

A concise synthesis of (*R*)-Bgugaine, a pyrrolidine alkaloid from *Arisarum vulgare*

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A new short method for the preparation of (*R*)-Bgugaine (**1**) has been described using Wittig condensation of a non stabilized ylide with N-carboethoxy prolinal followed by reduction of double bond and conversion of N-carboethoxy group to N-methyl.

Keywords: pyrrolidine alkaloids, bgugaine, Wittig reaction.

Nitrogen containing heterocycles including pyrrolidines, piperidines and related compounds, constitute an important structural motif in biologically active compounds¹ and effective chiral controllers in organocatalysis.²⁻⁴ This fact has lead to a great numbers of studies concerning to the development of new synthetic methodology towards these molecules over the years.⁵⁻⁷

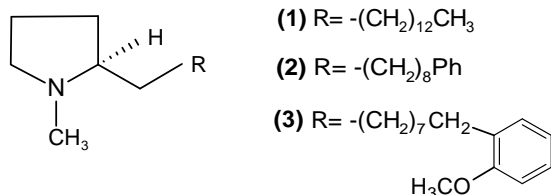
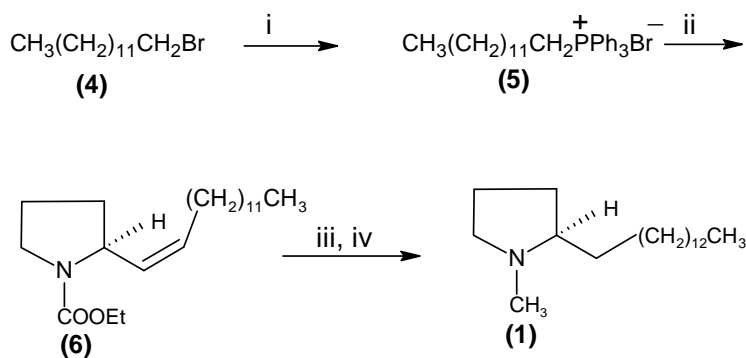


Fig. 1

(*R*)-Bgugaine (**1**) is a natural 2-alkyl pyrrolidine alkaloid, first isolated⁸ in 1993 from the tubers of *Arisarum vulgare*, a toxic araceae species that is found on the Mediterranean coasts of Morocco and Spain. (*R*)-Irniine (**2**),⁹ (*R*)-N-methyl-2-[9'(2''-methoxyphenyl) nonyl]pyrrolidine (**3**)¹⁰ are other related alkaloids isolated from the same source (Fig.1).

These alkaloids displays antibacterial and antimycotic activities,^{8,13} are active in brine shrimp assay showing an LC₅₀ of 1.5µg mL⁻¹ and have a strong binding affinity¹¹ for DNA. (*R*)-Bgugaine (**1**) is a potent hepatotoxin in rat and human liver cells and induces significant DNA damage in a human hepatoblastoma (HepG₂) cell line.¹²

So far, three syntheses of (*R*)-Bgugaine (**1**) have been reported. The first synthesis of **1** by Jossang *et. al.*¹³ required linear sequence of seven steps from tetradecylmethyl cuprate,⁹ while a second asymmetric synthesis based on a Sharpless asymmetric dihydroxylation approach comprising of six steps from 4-pentenylphthalimide is reported by Takahata *et. al.*¹⁴ The last by Enders *et. al.*¹⁵ employs their famous SAMP-hydrazone methodology towards synthesis of title compound **1** in six steps. In continuation of our interest^{16,17} in alkaloid containing proline motif, we now report an efficient three step synthesis of (*R*)-Bgugaine. We have used the existing pyrrolidine skeleton in L-proline to provide access to a (*R*)-Bgugaine (**1**).



Scheme 1. *Reagents and conditions:* i) PPh_3 , Toluene, refluxed, 24 h. ii) nBuLi , Et_2O , N-carboethoxy prolinal (2 steps 50%); iii) H_2 , Pd/C, EtOH, overnight; iv) LAH, Et_2O , refluxed (2 steps 80%).

Our approach to the synthesis commenced with (*S*)-N-carboethoxy prolinal.¹⁸ The necessary manipulation for the conversion of aldehyde group to tetradecane chain was

planned by application of Wittig reaction followed by reduction of the incipient double bond and reduction of carboethoxy group to methyl. Thus, freshly prepared (*S*)-*N*-carboethoxy prolinal was subjected to Wittig olefination in one vessel without isolating the intermediate salt **5** (Scheme 1) to get **6**. The double bond geometry of **6** was not of consequence towards further manipulation and was assumed to be *cis* based on ¹H NMR shift of both vinyl protons which appeared at same value around 5.39 ppm as multiplet. In the end, as expected reduction of compound **6** with H₂, Pd/C in ethanol followed by reduction with LAH in THF resulted in a facile formation of the title compound **1** with $[\alpha]_D^{27} -43.18$ (c 0.44, MeOH) and whose physical and spectroscopic data is in accordance with those reported.^{13,14}

In conclusion, we have accomplished a new concise synthesis of enantiomerically pure (*R*)-Bgugaine from (*S*)-*N*-carboethoxy prolinal in 2 steps. Furthermore, purification by column chromatography was required in only one step, proving it to be a particularly efficient route to this alkaloid.

