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Synthesis and Biological Activity of Dysiherbaine Model Compound

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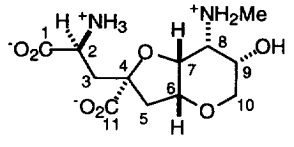
Abstract

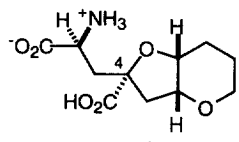
Synthesis of dysiherbaine model compound **2** and its diastereomer **3** is described. The structurally simplified model compound **2**, lacking the hydroxyl and *N*-methyl groups on the tetrahydropyran ring, induced convulsive behavior in mice upon intracerebral injections.

Key words: amino acids and derivatives; marine metabolites; natural products; toxins

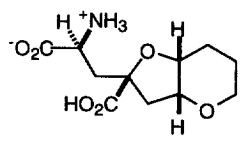
Dysiherbaine (**1**) was recently isolated as a neuroexitotoxin from a Micronesian marine sponge *Dysidea herbacea* [1]. Radioligand binding assay of **1** toward ionotropic glutamate receptors and electrophysiological experiments indicated that **1** is a potent agonist of non-NMDA (*N*-methyl-D-aspartate) subtype receptors in the central nervous system. 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 to be 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 neuroexitatory activity, dysiherbaine may become a useful leading compound for development of selective and powerful agonists or antagonists of glutamate receptors; however, its supply from natural source is limited. Therefore, total synthesis of **1** and its designed analogues is required for further physiological studies. In this letter, we describe a synthesis of the structurally simplified model compound **2**, which lacks two functional groups on the tetrahydropyran ring, and of its diastereomer **3** for their biological evaluations.



1: dysiherbaine



2



3

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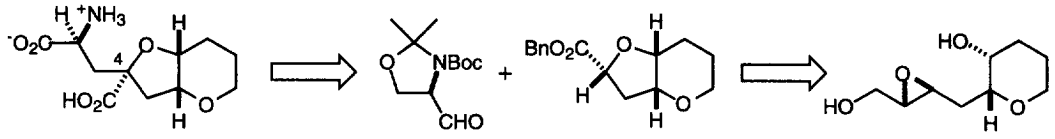
Our synthetic plan for **2** was based on a coupling of a protected D-serinal **4** [3], readily prepared from D-serine, onto *cis*-fused bicyclic ester **5** (Scheme 1). We anticipated that the *cis*-fused nature of **5** would allow an addition of **4** to occur preferentially from the convex face of the ester enolate of **5**, establishing the correct configuration at quaternary C4.[1] In turn, the 6/5-bicyclic ether skeleton of **5** was envisioned to be constructed through 5-*exo* selective cyclization of epoxy diol **6**.

Scheme 1



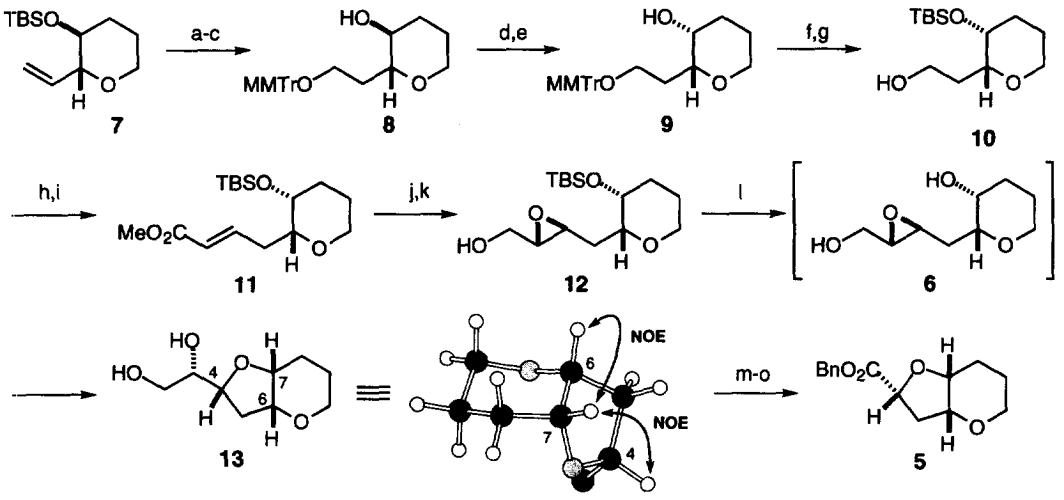
Synthesis of bicyclic ester **5** is summarized in Scheme 2. Hydroboration of the known **7** [4] with 9-BBN followed by oxidative workup gave a primary alcohol (88% yield), which was protected as its *p*-methoxyphenyldiphenylmethyl (MMTr), then desilylated to afford secondary alcohol **8**. The hydroxyl group was then inverted by an oxidation-reduction sequence to give **9** (74% yield over the four steps), which was converted to primary alcohol **10** in 58% overall yield. Oxidation of **10** with SO_3·pyridine to an aldehyde followed by Wittig olefination gave α,β-unsaturated ester **11** in 92% yield for the two steps. Ester **11** was reduced with diisobutylaluminum hydride (DIBAL), the resulting allylic alcohol being subjected to Sharpless asymmetric epoxidation using (+)-diethyl tartrate as the chiral auxiliary to give epoxy alcohol **12** in 80% yield for the two steps. The silyl group was removed with *n*-Bu_4NF to result in epoxy diol **6**, which underwent 5-*exo* selective cyclization during chromatography on silica gel, leading to *cis*-fused bicyclic diol **13** in 85% yield. The stereostructure of **13** was confirmed on the basis of prominent NOEs between H-4/H-7 and H-6/H-7. Oxidative cleavage of the *vic*-diol with $NaIO_4$ followed by further oxidation with $NaClO_2$ provided a carboxylic acid (75% yield for two steps), which was then benzylated with *N,N'*-diisopropyl-*O*-benzylisourea [5] to give ester **5** in 94% yield.

