Synthesis of dysiherbaine analogue

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Abstract—Synthesis of dysiherbaine analogue 4, which corresponds to 8,9-epi-neodysiherbaine A, is described. The synthesis features a concise route to the bicyclic ether skeleton through stereoselective C-glycosylation to set the C6 stereocenter and 5-exo ring-closure to form the tetrahydrofuran ring. The results of preliminary biological studies of 4 are also provided.

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Dysiherbaine (1), isolated from the Micronesian sponge, Dysidea herbacea, is a novel excitatory amino acid with potent convulsant activity.1,2 Dysiherbaine activates neuronal non-NMDA type glutamate receptors, namely, AMPA and kainic acid (KA) receptors, with considerable preference over KA receptors (Kᵢ values of 26 and 153 nM for KA and AMPA receptors, respectively).2 Moreover, it has been shown that dysiherbaine could differentially activate one of the activation sites within the subunit of a heteromeric GluR5/KA2 receptor complex.3 This discrete affinity of dysiherbaine has enabled characterization of the unexpectedly complex behavior of the heteromeric KA receptors. Neodysiherbaine A (2),4 isolated as a minor congener from the same sponge, differs from dysiherbaine in the functional group at the C8 position and is also a selective agonist for non-NMDA type glutamate receptors (Fig. 1).

Due to these unusual pharmacological properties of dysiherbaine to KA receptors and its potent epileptogenic activity, dysiherbaine and its designed analogues are anticipated to serve as useful tools for understanding the structure and functions of glutamate receptors in the central nervous system. Thus, the total synthesis of dysiherbaine has been reported by several research groups.5,6

Recently, Swanson and co-workers have characterized the pharmacological action of neodysiherbaine A and simplified synthetic analogue 37 on glutamate recep-

 tors.8 These studies revealed that neodysiherbaine A is similar to dysiherbaine in its pharmacological activity on KA receptors, albeit with slightly different binding affinities for individual receptor subunits, whereas analogue 3, lacking the hydroxyl and N-methyl groups on the tetrahydropyran ring, is a selective antagonist for GluR5 KA receptors. These results strongly suggest that the C₅ and C₉ functional groups are critical structural elements for specificity and selectivity for KA receptors. In order to reveal further the detailed structure–activity relationship profiles of dysiherbaine, we undertook a diverted synthesis of structural analogues of dysiherbaine. In this letter, we describe a synthesis of dysiherbaine analogue 4, corresponding to 8,9-epi-neodysiherbaine A, for the biological evaluation.

The synthesis started with C-glycosylation of allylsilane 69 with diacetyl-L-arabinal (5).10 Thus, reaction of 5
with 6 in the presence of Yb(OTf)3 (10 mol%), CH2Cl2, rt, 85%; (b) AD mix-β, MeSO3NH2, t-BuOH/H2O, 0 °C → rt; quant.; (c) TBSOTf, Et3N, DMAP, CH2Cl2, 0 °C, 87%; (d) K2CO3, MeOH, rt, 92%; (e) CH2Cl2, phosphate buffer, 0 °C, AD mix-β, methylsilyl (TBS) ether to give 9; (f) H2, Pd/C, hexane, rt, 89%; (g) NaH, CS2, MeI, THF, 0 °C → rt, then SiO2, 89%; (h) Me2C(OMe)2, CSA, CH2Cl2, 0 °C, 85%; (i) H2, Pd/C, hexane, rt, 80%; (j) TMS, 2-BuOH/H2O, 0 °C, 75%; (k) Bu3SnH, AIBN, toluene, 110 °C, 80%; (l) TBSOTf, 2,6-lutidine, CH2Cl2, 0 °C, 85%; (m) NaH, CS2, MeI, THF, 0 °C → rt, 80%; (n) Bu3SnH, AIBN, toluene, 110 °C, 75%; (o) LiBH4, THF, 0 → 60 °C, 74%; (p) TBSOTf, 2,6-lutidine, CH2Cl2, 0 °C, 87%. Oxidation of the major alcohol 11a with SO2-pyr/DMSO followed by Wittig reaction, gave enolate 12 in 88% overall yield (Scheme 2). DIBALH reduction and Sharpless asymmetric epoxidation using (+)-diisopropyl tartrate (DIPT) delivered epoxy alcohol 13 in 93% yield for the two steps. Stereoselective introduction of the amino group at the C3 position was carried out following the procedure of Kishi and co-workers.13 Thus, treatment of 13 with benzyl isocyanate (t-Pr2NET, benzene, 50 °C, 80%) followed by reaction of the resultant benzyl carbamate with KOr-Bu afforded cyclic carbamate 14 (61%). Subsequent deoxygenation was carried out according to the method of Barton and Macombie14 to provide 15 in 66% yield for the two steps.

Diastereomeric alcohol 11b was also converted to 15 as depicted in Scheme 3. Oxidation to the acid and subsequent esterification provided methyl ester 16 in 60% overall yield. Desilylation followed by oxidation with SO2-pyr/DMSO afforded an aldehyde, which was subjected to Wittig reaction to give 17 in 51% yield for the three steps. Selective reduction of the enone moiety of diester 17 was achieved by exposure to DIBALH in THF to yield an allylic alcohol (90%), which upon asym-

![Scheme 1](image1)

Scheme 1. Reagents and conditions: (a) compound 6, Yb(OTf)3 (10 mol%), CH2Cl2, rt, 85%; (b) AD mix-β, MeSO3NH2, t-BuOH/H2O, 0 °C → rt; quant.; (c) TBSOTf, Et3N, DMAP, CH2Cl2, 0 °C, 87%; (d) K2CO3, MeOH, rt, 92%; (e) m-CPBA, CH2Cl2/pH 7 phosphate buffer, 0 °C → rt, then SiO2, 89%; (f) Me2C(OMe)2, CSA, CH2Cl2, 0 °C, 85%; (g) H2, Pd/C, hexane, rt, 60% in 87% yield.

