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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 C_6 stereocenter and 5-*exo* ring-closure to form the tetrahydrofuran ring. The results of preliminary biological studies of **4** are also provided.

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 (K_i 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 C_8 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 **3**[7] on glutamate receptors.[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 C_8 and C_9 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.

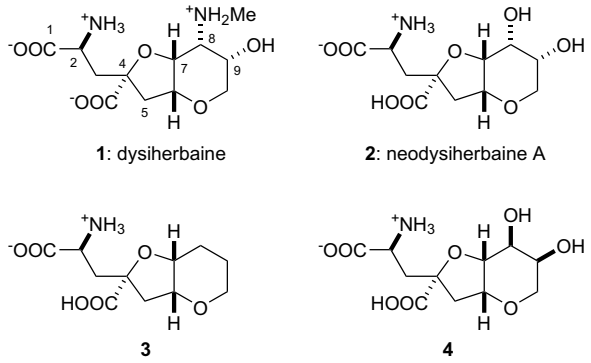

Figure 1. Structures of dysiherbaine and its analogues.

The synthesis started with C-glycosylation of allylsilane **6**[9] with diacetyl-L-arabinal (**5**).[10] Thus, reaction of **5**

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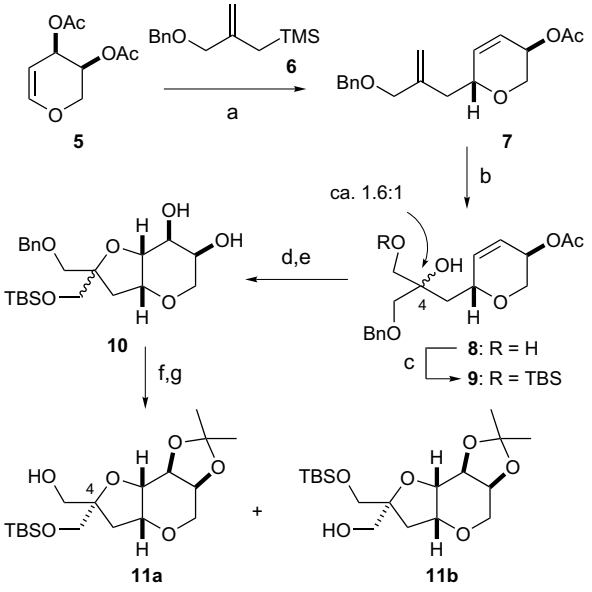
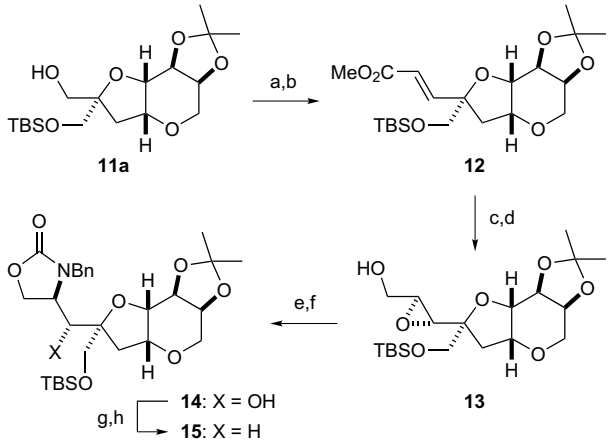


Scheme 1. Reagents and conditions: (a) compound **6**, $Yb(OTf)_3$ (10 mol%), CH_2Cl_2, rt, 85%; (b) AD mix-β, $MeSO_2NH_2$, *t*-BuOH/H_2O, 0 °C → rt, quant.; (c) TBSOTf, Et_3N, DMAP, CH_2Cl_2, 0 °C, 87%; (d) K_2CO_3, MeOH, rt, 92%; (e) *m*-CPBA, CH_2Cl_2/pH 7 phosphate buffer, 0 °C → rt, then SiO_2, 89%; (f) $Me_2C(OMe)_2$, CSA, CH_2Cl_2, 0 °C, 85%; (g) H_2, Pd/C, hexane, rt, **11a**, 60%; **11b**, 38%.

