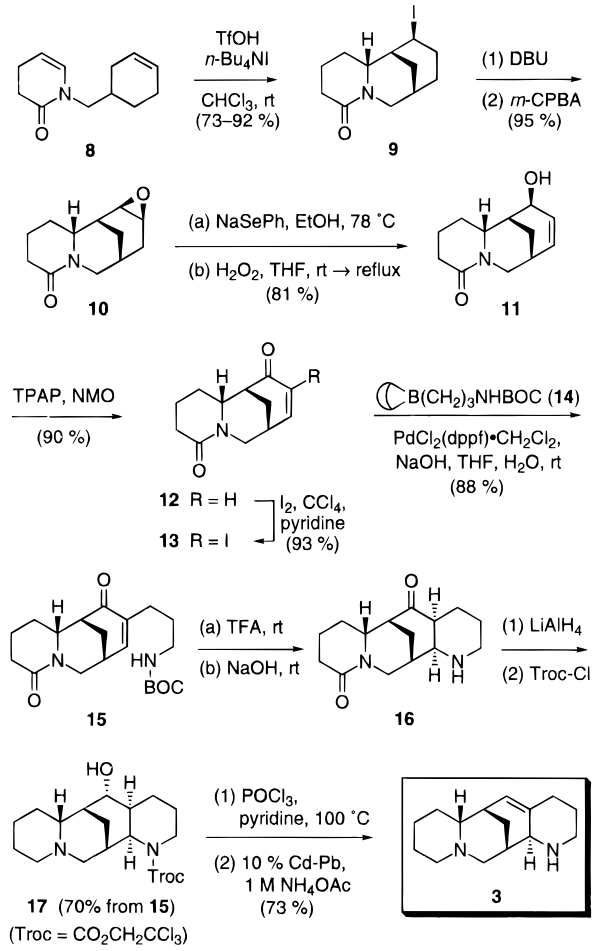
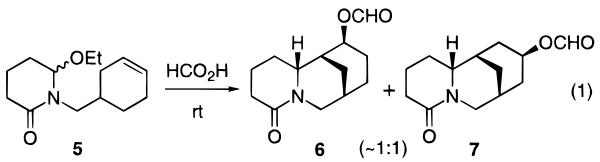
Aloperine, the parent member of a rare family of C_{15} *Lupine* alkaloids, was first reported in 1935 as a minor component of the seeds and leaves of *Sophora alopecuroides* L.[1,2] The related plant *Sophorae tonkinensis radix* is used effectively by doctors of traditional Chinese medicine in the treatment of inflammatory disorders.[3] Recent pharmacological investigations indicate that aloperine displays useful cardiovascular,[4,5] antiinflammatory, and antiallergic activities.[6] On the basis of chemical degradation, low-field NMR, and mass spectrometric data, structure **1** was formulated for aloperine in 1975.[7] Prompted by the promising medicinal activities of aloperine and the opportunity to further explore the participation of nucleophiles in Mannich cyclizations,[8] we recently initiated a program to synthesize the four diastereomers of **1**.[9] Herein we report establishment of **2** as the stereochemistry of natural aloperine and total syntheses of aloperine stereoisomers **3** and **4**.



Our approach to aloperine stereoisomers having a cis relationship of the angular methine hydrogen H_6 and the one-carbon bridge was based on seminal studies by Speckamp, who showed that the bridged azatricyclic formates **6** and **7** were formed in high yield by cyclization of α-ethoxy lactam **5** in formic acid (eq 1).[10] However, this mixture of formate regioisomers, which results from unusually fast 1,2-hydride migrations of the intermediate bicyclo[3.3.1]nonyl cation, is not a practical starting point for regiocontrolled elaboration of the additional piperidine ring of **1**. Our recent demonstration of the kinetic participation of iodide in iminium ion−alkyne cyclizations suggested that the presence of this strong nucleophile might prevent the undesired hydride migration.[8a]

Scheme 1





Our studies began with the ene lactam **8**,[10] which was conveniently prepared on a multigram scale from commercially available (±)-3-cyclohexene-1-methanol (Scheme 1).[11] After some experimentation, we found that exposure of a chloroform solution of **8** and excess tetrabutylammonium iodide to 2 equiv of TfOH at rt provided a single tricyclic iodide **9** (mp 145−145.5 °C), which was isolated in 73−92% yield after purification by chromatography and crystallization.[12] As a prelude to elaboration of the piperidine ring, this intermediate was converted to α-iodo enone **13** as depicted in Scheme 1. Iodide **9** was first dehydrohalogenated with DBU, and the resulting alkene was exposed to *m*-CPBA to provide a single epoxide **10**