Experimental

General

Solvents were purified and dried by standard procedure before use; column chromatography was performed on silica gel (60-120 mesh). IR spectra were recorded on Shimadzu FT-IR spectrophotometer. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker 300 MHz spectrometer using CDCl₃ as solvent and TMS as internal standard. The multiplicities of carbon signals were obtained from Distortionless Enhancement by Polarization Transfer (DEPT) experiment. Optical rotations were measured using sodium

D line on ADP220 polarimeter. High resolution mass spectra (HRMS) were recorded on a Micro Mass ES-QTOF Mass spectrometer.

Synthesis of (Z)-(2'R)-[N-carboethoxyproline]tetradec-1-ene (6): A solution containing PPh₃ (0.55 g, 2.09 mmol) and 1-bromotridecane (0.50 g, 1.90 mmol) in toluene (10 mL) was boiled under reflux for 24 h. Evaporation of toluene resulted in a white solid which was washed with Et₂O (3× 20 mL) and dried under high vacuum. A 1.6 M solution of n-BuLi (1.43 mL, 2.28 mmol) was added to this suspension of salt **5** in Et₂O (50 mL) with stirring under N₂. The resulting deep red mixture was stirred for 1 h. A solution of N-carboethoxy proline (0.33g, 1.93 mmol) in dried Et₂O (5 mL) was added and resulting solution was stirred at r.t. for 1 h. Water (30 mL) was added and the resultant mixture was extracted with Et₂O (3× 20 mL). The combined organic layers were dried over anhydrous Na₂SO₄, concentrated and subjected to column chromatography (silica gel, hexanes-EtOAc, 8:2) to get pure **6** as viscous liquid (0.33 g, 50%); [α]²⁷_D +84.96 (c 0.152, MeOH); IR (neat) ν_{max}: 1683 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 0.89 (3H, t, J = 6.6 Hz, H-14), 1.22-1.27 (23Hs, m, 10CH₂ and 1CH₃, H-4 to H-13, OCH₂CH₃), 1.61-1.69 (2H, m, H-3), 1.74-2.14 (4H, m, H-3', H-4'), 3.44 (2H, m, H-5'), 4.13 (2H, q, J = 6.9 Hz, OCH₂), 4.58 (1H, m, H-2'), 5.26-5.39 (2H, m, H-1, H-2); ¹³C NMR (CDCl₃, 75 MHz) δ 14.0 (CH₃, C-14), 14.1 (CH₃, CH₂CH₃), 22.6 (CH₂, C-13), 27.3 (CH₂, C-3'), 29.3 (CH₂, C-4'), 29.5 (CH₂, C-5 to C-12), 29.6 (CH₂, C-4), 31.9 (CH₂, C-3), 46.3 (CH₂, NCH₂), 54.2 (CH, NCH), 60.6 (CH₂, OCH₂CH₃), 130.7 (CH, C-1, C-2), 155.2 (C, COOCH₂); HRMS found 338.3054 (calcd for C₂₁H₄₀O₂N, [M + H]⁺ 338.3059).

Synthesis of (R)-Bgugaine (1): A solution of **6** (0.26 g, 0.75 mmol) in EtOH (20 mL) was stirred overnight at r.t. with 10 % Pd/C (30 mg) under hydrogen atmosphere (30 psi).

The catalyst was filtered off and washed with EtOH (20 mL). The combined organic layer was concentrated to afford N-carboethoxy-2-tetradecyl pyrrolidine as a thick liquid. To a suspension of lithium aluminium hydride (0.050 g, 1.31 mmol) in Et₂O (35 mL) was added solution of above N-carboethoxy-2-tetradecyl pyrrolidine in Et₂O (2 mL) and the reaction mixture was refluxed for 16 h. The 5% KOH (1 mL) and water (1 mL) were slowly added in succession. The precipitate formed was filtered, washed with Et₂O (3×20 mL) and the combined filtrate was dried over anhydrous Na₂SO₄ and concentrated to give pure **1** as viscous oil (173 mg, 80%); [α]_D²⁷ -43.18 (c 0.44, MeOH), [lit.¹⁴, [α]_D²⁷ -42.5 (c 1.65, MeOH)]; IR (neat) ν_{\max} : 2924, 2853, 2774, 1456, 804 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 0.89 (3H, t, J = 6.6 Hz, H-14'), 1.27 (25Hs, m, 1CH and 12CH₂, H-1' and H-2' to H-13'), 1.40-1.46 (1H, m, H-1'), 1.67-1.80 (2H, m, H-3), 1.84-1.94 (3H, m, 1H-5, 2H-4), 2.07-2.16 (1H, m, H-5); 2.31 (3H, s, NCH₃); 3.10 (1H, m, H-2); ¹³C NMR (CDCl₃, 75 MHz) δ 14.1 (CH₃, C-14'), 21.8, 22.7, 26.7, 29.4, 29.7, 30.1, 30.8, 31.9, 33.9 (CH₂, C-3, C-4, C-2' to C-13'), 40.4 (CH₃, NCH₃), 57.4 (CH₂, C-5), 66.5 (CH, C-2). HRMS found 282.3156 (calcd for C₁₉H₄₀N, [M + H]⁺ 282.3161).

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