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Formal Syntheses of (±)-Mesembrine and (±)-Dihydromaritidine

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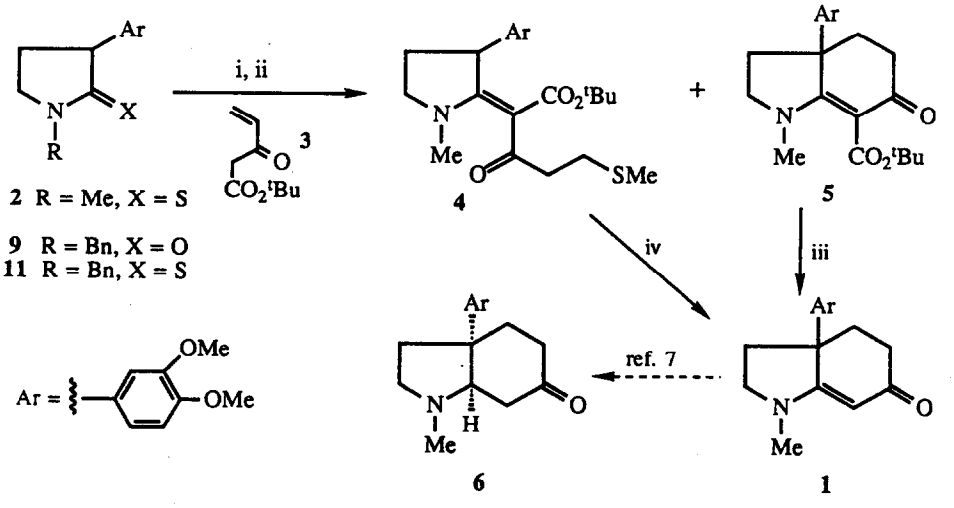
Key words: thiolactam; annulation; Δ^7-mesembrenone; mesembrine; dihydromaritidine

Abstract: Condensation of 3-arylated Δ^1-pyrrolinium salts with *t*-butyl 3-oxopent-4-enoate **3** followed by treatment with trifluoroacetic acid yielded the alkaloid Δ^7-mesembrenone **1** and its N-benzyl analogue **10**. These compounds are intermediates in formal syntheses of (±)-mesembrine **6** and (±)-dihydromaritidine **13**.

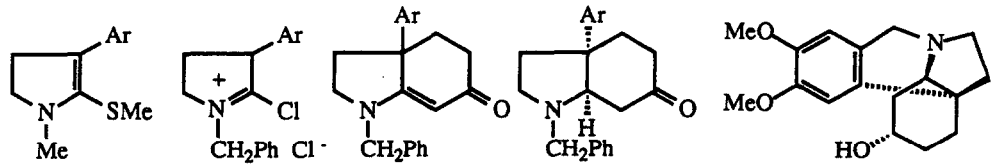
The alkaloid Δ^7-mesembrenone **1** is a minor constituent of *Sceletium namaquense*[1]. We previously reported an efficient synthesis of **1** (70% overall yield)[2] by a one-pot procedure involving alkylation of 1-methyl-3-arylpyrrolidine-2-thione **2** with chloromethyl vinyl ketone, spontaneous sulphide contraction[3], and cyclisation by a putative intramolecular conjugate addition. This method has since proved not to be general: the instability of the α-halocarbonyl compound and the rather vigorous conditions needed for the reaction (refluxing nitromethane) are experimental drawbacks, and the reaction fails for pyrrolidine-2-thiones lacking the 3-aryl group. We have recently described new methodology based on the condensation of alkyl 3-oxopent-4-enoates, *e.g.* **3**, with 2-methylthio-Δ^1-pyrrolinium salts that appears to be more flexible, if less efficient, for constructing the parent 1,2,3,3a,4,5-hexahydro-6*H*-indol-6-one nucleus of alkaloids such as **1**[4]. We now show the application of this methodology to the synthesis of (±)-Δ^7-mesembrenone **1** (Scheme).



Scheme. Reagents: (i) MeI, $CH_2C\ell_2$; (ii) **3**, NEt_3, $CH_2C\ell_2$, r.t.; (iii) TFA (3 eq), $CHC\ell_3$, ultrasound; (iv) neat TFA, ultrasound

Alkylation of thiolactam **2**[2] with iodomethane followed by reaction of the resulting 2-methylthio-Δ^1-pyrrolinium iodide with *t*-butyl 3-oxopent-4-enoate **3**[5] gave two products. Compound **4** (56%) results from the expected Knoevenagel-like condensation followed by interception of the enone by the liberated methanethiolate anion; and hexahydroindol-6-one **5** (17%) comes from conjugate addition of the competitively-formed enamine **7** to **3** followed by condensation. Both **4** and **5** yielded Δ^7-mesembrenone **1** after treatment with trifluoroacetic acid (71% from **4**, 82% from **5**), in accordance with the precedent we established previously[4]. The overall yield of the alkaloid from **2** is thus 53.3%. The synthesis of **1** also represents a formal synthesis of the popular target (±)-mesembrine **6**[6], since Takano and co-workers have demonstrated the reduction of **1** to **6** in 77% yield with lithium in liquid ammonia[7].

