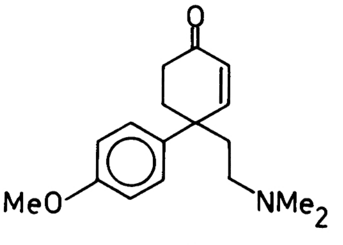
CHEMISTRY LETTERS, pp. 891-894, 1981. © The Chemical Society of Japan 1981

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

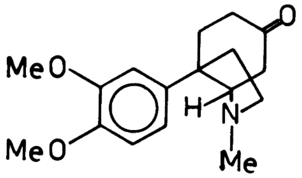
Ignacio H. SANCHEZ*
Departamento de Química Orgánica, División de Estudios de Posgrado,
Facultad de Química, Universidad Nacional Autónoma de México, México
20, D. F., MEXICO
F. Ramón TALLABS
División de Estudios Superiores, Facultad de Ciencias Químicas e
Industriales, Universidad Autónoma del Estado de Morelos, Cuernavaca,
Morelos, MEXICO.

A new method of synthesis of Sceletium (Aizoaceae) alkaloids based on the introduction of a "formyl anion" equivalent at the β-position of a cinnamonitrile, 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 interesting[3] preparation known as "Channa" or "Kougoed".[4] Such studies have culminated in the total synthesis of several representative mesembrane and seco-mesembrane alkaloids.[5]

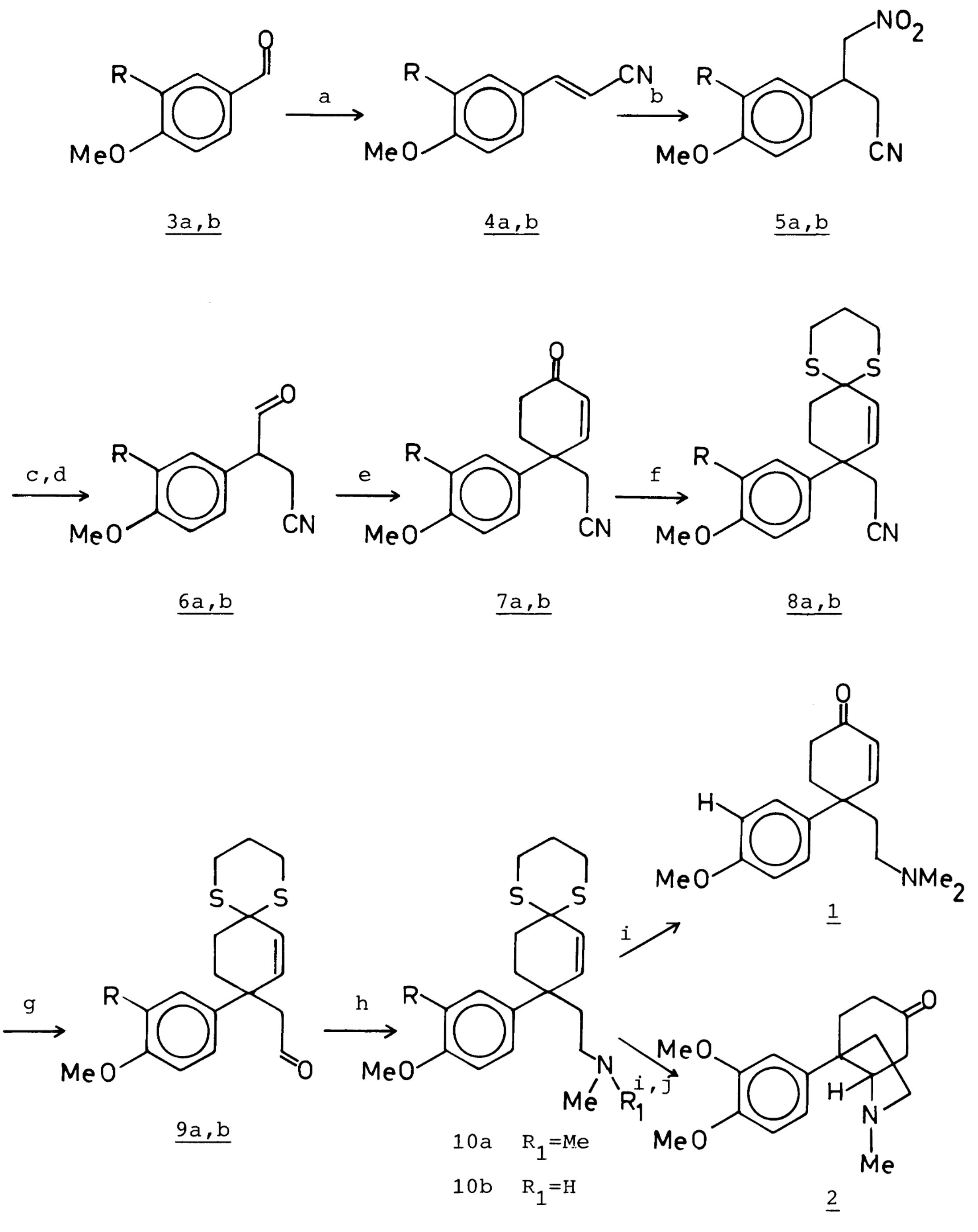


1



2

We now report a new method for the syntesis of such alkaloids based on the utilization of the readily available cinnamonitriles 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 cinnamonitrile 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).



