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Concise syntheses of racemic and enantiopure deoxydysibetaine

Bao Khanh Le Nguyen and Nicole Langlois*

Institut de Chimie des Substances Naturelles, CNRS, Avenue de la Terrasse, 91198 Gif-sur-Yvette, France

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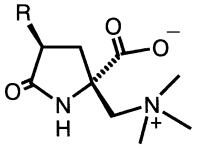
Abstract—Racemic deoxydysibetaine was efficiently obtained in few steps from methyl pyroglutamate. The 2*S* enantiomer was synthesized from (*S*)-pyroglutaminol as chiral starting material, through the key intermediate (*S*)-2-hydroxymethylglutamic acid recently prepared with complete stereoselectivity in our laboratory.

Dysibetaine **1** was isolated from an aqueous extract of the marine sponge *Dysidea herbacea* collected in Yap, Micronesia,[1] beside an original non-NMDA glutamate receptor agonist named dysiherbaine.[2] The betaine **1** is an α-amino acid α-substituted by a trimethylammoniomethyl group. The structure of **1** was established by NMR and X-ray crystal analysis but its absolute configuration (2*S*,4*S*) was assigned only two years later by the sole total synthesis of the four diastereomers.[3]



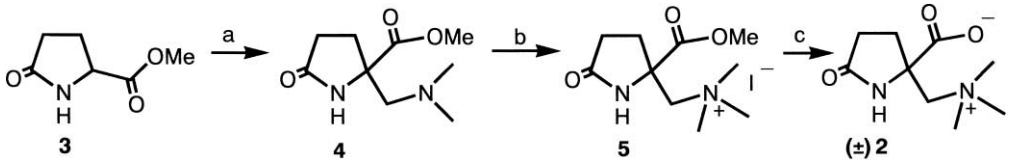
1: R = OH
2: R = H

As dysibetaine is able to induce a convulsive behaviour in mice, this compound was suspected of acting to glutamate receptors in central nervous system.[1] Thus, the synthesis of simpler analogues could be interesting for comparison purpose in further pharmacological studies. We designed deoxydysibetaine **2** as our first synthetic target and here are reported the main results in this field.

The preparation of racemic **2** was envisioned from pyroglutamic acid through a direct dimethylaminomethylation at C-2. This key step was achieved without protection of the nitrogen atom as carbamate, to avoid a reaction at α position of the lactam carbonyl.[4]

Accordingly, methyl pyroglutamate **3** was deprotonated by 2.1 equiv. of base (LiHMDS in THF) and alkylated with Eschenmoser salt at −60°C to afford the *N*,*N*-dimethylaminomethyl derivative **4** in 82% yield (Scheme 1).

However, the isolation of **4** needed careful and rapid extraction because the methyl ester function was shown to be rather unstable and particularly sensitive to water. Indeed, the ester was rapidly hydrolyzed by water at room temperature, probably with the assistance of the neighbouring amino group to give **6**, as outlined in the Scheme 2.



Scheme 1. *Reagents and conditions*: (a) LiHMDS, THF, Eschenmoser salt, 82%; (b) CH_3I, THF, 78%; (c) Dowex 550A, HO^-, 85%.

* Corresponding author. Fax: +33-1-6907-7247; e-mail: nicole.langlois@icsn.cnrs-gif.fr

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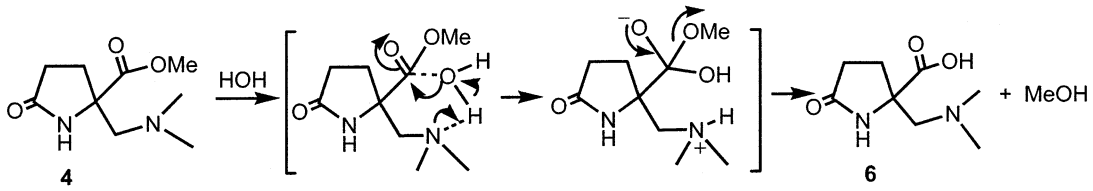


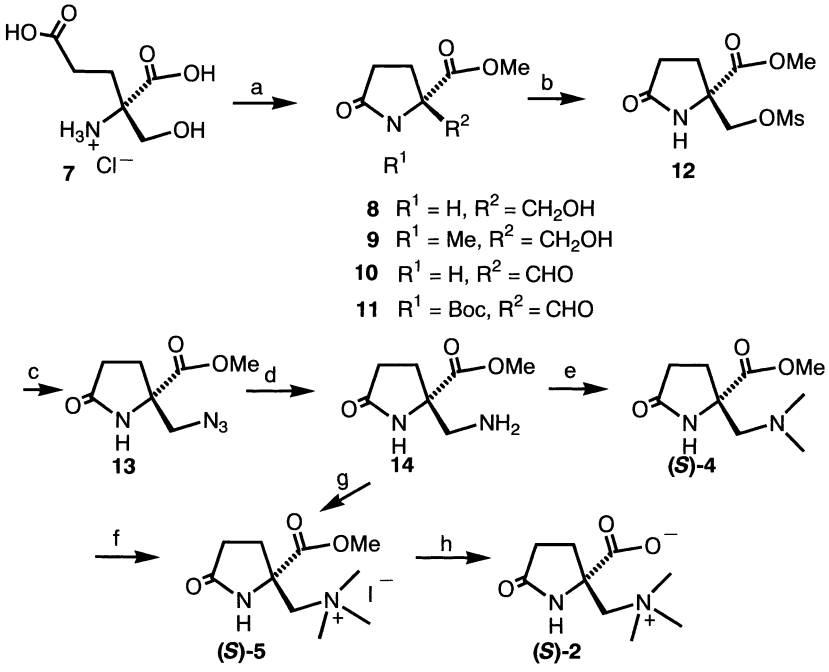
Scheme 2.

