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## FORMAL SYNTHESIS OF SCELETIUM ALKALOIDS, (±)-MESEMBRINE AND (±)-MESEMBRANOL<sup>†</sup>

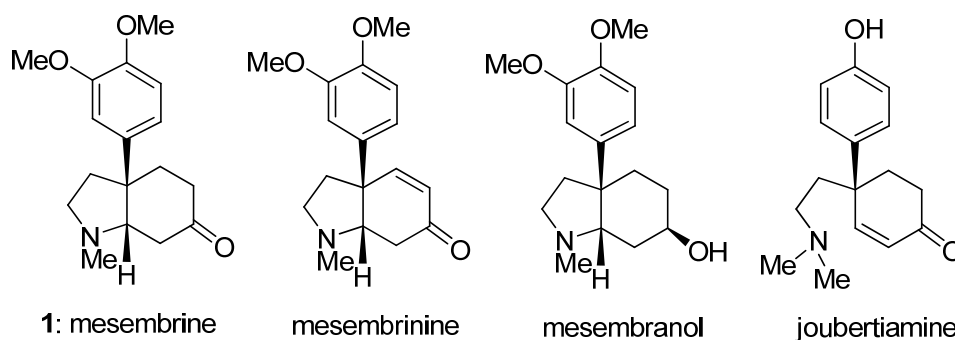
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**Abstract** – An intramolecular Mizoroki-Heck reaction was exploited for construction of a benzylic quaternary carbon center. The product obtained was further converted into the key intermediate for the synthesis of (±)-mesembrine and (±)-mesembranol.

Mesembrine (**1**), isolated from *Sceletium tortuosum* as the major active alkaloid,<sup>1</sup> was recently shown<sup>2</sup> to be a nanomolar inhibitor of serotonin re-uptake. Derivatives of mesembrine are, thus, expected to be alternative potential antidepressants with short half life properties worthy of further investigation.

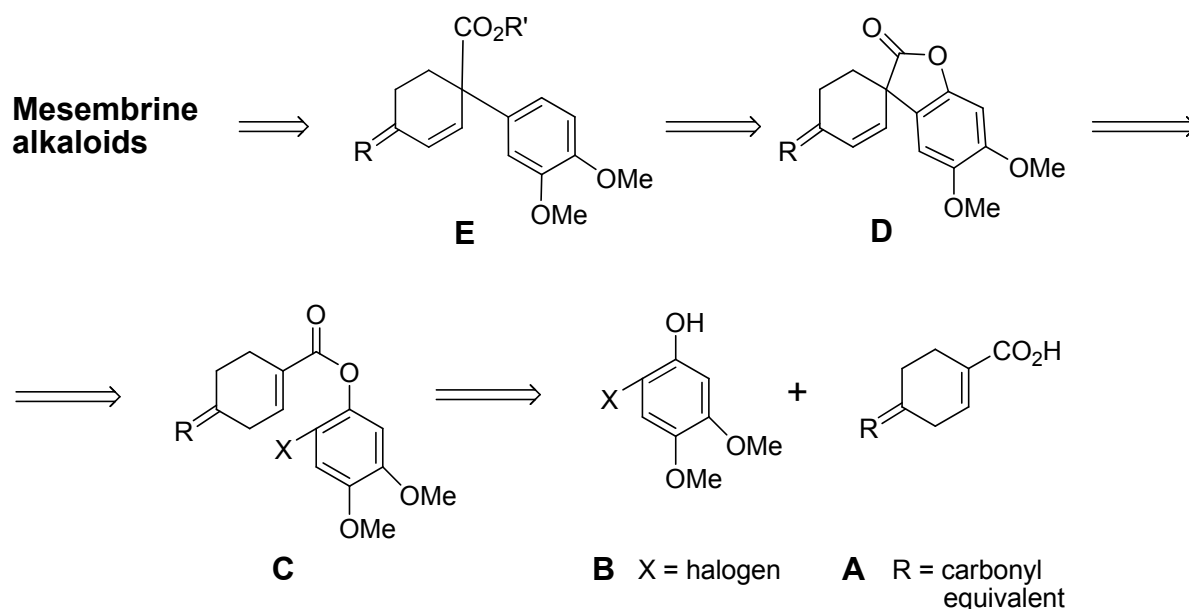
The key structural feature of this alkaloid is a saturated pyrrolidine ring fused to a cyclohexanone, with a benzylic quaternary carbon centre at the ring fusion (Figure 1). Mesembrine and its relatives having relatively simple structural features are popular synthetic targets, because they exhibit attractive biological activity and also provide further opportunities to develop new synthetic methods and strategies for this type of quaternary center observed as a common component in the alkaloids.<sup>3</sup>



**Figure 1.** Structures of mesembrine (**1**) and its relatives

To construct the desired quaternary center, we decided to exploit an intramolecular Mizoroki-Heck reaction<sup>4</sup> as the key step, since this coupling reaction could be expected to extend to its asymmetric version by means of appropriate chiral phosphine ligands.

