An Extremely Short, Stereoselective Synthesis of (±)-Tetraponerine-8

José Barluenga,* Miguel Tomás, Vladimir Kouznetsov, and Eduardo Rubio

Instituto Universitario de Química Organometálica "Enrique Moles", Campus del Cristo. Universidad de Oviedo, 33071 Oviedo, Spain

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In 1987 Braekman *et al.* reported the isolation and the structure determination of the tetraponerines,[1] a family of tricyclic alkaloids segregated as a defense mechanism by the New Guinean ant *Tetraponera* sp., whose main structural feature is a highly unusual aminal moiety. Soon afterward they presented the first total synthesis of tetraponerine-8 (**1**), the major constituent of this venom.[2] At the present time only three other multistep approaches have been described for this alkaloid, two by Jones[3] and the first enantioselective synthesis by Husson's group.[4]

We are currently engaged in developing new strategies for the construction of heteropolycyclic compounds of biological interest. In this context, we have recently reported the preparation of a new class of semicyclic azabutadienes **3** and tested their synthetic potential by preparing condensed pyrimidines[5] and pyrroles.[6] We have envisaged that a straightforward access to the tetraponerine skeleton would simply involve a tandem cyclization/reduction of the azadiene **3**, which is in turn readily available from δ-valerolactam, as shown in Figure 1. On the basis of this realization we report here that (±)-T-8 (**1**) is synthesized in one-pot by the sequential condensation of azabutadiene **3** with 4-bromobutyraldehyde, followed by reduction with sodium borohydride.

The preparation of the azadiene **3** is accomplished from the readily available imine **2**;[7] hence, slow addition of a solution of hexanenitrile to the metalated imine **2** at −78 °C, followed by stirring at the same temperature for 30 min, and aqueous workup resulted in the formation of pure azadiene **3** in nearly quantitative yield (Scheme 1).[8]

This material was not purified, but it was used in the crucial next step, which implies the assembling of the tricyclic structure in a one-pot procedure. Thus, **3** was allowed to react overnight with 4-bromobutyraldehyde[9] in refluxing tetrahydrofuran in the presence of anhydrous sodium sulfate as dehydrating agent; the sodium sulfate was then filtered off and the presumed pyrimidinium salt **4** was reduced at −20 °C with sodium borohydride in THF/MeOH. After workup and chromatographic purification, racemic tetraponerine-8 was isolated as the sole stereoisomer in 67% yield (Scheme 2).

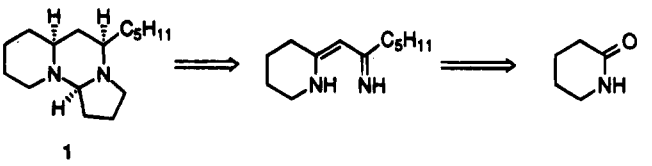
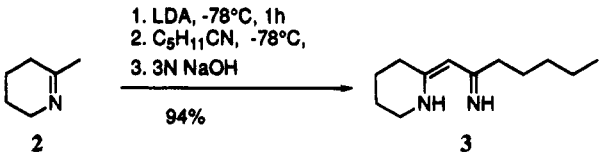
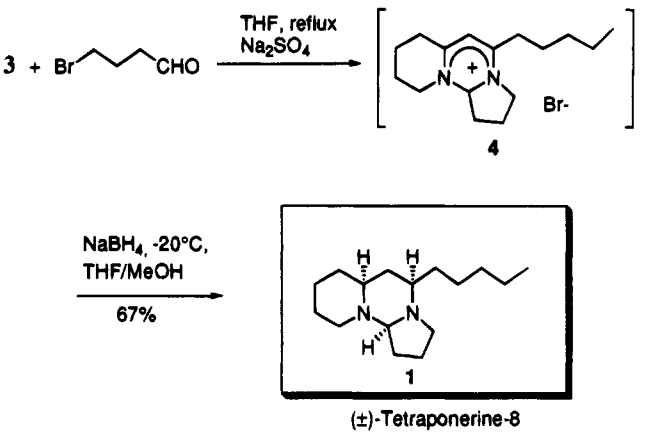


Figure 1.

Scheme 1



Scheme 2



In conclusion, we have achieved the most straightforward, high yield synthesis of the alkaloid tetraponerine-8 based on the facile cyclization of 4-amino-1-azadienes to the dihydropyrimidine ring and its hydride reduction.[5,10] Moreover, this methodology involves only inexpensive, readily available materials (δ-valerolactam, hexanenitrile, and 4-bromobutyraldehyde) and should allow the obtention of the product in multigram quantities.

