

TOTAL SYNTHESIS OF SCELETIUM (AIZOACEAE) ALKALOIDS.
 THE CINNAMONITRILE ROUTE. THE TOTAL SYNTHESIS OF RACEMIC O-METHYL
 JOUBERTIAMINE AND MESEMBRINE ^{1,2}

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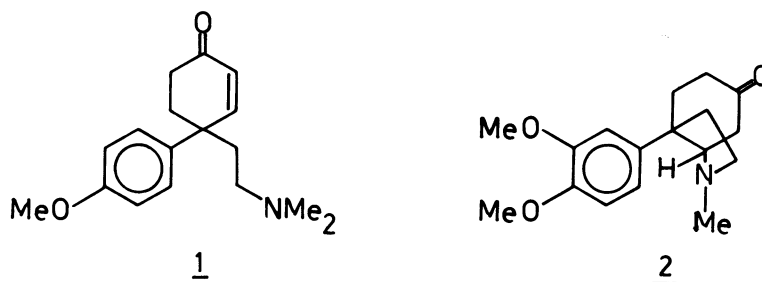
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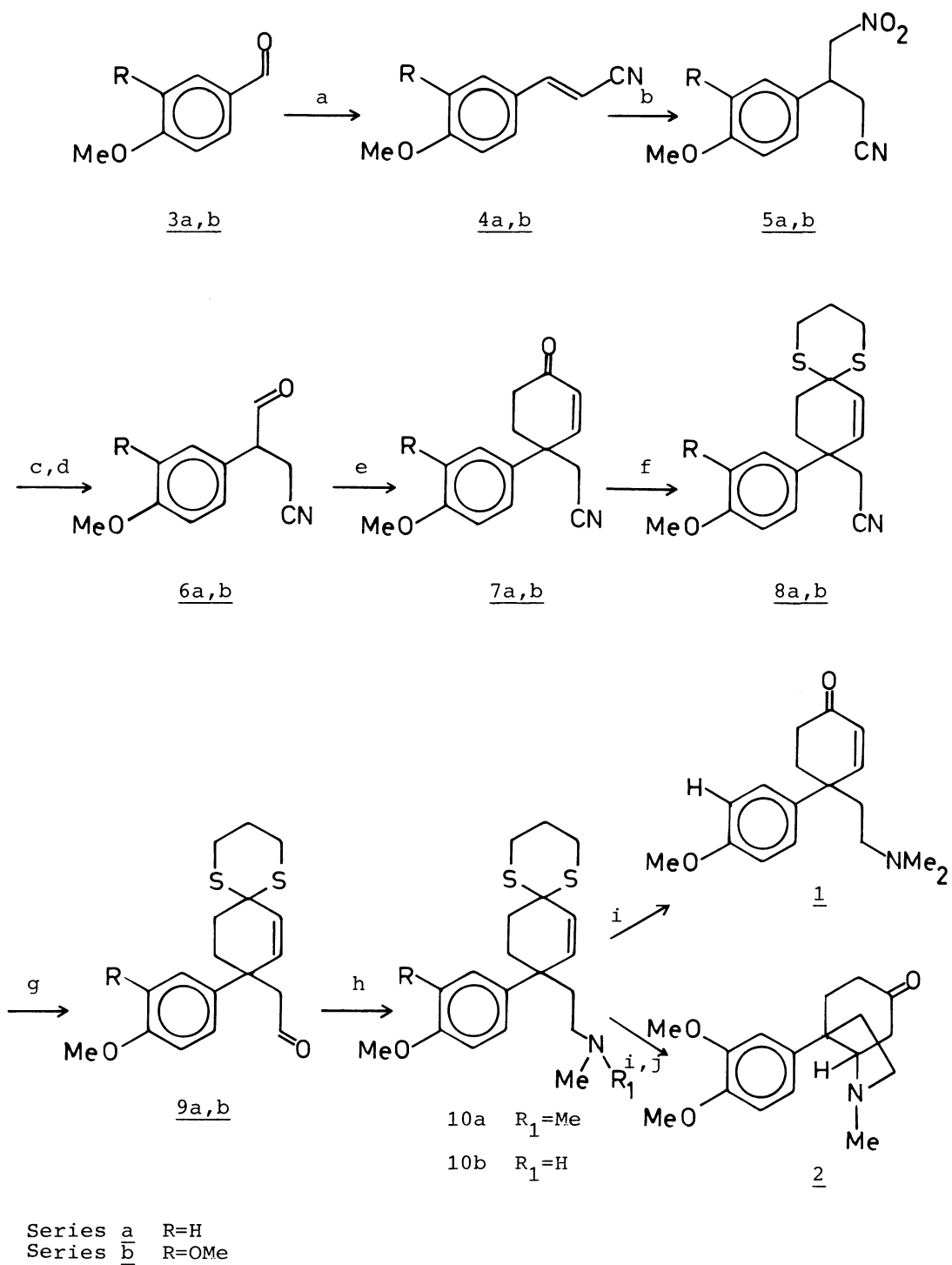
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A new method of synthesis of Sceletium (Aizoaceae) alkaloids based on the introduction of a "formyl anion" equivalent at the β -position of a cinnamitrile, followed by Robinson annulation and final modification of the resulting cyanomethyl side chain is described. The method has been successfully applied to the total synthesis of racemic O-methyljoubertiamine (1) and mesembrine (2).

