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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.

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*.[1] 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 ($^{2,3}J_{C,H}$) analysis,[2] 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.[1] 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.[3] Very recently, total syntheses of **1** have been achieved by two independent groups.[4] 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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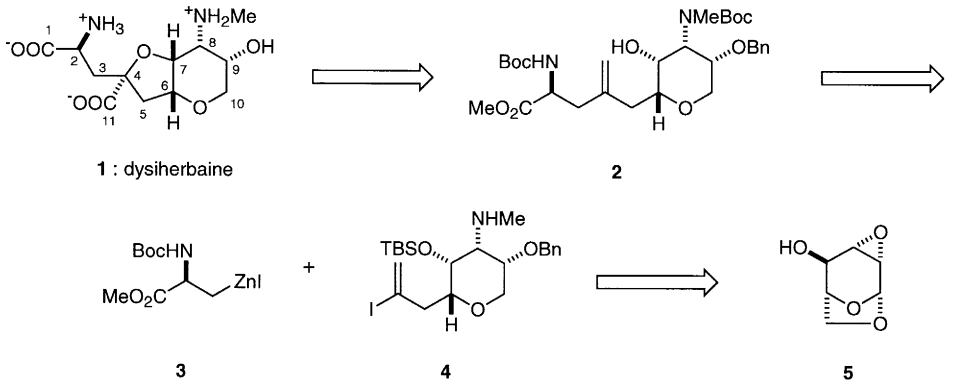
2 was envisioned to be synthesized by palladium(0)-catalyzed cross-coupling reaction of the known organozinc reagent **3**[5] with vinyl iodide **4**, which could be accessed from dianhydrohexose **5**. The use of a carbohydrate as a chiral starting material would allow for the synthesis of various analogues with respect to the bicyclic core structure.

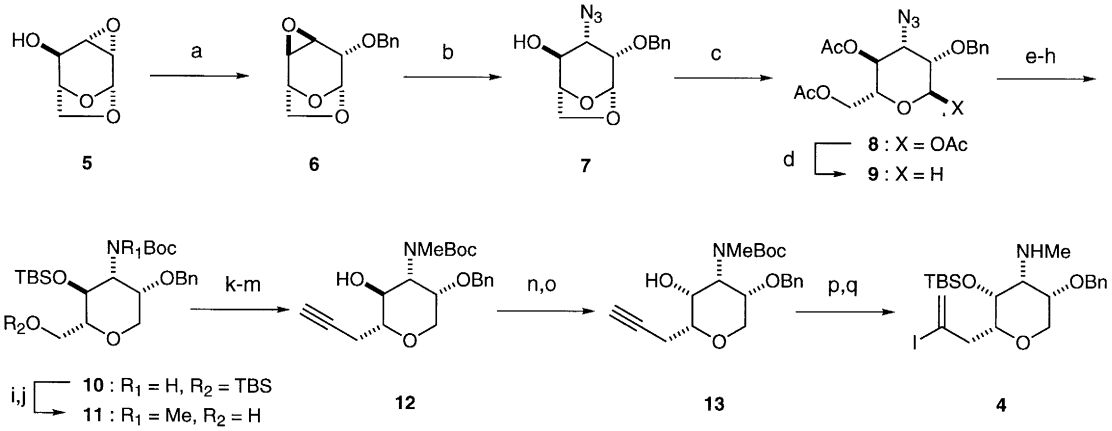


Scheme 1. Structure and retrosynthesis of dysiherbaine (**1**)

