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

Mahesh S. Majik[a], P.S. Parameswaran[b] and Santosh G. Tilve[a]*

[a]*Department of Chemistry, Goa University, Taleigao Plateau, Goa 403 206, India*

[b]*National Institute of Oceanography (CSIR), Dona Paula-Goa 403 004, India*

A new short method for the preparation of (*R*)-Bgugaine (**1**) has been described using Wittig condensation of a non-stabilised 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, include important biologically active compounds[1] and effective chiral catalysts.[2-4] There are a large number of studies concerning the development of new syntheses of these molecules.[5-7]

(*R*)-Bgugaine (**1**) is a natural 2-alkyl pyrrolidine alkaloid, first isolated[8] 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 display antibacterial and antimycotic activities,[8,13] and are active in the brine shrimp assay showing an LC_{50} of 1.5μg ml^{-1}. They have a strong binding affinity[11] for DNA. (*R*)-Bgugaine (**1**) is a potent hepatotoxin in rat and human liver cells and induces significant DNA damage in a human hepatoblastoma ($HepG_2$) 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, while a second asymmetric synthesis based on a Sharpless asymmetric dihydroxylation approach comprising of six steps from 4-pentenylphthalimide was reported by Takahata *et al.*[14] The last by Enders *et. al.*[15] employed their SAMP-hydrazone methodology towards synthesis of title compound **1** in six steps. In continuation with our interest[16,17] in alkaloid containing a proline motif, we now report an efficient three step synthesis of (*R*)-Bgugaine. We have used the existing pyrrolidine skeleton of L-proline to provide access to (*R*)-Bgugaine (**1**).

Our approach to the synthesis commenced with (*S*)-N-carboethoxyprolinal.[18] The necessary manipulation for the conversion of aldehyde group to tetradecane chain involved application of the Wittig reaction followed by reduction of the double bond and reduction of carboethoxy group to methyl.

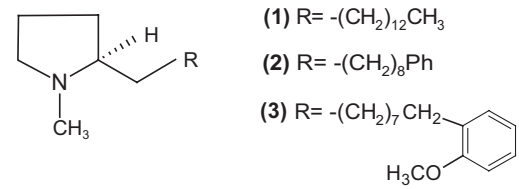


Fig. 1

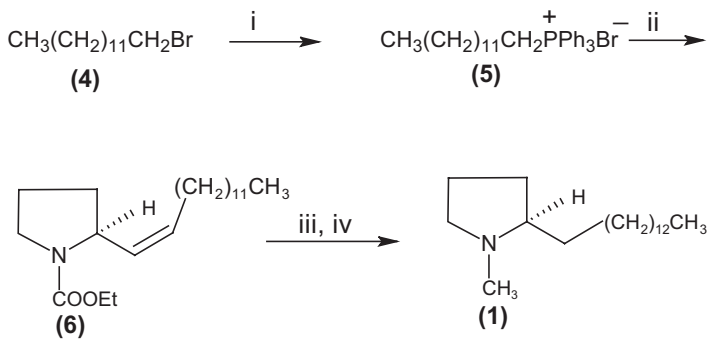
Thus, freshly prepared (*S*)-N-carboethoxy prolinal was subjected to Wittig olefination in one vessel without isolating the intermediate salt **5** (Scheme 1) to get **6**. The double bond geometry of **6** was not of consequence in the further manipulation and was assumed to be *cis* based on ^1H NMR shift of both vinyl protons which appeared at same value at δ 5.39 ppm as a multiplet. In the end, as expected reduction of compound **6** with H_2, 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-carboethoxyprolinal in three 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 ^{13}C NMR spectra were recorded on a Brucker 300 MHz spectrometer using $CDCl_3$ as solvent and TMS as internal standard. The multiplicities of carbon signals were obtained from Distortionless



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

* Correspondent. E-mail: stilve@unigoa.ac.in

Enhancement by Polarisation 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-carboethoxypyrrolidine]tetradec-1-ene (**6**)**:** A solution containing PPh_3 (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 Et_2O (3 × 20 ml) and dried under high vaccum. A 1.6 M solution of n-BuLi (1.43 ml, 2.28 mmol) was added to this suspension of salt **5** in Et_2O (50 ml) with stirring under N_2. The resulting deep red mixture was stirred for 1 h. A solution of N-carboethoxyprolinal (0.33 g, 1.93 mmol) in dried Et_2O (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 Et_2O (3 × 20 ml). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated and subjected to column chromatography (silica gel, hexanes–EtOAc, 8:2) to afford pure **6** as viscous liquid (0.33 g, 50%); $[\alpha]^{27}_D$ +84.96 (c 0.152, MeOH); IR (neat) ν_{max}: 1683 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (3H, t, *J* = 6.6 Hz, H-14), 1.22–1.27 (23Hs, m, 10CH_2 and 1CH_3, H-4 to H-13, OCH_2CH_3), 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, OCH_2), 4.58 (1H, m, H-2'), 5.26–5.39 (2H, m, H-1, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0 (CH_3, C-14), 14.1 (CH_3, CH_2CH_3), 22.6 (CH_2, C-13), 27.3 (CH_2, C-3'), 29.3 (CH_2, C-4'), 29.5 (CH_2, C-5 to C-12), 29.6 (CH_2, C-4), 31.9 (CH_2, C-3), 46.3 (CH_2, NCH_2), 54.2 (CH, NCH), 60.6 (CH_2, OCH_2CH_3), 130.7 (CH, C-1, C-2), 155.2 (C, $COOCH_2$); HRMS found 338.3054 (calcd for $C_{21}H_{40}O_2N$, $[M + H]^+$ 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 a 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-tetradecylpyrrolidine as a thick liquid. To a suspension of lithium aluminium hydride (0.050 g, 1.31 mmol) in Et_2O (35 ml) was added a solution of the above N-carboethoxy-2-tetradecylpyrrolidine in Et_2O (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 Et_2O (3 × 20 ml) and the combined filtrate was dried over anhydrous Na_2SO_4 and concentrated to give pure **1** as viscous oil (173 mg, 80%); $[\alpha]^{27}_D$ -43.18 (c 0.44, MeOH), [lit.[14], $[\alpha]^{27}_D$–42.5 (c 1.65, MeOH)]; IR (neat) ν_{max}: 2924, 2853, 2774, 1456, 804 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (3H, t, *J* = 6.6 Hz, H-14'), 1.27 (25Hs, m, 1CH and 12CH_2, 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, NCH_3); 3.10 (1H, m, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1 (CH_3, C-14'), 21.8, 22.7, 26.7, 29.4, 29.7, 30.1, 30.8, 31.9, 33.9 (CH_2, C-3, C-4, C-2' to C-13'), 40.4 (CH_3, NCH_3), 57.4 (CH_2, C-5), 66.5 (CH, C-2). HRMS found 282.3156 (calcd for $C_{19}H_{40}N$, $[M + H]^+$ 282.3161).

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