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A Concise Synthesis of (-)-Mesembrine

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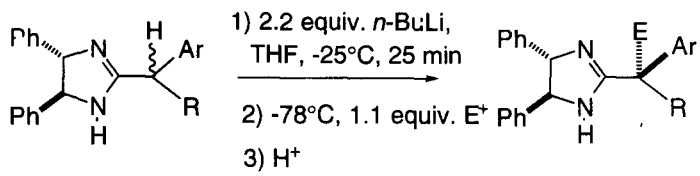
Abstract: (-)-Mesembrine **11** was synthesized in 7 steps, in 19.4% overall yield and with ee>95%. The key step of the sequence is a stereoselective alkylation reaction of dianion derived from C_2 symmetric imidazolines allowing efficient formation of quaternary benzylic center. Chiral auxiliaries derived from (*S,S*)-1,2-diamino-1,2-diphenylethane **1a** and (*S,S*)-1,2-diaminocyclohexane **1b** were compared. This synthesis provided unambiguous correlation of the newly formed stereocenter.

Keywords : Alkylation, sercocontrol, imidazoline, alkaloid.

We recently described[1] that the intermolecular alkylation of dianions derived from C_2 symmetric imidazolines proceeds with high acyclic stereoselectivity and affords quaternary carbon centers[2] by using as electrophiles either the particular 9-BBN triflate/THF system[3] or alkyl halides[1].



We wish to report herein our investigation extending this alkylation method to other C_2 symmetric imidazolines, and providing further synthetic goals. A concise synthesis of the natural isomer of mesembrine **11** allowed to establish the configuration of the newly formed stereocenter.

Although the natural (-)-mesembrine **11** is devoid of significant biological activity, it was selected over the years as a favourite target in organic synthesis[4]. In fact, the synthesis of this alkaloid, beyond a suitable ground to test new methodologies, provides access toward the more complex *Sceletium* alkaloids of pharmacological interest, such as tazettine, lycoramine or galanthamine[5].

The key steps of our sequence are (i) the stereoselective creation of the quaternary benzylic center and (ii) the hydrolysis of the imidazoline nucleus. Imidazolines, a masked carboxylic function, are indeed rather inert towards hydrolysis and this chemical stability probably precluded their wider use in synthesis. A mild methodology to overcome this difficulty and transform them to more flexible substrates is a long-time desired goal.

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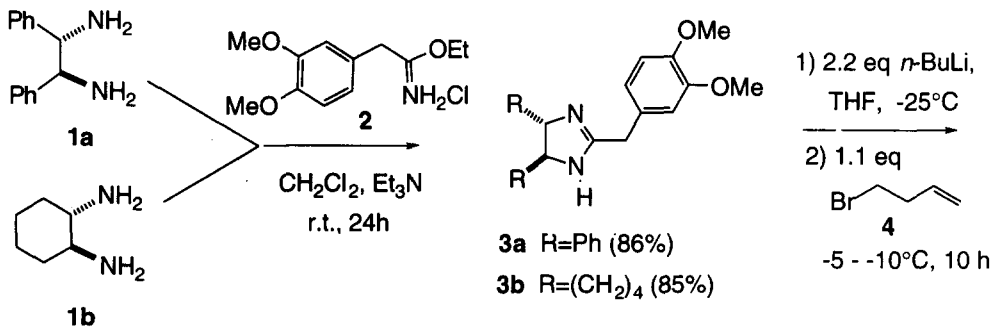
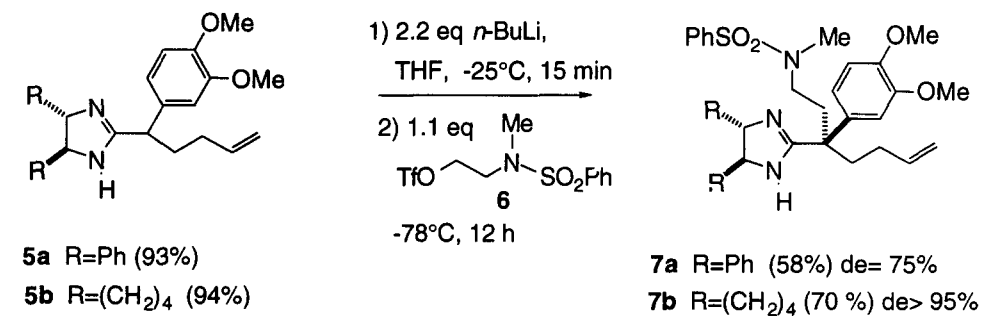
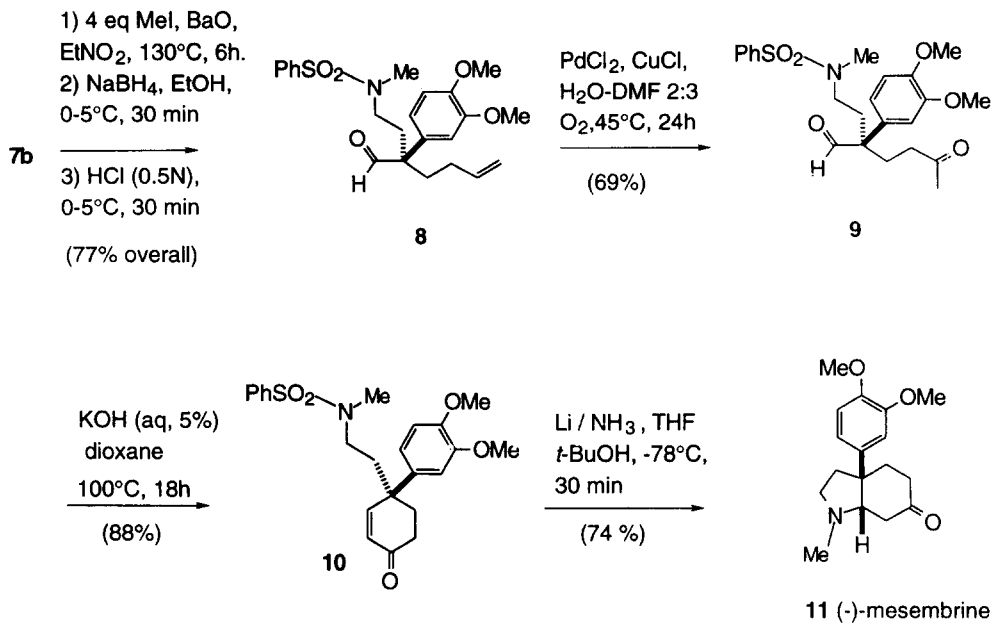
The starting imidazolines **5a** and **5b** were prepared in two steps using a classical condensation - alkylation sequence. Accordingly, compounds **3a** and **3b** were obtained by condensation reaction[3,6] of iminoether **2** with either the (*S,S*)-1,2-diamino-1,2-diphenylethane[7] **1a** and (*S,S*)-1,2-diaminocyclohexane[8] **1b**. Imidazoline derivatives **3a** and **3b**, after deprotonation using two equivalents of *n*-butyllithium at -25°C, were alkylated with 1.1 equiv of 4-bromobutene **4** at -5°C to -10°C and afforded imidazolines **5a**, **5b** in high yields after a regioselective side chain alkylation of imidazoline dianion intermediates.





