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SCELETIUM (AIZOACEAE) ALKALOIDS: TOTAL SYNTHESIS OF RACEMIC MESEMBRANONE, JOUBERTINAMINE AND EPIJOUBERTINAMINE[1,2]

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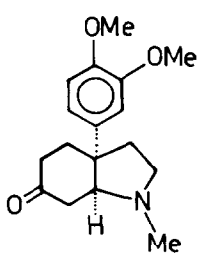
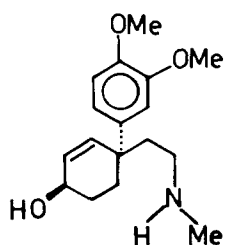
Abstract. The total synthesis of the *Sceletium* alkaloids mesembranone, joubertinamine and epijoubertinamine *via* the intramolecular cyclization of an enone to a benzensulfonamide grouping under the conditions of a dissolving metal reduction is described.

Chemical interest in the constituents of certain *Sceletium* (family Aizoaceae) species which are indigenous to Southwest Africa[3], has resulted from their occurrence in the preparation known as "Channa" or "Kougoed"[4]. Such studies have culminated in the total synthesis of several representative mesembrane[5] and seco-mesembrane alkaloids[6]. However, the synthetic significance of these alkaloids arises fully upon the recognition of its close structural relationship with the more complex 5, 10b-ethanophenanthridine (Amaryllidaceae) alkaloids[7]. Since both families incorporate a functionalized *cis*-3a-aryloctahydroindole nucleus, the development of efficient methodologies for its construction will result in general synthetic entries to either series.



I



II

We now report a short general method of synthesis, applicable to both the mesembrane and seco-mesembrane members of the *Sceletium* alkaloids, that allows the direct attachment of the required nitrogenous side chain, as a protected ethanolamine derivative, to a substituted arylacetonitrile.

In this manner, 3,4-dimethoxyphenylacetonitrile[8] (1) was reacted (THF, nBuLi, -25°) with O,N-bisbenzenesulfonyl-N-methylethanolamine, mp 59-60°[9,10] to furnish the oily sulfonamide 2 in 96% yield (Scheme). Subsequent reduction with diisobutylaluminum hydride[11] (DIBAL, benzene, 0°, 2h) generated aldehyde 3 as a viscous oil in 80% yield. Robinson annulation[12] of this intermediate (MVK in THF using a catalytic amount of DBN[13] at 0°, followed by heating with 20% (v/v) methanolic hydrochloric acid) afforded enone 4 in 67% overall yield.

In order to complete our synthetic scheme, enone 4 was submitted to a metal in liquid ammonia reduction[14] (excess sodium in dry DME-NH_3) to give racemic mesembranone (I) in 82% yield after purification by chromatography on grade III neutral alumina. To the best of our knowledge this is the first example of an intramolecular cyclization *via* displacement of benzenesulfinic acid (as its salt) from a properly located benzenesulfonamide grouping during the dissolving metal reduction of an enone to generate in one step the required *cis*-3a-aryloctahydroindol-6-one nucleus characteristic of the mesembrane alkaloids (Figure).

On the other hand, enone 4 was first reduced with DIBAL[11] (toluene, -78°, 3h) to the oily 4,4-disubstituted cyclohexenol 5 in 91% yield (isolated as an inseparable mixture of isomers in which the relevant methine proton was observed as a multiplet, W1/2=16 Hz, at δ 4.10-4.40 ppm). Treatment of this mixture with nBuLi (DME, -78°, 0.5h) afforded the corresponding lithium alkoxides, which upon reductive splitting[14] of the N-benzenesulfonyl moiety furnished an easily separable mixture of racemic joubertinamine[15] (11) and epijoubertinamine (6) in 94% overall yield. The ratio of 11:6 (colorless oils) was shown to be 81:19 by spectroscopic methods. Thus, the two isomers are clearly distinguishable from their pmr spectra since the C-1 methine in 11 appears as a dd at δ 4.40-4.30, showing J_{ae}=4 Hz and J_{aa}=9 Hz, while 6 shows instead a multiplet (W1/2=9 Hz) at 4.05-4.25 ppm.

As expected[16], active manganese dioxide oxidation[17] of the crude mixture of 11 and 6 afforded racemic I in 76% yield, identical in all respects to the sample obtained previously (*vide supra*) by our reductive method.