Series a R=H
Series b R=OMe

a) CH_3CN/KOH; b) Series a: CH_3NO_2/KF/18-crown-6; Series b: CH_3NO_2/Triton B; c) 1. MeONa/MeOH; 2. H_2SO_4/MeOH; d) $HCl-H_2O$; e) 1. MVK/DBN; 2. $C_5H_{11}N$-HOAc; f) $BF_3 \cdot Et_2O/HS(CH_2)_3SH$; g) iBu_2AlH; h) Series a: $Me_2NH.HCl/NaCNBH_3$; Series b: $MeNH_2.HCl/NaCNBH_3$; 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 Gokel[6] to produce in nearly quantitative yield an 85:15 mixture of the corresponding E- and Z-cinnamonitriles, 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 C_1-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 modification[10] 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 6b[9] 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-catalyzed[12] 1,4-addition of methylvinylketone (MVK) followed by an internal aldol condensation. When pyrrolidine-glacial acetic acid[13] 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 neccessary 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 9a[9] and 9b.[9]

In order to complete our synthetic scheme, aldehyde 9a (R=H) was first treated with dimethylamine hydrochloride and sodium cyanoborohydride ($NaCNBH_3$)[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 reagent[16] in wet acetonitrile yielded racemic O-methyljoubertiamine (1).[17]

On the other hand, aldehyde 9b (R=OMe) was reductively aminated[15] using methylamine hydrochloride/$NaCNBH_3$. The resulting amine 10b (crude) was deprotected as before[16] 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.

Aknowledgements. Financial support from Consejo Nacional de Ciencia y Tecnología CCONACYT), México, Grant PCCBNAL 790199 is greatly appreciated. One of us (F. R. T.)

thanks the Universidad Autónoma del Estado de Morelos, Cuernavaca, Morelos, and the Universidad Nacional Autónoma de México for a postgraduate scholarship.

References

1. Taken in part from the M. Sc. thesis of F. R. T. to the Universidad Autónoma del Estado de Morelos (1980).
2. Presented at the XIV Mexican Congress of Pure and Applied Chemistry of the Chemical Society of México, Monterrey, N. L., México, 1979.
3. J. M. Watt and M. G. Breyer-Brandwijk, "The Medicinal and Poisonous Plants of Southern and Eastern Africa", E. and S. Livingstone, Ltd., London, 1962, p. 11-12; T. Ohishi and H. Kugita, Japanese Patents 7143538 (Chem. Abstr., **76**, 59442t (1972)) and 7143539 (Chem. Abstr., **76**, 59443u (1972)).
4. E. M. Holmes, Pharm. J. Trans., **9**, 810 (1874); C. F. Juritz, Rep. Jt. Meet. Brit. Assn. Adv. Sci., **1**, 216 (1905).
5. For general methods of synthesis in the *Sceletium* alkaloid series see: R. V. Stevens, "Alkaloid Synthesis" in The Total Synthesis of Natural Products, J. ApSimon, editor, Wiley-Interscience, New York, 1977, vol. 3, p. 439; R. V. Stevens, Accts. Chem. Res., **10**, 193 (1977); S. F. Martin, Tetrahedron, **36**, 419 (1980); S. F. Martin, T. A. Puckette, and J. A. Colapret, J. Org. Chem., **44**, 3391 (1979) and references cited therein.
6. G. W. Gokel, S. A. Dibiase and B. A. Lipisko, Tetrahedron Lett., 3495 (1976); S. A. Dibiase, B. A. Lipisko, A. Haag, R. A. Wolak and G. W. Gokel, J. Org. Chem., **44**, 4640 (1979).
7. The crude *E*- and *Z*-cinnamonitrile mixture can also be used in the described sequences without modification of the reaction conditions.
8. I. Belsky, J. Chem. Soc. Chem. Comm., 237 (1977).
9. All new compounds were adequately characterized by spectral methods (IR, NMR and MS) and gave satisfactory high resolution mass spectral and/or combustion analytical data.
10. R. M. Jacobson, Tetrahedron Lett., 3215 (1974).
11. M. E. Jung, Tetrahedron, **32**, 3 (1976); R. E. Gawley, Synthesis, 777 (1976).
12. C. D. DeBoer, J. Org. Chem., **39**, 2426 (1974).
13. Ae. de Groot and B. J. M. Jansen, Tetrahedron Lett., 2709 (1976).
14. E. Winterfeldt, Synthesis, 617 (1975).
15. R. F. Borch, M. D. Bernstein and H. D. Durst, J. Am. Chem. Soc., **93**, 2897 (1971).
16. E. J. Corey and B. W. Erickson, J. Org. Chem., **36**, 3553 (1971).
17. We are indebted to Professors R. V. Stevens of Rice University and S. F. Martin of the University of Texas at Austin for kindly providing us with comparison spectra of O-methyljoubertiamine and mesembrine.

(Received April 13, 1981)