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LETTERS

## Total synthesis of (–)-dysiherbaine, a novel neuroexcitotoxic amino acid

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### Abstract

A total synthesis of (–)-dysiherbaine, a neuroexcitotoxic amino acid isolated from the Micronesian marine sponge *Dysidea herbacea*, starting from a carbohydrate precursor, is described. The present synthesis features a palladium(0)-catalyzed cross-coupling of the 6/5-bicyclic core with an amino acid residue. © 2000 Elsevier Science Ltd. All rights reserved.

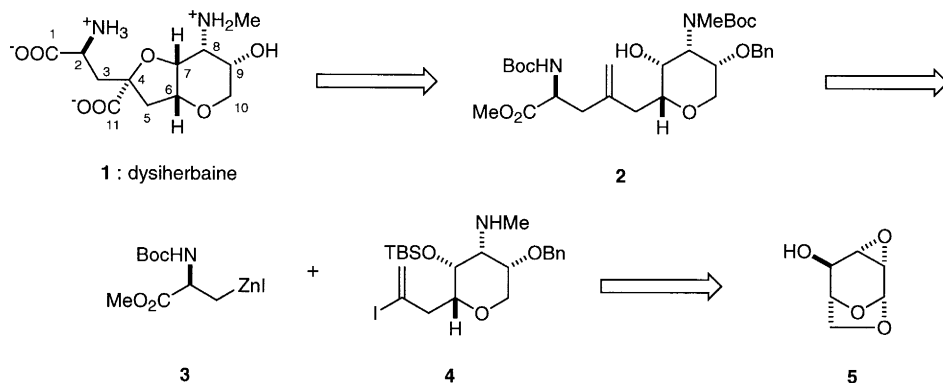
**Keywords:** amino acids and derivatives; marine metabolites; natural products; toxins.

Dysiherbaine (**1**) was recently isolated as a neuroexcitotoxin from the Micronesian marine sponge *Dysidea herbacea*.<sup>1</sup> Radioligand binding assay of **1** towards ionotropic glutamate receptors and electrophysiological experiments indicated that **1** is a potent agonist of non-NMDA (*N*-methyl-D-aspartate) subtype receptors in the central nervous system (CNS). On the basis of extensive spectroscopic studies including long-range carbon–proton coupling constants (<sup>2,3</sup>J<sub>C,H</sub>) analysis,<sup>2</sup> the structure of **1** was determined as an unprecedented diamino dicarboxylic acid, which is characterized by a structurally novel *cis*-fused hexahydrofuro[3,2-*b*]pyran ring system containing a glutamate substructure.<sup>1</sup> Due to its unique skeletal structure and potent neuroexcitatory activity, dysiherbaine may become a useful lead compound for the design of selective and powerful agonists or antagonists of glutamate receptors; however, its supply from natural sources is limited. Therefore, total synthesis of **1** and its designed analogues is required for further physiological studies. In connection with the synthetic studies on dysiherbaine, we have already reported the synthesis of a dysiherbaine model lacking the hydroxyl and methylamino groups.<sup>3</sup> Very recently, total syntheses of **1** have been achieved by two independent groups.<sup>4</sup> In this letter, we describe a total synthesis of dysiherbaine (**1**) by a convergent strategy that can be adopted to facilitate the synthesis of a variety of analogues.

Our retrosynthetic analysis for dysiherbaine (**1**) is shown in Scheme 1. We planned to construct the 6/5-*cis*-fused bicyclic ring system of **1** via a 5-*exo* ring closure of hydroxy *exo*-olefin **2**. The key intermediate

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**2** was envisioned to be synthesized by palladium(0)-catalyzed cross-coupling reaction of the known organozinc reagent **3**<sup>5</sup> with vinyl iodide **4**, which could be accessed from dianhydrohexose **5**. The use of a carbohydrate as a chiral starting material would allow for the synthesis of various analogues with respect to the bicyclic core structure.