Our retrosynthetic route to mesembrine alkaloids is depicted in Scheme 1.



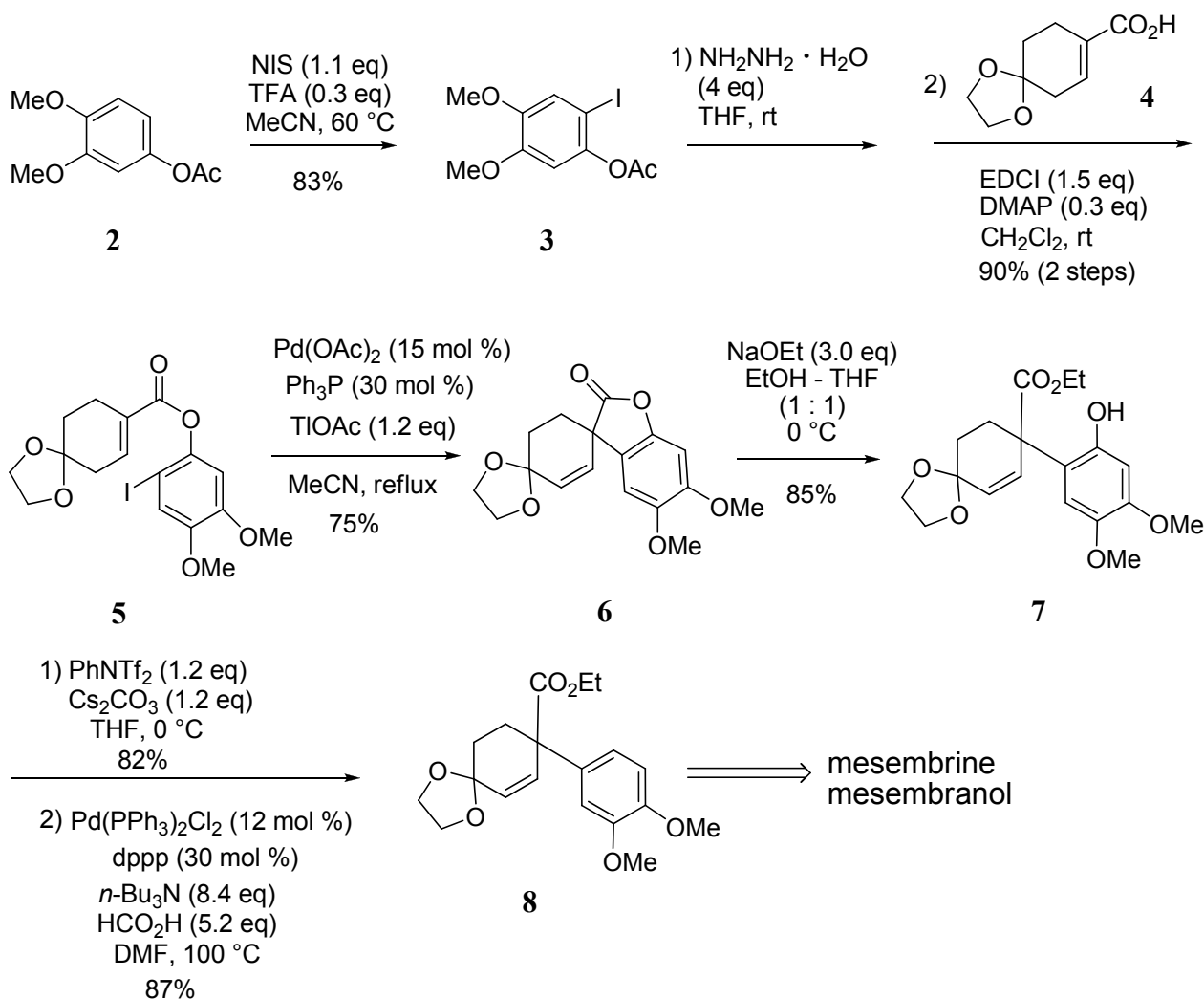
**Scheme 1.** Retrosynthetic route to mesembrine alkaloids

