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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 4691–4694

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

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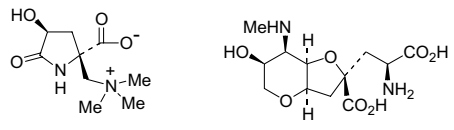
Received 14 April 2007; revised 1 May 2007; accepted 2 May 2007
Available online 6 May 2007

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

Keywords: (*R*)-Deoxydydibetaine; (−)-4-*epi*-Dysibetaine; Samarium iodide; Reductive carbon–nitrogen bond cleavage; α,α-Disubstituted amino acid.
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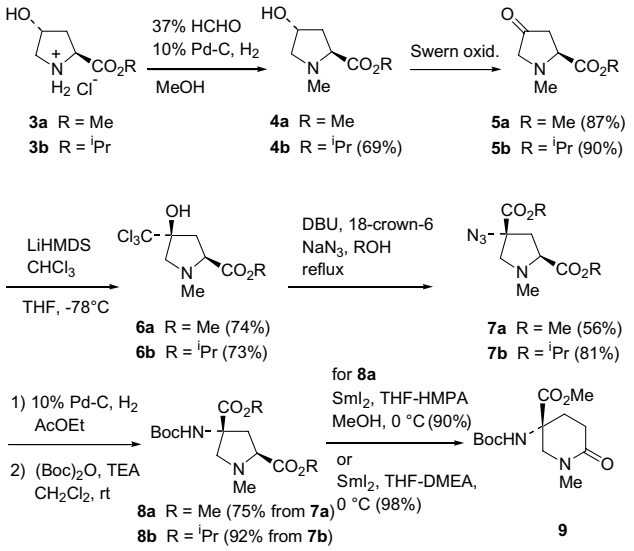
doi:10.1016/j.tetlet.2007.05.007



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).

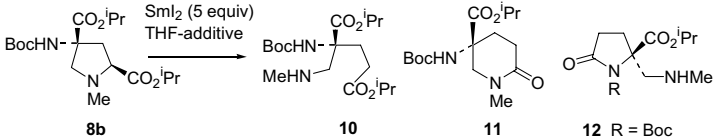
Although we were able to find the optimal reaction conditions to obtain the desired ring-opened product **14**, in reasonable yield,[15] by treatment of **8b** with 5 equiv of SmI_2 in THF at 0 °C for 5 min in the presence of 10 equiv of DMEA, followed by deprotection of Boc group with TFA, the subsequent 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.

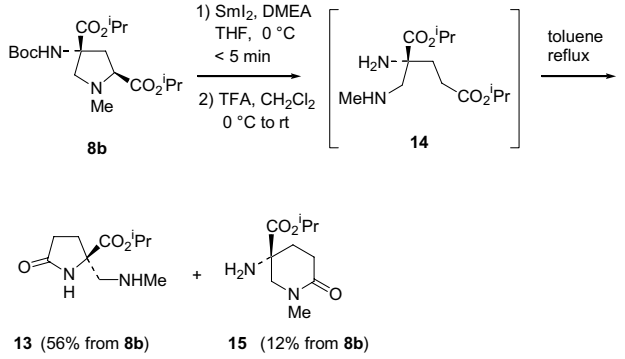
Thus, compound **8b** was treated with samarium iodide in THF in the presence of DMEA at 0 °C for 5 min to provide the fragmentation product, which, without further purification, was reacted with 37% formalin and 10% Pd–C under reduction conditions to give tertiary amine **16** in 91% yield from **8b**.

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).

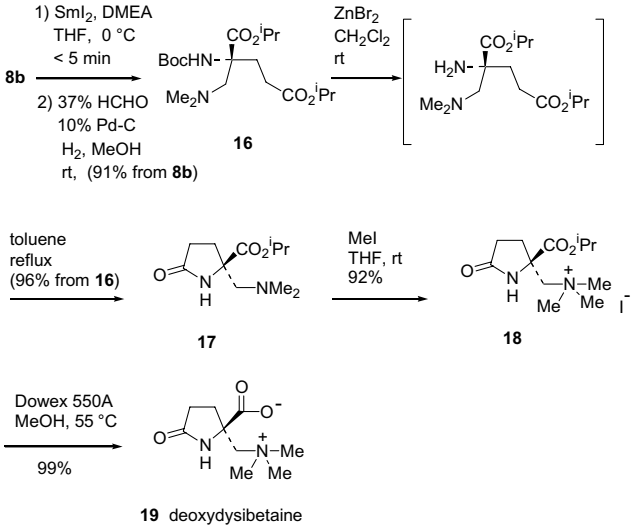
Table 1. Bond cleavage reaction of **8b** with SmI_2



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%)



Scheme 2. Conversion of **8b** to γ-lactam **13**.

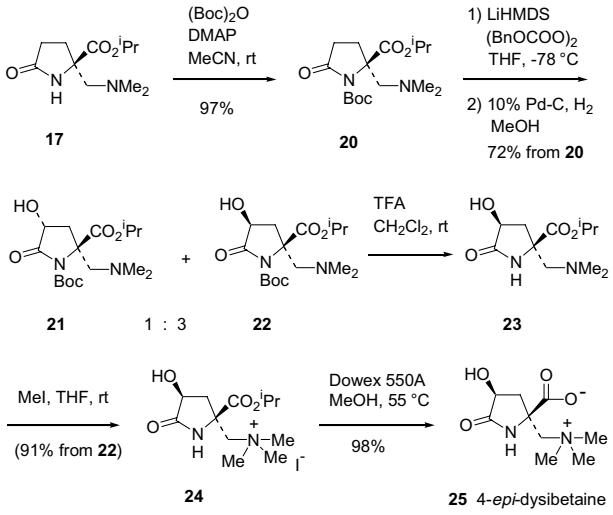


Scheme 3. Synthesis of (*R*)-deoxydysibetaine **19**.

