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Total Synthesis of (±)-Jamtine Using a Thionium/*N*-Acyliminium Ion Cascade

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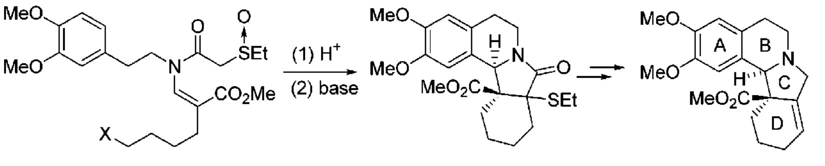
ABSTRACT



(±)-jamtine

The first total synthesis of (±)-jamtine (4), a tetrahydroisoquinoline alkaloid reputed for its therapeutic properties, is described. The key step involves a tandem thionium/*N*-acyliminium ion cyclization from enamido sulfoxide 13. The cascade process takes place with high diastereoselectivity and in excellent yield.

The development of new and general strategies for the synthesis of nitrogen-containing natural products constitutes an area of considerable interest in organic chemistry.[1−5] The Pummerer reaction followed by a π-cyclization was reported over 25 years ago and has been found to be a very effective method for the preparation of many diverse azapolycyclic systems.[6] This strategy was employed by Magnus[7] and others in some very elegant alkaloid syntheses.[8] In this context, we were attracted several years ago to the potential of employing a tandem Pummerer/Mannich ion cyclization sequence for the assembly of complex target molecules.[9] We came to realize that a linked thionium/iminium ion process could be used for a concise and stereocontrolled synthesis of the tetrahydroisoquinoline alkaloid jamtine (**4**). Jamtine is one of several alkaloids produced by the climbing shrub *Cocculus hirsutus*[10] commonly found throughout Pakistan and whose parts are reputed for their therapeutic properties in folk medicine.[11] Its isolation and structural elucidation, primarily by 2D-NMR spectra, was reported in 1987.[12] For our purposes, a synthesis of (±)-jamtine provided an opportunity to further develop the tandem Pummerer/Mannich sequence[13] and its application to tetrahydroisoquinoline alkaloids.[14] Our retrosynthetic analysis of this natural product is outlined in Scheme 1. The attractiveness of this stratagem involves the efficient use of the thioethyl group in each of the critical

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(1) Comins, D. L.; Killpack, M. O. *J. Am. Chem. Soc.* **1992**, *114*, 10973. Comins, D. L.; Joseph, S. P.; Goehring, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 4719.

(2) Grieco, P. A.; Larsen, S. C. *J. Am. Chem. Soc.* **1985**, *107*, 1768. Midland, M. M.; Koops, R. W. *J. Org. Chem.* **1992**, *57*, 1158.

(3) Flann, C.; Malone, T. C.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 6097. Tietze, L. F.; Bratz, M. *Chem. Ber.* **1989**, *122*, 997.

(4) Bonin, M.; Grierson, D. S.; Royer, J.; Husson, H. P. *Org. Synth.* **1991**, *70*, 54. Amat, M.; Llor, N.; Bosch, J. *Tetrahedron Lett.* **1994**, *35*, 2223. Munchhof, M. J.; Meyers, A. I. *J. Am. Chem. Soc.* **1995**, *117*, 5399.

(5) Boger, D. L.; Weinreb, S. M. *Hetero Diels−Alder Methodology in Organic Synthesis;* Academic Press: San Diego, 1987; Chapter 9.

(6) Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1974**, *30*, 2653. Oikawa, Y.; Yonemitsu, O. *J. Org. Chem.* **1976**, *41*, 1118.

(7) Gallagher, T.; Magnus, P.; Huffman, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 4750. Magnus, P.; Gallagher, T.; Brown, P.; Pappalardo, P. *Acc. Chem. Res.* **1984**, *17*, 35.

(8) For a review, see: Padwa, A.; Gunn, D. E.; Osterhout, M. H. *Synthesis* **1997**, 1353.

(9) Padwa, A.; Hennig, R.; Kappe, C. O.; Reger, T. S. *J. Org. Chem.* **1998**, *63*, 1144. Padwa, A.; Waterson, A. G. *Tetrahedron Lett.* **1998**, *39*, 8585.