![Scheme 2](image2)

Scheme 2. Reagents and conditions: (a) SO2-pyr, DMSO, Et3N, CH2Cl2, 0 °C; (b) Ph3P=CHCO2Me, CH2Cl2, rt, 88% (two steps); (c) DIBALH, CH2Cl2, –78 °C, 98%; (d) t-BuOOH, Ti(Oi-Pr)4 (+)-DIPT, 4 Å MS, CH2Cl2, –20 °C, 95%; (e) t-Pr2NET, benzene, 50 °C, 80%; (f) KOr-Bu, THF, –20 → 0 °C, 61%; (g) NaH, CS2, MeI, THF, 0 °C → rt, 80%; (h) Bu3SnH, AIBN, toluene, 110 °C, 82%.

![Scheme 3](image3)

Scheme 3. Reagents and conditions: (a) TEMPO, NaClO2, cat. NaClO, MeCN/pH 7.0 phosphate buffer, 75%; (b) K2CO3, MeI, DMF, rt, 80%; (c) TBAF, THF, rt, 85%; (d) SO2-pyr, DMSO, Et3N, CH2Cl2, 0 °C; (e) Ph3P=CHCO2Me, CH2Cl2, rt, 60% (two steps); (f) DIBALH, THF, –78 °C, 90%; (g) t-BuOOH, Ti(i-Pr)O2, (+)-DIPT, CH2Cl2, 4 Å MS, –20 °C, 83%; (h) NaH, CS2, MeI, THF, 0 °C → rt, 80%; (i) KOr-Bu, THF, –20 → 0 °C, 78%; (j) NaH, CS2, MeI, THF, 0 °C → rt, 80%; (k) Bu3SnH, AIBN, toluene, 110 °C, 75%; (l) LiBH4, THF, 0 → 60 °C, 74%; (m) TBSOTf, 2,6-lutidine, CH2Cl2, 0 °C, 87%.
metric epoxidation delivered epoxy alcohol 18 in 83% yield. Elaboration of 18 to cyclic carbamate 19 was readily accomplished as described above. The resultant ester 19 was then converted to 15 by ester reduction and protection.15

Cyclic carbamate 15 was subsequently transformed to diol 20 by a four-step sequence of protective group manipulations, including reductive debenzylation with lithium tert-butylbiphenylylde (LDBB),16 reprotection as the Boc group, ethanolysis of the cyclic carbamate and desilylation with TBAF (Scheme 4). Oxidation of 20 with KMnO4 (1 M NaOH, H2O) gave a mixture of diacid 21 and aminal 22, which without separation was further oxidized with catalytic amounts of tetra-n-propylammonium per ruthenate (TPAP) and N-methylmorpholine N-oxide (NMO)17 and subsequently treated with excess trimethylsilyl diazomethane to deliver dimethyl ester 23 in 61% yield over the three steps. Finally, global deprotection by acid hydrolysis (6 M HCl, 65 °C) furnished the target compound 4 in 90% yield.18 Thus, the synthesis of analogue 4 was completed in 23 steps and 3.4% overall yield from diacetyl-LL-arabinal via 11a. In addition, selective deprotection of the acetonide of 23 was realized by using DDQ (CH3CN/H2O, 50 °C) in 85% yield.19 Further modification of the C8 and C9 hydroxy groups of 24 should lead to various dysiherbaine analogues.

The toxicity of dysiherbaine analogue 4 was preliminarily tested on mice. Intracerebral injection of 4 against mice did not induce any behavioral effects such as violent scratching and head bobbing even at higher dose (20 μg/mouse).

In conclusion, we have developed a synthetic route to dysiherbaine analogue 4, which features a concise synthesis of the bicyclic ether skeleton through stereoselective C-glycosylation to set the C8 stereocenter and 5-exo cyclization for constructing the tetrahydrofuran ring. Further neurophysiological studies of compound 4 and synthesis of other analogues from a key intermediate 23 to probe the structure–activity relationship of dysiherbaine are in progress and will be reported in due course.

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References and notes


12. The stereochemistry at C4 position of each compound was determined by NOE experiments of the corresponding aldehydes (A and B).


15. Attempts to remove the benzyl group of compound 19 were unsuccessful.


18. Selected data for compound 4: $[\alpha]_D^{25} = -40.0$ (c 0.05, H2O); $^1$H NMR (600 MHz, D2O) $\delta$ 2.00 (dd, $J = 15.6$, 10.6 Hz, 1H, 3-H), 2.09 (dd, $J = 14.1$, 3.8 Hz, 1H, 5-H), 2.53 (dd, $J = 15.6$, 2.3 Hz, 1H, 3-H); 2.54 (d, $J = 14.1$ Hz, 1H, 5-H), 3.39 (dd, $J = 10.6$, 10.6 Hz, 1H, 10-H), 3.47 (dd, $J = 10.6$, 5.0 Hz, 1H, 10-H), 3.61 (dd, $J = 10.6$, 2.3 Hz, 1H, 2-H), 3.93 (ddd, $J = 10.6$, 5.0, 3.2 Hz, 1H, 9-H), 4.05 (m, 1H, 7-H), 4.09 (m, 1H, 8-H), 4.13 (m, 1H, 6-H); $^{13}$C NMR (125 MHz, D2O) $\delta$ 178.57, 174.12, 86.89, 83.97, 74.24, 67.42, 65.11, 64.43, 53.79, 44.31, 39.70; HRMS (FAB) calcd for C11H16NO8 [(M+H)+]: 290.0876. Found: 290.0881.