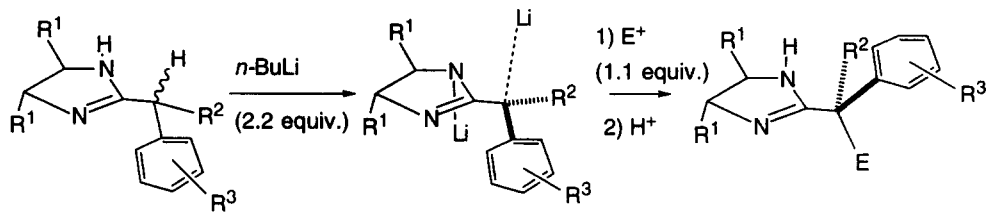
Dimetalation of **5a** and **5b**, using two molar equiv. of *n*-BuLi at -25°C, was performed as described previously[1]. After 15 minutes at this temperature, the reaction medium was cooled to -78°C and the triflate derivative **6**[9] was added. After 12 hours at -78°C, quaternary substituted imidazolines **7a** and **7b** were isolated in acceptable yields and in diastereomeric excess of 75% and more than 95% respectively[10].

For the synthesis of (-)-mesembrine **11**, the cyclohexyl derivative **7b** was selected. Attempted acidic hydrolysis of **7b** under "classical" conditions (5N H_2SO_4, reflux) resulted in the decomposition of the product. Although transformation of imidazolines to imidazolidines was reported recently[11] under Bouveault-Blanc conditions, **7b** stayed inert under these conditions. Nevertheless, the aldehyde **8** was obtained in a "one pot" three step sequence. Accordingly, imidazoline **7b** was *N*-permethylated using an excess of methyl iodide under pression in a sealed tube and the resulting imidazolinium derivative was in turn reduced with sodium borohydride. Without isolation, the aminal obtained was then converted in good overall yield to the desired aldehyde **8**[10] using 0.5N HCl.



The terminal olefin of **8** was subsequently converted to the corresponding methyl ketone **9**[10] under Wacker's conditions. The synthesis was completed by an intramolecular aldol reaction followed by cleavage of the phenylsulphonyl protecting group under Birch conditions, thus affording *in situ* the desired (-)-mesembrine **11**[12]. Beyond the access of the natural product this sequence allowed to establish unambiguously the absolute configuration of the quaternary carbon center.

Perhaps is it pertinent to speculate on the mechanism of the alkylation step. Recent investigations from our laboratory[1] showed that dilithiation occurs on the nitrogen of the cycle and the α-carbon, respectively and give rise a pyramidalized, thus stereogenic, metalled benzylic (carbon) center. The formation of such a chiral organolithium compound may be the consequence of either kinetic or thermodynamic factors. In the latter case the configuration of the carbometallated benzylic center would be determined by an optimal spatial and polar arrangement between the aryl group of the lateral chain, the functionalized heterocycle and the (coordinated and/or solvated) metal. The asymmetric induction of the alkylation is determined by the configuration of the lithiated benzylic carbon. According to earlier observations[13], alkylation could proceed with inversion of configuration in the benzylic position with regard to the lithium, using non complexing electrophiles[14], as depicted in the scheme. However, the origin of the difference of selectivity observed in the alkylation of imidazolines **5a** and **5b** is difficult to rationalise.



