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Enantioselective synthesis of (*R*)-deoxydysibetaine and (−)-4-*epi*-dysibetaine

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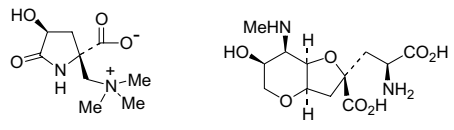
Abstract—Enantioselective synthesis of (*R*)-deoxydysibetaine and (−)-4-*epi*-dysibetaine was achieved by employing a samarium iodide-promoted reductive carbon–nitrogen bond cleavage of a proline derivative, as a key reaction.

Dysibetaine **1**, a novel α,α-disubstituted amino acid, was isolated from the marine sponge *Dysidea herbacea*, and its structure including the relative stereochemistry was elucidated by spectral methods and also by X-ray crystallography.[1] The absolute configuration of **1** was unambiguously determined by its total synthesis.[2] Due to its unique structural feature and also potential biological activity related to a non-NMDA type glutamate receptor antagonist, dysiherbaine **2**,[3] three total synthesis of (*R*)-dysibetaine have so far been reported[2,4,5] (Fig. 1).

In relation to our synthetic work on biologically active natural products by employing a samarium iodide-promoted reductive carbon–nitrogen bond cleavage reaction,[6] we are also interested in the synthesis of dysibetaine.

In our synthetic strategy for **1**, we focused our attention on the synthesis of deoxydysibetaine[5,7,8] through construction of the quaternary carbon center stereoselectively, since an introduction of a secondary hydroxy group would be achieved at the later stage of the synthesis based on the previous synthetic procedures.



dysibetaine **1** dysiherbaine **2**

Figure 1. Structures of dysibetaine and dysiherbaine.

Thus, methyl 4*R*-hydroxyprolinate hydrochloride **3a** was converted to the corresponding N-methyl derivative **4a**,[9] which, on Swern oxidation, afforded 4-oxo-compound **5a** in good yield.

Although both Bucherer–Bergs and Strecker reactions of 4-oxo-L-proline derivative would be expected to provide the corresponding α,α-disubstituted amino acid with the desired stereochemistry,[10,11] we chose an alternative synthetic path for construction of the quaternary carbon center to circumvent the use of cyanide ion with the aim of establishing a synthetic strategy for deoxydysibetaine,[5,7,8] where the final product would be an antipodal form of the natural product.

Addition of trichloromethyl function to **5a** on treatment with LiHMDS and chloroform gave the desired adduct **6a**, stereoselectively, in 74% yield[11] (Scheme 1). Construction of the α,α-disubstituted amino acid moiety was successfully achieved as follows. Treatment of **6a** with DBU and sodium azide in MeOH in the presence of 18-crown-6 under the modified Corey–Link reaction[11,12] gave azide-ester **7a** in 56% yield. Reduction of the azide group of **7a**, followed by protection of the resulting primary amine with $(Boc)_2O$ gave methyl ester **8a** in 75% yield from **7a**.

With the desired compound **8a** in hand, we attempted a reductive carbon–nitrogen bond cleavage reaction by

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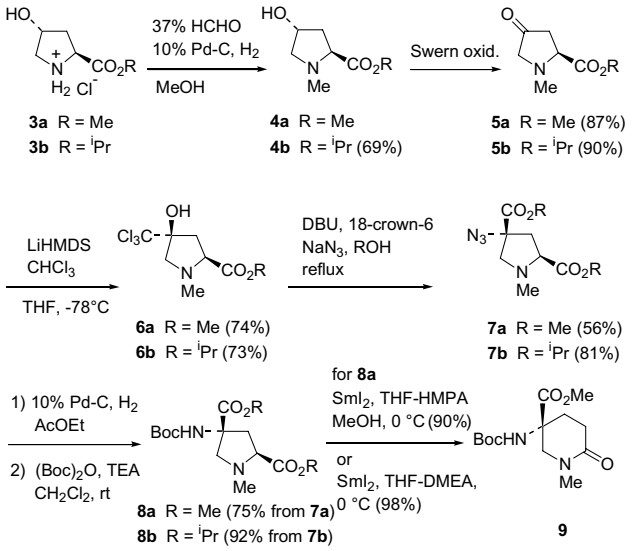


Scheme 1. Preparation of **8a**,**b** and the reaction of **8a** with SmI_2.

treatment with samarium iodide in THF-HMPA at 0 °C in the presence of MeOH as a proton source. However, the isolated product was δ-lactam **9**, in 90% yield, instead of the desired bond cleaved product. Even in the presence of dimethylethanolamine (DMEA) in this reaction, **9** was obtained as a sole product in 98% yield. The transformation of proline derivatives to δ-lactams under these reaction conditions were already observed in our previous works, where a reductive carbon–nitrogen bond cleavage reaction and subsequent recyclization occurred, simultaneously.[6] For obtaining a carbon–nitrogen bond cleaved compound as a major product, we planned to change methyl ester to sterically bulky isopropyl ester.