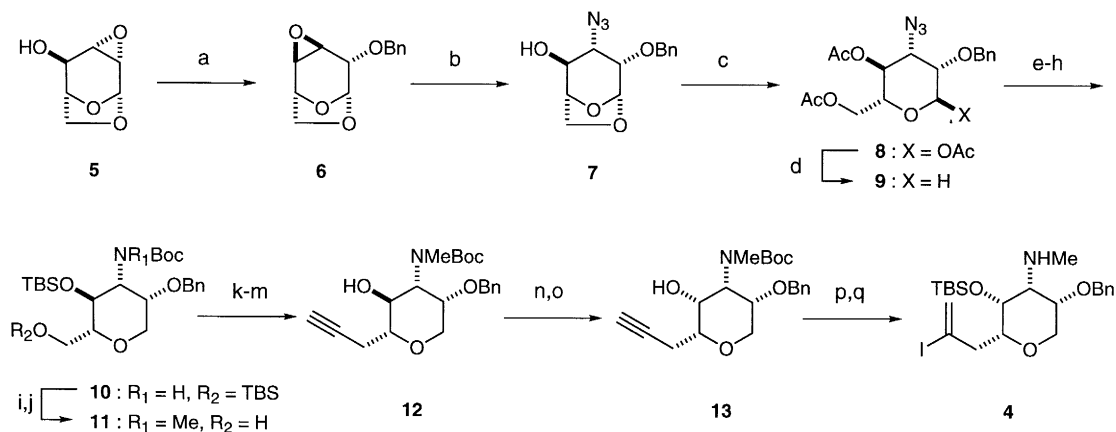


Scheme 1. Structure and retrosynthesis of dysiherbaine (**1**)

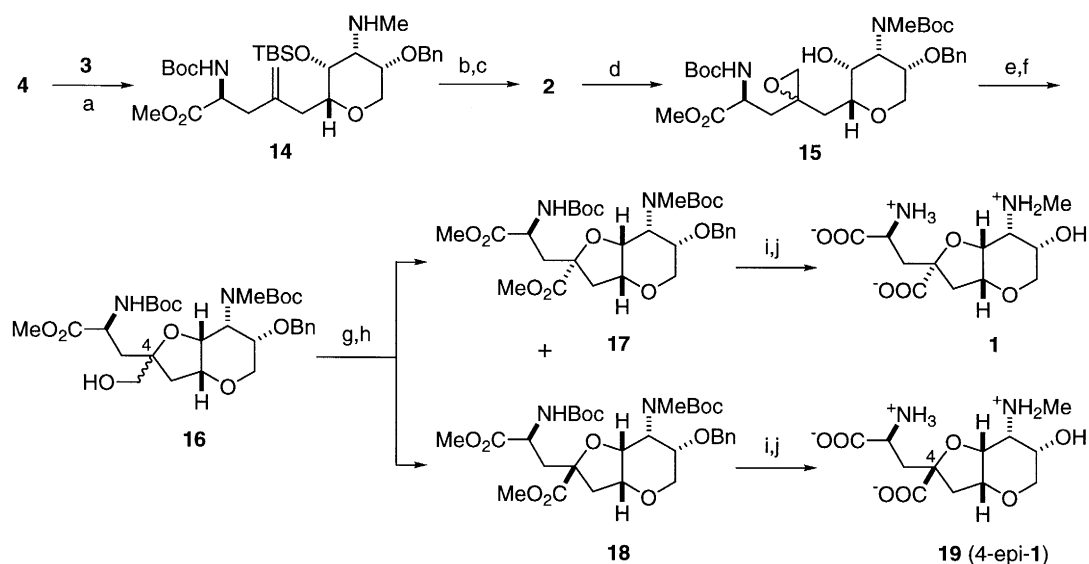
Synthesis of vinyl iodide **4** commenced with the known 1,6:2,3-dianhydrohexose **5**<sup>6</sup> (Scheme 2). Benzylation of **5** under the usual conditions was accompanied with migration of the epoxide ring<sup>6</sup> to give benzyl ether **6** in 86% yield. Epoxide ring-opening in **6** with sodium azide proceeded regioselectively to give azide alcohol **7**, which was then treated with acetic anhydride in the presence of  $\text{BF}_3 \cdot \text{OEt}_2$  to yield triacetate **8** as a single stereoisomer in 84% yield for the two steps. Reduction of the anomeric acetoxy group was effected with  $\text{Et}_3\text{SiH}$  in the presence of TMSOTf and  $\text{BF}_3 \cdot \text{OEt}_2$  to give diacetate **9** in 78% yield. The acetyl groups were exchanged to *t*-butyldimethylsilyl (TBS) groups and reduction of the azide group with  $\text{PPh}_3$ , followed by protection of the resulting amino group as the *t*-butyl carbamate, gave *N*-Boc derivative **10** in 84% overall yield for the four steps. *N*-Methylation of **10** and selective cleavage of the primary silyl group gave alcohol **11** in 96% yield, which was converted to the corresponding triflate and then treated with lithium trimethylsilylacetylide in THF–HMPA to give, after desilylation, alkyne **12** in 76% overall yield. The hydroxyl group of **12** was inverted by using an oxidation–reduction sequence to give alcohol **13** as a single stereoisomer in 95% yield. After silylation of **13**, iodoboration of the resulting alkyne with B-iodo-9-BBN followed by treatment with acetic acid was accompanied with deprotection of the Boc group to produce vinyl iodide **4** in 60% yield.<sup>7</sup>