Obviously the synthetic strategy outlined in these transformations may be applied to the total synthesis of a number of mesembrane and/or seco-mesembrane-like *Sceletium* alkaloids[18] and such results, together with their conversion to 5,10b-ethanophenanthridines will be reported elsewhere.

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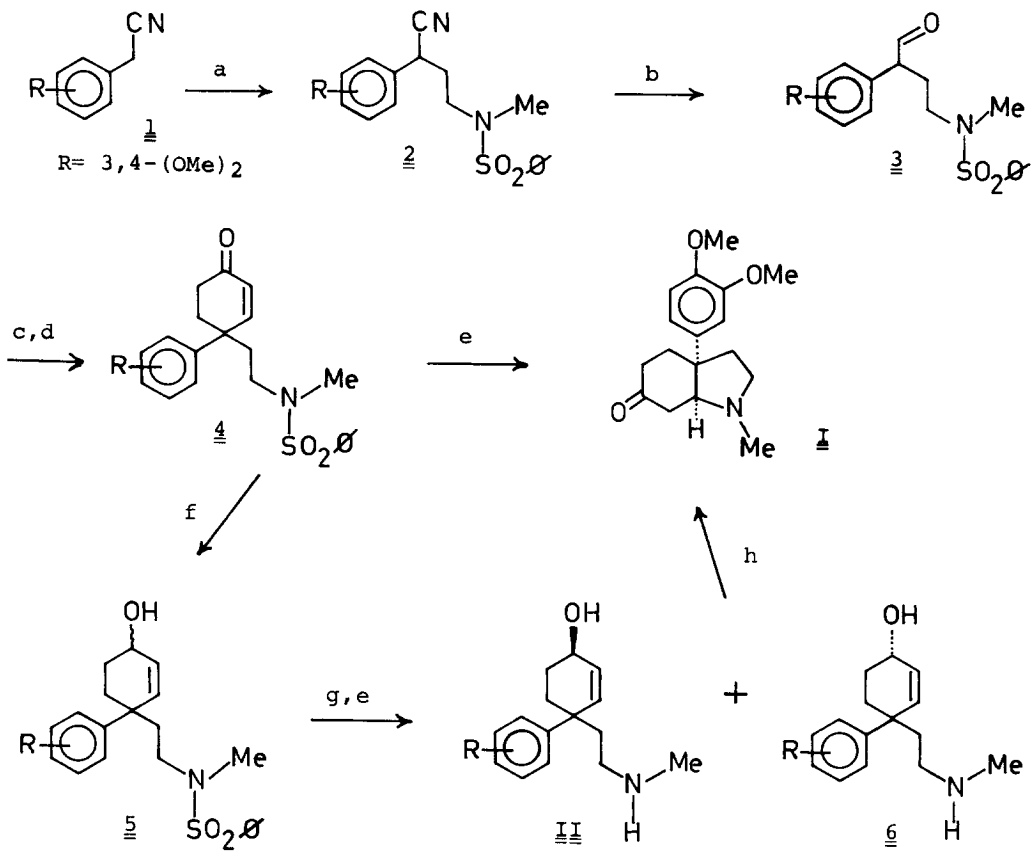
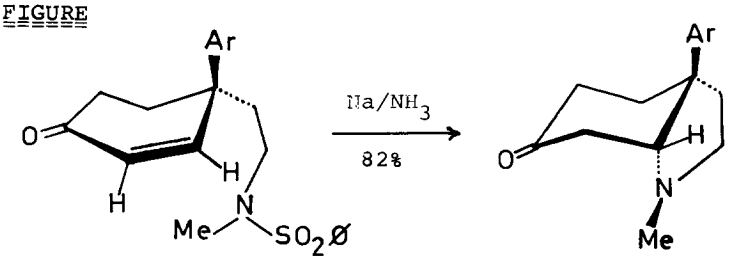
Scheme:



a) nBuLi/ $C_6H_5SO_2O-(CH_2)_2N(CH_3)SO_2C_6H_5$; b) DIBAL, 0°; c)MVK/DBN; d) HCl/MeOH; e) Na/NH_3-DME; f) DIBAL, -78°; g) nBuLi; h) MnO_2.

FIGURE



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