with **6** in the presence of $Yb(OTf)_3$ (CH_2Cl_2, room temperature)[11] led to *C*-glycoside **7** as the sole product in 85% yield (Scheme 1). Subsequent treatment of **7** with AD mix-β® ($MeSO_2NH_2$, *t*-BuOH/H_2O, 0 °C → rt) effected regioselective dihydroxylation of the exocyclic double bond to afford diol **8** in quantitative yield as an approximately 1.6:1 mixture of diastereomers, which was carried forward without separation through the subsequent transformations. The primary hydroxy group of **8** was selectively protected as the *tert*-butyldimethylsilyl (TBS) ether to give **9** in 87% yield. After removal of the acetyl group (92%), treatment of the resultant allylic alcohol with *m*-CPBA led exclusively to the corresponding β-epoxide. When the crude epoxide was subjected to purification by column chromatography on silica gel, epoxide ring-opening by an intramolecular attack of the tertiary alcohol occurred to generate diol **10** in 89% yield. Protection of the diol as the acetonide (85%) followed by removal of the benzyl group under hydrogenolysis afforded alcohols **11a** (60%) and **11b** (38%), which were readily separable by flash column chromatography.[12] Thus, the synthesis of the bicyclic ether skeleton was realized in only seven steps from **5**.

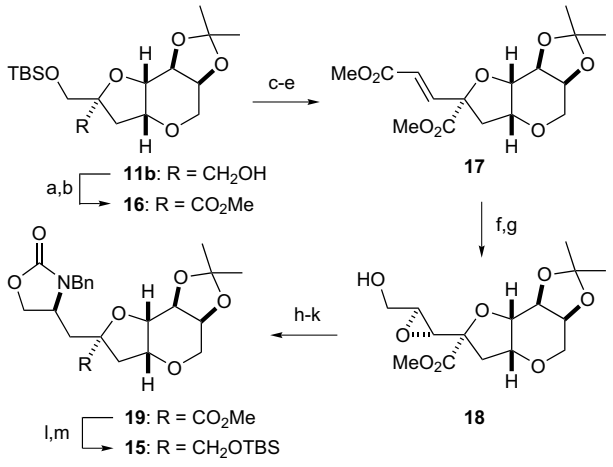
Oxidation of the major alcohol **11a** with SO_3·pyr/DMSO followed by Wittig reaction, gave enoate **12** in 88% overall yield (Scheme 2). DIBALH reduction and Sharpless asymmetric epoxidation using (+)-diisopropyl tartrate (DIPT) delivered epoxy alcohol **13** in 93% yield for the two steps. Stereoselective introduction of the amino group at the C_2 position was carried out following the procedure of Kishi and co-workers.[13] Thus, treatment of **13** with benzyl isocyanate (*i*-Pr_2NEt, benzene, 50 °C, 80%) followed by reaction of the resultant benz-



Scheme 2. Reagents and conditions: (a) SO_3·pyr, DMSO, Et_3N, CH_2Cl_2, 0 °C; (b) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, rt, 88% (two steps); (c) DIBALH, CH_2Cl_2, −78 °C, 98%; (d) *t*-BuOOH, Ti(O*i*-Pr)$_4$, (+)-DIPT, 4 Å MS, CH_2Cl_2, −20 °C, 95%; (e) BnNCO, *i*-Pr_2NEt, benzene, 50 °C, 80%; (f) KO*t*-Bu, THF, −20 → 0 °C, 61%; (g) NaH, CS_2, MeI, THF, 0 °C → rt, 80%; (h) Bu_3SnH, AIBN, toluene, 110 °C, 82%.

ylcarbamate with KO*t*-Bu afforded cyclic carbamate **14** (61%). Subsequent deoxygenation was carried out according to the method of Barton and MaCombie[14] to provide **15** in 66% yield for the two steps.

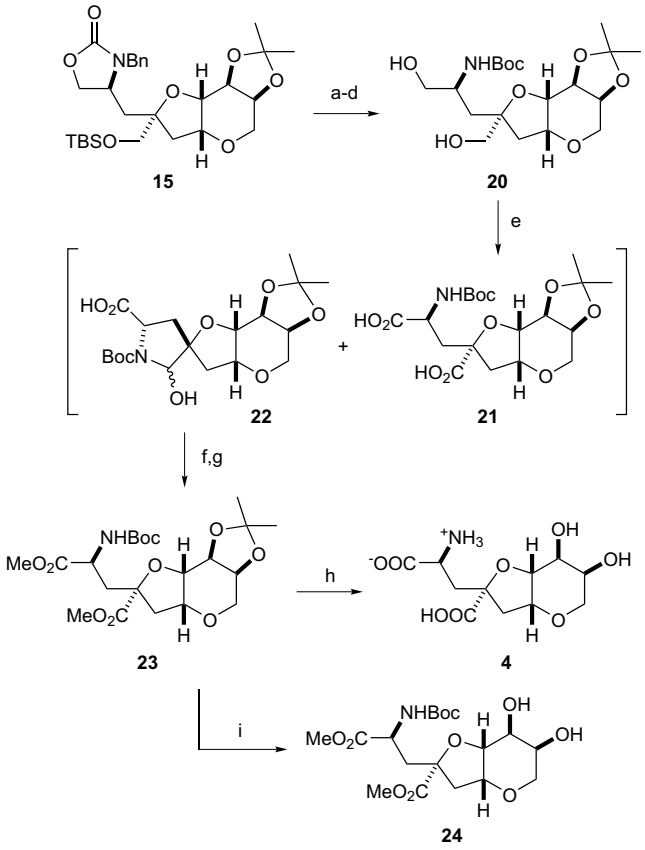
Diastereomeric alcohol **11b** was also converted to **15** as depicted in Scheme 3. Oxidation to the acid and subsequent esterification provided methyl ester **16** in 60% overall yield. Desilylation followed by oxidation with SO_3·pyr/DMSO afforded an aldehyde, which was subjected to Wittig reaction to give **17** in 51% yield for the three steps. Selective reduction of the enoate moiety of diester **17** was achieved by exposure to DIBALH in THF to yield an allylic alcohol (90%), which upon asym-



