Pergamon

Tetrahedron Letters, Vol. 35, No. 44, pp. 8145-8146, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01797-2

A Short Synthesis of (±)-Tortuosamine

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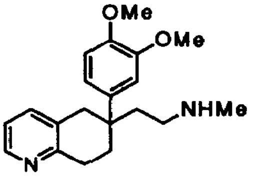
Key Words: Intramolecular $S_{RN}1$, Sceletium Alkaloid, (±)-Tortuosamine.

Abstract: A four-step synthesis of (±)-tortuosamine (1) is described. The key ring closure was an intramolecular $S_{RN}1$ reaction between a ketone enolate and a 2-halopyridine.

Tortuosamine (1) is one of the Sceletium alkaloids isolated in 1971.[1] To date there have been three syntheses of 1 reported in the literature, all of which involve fabrication of the pyridine ring.[2] Herein, we would like to describe our work in this area which has lead to an efficient synthesis of this natural product employing a completely different strategy.



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Our synthesis was guided by our continuing interest in intramolecular $S_{RN}1$ reactions.[3] Thus, addition of the anion of 3,4-dimethoxyphenylacetone (2) (LDA, THF, -23°C) to a solution of the chloroamine free-base 3[4] gave the aminoketone 4 in 64% yield.[5] Alkylation of the anion of 4 (LDA, THF, -78°C) with 2-bromo-3-bromomethylpyridine (5)[6] gave the pyridylketone 6 in 83% yield, providing us with the substrate for our intramolecular $S_{RN}1$ reaction.[7,8] Treatment of 6 with 2.5 equivalents of LDA (THF, 0°C) and irradiation[9,10] effected cyclization to afford the product (as its enolate 7) which was trapped by reaction with N-phenyltriflimide to give the vinyl triflate 8 in 59% yield. Hydrogenation reduced the vinyl triflate to the saturated hydrocarbon with concomitant removal of the benzyl group to give a 91% yield of (±)-tortuosamine (1) whose spectral data were in agreement with those reported in the literature.[2a]

In summary, we have completed a short, photochemical-based synthesis of (±)-tortuosamine (1). This is one of a growing number of applications of the intramolecular $S_{RN}1$ reaction to the synthesis of natural products.[11]

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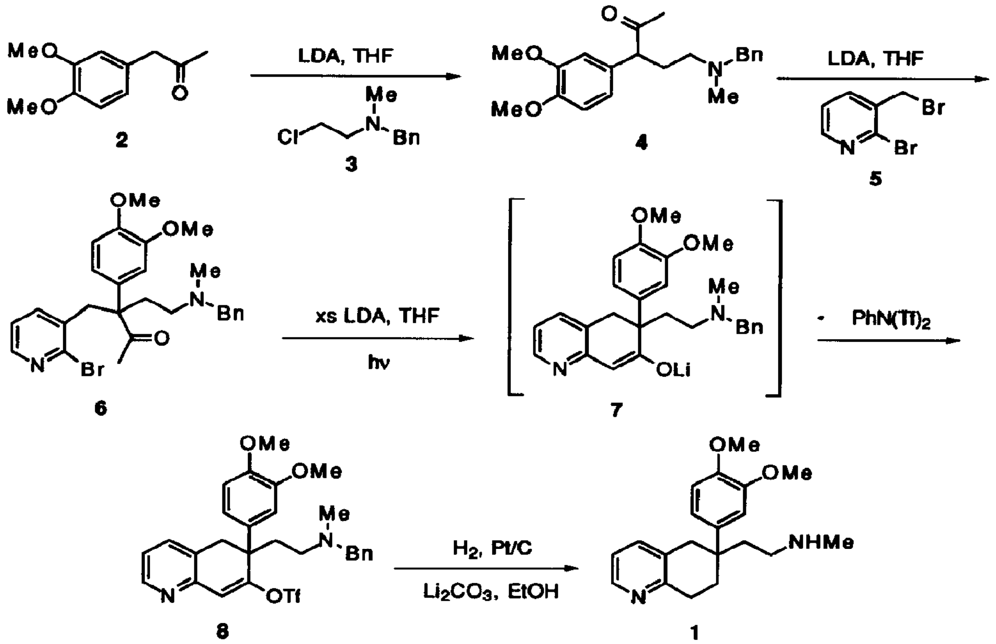

Acknowledgement. We thank the Faculty Research and Professional Development Fund (North Carolina State University) for financial support and Professor D.L. Comins for the use of equipment and laboratory space.

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4. Chloroamine free-base **3** was prepared in situ by neutralization of the HCl salt (Aldrich) with LDA (THF, -78°C).
5. All yields refer to chromatographically pure compounds for which satisfactory ^{1}H and ^{13}C NMR, IR and combustion analyses were obtained.
6. Prepared from 2-bromopyridine (i. LDA, formaldehyde; ii. PBr_3). See also: Rebek, Jr., J.; Costello, T.; Wattley, R. J. Amer. Chem. Soc. **1985**, 107, 7487.
7. For the intermolecular $S_{RN}1$ reaction of halopyridines with ketone enolates, see: Komin, A.P.; Wolfe, J.F. J. Org. Chem. **1977**, 42, 2481.
8. For the intramolecular $S_{RN}1$ reaction of carboaromatic halides with ketone enolates, see: Semmelhack, M.F.; Bargar, T. J. Amer. Chem. Soc. **1980**, 102, 7765, and references cited therein.
9. Irradiation was performed with a Hanovia 450-W high-pressure Hg-vapor lamp.
10. When the cyclization reaction was run in the dark or in the presence of a catalytic amount of di-tert-butyl nitroxide, only trace amounts of product were detected by ^{1}H NMR.
11. For recent examples of the application of intramolecular $S_{RN}1$ reactions to the synthesis of natural products, see: (a) Ref. 3c. (b) Staskun, B.; Wolfe, J.F. S. Afr. J. Chem. **1992**, 45, 5 (Chem. Abstr. **1992**, 117, 90001n). (c) Martin, S.F.; Liras, S. J. Amer. Chem. Soc. **1993**, 115, 10450.

(*Received in USA* 17 *August* 1994; *accepted* 8 *September* 1994)