Coupling of the lithium enolate generated from ester **5** (LDA, THF-HMPA, -78 °C) with aldehyde **4** provided a mixture of diastereomeric alcohols, which were easily separated by column chromatography on silica gel to give **14a** (18%) and **14b** (75%) (Scheme 3). The next sequence of reactions were carried separately from each diastereomer without their stereochemical assignment. Deoxygenation by the method of Barton-McCombie [6] provided diastereomeric **15a** (81%) or **15b** (68%). Selective removal of the acetonide group was accomplished with $FeCl_3$-SiO_2 [7] in each case. The oxidation with Jones reagent and following esterification with trimethylsilyldiazomethane provided methyl ester **16a** (43%) or its C4

[1] The numbering of carbon atoms in all compounds in this letter corresponds to that of dysiherbaine (**1**).

epimer **16b** (61%). At this stage, their structures were unambiguously determined by X-ray crystallographic analysis of dimethyl ester **17** corresponding to **16b**. The unexpected stereochemical outcome in this coupling of **4** to **5** is yet to be explained.

Scheme 2



Reagents and conditions: (a) 9-BBN, THF, then H_2O_2, $NaHCO_3$, 88%; (b) MMTrCl, Et_3N, DMAP, CH_2Cl_2; (c) *n*-Bu_4NF, THF; (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C to r.t.; (e) *L*-Selectride, THF, -78 °C, 74% (4 steps); (f) TBSCl, imidazole, DMAP, DMF, 50 °C; (g) PPTS, MeOH, 58% (2 steps); (h) SO_3·Pyr, Et_3N, DMSO, CH_2Cl_2, 0 °C; (i) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, 92% (2 steps); (j) DIBAL, CH_2Cl_2, -78 °C, quant.; (k) *t*-BuOOH, $Ti(O\text{-}i\text{-}Pr)_4$, (+)-diethyl tartrate, 4Å molecular sieve, CH_2Cl_2, -20 °C, 80%; (l) *n*-Bu_4NF, THF, then silica gel, 85%; (m) $NaIO_4$, THF-H_2O; (n) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, 75% (2 steps); (o) *i*-PrNHC(OBn)=N*i*-Pr, $PhCH_3$, 94%.