Organozinc reagent **3**<sup>5</sup> was prepared from the protected iodoalanine (5 equiv.) following the procedure of Jackson et al.<sup>8</sup> and in situ treated with **4** in the presence of  $\text{PdCl}_2(\text{PPh}_3)_2$  (17 mol%) at 35°C to furnish the desired cross-coupled product **14** (Scheme 3). Removal of the TBS group followed by protection of the amino group gave alcohol **2** in 58% overall yield from **4**. Epoxidation of the *exo*-olefin of **2** with *m*-chloroperbenzoic acid (*m*CPBA) in  $\text{CH}_2\text{Cl}_2$ :pH 7.0 phosphate buffer (1:1) provided epoxide **15** as an approximately 1:1 mixture of diastereomers in 92% yield. Upon treatment of this mixture with camphorsulfonic acid (CSA), 5-*exo*-ring closure proceeded smoothly to yield an inseparable mixture of 6/5-bicyclic alcohol **16** and its  $\delta$ -lactone, which was then hydrolyzed with 1 N aqueous NaOH to give **16**<sup>9</sup> as a mixture of diastereomers at C4.

Conversion of **16** into dysiherbaine (**1**) and its C4 epimer **19** required oxidation of the primary hydroxyl group to the carboxylic acid and removal of the protective groups. We found unexpected transformation of **16** into fully protected dysiherbaine **17** and its C4 epimer **18**. Thus, oxidation of crude **16** with TPAP/NMO,<sup>10</sup> concentration of the reaction mixture under reduced pressure, and treatment of the residue with trimethylsilyldiazomethane provided **17** and **18** (24 and 16% isolated yields, respectively, from **15**), which were separated by chromatography on silica gel.<sup>11</sup> Finally, hydrogenolysis of the benzyl group



Scheme 2. Synthesis of vinyl iodide **4**. Reagents and conditions: (a) NaH, BnBr, DMF, 0°C→rt, 86%; (b) NaN<sub>3</sub>, NH<sub>4</sub>Cl, MeOCH<sub>2</sub>CH<sub>2</sub>OH–H<sub>2</sub>O, reflux; (c) BF<sub>3</sub>·OEt<sub>2</sub>, Ac<sub>2</sub>O, rt, 84% (two steps); (d) Et<sub>3</sub>SiH, TMSOTf, BF<sub>3</sub>·OEt<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>–CH<sub>3</sub>CN, rt, 78%; (e) NaOMe, MeOH, rt; (f) TBSOTf, 2,6-lutidine, CH<sub>2</sub>Cl<sub>2</sub>; (g) Ph<sub>3</sub>P, THF, rt, then H<sub>2</sub>O, 45°C; (h) Boc<sub>2</sub>O, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, rt, 84% (four steps); (i) NaH, MeI, DMF, 0°C, 96%; (j) CSA, CH<sub>2</sub>Cl<sub>2</sub>–MeOH, rt, 99%; (k) Tf<sub>2</sub>O, 2,6-lutidine, CH<sub>2</sub>Cl<sub>2</sub>, –78°C; (l) trimethylsilylacetylene, BuLi, THF–HMPA, –78°C; (m) Bu<sub>4</sub>NF, THF, rt, 76% (three steps); (n) (COCl)<sub>2</sub>, DMSO, *i*-Pr<sub>2</sub>NEt, CH<sub>2</sub>Cl<sub>2</sub>, –78°C→rt; (o) NaBH<sub>4</sub>, THF–MeOH, –78→0°C, 95% (two steps); (p) TBSOTf, 2,6-lutidine, CH<sub>2</sub>Cl<sub>2</sub>, 0°C; (q) B-1-9-BBN, pentane, –20°C, then AcOH, 60% (two steps)