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(8) For recent studies of the participation of nucleophiles in Mannich cyclizations of alkynes, see, *inter alia*: (a) Overman, L. E.; Sharp, M. J. *J. Am. Chem. Soc.* **1988**, *110*, 612. (b) Lin, N.-H.; Overman, L. E.; Rabinowitz, M. H.; Robinson, L. A.; Sharp, M. J.; Zablocki, J. *J. Am. Chem. Soc.* **1996**, *118*, 9062. (c) Caderas, C.; Lett, R.; Overman, L. E.; Rabinowitz, M. H.; Robinson, L. A.; Sharp, M. J.; Zablocki, J. *J. Am. Chem. Soc.* **1996**, *118*, 9073.
(9) There have been no reports of synthetic approaches to the aloperine alkaloids. For pioneering syntheses of related C_{20} *Ormosia* alkaloids, see: (a) Liu, H.-J.; Valenta, Z.; Wilson, J. S.; Yu, T. T.-J. *Can. J. Chem.* **1969**, *47*, 509. (b) Liu, H.-J.; Valenta, Z.; Yu, T. T.-J. *Chem. Commun.* **1970**, 1116. (c) Liu, H.-J.; Sato, Y.; Valenta, Z.; Wilson, J. S.; Yu, T. T.-J. *Can. J. Chem.* **1976**, *54*, 97.
(10) Schoemaker, H. E.; Dijkink, J.; Speckamp, W. N. *Tetrahedron* **1978**, *34*,163.
(11) (a) TsCl, pyridine, rt (b) glutarimide, K_2CO_3, 18-crown-6, benzene, reflux (c) $NaBH_4$, HCl, EtOH, −12 °C (d) TFAA, THF, rt.
(12) No isomers of **9** were detected in the crude cyclization product; however, trace amounts of the tricyclic alkene that is formed upon treatment of **9** with DBU were seen.

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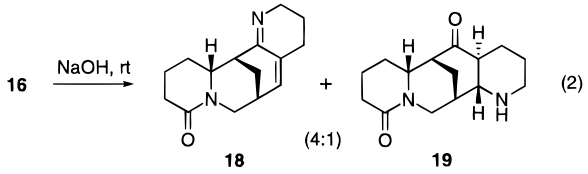
in excellent yield. Isomerization of **10** to allylic alcohol **11** was best accomplished by the method of Sharpless.[13] Oxidation of **11** with tetra-*n*-propylammonium perruthenate−*N*-methylmorpholine *N*-oxide (TPAP-NMO)[14] yielded enone **12**, which was iodinated to deliver α-iodo enone **13**.[15] Introduction of the remaining aminopropyl fragment was then achieved in 88% yield by Suzuki coupling[16] of **13** with borane **14**, which was generated *in situ* by hydroboration of *N*-BOC-allylamine with 1 equiv of 9-BBN-H.[17,18]

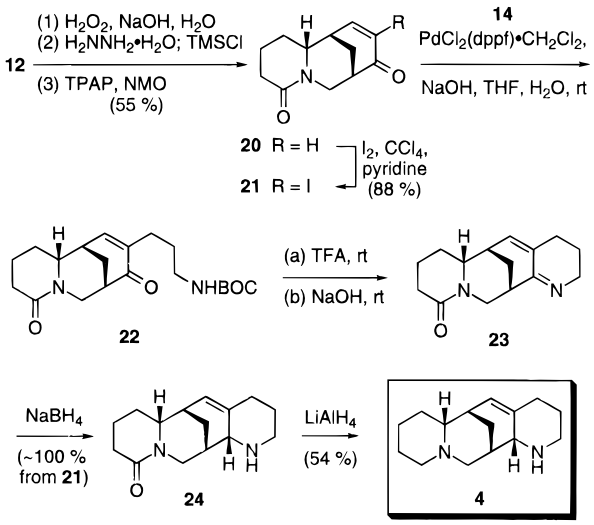
To close the final ring, **15** was treated with TFA to remove the BOC protecting group, and the resulting amine salt was exposed to aqueous NaOH. After 5 min, a single cis-fused tetracycle **16** was produced. However, if base treatment was allowed to proceed for several days, or if tetracycle **16** was re-exposed to aqueous base, a 4:1 mixture of tetracyclic imine **18** and trans-fused tetracycle **19** was formed (eq 2).[19] Treatment of crude **16** with