As mentioned above, we envisaged that exploitation of an intramolecular Mizoroki-Heck reaction of ester (**C**), readily derived from acid (**A**) and phenol derivative (**B**), for assembling a quaternary carbon center and subsequent manipulation of a lactone moiety involving a deoxygenation of the coupling product (**D**) to the corresponding ester (**E**), would be the most straightforward way to achieve the goal for constructing the basic carbon framework of this type of alkaloids. Moreover, this strategy is expected to have broad utility in searching for new potential antidepressant compounds.

Thus, our synthesis commenced with the preparation of ester (**5**).

3,4-Dimethoxyphenyl acetate (**2**) was treated with *N*-iodosuccinimide (NIS) in acetonitrile at 60 °C to give iodide (**3**)<sup>5</sup> in 83% yield. Mild hydrolysis of iodo-acetate (**3**) was achieved by using hydrazine hydrate furnishing the corresponding phenol derivative,<sup>6</sup> which, without further purification, was used in the next reaction. Condensation of phenol derivative obtained above with acid (**4**)<sup>7</sup> in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) and *N,N*-dimethylaminopyridine (DMAP) in CH<sub>2</sub>Cl<sub>2</sub> afforded the desired ester (**5**) in 90% yield from **3**. Mizoroki-Heck reaction of **5** was carried out under the similar reaction conditions as described for the corresponding lactam.<sup>8</sup> Treatment of **5** with palladium(II) acetate as the catalyst in the presence of triphenylphosphine and thallium acetate in refluxing acetonitrile afforded the spiro-lactone in 75% yield.

Solvolysis of **6** with sodium ethoxide in a mixture of ethanol-THF (1:1, v/v) at 0 °C gave ester (**7**) in 85% yield. To accomplish the synthesis of mesembrine alkaloids, deoxygenation of a phenolic hydroxyl group of **7** would be required. Thus, ester (**7**) was first converted to its triflate under the usual reaction conditions, which, on treatment with formic acid in the presence of bis(triphenylphosphine)palladium chloride under the reaction conditions designed for highly congested aryl triflates,<sup>9</sup> provided the desired ester (**8**) in 87% yield (Scheme 2). The spectroscopic data of the synthesized compound were comparable with those reported in the literature.<sup>10</sup> Ester (**8**) was already transformed to mesembrine and mesembranol.<sup>10</sup> Thus, we have accomplished a formal synthesis of those alkaloids.<sup>10</sup>



**Scheme 2.** Synthesis of the key intermediate for mesembrine alkaloids

In summary, we were able to establish an alternative synthetic route to mesembrine alkaloids by employing Mizoroki-Heck reaction as the key step for constructing the desired quaternary center with

reasonably high yield. The key intermediate (**8**) was synthesized from the known 2-iodo-4,5-dimethoxyphenyl acetate (**3**) in 41% overall yield in 6 steps.

This methodology seems to be applicable to the synthesis of various types of Scelletium and Amaryllidaceae alkaloids. Asymmetric version of this synthesis is now under investigation in our laboratory.