Scheme 3. Total synthesis of dysiherbaine (**1**) and its C4-epimer **19**. Reagents and conditions: (a) PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, THF–DMA, 35°C; (b) Bu<sub>4</sub>NF, THF, rt; (c) Boc<sub>2</sub>O, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, rt, 58% (three steps); (d) *m*CPBA, CH<sub>2</sub>Cl<sub>2</sub>–pH 7.0 phosphate buffer, rt, 92%; (e) CSA, CH<sub>2</sub>Cl<sub>2</sub>, rt; (f) 1N NaOH, THF, rt; (g) TPAP, NMO, 4 Å molecular sieves, CH<sub>3</sub>CN, rt; (h) TMSCHN<sub>2</sub> (20 equiv.), MeOH, rt; **17**: 24% from **15**, **18**: 16% from **15**; (i) H<sub>2</sub>, Pd/C, MeOH, rt; (j) 6N HCl, 120°C, **1**: 90% (two steps), **19**: 89% (two steps)

followed by acid hydrolysis with 6N HCl furnished synthetic dysiherbaine (**1**) and its C4 epimer **19** as their hydrochloride salts in 90 and 89% yields, respectively. Each compound **1** and **19** was further purified by TOSO HW40 column (1.5×160 cm; eluent H<sub>2</sub>O; UV 210 nm; flow rate 0.25 mL/min).<sup>12</sup> The synthetic dysiherbaine was confirmed to be identical to natural dysiherbaine by <sup>1</sup>H NMR, ESIMS, and HPLC analysis.

The convulsant activity of synthetic dysiherbaine (**1**) in mice after an intracerebral injection (ED<sub>50</sub>=9.8

pmol/mouse) was virtually identical with that of the natural sample ( $ED_{50}=13$  pmol/mouse). The diastereomeric compound **19** was also found to be active in vivo although the potency ( $ED_{50}=385$  pmol/mouse) was about 40 times less than that of **1**. These results are somewhat surprising since the C4 epimer of dysiherbaine model compound was virtually inactive, whereas the model compound with native stereochemistry at C4 displayed CNS activity.<sup>3</sup> Detailed pharmacological properties of **19** along with the model compounds will be published elsewhere.

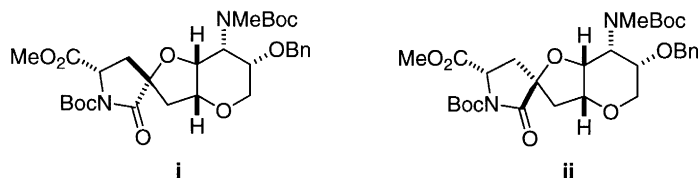
In summary, a total synthesis of (–)-dysiherbaine (**1**) was accomplished from readily available dianhydrohexose **5**. The synthesis described herein should allow for the preparation of a variety of analogues of this neuroexcitotoxin for further neurobiological studies. Further synthetic studies along this line are currently underway.

## Acknowledgements

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9. Hydroxy carboxylic acid **16** was easily cyclized to the corresponding  $\delta$ -lactone under weakly acidic conditions. Therefore, crude **16** was passed through a short column of neutral  $SiO_2$  (10% MeOH– $CHCl_3$  containing 1%  $Et_3N$ ) and immediately used in the next oxidation reaction.
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11. Following the oxidation of **16** with TPAP/NMO, the usual workup followed by purification by chromatography on silica gel and esterification with trimethylsilyldiazomethane provided a mixture of spiro lactam methyl esters **i** and **ii**.



12. <sup>1</sup>H NMR data (400 MHz, D<sub>2</sub>O) for compound **19**:  $\delta$  4.04 (1H, brdd,  $J=5.6, 1.7$  Hz, 6-H), 3.96 (1H, brs, 9-H), 3.96 (1H, brd,  $J=4.3$  Hz, 7-H), 3.83 (1H, d,  $J=13.2$  Hz, 10-H), 3.80 (1H, dd,  $J=11.7, 1.5$  Hz, 2-H), 3.49 (1H, m, 8-H), 3.46 (1H, d,  $J=13.2$  Hz, 10-H), 2.64 (3H, s, NMe), 2.50 (1H, dd,  $J=15.4, 5.6$  Hz, 5-H), 2.36 (1H, dd,  $J=15.8, 1.5$  Hz, 3-H), 2.10 (1H, d,  $J=15.4$  Hz, 5-H), 2.01 (1H, dd,  $J=15.8, 11.7$  Hz, 3-H).