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Asymmetric Total Synthesis of the Proposed Structure of the Medicinal Alkaloid Jamtine Using the Chiral Base Approach

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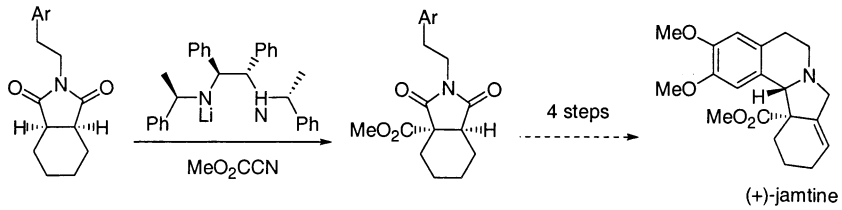
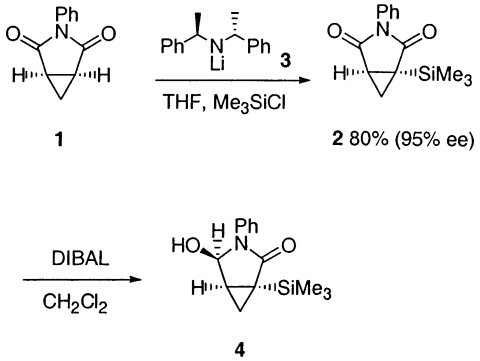
ABSTRACT



A highly step-economic asymmetric synthesis of the tetracyclic structure assigned to the medicinal alkaloid jamtine has been accomplished using a chiral lithium amide base desymmetrization of a ring-fused imide. The structure synthesized appears to be different from that of the natural product originally reported.

As part of our ongoing program aimed at developing the chemistry of chiral lithium amide bases, we have recently described highly enantioselective desymmetrization reactions of certain types of cyclic imide.[1,2] Typically, reaction of a ring-fused imide, e.g. cyclopropane derivative **1**, with chiral base **3** gave substituted products such as **2** in high yield and enantioselectivity (Scheme 1).

Scheme 1



A particularly important aspect of this type of desymmetrization is that the silyl or alkyl groups installed completely control the regiochemistry of subsequent imide reaction. Thus, reaction of silylimide **2** with DIBAL occurred only at the carbonyl function distal to the silicon substituent, leading to hydroxylactam **4**.[3] This approach allows efficient enantioselective access to a range of substituted lactams and related products.

In seeking to apply this chemistry to interesting alkaloid targets we were attracted to a recent report from the group of Padwa,[4] describing the first synthesis of an unusual alkaloid called jamtine **5**. This compound was originally reported, in the form of an *N*-oxide, as one of a small group of isoquinoline alkaloids isolated from the climbing shrub Cocculus hirsutus.[5] This plant is commonly found in parts of Pakistan and its various parts are reputed to have therapeutic properties according to local folk medicine.[6]

(1) Adams, D. J.; Blake, A. J.; Cooke, P. A.; Gill, C. D.; Simpkins, N. S. *Tetrahedron* **2002**, *58*, 4603 (part of a special issue dedicated to chiral lithium amides).

(2) For a review, see: O'Brien, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1439.

(3) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367.

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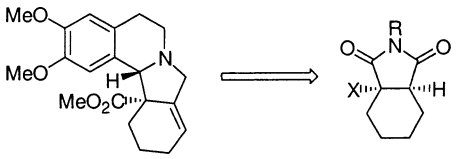
We were interested in the asymmetric synthesis of jamtine, starting from a chiral imide **6**, in which the substituent X would become the carbomethoxy substituent present in the natural product (Scheme 2).