(10) Ahmad, V. U.; Iqbal, S. *Phytochemistry* **1993**, *3*, 735. Ahmad, V. U.; Iqbal, S. *Nat. Prod. Lett.* **1993**, *2*, 105. Chopra, R. N.; Chopra, I. C.; Handa, K. L.; Kapoor, L. D. *Indigenous Drugs of India*; U. N. Dhar and Sons Pvt. Ltd.: Calcutta, India, 1958; p 501. Kirtikar, K. R.; Basu, B. D. *The Indian Medicinal Plants*; L. M. Basu Allahabad; 1933; Vol. 1, p 86. Nadkarni, K. M. *Indian Materia Medica*; Popular Prakashan Pvt. Ltd.: New Delhi, 1976; Vol. 1, p 362.

(11) Rao, K. V. J.; Rao, L. R. C. *J. Sci. Ind. Res.* **1981**, *20B*, 125.

(12) Ahmad, V. U.; Rahman, A.; Rasheed, T.; Rehman, H. *Heterocycles* **1987**, *26*, 1251.

(13) Padwa, A.; Heidelbaugh, T. M.; Kuethe, J. T. *J. Org. Chem.* **2000**, *65*, 2368. Padwa, A.; Heidelbaugh, T. M.; Kuethe, J. T.; McClure, M. S. *J. Org. Chem.* **1998**, *63*, 6778.

(14) *The Isoquinoline Alkaloids*; Bentley, K. W., Ed.; Harwood Academic Press: Amsterdam, The Netherlands, 1998.

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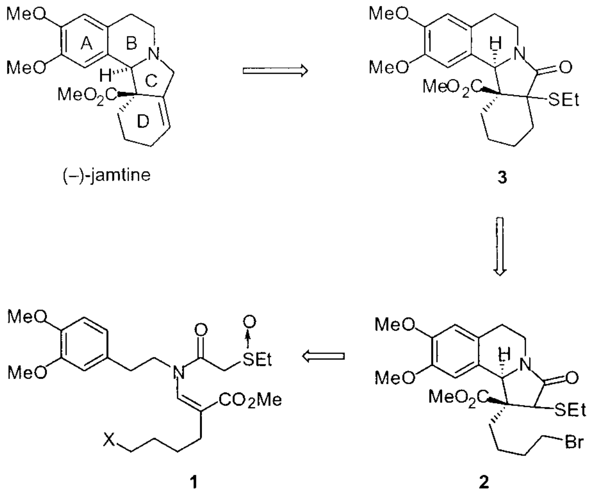
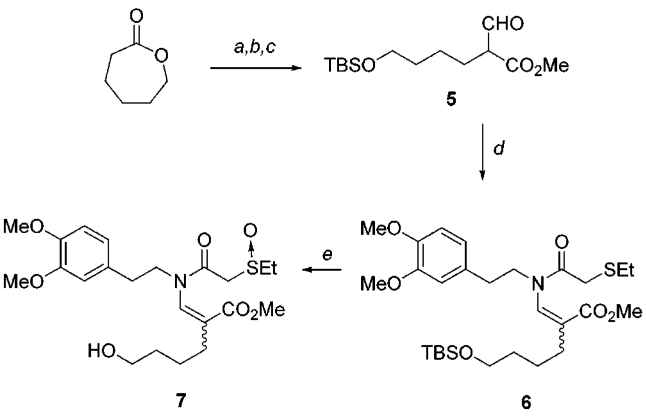
Scheme 1



stages of the synthesis. The first step in this highly convergent synthesis involves the domino ring closure of enamido sulfoxide **1** to provide the tricyclic ring skeleton **2**. Assembly of the D ring should proceed uneventfully by a base-induced cyclization and furnish the tetracyclic core of jamtine. Finally, standard functional group manipulations and selective reduction of the lactam would lead to the desired alkaloid. Summarized below is the successful reduction of these ideas to practice.

Our approach starts from commercially available ε-caprolactone, which was transformed into the open chain hydroxy methyl ester under mild acidic conditions.[15] The free alcohol was protected as the *tert*-butyldimethylsilyl ether,[16] and this compound was formylated by treatment with LDA and ethyl formate to give a 90% yield of aldehydic ester **5**. Condensation with 3,4-dimethoxy-phenethylamine led to the expected enamine, which was in turn acylated with ethyl sulfenylacetyl chloride[17] to provide enamide **6** in 94% isolated yield as a 4:1 (*Z/E*) mixture of isomers (Scheme 2). The *tert*-butyldimethylsilyl group was removed under the oxidative conditions required for the formation of sulfoxide **7**, thereby allowing for an effortless purification of this highly polar intermediate.