The compound **4** in THF was then converted into the trimethylammonium iodide **5** with an excess of methyl iodide under standard conditions (78%). The treatment of **5** with Dowex 550A resin in the hydroxide form (in methanol at 55°C)[3] allowed to obtain racemic deoxydysibetaine (±)-**2** in 85% yield (Scheme 1).

Next, the synthesis of the enantiomer (2*S*)-**2** (the configuration of natural dysibetaine **1** at C-2) was planned as described in the Scheme 3.

This synthesis started from (*S*)-2-hydroxymethylglutamic acid hydrochloride **7**, recently synthesized in our laboratory with complete stereoselectivity.[5] This amino diacid failed to provide 2-hydroxymethylpyroglutamic acid by lactamization under mild conditions, after the displacement of the hydrochloride with triethylamine. Thus, the diacid was methylated with trimethylsilyldiazomethane or more simply with diazomethane in excess (in a mixture of MeOH–Et_2O) to afford directly the methyl (*S*)-2-hydroxymethylpyroglutamate **8** in 67% yield.[6] Some amounts (10%) of a side product **9** resulting from nitrogen methylation was also isolated, but the formation of lactim ether was not observed.[7] The *N*-methylation of **8** could be due not only to the excess of diazomethane employed but especially to the presence of methanol in this methylation to increase the solubility of the starting product.[8] Formation of the aminomethyl group at C-2 by reductive amination[9] of either aldehyde **10** or *N*-Boc protected **11**, both obtained with Dess–Martin reagent,[10] gave disappointing results.

Thus, an alternative classical route was investigated (Scheme 3). Mesylation of the primary alcohol **8** (MsCl, CH_2Cl_2–Et_3N, 0°C) gave the mesylate **12** (86%) which was substituted with NaN_3 at 65°C providing the azidomethyl derivative **13** in 91% yield. The compound **13** was quantitatively reduced with hydrogen and Pd–10%/C as catalyst. The resulting primary amine **14**, characterized as its hydrochloride, was dimethylated with aqueous formol under hydrogen (Pd–10%/C, 40–50 psi) giving rise to (*S*)-**4** (64%), which was in turn converted into trimethylammonium iodide (*S*)-**5** according a common protocol (86%, Scheme 3).[3,11] It is worthy of note that the same intermediate (*S*)-**5** could be obtained also by a more direct and more efficient way (94%) from the aminomethyl derivative **14**, provided that diisopropylethylamine was added to the reaction with methyl iodide in excess. This 2-methoxycarbonyl-2-trimethyl-



Scheme 3. *Reagents and conditions*: (a) CH_2N_2, MeOH–Et_2O, 67%; (b) MsCl, CH_2Cl_2, Et_3N, 86%; (c) NaN_3, DMF, 65°C, 91%; (d) H_2, Pd–10%/C, MeOH, 100%; (e) CH_2O, H_2 40–50 psi, Pd–10%/C, 64%; (f) CH_3I, THF, 86%; (g) CH_3I, $EtN(iPr)_2$, THF, 94%); (h) Dowex 550A, HO^-, 100%.

ammoniomethylpyrrolidin-5-one was hydrolyzed quantitatively into deoxydysibetaine (*S*)-**2**, as described above for the racemic counterpart.[12]

In conclusion, two simple routes were developed to prepare racemic and enantiopure deoxydysibetaine respectively, in high yields. The synthesis of further analogues of dysibetaine is currently under investigation.

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12. Data of (*S*)-**2**: Mp: 226°C; $[\alpha]_D^{24} = -9$ (*c* 0.84, MeOH). ^{1}H NMR (300 MHz, D_2O $\delta = 4.65$ ppm): 3.92 (d, 1H, $J = 15$ Hz, Ha-6), 3.56 (d, 1H, $J = 15$ Hz, Hb-6), 3.08 (s, 9H, $N(CH_3)_3$), 2.41 (m, 1H), 2.30 (m, 1H), 2.20 (m, 1H), 2.04 (m, 1H): H_2-4, H_2-3. ^{13}C NMR (75.0 MHz, CD_3OD $\delta = 49.00$ ppm): 182.05 (CO), 177.75 (CO), 71.80 (C-6), 66.27 (C-2), 55.46 ($N(CH_3)_3$), 34.11 (C-4), 29.78 (C-3). MS (ESI): 223 $(M+Na)^+$, 201 [$(M+H)^+$, 100%)]. HRMS (ESI) calcd for $C_9H_{17}N_2O_3$ $(M+H)^+$: 201.1239. Found: 201.1267.