Scheme 2



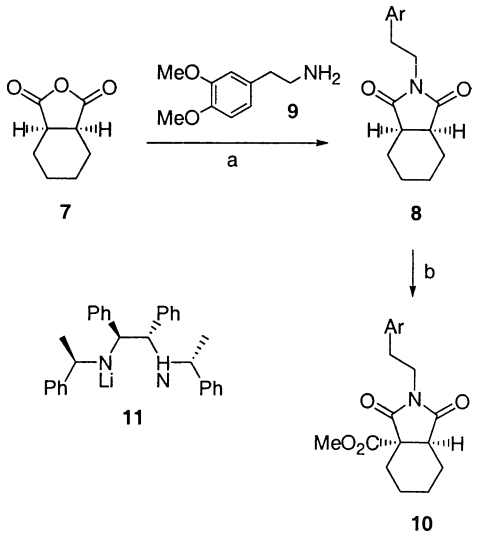
5 **6**

This idea presented two specific issues to be overcome. First, in our previous work succinimides having a fused cyclohexane ring proved to be the sole substrates that did *not* give good results on reaction with base **3**. Second, the elaboration of **6** toward jamtine requires regioselective reaction at the imide carbonyl *proximal* to the installed group X. This complementary mode of reaction, compared to that seen in reduction of **2** to give **4**, has little precedent, but appeared viable through electronic or chelation modes of activation.

Herein we describe the successful application of this strategy to a new and very concise asymmetric synthesis of alkaloid **5**, and we conclude that this is probably *not* the correct structure of the alkaloid originally isolated.

Our synthesis started with the construction of an appropriately substituted *meso*-imide **8** by the straightforward combination of commercially available anhydride **7** and the amine **9** (Scheme 3). As mentioned above, this type of system (i.e. with NMe or NPh substituents) had not given good results with base **3**, and indeed imide **8** gave similarly poor chemical yield and enantioselectivity under our usual conditions. Instead, use of base **11**, a monolithiated diamine base, proved much more effective and allowed highly enantioselective carboxymethylation to give (−)-**10** on quenching the reaction with Mander's reagent.[7]

Scheme 3[a]

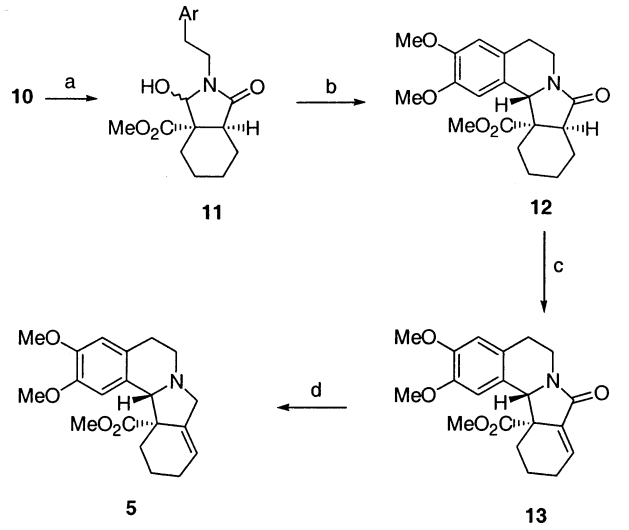


7 **8** **9** **10** **11**

[a] Reagents: (a) AcOH, reflux, 87%; (b) base **11**, THF, −78 °C then MeO_2CCN, 85%, 95 to 98% ee.

With imide **10** available in essentially enantiopure form we next probed possibilities for regioselective imide reduction as a prelude to cyclization to form the isoquinoline. Efficient and completely regioselective reduction was achieved simply by reaction of **10** with $NaBH_4$ in EtOH (Scheme 4).[8]

Scheme 4[a]



10 **11** **12** **13** **5**

[a] Reagents: (a) $NaBH_4$, EtOH, −5 °C, 89%; (b) camphorsulfonic acid, toluene, 80 °C, 69%; (c) KH, PhSeSePh, THF, 50 °C, then H_2O_2, py, CH_2Cl_2, rt, 65% overall; (d) Me_3OBF_4, 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2, rt, then $NaBH_4$, MeOH, 0 °C, 69%.

Since metal chelation is unlikely under such conditions we attribute the high regiocontrol to the inductive effect of the ester enhancing the electrophilicity of the proximal imide carbonyl.

