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A Reinvestigation of the Reported Synthesis of the Spirobenzyl Isoquinoline Alkaloid, Iso-Ochotensine

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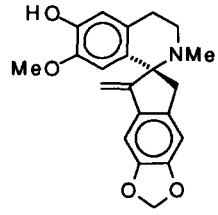
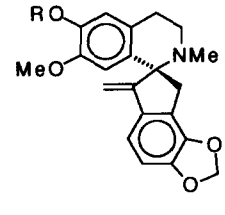
Summary: *Attempts to repeat the spirocyclization of isoquinoline carboxylic acids,* ***4****,* ***5****,* ***8****, and* ***9*** *to the spiroketones,* ***6*** *led only to the formation of the N-carboxyanhydrides,* ***7****.* © 1997 Elsevier Science Ltd.

During our continuing studies to reach a number of non-racemic indole and isoquinoline alkaloids *via* asymmetric total syntheses,[1] we were attracted to the spirobenzyl isoquinoline family, *Fumariaceae*.[2] In this group are two members which we were particularly interested in, namely iso-ochotensine **1** and ochotensine, **2.** Our interest was driven by our earlier report which described an asymmetric route to 1,1-dialkyl-1,2,3,4 tetrahydroisoquinolines, a chiral quaternary carbon system, in high enantiomeric excess.[3] The asymmetric stereogenic quaternary center in **1**



1 (isoochotensine)

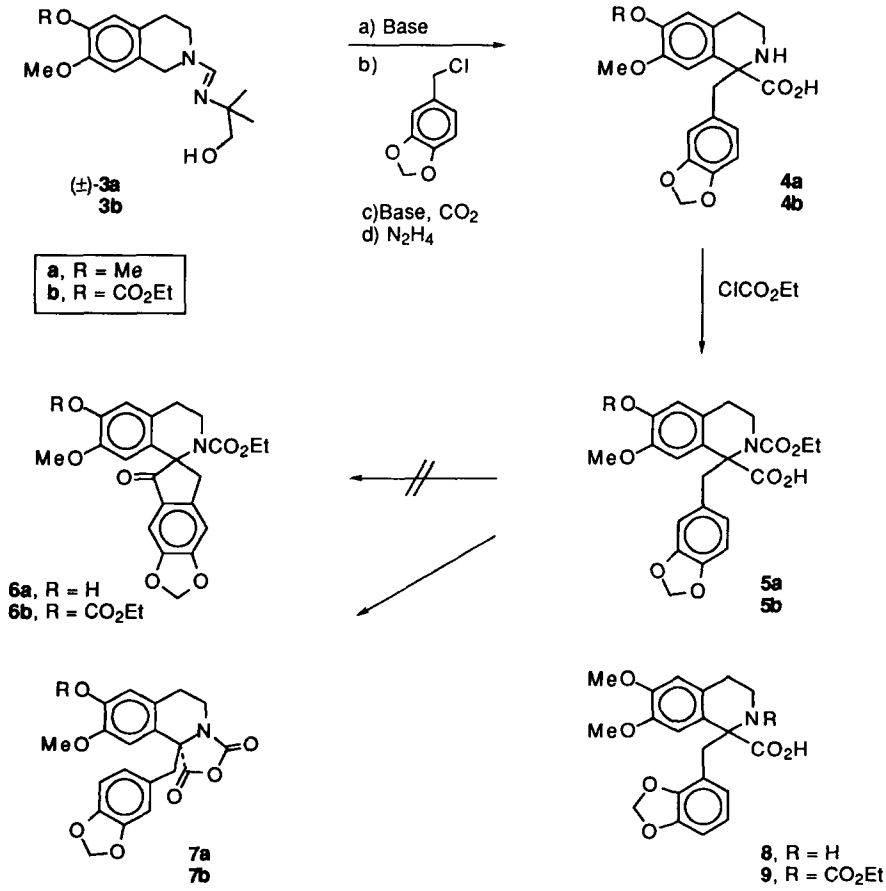


2 [R = H, ochotensine; R = Me, ochotensimine]

and **2** seemed to be quite amenable to our formamidine carbanion alkylation. Although there are three reported total synthetic routes to **1** and/or **2**,[4-6] none provide the enantiomerically pure alkaloids. A biogenetic route to this family has also been described by Shamma.[7] The Kametani

synthesis[6] was appealing to us since it employed a spirocyclization of 1-benzyl-1-carboxyisoquinoline **5b** using polyphosphoric acid ester (PPE) to afford the ketone, **6b**.

Our approach to a close analog of **5b** was initially to use the dimethoxy derivative **3a** in a racemic model to assess the efficiency of the route to iso-ochotensine, **1**, and presumably to ochotensimine **2** (R = Me).[2g] We utilized the formamidine **3a**[3] which was first metalated (*n*-BuLi, THF, -78 °C) and then treated with 3,4-methylenedioxybenzyl chloride. Immediately thereafter it was metalated again (*s*-BuLi, -78 °C, THF) and allowed a stream of CO_2 to pass through the solution at -78 °C. The reaction was immediate and after hydrazine treatment to remove the formamidine moiety, we had obtained the amino acid, **4a** in 76% overall yield from **3a**. The insoluble amino acid was transformed into the urethane, **5a** and then subjected to the conditions