References and notes:

1. Dalko, P.I.; Langlois, Y. *J. Chem. Soc., Chem. Commun.* **1998**, 331-332.
2. For a reviews concerning asymmetric creation of quaternary carbon centers, see, a) Corey, E. J.: Guzman-Perez, A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 388-401; b) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037- 2066.
3. Dalko, P.I.; Langlois, Y. *Tetrahedron Lett.* **1992**, *33*, 5213-5216.
4. For recent enantioselective syntheses of mesembrine, see: a) Denmark, S.E.; Marcin, L. R. *J. Org. Chem.* **1997**, *62*, 1675-1686; b) Mori, M.; Kuroda, S.; Zhang, C. S.; Sato, Y. *J. Org. Chem.* **1997**, *62*, 3263- 3270; c) Yoshimitsu, T.; Ogasawara, K. *Heterocycles*, **1996**, *42*, 135-139; d) Nemoto, H.; Tanabe, T.; Fukumoto, K. *J. Org. Chem.* **1995**, *60*, 6788-6790. e) Kosugi, H.; Miura, Y.; Kanna, H.; Uda, H. *Tetrahedron: Asymmetry*, **1993**, *4*, 1409-1412. f) Yokomatsu, T.; Isawa, H.; Shibuya, S. *Tetrahedron Lett.* **1992**, *33*, 6999-7002.
5. Lewis, J. R. *Nat. Prod. Reports*, **1998**, *15*, 107-110 and references therein.
6. a) Dunn, P. J. "Amides and *N*-Substituted Amides" in *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R.; Meth-Cohn, O.; Rees, C. W. ed, Elsevier, Cambridge, UK., 1995; b) Meyers, A.I.; Knaus, G.; Kamata, K.; Ford, M. E. *J. Am. Chem. Soc.* **1976**, *98*, 567-576; c) Delaby, R.; Reynaud, P.; Lilly, F. *Bull. Soc. Chim. Fr.* **1961**, 2067-2071; d) Pridgen, L. N.; Killmer, L. B.; Webb, R. L. *J. Org. Chem.* **1982**, *47*, 1985-1989; e) Dox, A. V., *Organic Syntheses* Coll. Vol. I, 5-7, Wiley, New York, **1948**.
7. For a review of other applications of chiral 1,2-diphenyl-1,2-diaminoethane-derived reagents, see: Corey, E.J. *Pure Appl. Chem.* **1990**, *62*, 1209-1216.
8. For a review of other applications of *trans* 1,2-diaminocyclohexane derivatives, see: Bennani, Y.L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161-3195.
9. Other electrophiles such as iodide and *N*-Bn, *N*-OMe, *N*-Boc, *N*-Cbz, *N*-$COCF_3$ or *N*-Ts derivatives were useless in this reaction.
10. ^1H NMR, 250MHz, $CDCl_3$: **7b** : 7.6-7.3, m, 5H; 6.75, m, 3H; 5.8, m, 1H; 4.85-5.05, 2d, 2H; 4.2, m, 1H; 3.82, 3.78, 2s, 3H; 2.65, s, 3H. $[\alpha]_D$ -57 (c = 1.72, MeOH). **8** : 9.45, s, 1H; 7.70-7.25, m, 5H; 6.85-6.6, m, 3H; 3.65, s, 6H; 2.65, s, 3H; 2.05, s, 3H. **10** : 7.7-7.3, m, 5H; 7, d, 1H; 6.75, m, 3H; 6.1, d, 1H; 3.72, 3.68, 2s, 3H; 2.65, s, 3H.
11. Shi, Z.; Gu, H. *Synth. Commun.* **1997**, *27*, 2701-2707.
12. **11** : $[\alpha]_D$ -62 (c = 0.5, MeOH). Takano, S.; Imamura, Y.; Ogasawara, K. *Tetrahedron Lett.* **1981**, *22*, 4479-4482 : $[\alpha]_D$ -62.8 (c = 1.4, MeOH).
13. a) Thayumanavan, S.; Basu A.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 8209-8216; b) Hammerschmidt, F.; Hanninger, A.; Völlenkle H. *Chem. Eur. J.* **1997**, *3*, 1728-1732 and references cited.
14. a) Norsikian, S.; Marek, I.; Poisson, J.-F.; Normant, J.-F., *J. Org. Chem.* **1997**, *62*, 4898-4899; b) Klein, S.; Marek, I.; Poisson, J.-F.; Normant, J.-F. *J. Am. Chem. Soc.* **1995**, *117*, 8853-8854; c) Mück-Lichtenfeld, C.; Ahlbrecht, H., *Tetrahedron*, **1996**, *52*, 10025-10042.