Chemical interest in the constituents of certain Sceletium species (family Aizoaceae), which are indigenous to Southwest Africa, has resulted from their occurrence in the pharmacologically interesting³ preparation known as "Channa" or "Kougloed".⁴ Such studies have culminated in the total synthesis of several representative mesembrane and seco-mesembrane alkaloids.⁵



We now report a new method for the synthesis of such alkaloids based on the utilization of the readily available cinnamitriles as precursors of both the aromatic ring and the nitrogenous side chain. The hydroaromatic portion of the molecule will be then constructed via the introduction of a "formyl anion" equivalent at the β -position of the starting cinnamitrile followed by a Robinson annulation and final modification of the resulting cyanomethyl side chain. The method has been successfully applied to the total synthesis of racemic O-methyljoubertiamine (1) and mesembrine (2).



a) $\text{CH}_3\text{CN}/\text{KOH}$; b) Series a: $\text{CH}_3\text{NO}_2/\text{KF}/18\text{-crown-6}$; Series b: $\text{CH}_3\text{NO}_2/\text{Triton B}$; c) 1. MeONa/MeOH ; 2. $\text{H}_2\text{SO}_4/\text{MeOH}$; d) $\text{HCl}-\text{H}_2\text{O}$; e) 1. MVK/DBN ; 2. $\text{C}_5\text{H}_{11}\text{N}-\text{HOAc}$; f) $\text{BF}_3 \cdot \text{Et}_2\text{O}/\text{HS}(\text{CH}_2)_3\text{SH}$; g) $i\text{Bu}_2\text{AlH}$; h) Series a: $\text{Me}_2\text{NH} \cdot \text{HCl}/\text{NaCNBH}_3$; Series b: $\text{MeNH}_2 \cdot \text{HCl}/\text{NaCNBH}_3$; i) NCS/AgNO_3 ; j) Amberlyst-15

In this manner, the appropriate substituted benzaldehyde 3a (R=H) or 3b (R=OMe) was condensed with acetonitrile under the conditions described by Gokel⁶ to produce in nearly quantitative yield an 85:15 mixture of the corresponding *E*- and *Z*-cinnamitriles, respectively. Pure 4a, mp 64-65°, and 4b, mp 97-98°, were obtained by direct crystallization of the reaction mixture from ether-hexane and were used in all subsequent reactions.⁷

Next, and in order to introduce the missing C₁-unit, a 1,4-addition using nitromethane as the required "formyl anion" equivalent was attempted (Scheme). The reaction proceeded well either under anhydrous potassium fluoride/18-crown-6 ("naked" fluoride) catalysis (series a, 90% yield) or in the presence of a catalytic amount of Triton B in refluxing acetonitrile (series b, 70% yield). The resulting nitromethyl derivatives 5a (oily)⁹ and 5b, mp 101-103° (ethyl acetate-hexane),⁹ were then submitted to Jacobson's modification¹⁰ of the Nef reaction followed by immediate hydrolysis of the corresponding (crude) acetal intermediates with 10% HCl in refluxing acetone overnight. The oily cyanoaldehydes 6a (2,4-dinitrophenylhydrazone mp 179.5-180.5°)⁹ and 6b⁹ were isolated in 60 and 73% overall yield, respectively.

The characteristic 4,4-disubstituted cyclohex-2-en-1-one system of the seco-mesembrane alkaloids was then constructed via a normal Robinson annulation,¹¹ namely an initial DBN-catalyzed¹² 1,4-addition of methylvinylketone (MVK) followed by an internal aldol condensation. When pyrrolidine-glacial acetic acid¹³ was used as the catalyst for the final cyclization step, an overall 50 and 48% yield of the crystalline enones 7a, mp 107-108° (ether-hexane)⁹ and 7b, mp 131-132° (ethyl acetate-hexane),⁹ respectively, was realized.

Before the final modification of the side chain was attempted, it became necessary to protect the enone grouping and this was readily achieved by treatment with 1,3-propanedithiol and boron trifluoride etherate in dry dichloromethane at 0°. In this manner, the corresponding propilenedithioketals 8a (mp 76-78°, 59% yield)⁹ and 8b (oily, 73% yield)⁹ were isolated after preparative layer chromatography on silica gel, and were further reduced with diisobutylaluminum hydride (DIBAL)¹⁴ in dry toluene at -78° to the oily acetaldehyde derivatives 9a⁹ and 9b.⁹

In order to complete our synthetic scheme, aldehyde 9a (R=H) was first treated with dimethylamine hydrochloride and sodium cyanoborohydride (NaCNBH₃)¹⁵ in dry *t*-butanol to afford a 53% yield of the oily amine 10a,⁹ which upon deprotection with the *N*-chlorosuccinimide-silver nitrate reagent¹⁶ in wet acetonitrile yielded racemic *O*-methyljoubertiamine (1).¹⁷

On the other hand, aldehyde 9b (R=OMe) was reductively aminated¹⁵ using methylamine hydrochloride/NaCNBH₃. The resulting amine 10b (crude) was deprotected as before¹⁶ and further treated with a catalytic amount of the sulfonic resin Amberlyst-15 in warm benzene to produce racemic mesembrine (2), identical in all respects with authentic material,¹⁷ in 35% overall yield.

Obviously, the chemistry and synthetic strategy involved in these reaction sequences may be conveniently applied to the total synthesis of a number of Sceletium alkaloids possessing the seco-mesembrane or mesembrane skeleton and such results will be reported independently.

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