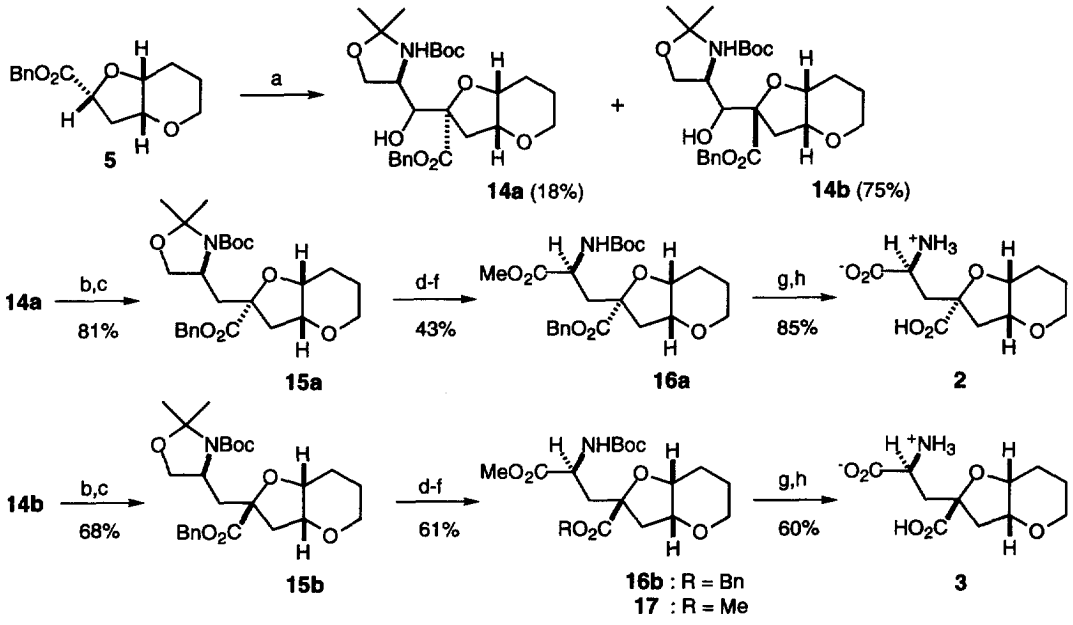
Finally, hydrolysis of the ester groups with aqueous 1N NaOH followed by removal of the Boc group with trifluoroacetic acid gave rise to the targeted model compound **2** and its C4 diastereomer **3** in 85% and 60% yield for the two steps from the respective precursors.

The toxicity of these model compounds **2** and **3** was tested on mice as a preliminary investigation. Intracerebral injection of **2** (20 μg/mouse) in mice (n=3) induced typical convulsive behaviors such as violent scratching and head bobbing for about 4 minutes, which was also observed for dysiherbaine (10-40 pmol/mouse). Interestingly, however, mice became hypoactive and rigid with occasional scratching behavior and eventually went into a deep sleeplike state about 5 minutes after the injection. This state lasted for up to 6 h. All mice recovered from these symptoms gradually and behaved apparently normal on the next day. Lower dose (2 μg /mouse) of **2** induced a moderate sleeper effect with faster recovery (2 h). The lowest dose tested (0.2 μg/mouse) only induced hypoactivity and moderate scratching behavior. Diastereomeric compound **3** did not induce neither typical convulsive behavior nor "sleeper" activity at 20 μg/mouse, suggesting that the stereochemistry at C4 quaternary carbon is important for this activity. Since dysiherbaine and other excitatory amino acids, such as

kainic acid or domoic acid, do not exhibit the "sleeper" activity, compound **2** may have some other actions at least in part differing from glutamate receptors on the central nervous system.

Further studies directed toward a total synthesis of dysiherbaine and its other analogues are currently under way and will be reported in due course.

Scheme 3



Reagents and conditions: (a) LDA, THF, -78 °C, then **4**; (b) NaH, CS_2, MeI, THF; (c) *n*-Bu_3SnH, AIBN, $PhCH_3$, 110 °C; (d) $FeCl_3$-SiO_2, $CHCl_3$; (e) Jones reagent, acetone; (f) $TMSCHN_2$, PhH-MeOH; (g) 1N NaOH, MeOH; (h) TFA, CH_2Cl_2.

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References

[1] Sakai R, Kamiya H, Murata M, Shimamoto K. J. Am. Chem. Soc. 1997; 119: 4112-4116.
[2] Matsumori N, Kaneno D, Murata M, Nakamura H, Tachibana K. J. Org. Chem. in press.
[3] Dondoni A, Perrone D. Synthesis 1997; 527-529 and references cited therein.
[4] Nicolaou KC, DeFrees SA, Hwang C-K, Stylianides N, Carroll PJ, Snyder, JP. J. Am. Chem. Soc. 1990; 112: 3040-3054.
[5] Mathias, LJ. Synthesis 1979; 561-576.
[6] Barton DHR, McCombie SW. J. Chem. Soc., Perkin Trans I 1975; 1574-1585.
[7] Kim K, Song Y, Lee B, Hahn C. J. Org. Chem. 1986; 51: 404-407.