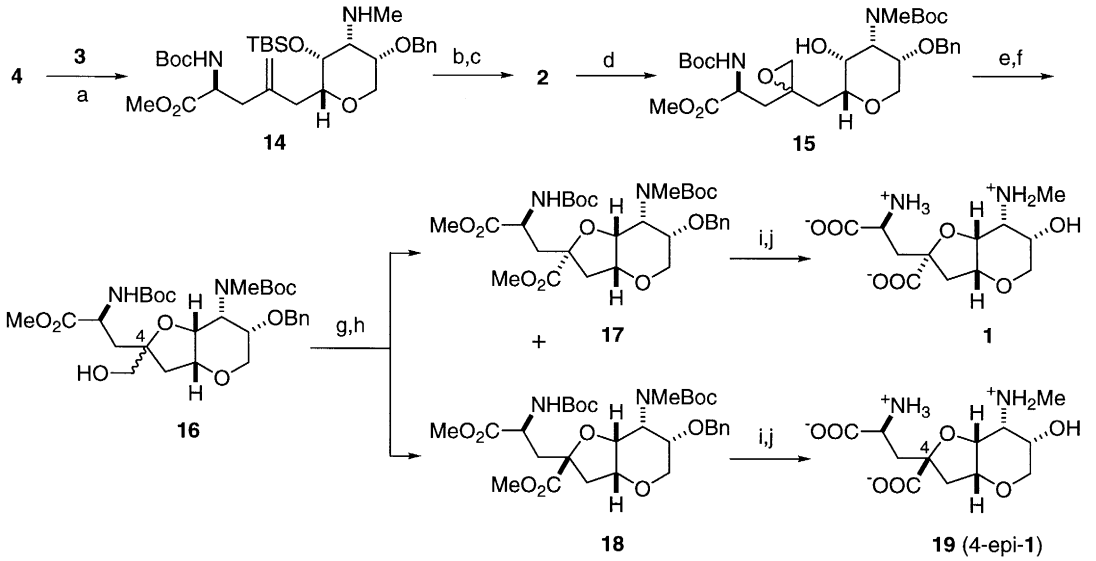
Synthesis of vinyl iodide **4** commenced with the known 1,6:2,3-dianhydrohexose **5**[6] (Scheme 2). Benzylation of **5** under the usual conditions was accompanied with migration of the epoxide ring[6] to give benzyl ether **6** in 86% yield. Epoxide ring-opening in **6** with sodium azide proceeded regioselectively to give azide alcohol **7**, which was then treated with acetic anhydride in the presence of $BF_3 \cdot OEt_2$ to yield triacetate **8** as a single stereoisomer in 84% yield for the two steps. Reduction of the anomeric acetoxyl group was effected with Et_3SiH in the presence of TMSOTf and $BF_3 \cdot OEt_2$ to give diacetate **9** in 78% yield. The acetyl groups were exchanged to *t*-butyldimethylsilyl (TBS) groups and reduction of the azide group with 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.[7]

Organozinc reagent **3**[5] was prepared from the protected iodoalanine (5 equiv.) following the procedure of Jackson et al.[8] and in situ treated with **4** in the presence of $PdCl_2(PPh_3)_2$ (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 CH_2Cl_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 δ-lactone, which was then hydrolyzed with 1 N aqueous NaOH to give **16**[9] 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,[10] 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.[11] 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_3, NH_4Cl, $MeOCH_2CH_2OH$–H_2O, reflux; (c) $BF_3{\cdot}OEt_2$, Ac_2O, rt, 84% (two steps); (d) Et_3SiH, TMSOTf, $BF_3{\cdot}OEt_2$, CH_2Cl_2–CH_3CN, rt, 78%; (e) NaOMe, MeOH, rt; (f) TBSOTf, 2,6-lutidine, CH_2Cl_2; (g) Ph_3P, THF, rt, then H_2O, 45°C; (h) Boc_2O, Et_3N, CH_2Cl_2, rt, 84% (four steps); (i) NaH, MeI, DMF, 0°C, 96%; (j) CSA, CH_2Cl_2–MeOH, rt, 99%; (k) Tf_2O, 2,6-lutidine, CH_2Cl_2, −78°C; (l) trimethylsilylacetylene, BuLi, THF–HMPA, −78°C; (m) Bu_4NF, THF, rt, 76% (three steps); (n) $(COCl)_2$, DMSO, *i*-Pr_2NEt, CH_2Cl_2, −78°C→rt; (o) $NaBH_4$, THF–MeOH, −78→0°C, 95% (two steps); (p) TBSOTf, 2,6-lutidine, CH_2Cl_2, 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) $PdCl_2(PPh_3)_2$, THF–DMA, 35°C; (b) Bu_4NF, THF, rt; (c) Boc_2O, Et_3N, CH_2Cl_2, rt, 58% (three steps); (d) *m*CPBA, CH_2Cl_2–pH 7.0 phosphate buffer, rt, 92%; (e) CSA, CH_2Cl_2, rt; (f) 1N NaOH, THF, rt; (g) TPAP, NMO, 4 Å molecular sieves, CH_3CN, rt; (h) $TMSCHN_2$ (20 equiv.), MeOH, rt, **17**: 24% from **15**, **18**: 16% from **15**; (i) H_2, 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_2O; UV 210 nm; flow rate 0.25 mL/min).[12] The synthetic dysiherbaine was confirmed to be identical to natural dysiherbaine by ^1H NMR, ESIMS, and HPLC analysis.

The convulsant activity of synthetic dysiherbaine (**1**) in mice after an intracerebral injection (ED_{50}=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.[3] 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 δ-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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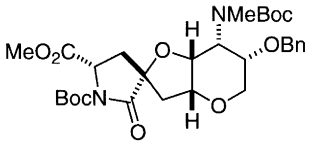
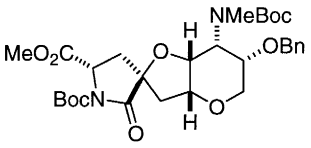
11. Following the oxidation of **16** with TPAP/NMO, the usual workup followed by purification by chromatography on silica gel and esterification with trimethylsilyldiazomethane provided a mixture of spirolactam methyl esters **i** and **ii**.



i



ii

12. ^{1}H NMR data (400 MHz, D_2O) for compound **19**: δ 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).