as described by Kametani.[6a] After a number of attempts, it soon became clear that none of the expected spiroketone **6a** (R = Me) was present, nor could the spiroketone be produced under other Friedel-Crafts acylation conditions (AgOTf,[8] Nafion-H,[9] triflic anhydride[10]). In the unlikely event that the methoxyl group in **5a** (R = Me) was interfering with the intramolecular acylation, we prepared the carbonate **5b** (R = CO_2Et); the exact compound reported[6] to cyclize to the spiroketones, **6a**, **6b**. In order to access the appropriate precursor for **5b**, we prepared the formamidine **3b** from the corresponding 6-hydroxy-7-methoxytetrahydroisoquinoline.[11] With **5b** in hand we carried out the experiment according to the conditions described[6a] (PPE, $CHCl_3$, 65 °, 5 h). As before, no spiroketone **6a** or **6b** could be isolated. The only product obtained (in 60-70% yield) after numerous attempts was shown to be the N-carboxyanhydride **7a** (R = Me) or **7b** (R = CO_2Et) which was verified by complete nmr, ir, mass spectral and finally X-ray crystal analyses. Using the same route, we also prepared the isomeric system **8** and **9** which would lead to the related alkaloids, **2**. Attempted cyclization to the spiroketones under the conditions described above also led to the N-carboxyanhydrides as the only product.[12]

It is quite interesting that Shamma[13] working with a rather similar system was unsuccessful in using the Kametani procedure to form the spiroketone, whereas Uyeo[5] also failed to effect spirocyclization, but before the Kametani paper appeared. It is further noteworthy to mention that McLean,[4] Uyeo,[5] and Kametani[6] all published synthetic routes to the ochotensines within an eight-month period in 1968 and none of them commented on the nmr assignments of the other. Although McLean and Uyeo's spectroscopic data are consistent with the structures,[2h] the Kametani spectral data are not well-matched and the reported values are rather vaguely presented so comparisons are not easily made.[14]

In summary, the intramolecular acylation to the spirobenzyl isoquinoline alkaloids does not appear to proceed as reported and the reasons for this remain unclear.

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References

1. Highsmith, T. K.; Meyers, A. I. *Advances in Heterocyclic Natural Product Synthesis*; JAI: 1990; Vol. 1, pp 95-135. For details on the procedure, see, Meyers, A. I.; Bos, M.; Dickman, D. A. *Org. Syn.* Coll. Vol. VIII, p. 573, J. Wiley, 1993.

2. (a) Manske, R. H. F. *The Alkaloids* **1971** *13*, p. 166, Academic. (b) Manske, R. H. F. *Can J. Res.* **1936** *14B*, 354. (c) Manske, R. H. F. *Can. J. Res.* **1940** *18B*, 75. (d) Ito, S. *Natural Products Chemistry*; Nakanishi, K.; Goto, T.; Ito, S.; Natori, S.; Nozoe, S., Ed.; Academic: New York, 1975; Vol. 2, pp 310-313. (e) Saunders, J. K.; Bell, R. A.; Chen, C.-Y.; MacLean, D. B.; Manske, R. H. F. *Can. J. Chem.* **1968**, *46*, 2873. (f) *ibid.* **1968**, *40*, 2876. (g) McLean, S.; Lin, M. S. *Tetrahedron Lett.* **1964**, 3819. (h) The X-ray structure of ochotensine has been reported: McLean, S.; Lin, M. S.; MacDonald, A. C.; Trottel, J. *Tetrahedron Lett.* **1966**, 185.

3. Meyers, A. I.; Gonzalez, M. A; Struzka, V.; Akahane, A.; Guiles, J.; Warmus, J. S. *Tetrahedron Lett.* **1991**, *32*, 5501.

4. McLean, S.; Lin, M. S.; Whelan, J. *Tetrahedron Lett.* **1968**, 2425.

5. Irie, H.; Kishimoto, T.; Uyeo, S. *J. Chem. Soc. (C)* **1968**, 3051.

6. (a) Kametani, T.; Takano, S.; Hibino, S.; Terui, T. *J. Heterocyclic Chem.* **1969**, *6*, 49. (b) Kametani, T.; Takano, S.; Hibino, S. *J. Pharm. Soc. Japan* **1968**, *88*, 1123.

7. Shamma, M.; Jones, C. D. *J. Am. Chem. Soc.* **1969**, *91*, 4009.

8. Effenberger, F.; Steegmüller, D.; Null, V.; Ziegler, T. *Chem. Ber.* **1988**, *121*, 125.

9. Yamato, T.; Hideshima, C.; Prakash, G. K. S.; Olah, G. A. *J. Org. Chem.* **1991**, *56*, 3955.

10. Hulin, B.; Koreeda, M. *J. Org. Chem.* **1984**, *49*, 207.

11. Bobbitt, J. M.; Sih, J. C.; *J. Org. Chem.* **1968**, *43*, 2115.

12. The N-carboxyanhydrides **7a**, **7b** as well as the cyclization products from **8** and **9** all showed very similar IR stretching frequencies (1840 ±1; 1777 ±1 cm^{-1}) characteristic of this moiety. The X-ray structure (S. Miller, Colorado State University Department of Chemistry) of the cyclization product of **8** confirmed the N-carboxyanhydrides were indeed the only products formed when cyclization was attempted under the reported (ref 6b) or other comparable conditions. ^{1}H-NMR of **7b**: (270 MHz, $CHCl_3$, δ) 1.40 (t, 3), 2.74 (dd, 1), 3.06 (m, 1), 3.17 (d, 1), 3.31 (dt, 1), 3.41 (d, 1), 3.94 (s, 3), 4.26 (m, 1), 4.33 (q, 2), 5.96 (s, 2), 6.59 (s, 1), 6.60 (d, 1) 6.75 (d, 1), 6.97 (s, 1), 7.38 (s, 1).

13. Shamma, M.; Jones, C. D. *J. Org. Chem.* **1970**, *35*, 3119.

14. Attempts to secure samples or spectra from the late Professor Kametani's laboratory did not meet with any success.

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