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## REFERENCES

- † This paper is dedicated to Professor Albert Padwa on the occasion of his 75th birthday.
- (a) K. Bodendorf and W. Krieger, *Archiv. Pharm.*, 1957, **290**, 441; (b) A. Popelak, E. Haack, G. Lettenbauer, and H. Spingler, *Naturwissenschaften*, 1960, **47**, 156; (c) P. Coggon, D. S. Farrier, P. W. Jeffs, A. T. McPhail, and P. M. Gross, *J. Chem. Soc. B*, 1970, 1267.
  - (a) M. T. Smith, N. Crouch, N. Gericke, and M. Hirst, *J. Ethnopharmacol.*, 1996, **50**, 119; (b) N. P. Gericke and B.-E. VanWyk, PCT Int. Appl., WO 9746234 CAN 128: 80030, 1997.
  - For reviews, see: (a) J. R. Lewis, *Nat. Prod. Rep.*, 1998, **15**, 107; (b) J. R. Lewis, *Nat. Prod. Rep.*, 1999, **16**, 389; (c) Z. Jin, Z. Liu, and R. Huang, *Nat. Prod. Rep.*, 2002, **19**, 454; (d) Z. Jin, *Nat. Prod. Rep.*, 2003, **20**, 606; (e) Z. Jin, *Nat. Prod. Rep.*, 2007, **24**, 886; (f) Z. Jin, *Nat. Prod. Rep.*, 2009, **26**, 363; (g) Y. Zhao, Y. Zhou, F. Du, L. Liang, and H. Zhang, *Youji Huaxue*, 2010, **30**, 47 and references cited therein. For selected recent syntheses of mesembrine, see: (a) J. H. Rigby and W. Dong, *Org. Lett.*, 2000, **2**, 1673; (b) D. F. Taber and Y. He, *J. Org. Chem.*, 2005, **70**, 7711; (c) T. Paul, W. P. Malachowski, and J. Lee, *Org. Lett.*, 2006, **8**, 4007; (d) S. Arns, M.-E. Lebrun, C. M. Grise, I. Denissova, and L. Barriault, *J. Org. Chem.*, 2007, **72**, 9314; (e) C. Roe, E. J. Sandoe, G. R. Stephenson, and C. E. Anson, *Tetrahedron Lett.*, 2008, **49**, 650; (f) Y. Zhao, Y. Zhou, L. Liang, X. Yang, F. Du, L. Li, and H. Zhang, *Org. Lett.*, 2009, **11**, 555; (g) E. A. Ilardi, M. J. Isaacman, Y.-C. Qin, S. A. Shelly, and A. Zakarian, *Tetrahedron*, 2009, **65**, 3261; (h) Y. Zhao, Y. Zhou, F. Du, L. Liang, and H. Zhang, *Youji Huaxue*, 2009, **29**, 1829. For selected recent syntheses of mesembranol, see: (a) N. Chida, K. Sugihara, S. Amano, and S. Ogawa, *J. Chem. Soc., Perkin Trans. 1*, 1997, 275; (b) J. B. Everts and P. L. Fuchs, *Tetrahedron Lett.*, 2001, **42**, 3673.
  - (a) A. de Meijere and F. E. Meyer, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 2379; (b) A. de Meijere and S. Bräse, Palladium-Catalyzed Coupling of Organyl Halides to Alkenes - The Heck Reaction. In *Metal Catalyzed Cross-Coupling Reactions*; ed. by P. J. Stang and F. Diederich, Wiley-VCH, New

- York, 1998; (c) L. E. Overman and J. T. Link, Intramolecular Heck Reactions in Natural Products Chemistry. In *Metal Catalyzed Cross-Coupling Reactions*; ed. by P. J. Stang and F. Diederich, Wiley-VCH, New York, 1998; (d) I. P. Beletskaya and A. B. Cheprakov, *Chem. Rev.*, 2000, **100**, 3009; (e) J. T. Link, The Intramolecular Heck Reaction. In *Organic Reactions*; ed. by L. E. Overman, John Wiley and Sons, New York, 2002, Vol. 60, pp. 157-534; (f) A. B. Dounay and L. E. Overman, *Chem. Rev.*, 2003, **103**, 2945.
5. F. G. Schreiber and R. Stevenson, *Org. Prep. Proced. Int.*, 1978, **10**, 137.
  6. (a) W. Steglich and L. Zechlin, *Chem. Ber.*, 1978, **111**, 3939; (b) S. P. Bew and D. W. Knight, *Chem. Commun.*, 1996, 1007; (c) L.-Y. Yang, C.-F. Chang, Y.-C. Huang, Y.-J. Lee, C.-C. Hu, and T.-H. Tseng, *Synthesis*, 2009, 1175.
  7. (a) J. H. Rigby and N. Balasubramanian, *J. Org. Chem.*, 1989, **54**, 224; (b) J. H. Rigby, D. D. Holsworth, and K. James, *J. Org. Chem.*, 1989, **54**, 4019.
  8. (a) M. W. Abelman, T. Oh, and L. E. Overman, *J. Org. Chem.*, 1987, **52**, 4130; (b) A. Ashimori and L. E. Overman, *J. Org. Chem.*, 1992, **57**, 4571; (c) A. Ashimori, B. Bachand, L. E. Overman, and D. J. Poon, *J. Am. Chem. Soc.*, 1998, **120**, 6477.
  9. J. M. Saa, M. Dopico, G. Martorell, and A. G. Garcia-Raso, *J. Org. Chem.*, 1990, **55**, 991.
  10. C. J. Parkinson and J. T. Pinhey, *J. Chem. Soc., Perkin Trans. 1*, 1991, 1053.