With the two key steps accomplished, the synthesis of alkaloid **5** from hydroxylactam **11** proved quite straightforward. Thus, completely stereoselective cyclization of **11** was effected under standard *N*-acyliminium ion conditions to give the complete alkaloid skeleton in the form of lactam (+)-**12**. Dehydrogenation using a selenoxide *syn*-elimination gave

(4) Padwa, A.; Danca, M. D. *Org. Lett.* **2002**, *4*, 715.

(5) Ahmad, V. U.; Rahman, A.; Rasheed, T.; Rehman, H. *Heterocycles* **1987**, *26*, 1987. See also: Rasheed, T.; Khan, M. N. I.; Zhadi, S. S. A.; Durrani, S. *J. Nat. Prod.* **1991**, *54*, 582. Ahmad, V. U.; Iqbal, S. *Nat. Prod. Lett.* **1993**, *2*, 105.

(6) 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.

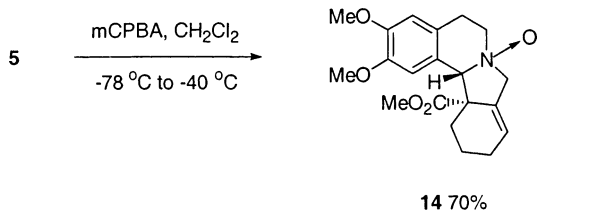
(7) Base **11**, in either mono- or dilithiated form always gives enantiocomplementary results to base **3**. At present our assignment of absolute stereochemistry for **10** rests on this fact, along with a firmly established pattern of enantioselectivity for base **3** (see ref 1).

(8) For related examples of regioselective imide reduction, see: Pilli, R. A.; Russowsky, *J. Org. Chem.* **1996**, *61*, 3187. Hsu, R.-T.; Cheng, L.-M.; Chang, N.-C.; Tai, H.-M. *J. Org. Chem.* **2002**, *67*, 5044.

13, which is an intermediate in the Padwa synthesis of **5**. Finally, we used a method for selective lactam reduction reported by Martin and co-workers to transform **13** into jamtine **5**.[9]

On exposure to mCPBA in CH_2Cl_2 at low temperature **5** was converted into the corresponding *N*-oxide **14** (Scheme 5).

Scheme 5



14 70%

At this stage it became clear that there are substantial differences between the NMR data for **14** and those reported for the natural product "jamtine oxide". That our synthesis has delivered the structure **5** is beyond doubt, given the excellent agreement between our data and those of Padwa and Danca.[10] That the natural product "jamtine oxide" could be the opposite *N*-oxide diastereomer to the one that we have prepared appears a remote possibility. A more likely explanation is that the original structural assignment is incorrect.

In conclusion, we have demonstrated the utility of the chiral base desymmetrization of imides in the synthesis of a simple alkaloid. The route delivers the tetracyclic isoquinoline structure **5** in six steps from commerical materials and in an overall yield of around 20%. Further applications of this approach are underway.

Acknowledgment. We thank the Engineering and Physical Sciences Research Council (EPSRC) for a Fellowship to C.D.G. We also thank Professor Albert Padwa, Emory University, for helpful exchanges of information.

Supporting Information Available: Description of the key chiral base reaction leading to **10**, and NMR and $[\alpha]_D$ data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL027447S

(9) Martin, S. F.; Clark, C. W.; Ito, M.; Mortimore, M. *J. Am. Chem. Soc.* **1996**, *118*, 9805.

(10) The ^{1}H NMR spectra obtained by us for compounds **13**, **5**, and **14** are virtually identical with those kindly forwarded to us by Prof. Padwa. In a personal communication Prof. Padwa has also indicated that the structure of "jamtine" **5** has been secured by X-ray crystallography. A full report by this group, in which they reach similar conclusions to ours, has been recently published; see: Padwa, A.; Danca, M. D.; Hardcastle, K. I.; McClure, M. S. *J. Org. Chem.* **2003**, *68*, 929.