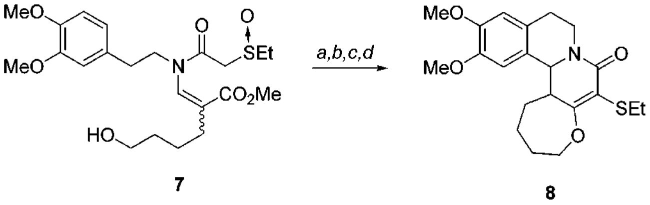
Scheme 2[a]



[a] Reagents: (a) H^+, MeOH, 95%; (b) TBSCl, DMAP, 98%; (c) LDA, HCO_2Et, 90%; (d) 3,4-dimethoxyphenethylamine, $EtSCH_2COCl$, 92%; (e) $NaIO_4$, $MeOH/H_2O$, 99%.

Studies dealing with the conversion of the hydroxyl functionality into an appropriate leaving group were carried out at this junction. Our intention was to first prepare an appropriate alcohol derivative that would be carried through the Pummerer/Pictet–Spengler cascade and then perform an anionic intramolecular cyclization (i.e., **2** → **3**) so as to install the D-ring of jamtine. Most surprisingly, an intriguing and totally unexpected product was obtained when the following reaction sequence was executed (Scheme 3). Treatment of alcohol **7** with methane-sulfonyl chloride and Et_3N was expected to furnish a mesylate, which we would then subject to camphorsulfonic acid in refluxing benzene in order to induce the desired tandem thionium/*N*-acyliminium ion cascade (vide infra). Without isolation, the crude reaction mixture was treated with NaI in acetone so as to replace the mesylate with an iodo group, and this was followed by treatment with NaH. Surprisingly, the only product isolated in 34% overall yield corresponded to the unusual cyclic enol ether **8**, whose structure was unequivocally established by an X-ray crystallographic study.

Scheme 3[a]



[a] Reagents: (a) MsCl, Et_3N; (b) CSA, benzene, reflux; (c) NaI, acetone; (d) NaH, THF, reflux.

Scheme 4 outlines a working mechanistic hypothesis to rationalize the formation of **8**. Under the conditions used to convert the hydroxyl functionality to the corresponding mesylate, reduction of the sulfoxide to the corresponding sulfide **9** also occurred, an event not unprecedented in the literature.[18] In fact, we have been able to isolate sulfide **9** in 68% yield from this reaction. When treated with camphorsulfonic acid, **9** underwent Pictet–Spengler cyclization to give the tetrahydroisoquinoline substructure **10** in 75% yield. After conversion of **10** to iodide **11**, treatment with NaH resulted in a Dieckmann condensation to first give **12** as a transient intermediate that underwent further O-alkylation under the basic conditions to furnish the observed product.

Because the attempted thionium ion cascade of alcohol **7** failed because of the ease with which the sulfoxide group

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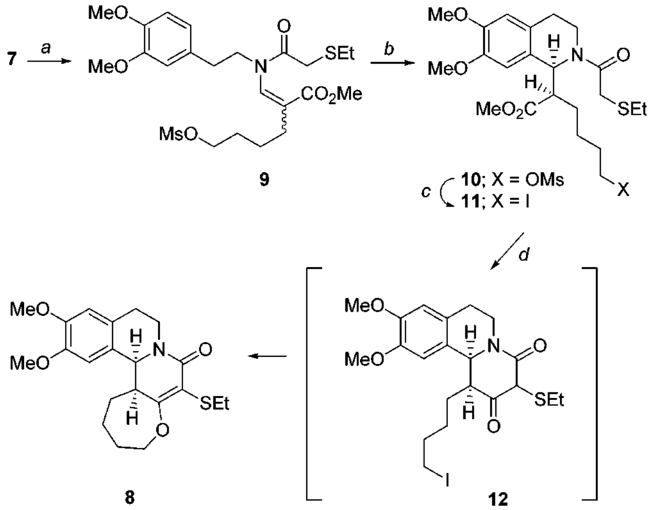
(15) King, S. A. *J. Org. Chem.* **1994**, *59*, 2253.

(16) Bookser, B. C.; Kasibhatla, S. R.; Applemann, J. R.; Erion, M. D. *J. Med. Chem.* **2000**, *43*, 1495.

(17) Mooradian, A.; Cavallito, C. J.; Bergman, A. J.; Lawson, E. J.; Suter, C. M. *J. Am. Chem. Soc.* **1949**, *71*, 3372.

(18) Madesclaire, M. *Tetrahedron* **1988**, *44*, 6537.