$LiAlH_4$ furnished a diamino alcohol ($J_{16,17}$ = 10.8 Hz), which was selectively protected on nitrogen by reaction with 2,2,2-trichloroethyl chloroformate (Troc-Cl)[20] to provide **17** in 70% overall yield from **15**. Finally, syn dehydration of the equatorial alcohol with $POCl_3$ and pyridine at 100 °C, followed by cleavage of the Troc functionality with 10% Cd−Pb,[21] afforded **3**. The ^{1}H NMR spectrum of this *syn-anti* isomer was not consistent with the published spectrum of aloperine.[7,22]

Tricyclic enone **12** also proved to be a useful intermediate for preparing the *syn-syn* aloperine isomer **4** (Scheme 2).[22] Our approach to constructing the piperidine ring drew upon the observation that imine **18** was the thermodynamic product of base-promoted cyclization of the primary amine derivative of **15** (eq 2). To exploit this thermodynamic preference in the synthesis of **4**, isomeric enone **20** was required. This intermediate was accessed by nucleophilic epoxidation of enone **12**, followed by Wharton rearrangement of the derived β-epoxide[23] and oxidation of the resulting crude allyl alcohol with TPAP-NMO.[14] The resulting enone **20** was iodinated and cross-coupled with borane **14** to afford enone **22**. When **22** was deprotected with TFA and the crude product exposed to NaOH in MeOH for 24 h at rt, imine **23** was produced as virtually the sole product. Without purification, this intermediate was reduced stereoselectively with $NaBH_4$ from the convex β-face to provide **24** in essentially quantitative yield from **21**. Finally, reduction of **24** with $LiAlH_4$ provided *syn-syn* aloperine isomer **4**, whose ^{1}H NMR spectrum was also not consistent with that of aloperine.[7]

Scheme 2



Shortly after initiating the synthesis of **4**, we obtained a sample of natural aloperine **2**, which was converted to the crystalline dihydrochloride monohydrate salt, mp 280 °C dec. Single-crystal X-ray analysis of this material demonstrated that natural aloperine was the *anti-syn* isomer and established that the absolute configuration was 6*R*,7*R*,9*R*,11*S* as depicted in **2**.[24−26]

In summary, this study demonstrates that iodide can be employed to control the outcome of *N*-acyliminium ion−alkene cyclizations. Using this approach, racemic aloperine stereoisomers **3** and **4** were prepared in stereocontrolled fashion in 12−13 steps and 13−27% overall yield from ene amide **8**. An enantioselective synthesis of aloperine and preliminary pharmacological characterization of **3** and **4** will be described in due course.

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Supporting Information Available: Experimental procedures and characterization data for new compounds reported in Schemes 1 and 2, copies of ^{1}H−^{1}H COSY spectra for **16** and **19**, and copies of ^{1}H (500 MHz) and ^{13}C (125 MHz) spectra for **2** (31 pages).

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(19) The stereochemistry of tetracycles **16** and **19** was determined by ^{1}H−^{1}H COSY experiments. Copies of these spectra are provided in the Supporting Information. The constitution of imine **18** was established by ^{1}H and ^{13}C NMR analyses.
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(22) The terms *syn-anti* and *syn-syn* refer to the orientation of the angular methine hydrogens H_6 and H_{11}, respectively, with respect to the methano bridge.
(23) (a) Di Grandi, M. J.; Coburn, C. A.; Isaacs, R. C. A.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 7728. (b) Maas, D. D.; Blagg, M.; Wiemer, D. F. *J. Org. Chem.* **1984**, *49*, 853. (c) Wharton, P. S.; Bohlen, D. H. *J. Org. Chem.* **1961**, *26*, 3615.
(24) Absolute configuration was assigned by refinement of the Flack parameter.[25]
(25) Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876.
(26) The authors have deposited atomic coordinates for **2** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.