Experimental Section

General Methods. All reagents were of commercial quality (Aldrich). Solvents used in reactions were dried and distilled before use according to standard procedures. Solvents used in extractions were distilled prior to use. Flash column chromatography was performed on silica gel (grade 60, Merck). ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ (compound **3**) and C_6D_6 (compound **1**) at 300 and 75 MHz, respectively. Mass spectra were obtained by EI (70 eV).

4-Amino-1-azabutadiene (3). To freshly prepared LDA (11 mmol) in THF (10 mL) was added at −78 °C imine **2** (0.97 g, 10 mmol) in anhydrous THF (25 mL) during 30 min. Then hexanenitrile (1.2 g, 12 mmol) in THF (25 mL) was slowly added over a period of 2 h. After the addition was complete, the reaction was stirred for another 30 min, keeping the temperature constant at −78 °C, and then quenched with 3 N NaOH, extracted with ether (3 × 25 mL), and dried over anhydrous sodium sulfate. The organic layer was concentrated at reduced pressure to afford **3** (1.8 g, 94%) as an orange oil which was used without purification in the next step: ^1H NMR ($CDCl_3$) δ 0.8 (t, 3H), 1.2–1.6 (m, 10H), 2.1 (t, 2H), 2.3 (t, 2H), 3.5 (t, 2H), 4.3 (s, 1H); ^{13}C NMR ($CDCl_3$)

(1) Merlin, P.; Braekman, J.-C.; Daloze, D.; Pasteels, J.-M. *J. Chem. Ecol.* **1988**, *14*, 517.
(2) (a) Merlin, P.; Braekman, J.-C.; Daloze, D. *Tetrahedron Lett.* **1988**, *29*, 1691. (b) Merlin, P.; Braekman, J.-C.; Daloze, D. *Tetrahedron* **1991**, *47*, 3805.
(3) (a) Jones, T. H. *Tetrahedron Lett.* **1990**, *31*, 1535. (b) Jones, T. H. *Tetrahedron Lett.* **1990**, *31*, 4543.
(4) Yue, C.; Royer, J.; Husson, H.-P. *J. Org. Chem.* **1990**, *55*, 1140.
(5) Barluenga, J.; Tomás, M.; Kouznetsov, V.; Rubio, E. *Synlett* **1992**, 563.
(6) Barluenga, J.; Tomás, M.; Kouznetsov, V.; Rubio, E. *J. Chem. Soc., Chem. Commun.* **1992**, 1419.
(7) Imine **2** is easily made from δ-valerolactam, see: Hua, D. H.; Miao, S. W.; Bharathi, S. N.; Katsuhira, T.; Bravo, A. A. *J. Org. Chem.* **1990**, *55*, 3682.
(8) Strict control of the reaction conditions is crucial in order to avoid contamination with products derived from an acid–base equilibrium between the metalated imine and the nitrile.
(9) For the synthesis of 4-bromobutyraldehyde, see: Stork, G.; Kobayashi, Y.; Suzuki, T.; Zhao, K. *J. Am. Chem. Soc.* **1990**, *112*, 1661.
(10) Barluenga, J.; Tomás, M. *Adv. Heterocycl. Chem.* **1993**, *57*, 1.

0022-3263/94/1959-3699$04.50/0

δ 13.7 (CH_3), 19.6 (CH_2), 21.1 (CH_2), 22.3 (CH_2), 27.6 (CH_2), 30.2 (CH_2), 31.2 (CH_2), 37.2 (CH_2), 46.9 (CH_2), 93.0 (CH), 157.5 (C), 166.5 (C).

(±)-Tetraponerine-8 (1). To diene **3** (0.5 g, 2.6 mmol) in THF (25 mL) and anhydrous sodium sulfate (1.0 g) was added 4-bromobutyraldehyde (0.4 g, 3.0 mmol). The mixture was heated at reflux for 14 h and then allowed to cool to room temperature, and the solution was transfered to another flask. Methanol (15 mL) was added and the temperature lowered to −20 °C. Sodium borohydride (0.12 g, 3 mmol) was then added and the reaction was stirred for 6 h at that temperature. The reaction was quenched with $Na_2SO_4 \cdot 10H_2O$, the sodium sulfate was filtered off, and the solution was concentrated. The oily residue was subjected to flash silica gel chromatography (20 g) with a 9:1 mixture of $CHCl_3$ and EtOH as the eluent. In this way, (±)-tetraponerine-8 (0.4 g, 67%) was obtained. All analytical data were in full agreement with those reported for the natural product.[2b]

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Supplementary Material Available: Copies of spectra of tetraponerine-8 (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.