Thus, isopropyl 4*R*-hydroxyprolinate **3b**[6a] was converted to trichloro derivative **6b** by three steps, involving N-methylation with 37% HCHO under reduction conditions, Swern oxidation of alcohol **4b**, and trichloromethylation of ketone **5b**, by the same procedure as described for the preparation of **6a**.

Introduction of azide group to **6b** gave **7b**, which, on catalytic reduction over 10% Pd–C, followed by protection of the corresponding primary amine with $(Boc)_2O$ gave **8b**[13] (Scheme 1).

By using isopropyl ester **8b**, a reductive bond cleavage reaction with samarium iodide was investigated under the various reaction conditions, and the results obtained were summarized in Table 1.

Reaction of **8b** with 5 equiv of SmI_2 in THF-HMPA at 0 °C in the presence of MeOH gave δ-lactam **11** and γ-lactam **12**, in 28% and 24% yields, respectively (entry 1). When this reaction was carried out in THF at 0 °C for 15 min in the presence of DMEA, the desired product **10** was obtained together with δ-lactam **11** as an inseparable mixture,[14] in quantitative yield (entry 2). The similar reaction in THF in the presence of MeOH at 0 °C to room temperature for 2 h gave γ-lactam **12**, as a major product, in addition to deprotected γ-lactam **13** (entry 3).

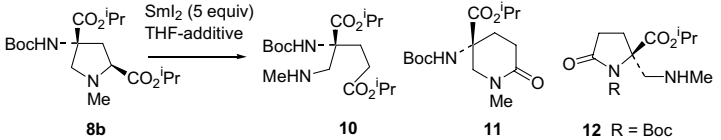
Although we were able to find the optimal reaction conditions to obtain the desired ring-opened product **14**, in reasonable yield,[15] by treatment of **8b** with 5 equiv of SmI_2 in THF at 0 °C for 5 min in the presence of 10 equiv of DMEA, followed by deprotection of Boc group with TFA, the subsequent recyclization in refluxing toluene gave γ-lactam **13** in 56% yield from **8b**, together with δ-lactam **15** in 12% yield (Scheme 2).

To avoid δ-lactam formation, we decided to convert the secondary amine obtained by bond cleavage reaction of **8b** to tertiary amine **16** prior to deprotection of Boc group and subsequent recyclization.

Thus, compound **8b** was treated with samarium iodide in THF in the presence of DMEA at 0 °C for 5 min to provide the fragmentation product, which, without further purification, was reacted with 37% formalin and 10% Pd–C under reduction conditions to give tertiary amine **16** in 91% yield from **8b**.

Deprotection of the Boc group of **16** with zinc bromide afforded the tertiary amine, which, on heating in toluene provided the desired γ-lactam **17**[16] in 96% yield from **16**, as the sole product. Quaternary ammonium iodide **18** was prepared by treatment of **17** with methyl iodide in 92% yield, which on hydrolysis with Dowex 550A in MeOH afforded (*R*)-deoxydysibetaine **19**, in 99% yield, whose spectroscopic data were identical with those reported[5,7] except for the sign of optical rotation, mp 230–231 °C; $[\alpha]_D$ +9.14 (*c* 0.98, MeOH), [*ent*-**19**: lit.,[7] mp 226 °C; $[\alpha]_D$ −9 (*c* 0.84, MeOH)] (Scheme 3).

Table 1. Bond cleavage reaction of **8b** with SmI_2



Entry	Additive (equiv)	Time	Temperature	Products (yield)
1	HMPA (5.0) + MeOH (2.5)	30 min	0 °C	**11** (28%), **12** (24%)
2	DMEA (10)	15 min	0 °C	**10** + **11** (3.5:1) (quant.)
3	MeOH (2.5)	2 h	0 °C to rt	**11** (trace), **12** (36%), **13** (9%)