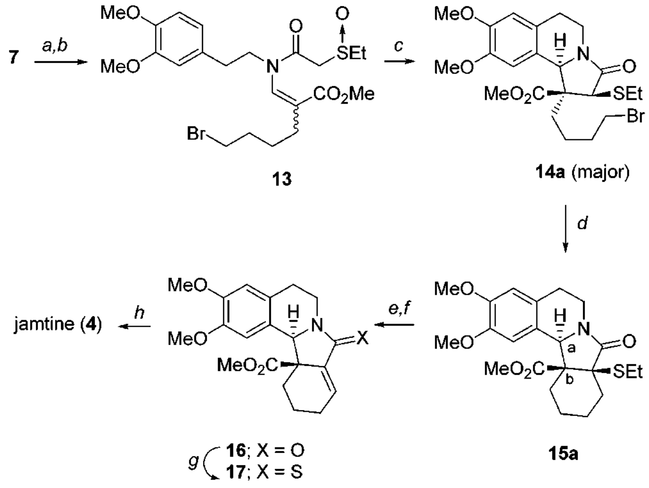
Scheme 4[a]



[a] Reagents: (a) MsCl, Et_3N, 68%; (b) CSA, benzene, reflux, 75%; (c) NaI, acetone, 93%; (d) NaH, THF, reflux, 72%.

was reduced, we decided to proceed in a stepwise manner. The hydroxyl group present in **7** was first converted to the corresponding bromide,[19] which also resulted in the simultaneous reduction of the sulfoxide functionality. Subsequent reoxidation with $NaIO_4$ delivered the required bromoenamide **13** as a 4:1 (*Z/E*) mixture of isomers in high yield. Heating a sample of **13** with camphorsulfonic acid afforded the desired tricyclic core of jamtine in excellent yield (88%) but as a 5:2:1:1 mixture of diastereomers (Scheme 5). Two of the diastereomers could be separated from the crude reaction mixture, and their structures were established by X-ray crystallographic analysis. The major product obtained corresponded to the desired diastereomer **14a**. The preferential formation of **14a** is consistent with our earlier stereochemical observations,[10] suggesting that a 4π-Nazarov type electrocyclization[20] controls the direction of closure from the α-acylthionium ion intermediate. The subsequent Pictet–Spengler step involves attack of the proximal aromatic ring from the less hindered side of the iminium ion. Deprotonation of **14a** with NaH resulted in quantitative cyclization to give **15a**, which contains the fully assembled skeleton of jamtine and whose structure was verified by X-ray analysis. It should be noted that treating the crude mixture of diastereomers **14** obtained from **13** with NaH not only afforded **15a** (67%) but also gave some of the corresponding *cis*-(*a*,*b*)-isomer **15b** (25%).

Scheme 5[a]



[a] Reagents: (a) CBr_4, PPh_3, 83%; (b) $NaIO_4$, $MeOH/H_2O$, 99%; (c) CSA, toluene, reflux, 98%; (d) NaH, THF, reflux, 99%; (e) $NaIO_4$, $MeOH/H_2O$; (f) heat, 90%; (g) Lawesson's reagent, 99%; (h) Meerwein's salt, $NaBH_4$, MeOH, 61%.

Completion of the synthesis entailed installation of the double bond and reduction of the lactam. This was accomplished by oxidation of the sulfide to the sulfoxide followed by thermal elimination to furnish the unsaturated lactam **16** in 89% overall yield. Conversion of **16** to thioamide **17** using Lawesson's reagent was followed by reduction to jamtine (**4**) using Meerwein's salt and $NaBH_4$[21] in a respectable 61% yield. The analytical and spectroscopic data are in full agreement with those reported in the literature.[9] This completes the first total synthesis of this interesting alkaloid.

In summary, this approach to jamtine demonstrates the utility of the thionium/*N*-acyliminium ion cascade for preparing stereochemically complex tetrahydroisoquinoline ring systems. Further studies on the synthesis of related alkaloids using this methodology are in progress and will be reported in due course.

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Supporting Information Available: Complete description of the synthesis and characterization of all compounds prepared in this study and ORTEP drawings for compounds **8**, **15a**, **15b** and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[19] Nakano, H.; Inoue, T.; Kawasaki, N.; Miyataka, H.; Matsumoto, H.; Taguchi, T.; Inagaki, N.; Nagai, H.; Satoh, T. *Bioorg. Med. Chem.* **2000**, *8*, 373.

[20] Denmark, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991, Vol. 5, p 751.

[21] Raucher, S.; Klein, P. *Tetrahedron Lett.* **1980**, *21*, 4062.