Since we were able to establish the synthetic strategy for (*R*)-deoxydysibetaine, our attention was focused on the introduction of a hydroxy group to synthesize dysibetaine as follows.

After protection of the amide nitrogen of **17** with $(Boc)_2O$, the resulting carbamate **20** was treated with LiHMDS and dibenzyl peroxydicarbonate in THF to give two hydroxy compounds **21** and **22**,[17] in 72% yield, in a ratio of 1:3. The stereochemistries of the products were determined by the comparison of their ^1H NMR data with those of the corresponding methyl esters.[5] Although the desired compound was obtained as a minor product to our dismay, we attempted a further conversion of the major alcohol **22** to (−)-4-*epi*-dysibetaine.

After deprotection of the Boc group of **22** with trifluoroacetic acid, the resulting amide **23** was methylated with methyl iodide to provide quaternary amine **24** in 91% yield from **22**. Finally, hydrolysis of **24** was carried out by the same procedure as for the preparation of (*R*)-deoxydysibetaine to furnish (−)-4-*epi*-dysibetaine **25**, in 98% yield, whose spectroscopic data including its specific optical rotation were again identical with those



Scheme 4. Synthesis of (−)-4-*epi*-dysibetaine **25**.

reported[2,5] mp >200 °C; $[\alpha]_D$ −16.6 (*c* 0.23, MeOH), [lit.,[2] $[\alpha]_D$ −11.2 (*c* 0.34, MeOH)] [*ent*-**25**: lit.,[2] $[\alpha]_D$ +9.5 (*c* 0.30, MeOH)] (Scheme 4).

In summary, starting from easily available 4*R*-hydroxyproline, an alternative synthetic path to (*R*)-deoxydysibetaine and (−)-4-*epi*-dysibetaine has been achieved, where a samarium-promoted carbon–nitrogen bond cleavage reaction was involved as the key step.

Acknowledgment

This work was supported by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

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13. *Selected data for* **8b**: mp 94–96 °C. $[\alpha]_D^{26}$ −39.6 (*c* 1.02, $CHCl_3$); FT-IR (film) ν_{max} 3360, 2980, 1740, 1730, 1715, 1175, 1105 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.98–5.14 (m, 3H), 3.64 (d, $J = 10.2$ Hz, 1H), 3.33 (t, $J = 8.1$ Hz, 1H), 2.74 (dd, $J = 8.1$, 13.6 Hz, 1H), 2.58 (d, $J = 10.2$ Hz, 1H), 2.43 (s, 3H), 2.32 (dd, $J = 8.1$, 13.6 Hz, 1H), 1.42 (s, 9H), 1.21–1.26 (m, 12H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 171.6, 171.4, 154.8, 69.1, 68.1, 66.2, 63.5, 40.6, 40.3, 28.2, 21.7, 21.6, 21.5; MS *m*/*z* 373 (M^++1). Anal. Calcd for $C_{18}H_{32}N_2O_6$: C 58.08, H 8.60, N 7.52. Found C 57.88, H 8.40, N 7.55.
14. The ratio of **10** and **11** was determined to be 3.5:1 based on its ^1H NMR analysis.
15. In this reaction, all the starting materials were converted to the desired compound on TLC monitoring, however, the yield of γ-lactam **13** might be decreased during deprotection of Boc group with TFA and subsequent recyclization sequences.
16. *Selected data for* **17**: mp 105–107 °C. $[\alpha]_D^{23}$ −20.2 (*c* 1.01, $CHCl_3$); FT-IR (film) ν_{max} 3245, 2982, 2945, 2827, 2775, 1738, 1704, 1262, 1182, 1106 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.40 (br s, 1H), 5.07 (sept, $J = 6.3$ Hz, 1H), 2.87 (d, $J = 13.3$ Hz, 1H), 2.52 (d, $J = 13.3$ Hz, 1H), 2.25–2.41 (m, 3H), 2.26 (s, 6H), 1.96–2.10 (m, 1H), 1.27 (d, $J = 6.3$ Hz, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 176.7, 173.0, 69.3, 66.6, 66.1, 47.2, 29.7, 29.4, 21.6; MS *m*/*z* 229 (M^++1); HR-MS Calcd for $C_{11}H_{21}N_2O_3$ (M^++1): 229.1560. Found 229.1552.
17. *Selected data for* **22**: $[\alpha]_D^{21}$ −7.52 (*c* 1.95, $CHCl_3$); FT-IR (film) ν_{max} 3460, 2980, 1940, 1790, 1760, 1738, 1722, 1307, 1268, 1154, 1108 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.03 (sept, $J = 6.3$ Hz, 1H), 4.86 (t, $J = 9.1$ Hz, 1H), 3.11 (d, $J = 14.6$ Hz, 1H), 2.94 (d, $J = 14.6$ Hz, 1H), 2.56 (dd, $J = 9.1$, 12.5 Hz, 1H), 2.27 (s, 6H), 2.02 (dd, $J = 9.1$, 12.5 Hz, 1H), 1.51 (s, 9H), 1.25 (d, $J = 6.3$ Hz, 3H), 1.23 (d, $J = 6.3$ Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 174.9, 170.6, 149.1, 84.1, 69.2, 68.8, 66.9, 61.0, 48.0, 37.6, 27.8, 21.4; MS *m*/*z* 344 (M^+); HR-MS Calcd for $C_{16}H_{28}N_2O_6$ (M^+): 344.1947. Found 344.1946.