Scheme 3. Reagents and conditions: (a) TEMPO, $NaClO_2$, cat. NaClO, MeCN/pH 7.0 phosphate buffer, 75%; (b) K_2CO_3, MeI, DMF, rt, 80%; (c) TBAF, THF, rt, 85%; (d) SO_3·pyr, DMSO, Et_3N, CH_2Cl_2, 0 °C; (e) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, rt, 60% (two steps); (f) DIBALH, THF, −78 °C, 90%; (g) *t*-BuOOH, Ti(*i*-PrO)$_4$, (+)-DIPT, CH_2Cl_2, 4 Å MS, −20 °C, 83%; (h) BnNCO, *i*-Pr_2NEt, benzene, 50 °C, 95%; (i) KO*t*-Bu, THF, −20 °C, 78%; (j) NaH, CS_2, MeI, THF, 0 °C → rt, 80%; (k) Bu_3SnH, AIBN, toluene, 110 °C, 75%; (l) $LiBH_4$, THF, 0 → 60 °C, 74%; (m) TBSOTf, 2,6-lutidine, CH_2Cl_2, 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*-butylbiphenylide (LDBB),[16] reprotection as the Boc group, ethanolysis of the cyclic carbamate and desilylation with TBAF (Scheme 4). Oxidation of **20** with $KMnO_4$ (1 M NaOH, H_2O) gave a mixture of diacid **21** and aminal **22**, which without separation was further oxidized with catalytic amounts of tetra-*n*-propylammonium perruthenate (TPAP) and *N*-methylmorpholine *N*-oxide (NMO)[17] and subsequently treated with excess trimethylsilyldiazomethane 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-L-arabinal via **11a**. In addition, selective deprotection of the acetonide of **23** was realized by using DDQ (CH_3CN/H_2O, 50 °C) to give diol **24** in 85% yield.[19] Further modification of the C_8 and C_9 hydroxy groups of **24** should lead to various dysiherbaine analogues.



Scheme 4. Reagents and conditions: (a) LDBB, THF, −78 °C, 76%; (b) Boc_2O, Et_3N, DMAP, CH_2Cl_2, 85%; (c) Cs_2CO_3, EtOH, rt, 95%; (d) TBAF, THF, 4 Å MS, rt, 94%; (e) $KMnO_4$, aq NaOH, rt; (f) TPAP, NMO, 4 Å MS, CH_2Cl_2, rt; (g) $TMSCHN_2$, MeOH, rt, 61% (three steps); (h) 6 M HCl, 65 °C, 90%; (i) DDQ, CH_3CN/H_2O, 50 °C, 85%.

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 C_6 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.

Acknowledgments

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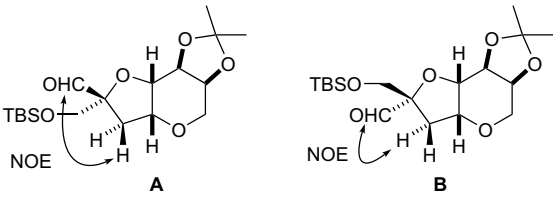

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18. Selected data for compound **4**: $[\alpha]_D^{25}$ −40.0 (*c* 0.05, H_2O); ^1H NMR (600 MHz, D_2O) δ 2.00 (dd, J = 15.6, 10.6 Hz, 1H, 3-H), 2.09 (dd, J = 14.1, 3.8 Hz, 1H, 5-H), 2.53 (dd, J = 15.6, 2.3 Hz, 1H, 3-H); 2.54 (d, J = 14.1 Hz, 1H, 5-H), 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, D_2O) δ 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 $C_{11}H_{16}NO_8$ [$(M-H)^-$]: 290.0876. Found: 290.0881.
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