Although 2-alkylthio-Δ^1-pyrrolinium iodides are the preferred substrates for our studies owing to their accessibility and comparative stability, pyrrolinium salts with other leaving groups[8] may also be used. The sensitive 2-chloro-Δ^1-pyrrolinium chloride **8**, prepared *in situ* from lactam **9**[9] and phosgene, condensed sluggishly with **3** ($CHC\ell_3$, NEt_3, reflux, 48 h). Rather than isolating the condensation products, we added TFA (3 eq) directly to the reaction mixture, then subjected it to ultrasonic radiation. Lactam **9** was recovered in variable yield, but it was always accompanied by the desired hexahydroindol-6-one **10** (best result: **9**, 57% and **10**, 29%). This effectively represents an improved yield of **10** compared with our original annulation procedure, *viz.* heating thiolactam **11** with chloromethyl vinyl ketone[10] in nitromethane (37% yield). Bicyclic enaminone **10** was easily reduced to octahydroindol-6-one **12** with lithium in ammonia (76%). Other workers[11] have converted **12** into the Amaryllidaceae alkaloid[12] dihydromaritidine **13** by reduction, debenzylation and Pictet-Spengler cyclisation. Our preparation of **12** thus constitutes a formal synthesis of (±)-dihydromaritidine[13].



7 **8** **10** **12** **13**

References and Notes

1. Jeffs, P. W.; Capps, T.; Johnson, D. B.; Karle, J. M.; Martin, N. H.; Rauckman, B. *J. Org. Chem.* **1974**, *39*, 2703-2710.
2. Howard, A. S.; Katz, R. B.; Michael, J. P. *Tetrahedron Lett.* **1983**, *24*, 829-830.
3. (a) Roth, M.; Dubs, P.; Götschi, E.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 710-734; (b) Shiosaki, K. In *Comprehensive Organic Synthesis*; Trost, B. M. Ed.; Pergamon Press: Oxford, 1991; Volume 2, pp. 865-892.
4. Michael, J. P.; Zwane, M. I. *Tetrahedron Lett.*, in press.
5. Ohta, S.; Shimabayashi, A.; Hatano, S.; Okamoto, M. *Synthesis* **1983**, 715-716.
6. (a) Parkinson, C. J.; Pinhey, J. T. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1053-1057; (b) Gelas-Mialhe, Y.; Gramain, J.-C.; Hajouji, H.; Remuson, R. *Heterocycles* **1992**, *34*, 37-49; and references cited in both.
7. (a) Takano, S.; Imamura, Y.; Ogasawara, K. *Chemistry Lett.* **1981**, 1385-1386; (b) Takano, S.; Imamura, Y.; Ogasawara, K. *Tetrahedron Lett.* **1981**, *22*, 4479-4482.
8. Pommelet, J.-C.; Dhimane, H.; Chuche, J.; Celerier, J.-P.; Haddad, M.; Lhommet, G. *J. Org. Chem.* **1988**, *53*, 5680-5685, and references cited therein.
9. Made from the dianion of N-benzyl-(3,4-dimethoxyphenyl)acetamide and $BrCH_2CH_2Cl$ in THF - HMPA at -70°C. Subsequent thionation with Lawesson's reagent in toluene gave a 51% yield of **11**.
10. Made by appropriate modification of the method described by Danishefsky, S.; Migdalof, B. H. *J. Am. Chem. Soc.* **1969**, *91*, 2806-2807.
11. (a) Hoshino, O.; Sawaki, S.; Shimamura, N.; Onotlera, A.; Umezawa, B. *Chem. Pharm. Bull.* **1987**, *35*, 2734-2743; (b) Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1978**, *34*, 2579-2586. We are grateful to Professor Speckamp for supplying copies of the spectra of **12**.
12. Martin, S. F. The Amaryllidaceae Alkaloids. In *The Alkaloids. Chemistry and Pharmacology*; Brossi, A. Ed; Academic Press: New York, 1987; Volume 30, pp. 252-376.

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