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Total synthesis of dysiherbaine

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Abstract—An efficient total synthesis of dysiherbaine, a potent and subtype-selective agonist for ionotropic glutamate receptors, has been achieved. An advanced key intermediate in the previous synthesis of neodysiherbaine A and its analogues was selected as the starting point, and cis-oriented amino alcohol functionality on the tetrahydropyran ring was installed by using an intramolecular S_N2 cyclization of *N*-Boc-protected amino alcohol. The amino acid appendage was constructed by catalytic asymmetric hydrogenation of enamide ester.

Ionotropic glutamate receptors (iGluRs) form a family of ligand-gated ion channels that mediate fast synaptic transmission in the mammalian central nervous system.[1] The iGluRs can be divided, based on their affinities for the selective agonists, into three subclasses: *N*-methyl-D-aspartate (NMDA), (*S*)-2-amino-3-(3-hydroxy-5-methyl-4-isoxazolyl)propionic acid (AMPA), and kainate receptors. These receptors play important roles in many processes, including learning and memory, and are also implicated in a number of neuronal disorders. There are seven NMDA receptor genes (NR1, NR2A-2D, NR3A, and NR3B), four AMPA receptor genes (GluR1-4), and five kainate receptor genes (GluR5-7 and KA1-2). This diversity makes the functional analysis of native glutamate receptors a formidable task. Therefore, the development of selective ligands that can discriminate between different glutamate receptors has been the focus of extensive research.

Dysiherbaine (**1**)[2] and its congener, neodysiherbaine A (**2**),[3] isolated by Sakai et al. from the Micronesian sponge *Dysidea herbacea*, are remarkable excitatory amino acids with potent convulsant activity (Fig. 1).[4] Structurally, these amino acids consist of a cis-fused hexahydrofuro[3,2-*b*]pyran ring system containing a glutamic acid substructure. Dysiherbaine activates the AMPA and kainate classes of receptors, with a higher affinity for the latter, but shows no detectable affinity for NMDA receptors.[5] Furthermore, it has been revealed that dysiherbaine had extremely high affinity for recombinant GluR5 or GluR6 kainate receptors but very low affinity for KA2 receptors, and this difference of affinities produced unusual biophysical behavior from heteromeric kainate receptors.[6] Neodysiherbaine A is also a selective agonist for AMPA and kainate receptors, with slightly different binding affinities for kainate receptor subunits.[7] The high affinity and selectivity of dysiherbaines for certain kainate receptor subtypes made these natural products useful tools for exploring the complex biophysical functions of glutamate receptor ion channels; however, the exact mode of interaction is still elusive.[8]

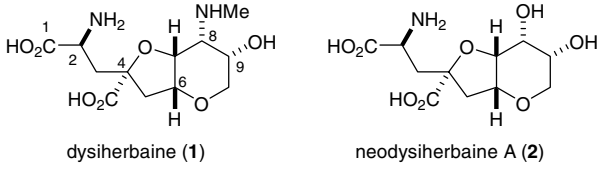

Figure 1. Structures of dysiherbaine and neodysiherbaine A.

In addition to their unique biological profiles, the unprecedented molecular structures of dysiherbaines have attracted considerable attention from synthetic chemists. Thus, several total syntheses and synthetic approaches have been reported, including structure–activity relationship studies of neodysiherbaine A from this

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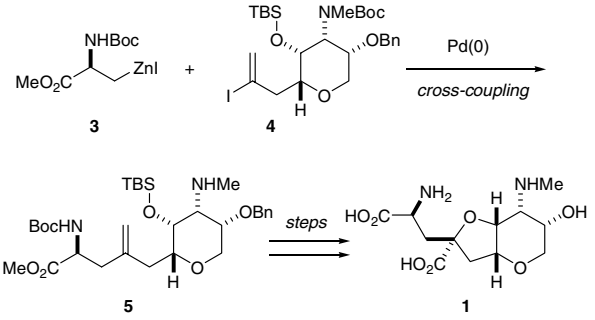
laboratory.[3,9–12] Here, we describe an efficient synthetic route to dysiherbaine that would allow for the preparation of analogues to elucidate the detailed structure–activity relationships.

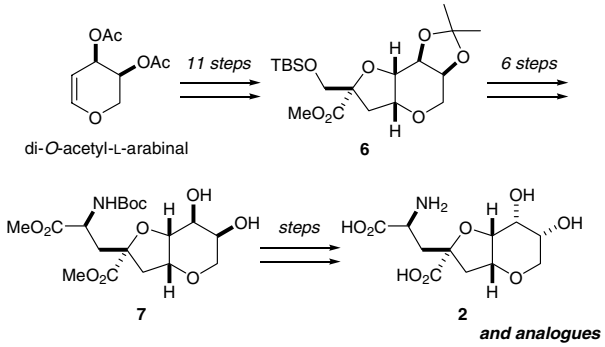
We previously reported the total synthesis of dysiherbaine (**1**), which featured the palladium(0)-catalyzed cross-coupling reaction of organozinc compound **3** with vinyl iodide **4**.[9b] This first-generation synthesis, however, required a multi-step sequence of reactions (32 steps from commercially available 1,6-anhydro-D-glucose) (Scheme 1).

Recently, we developed an efficient synthetic route to neodysiherbaine A (**2**) and its analogues starting from a common intermediate **7** (Scheme 2).[10d,11b] The synthesis of **7** featured (i) a concise synthesis of bicyclic ether **6** and (ii) a catalytic asymmetric hydrogenation to construct the amino acid appendage.

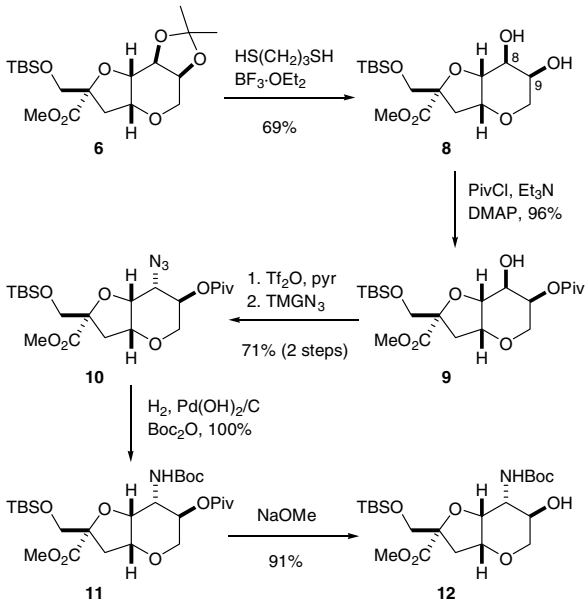
We envisioned constructing dysiherbaine (**1**) from ester **6**,[10d] which would have required the introduction of an amino functionality at the C8 position. For this purpose, the acetonide from ester **6** was selectively deprotected by exposure to 1,3-propanedithiol in the presence of boron trifluoride etherate (CH_2Cl_2, −30 °C) to afford diol **8** in 69% yield (Scheme 3). Treatment of diol **8** with pivaloyl chloride and triethylamine (CH_2Cl_2, −78 °C) afforded monopivaloate ester **9** selectively (96%) due to the equatorial disposition of the C9 alcohol and the steric congestion of the axial-oriented C8 alcohol. The remaining alcohol was converted to the corresponding triflate (trifluoromethanesulfonic anhydride, pyridine,



Scheme 1. First-generation total synthesis of dysiherbaine.



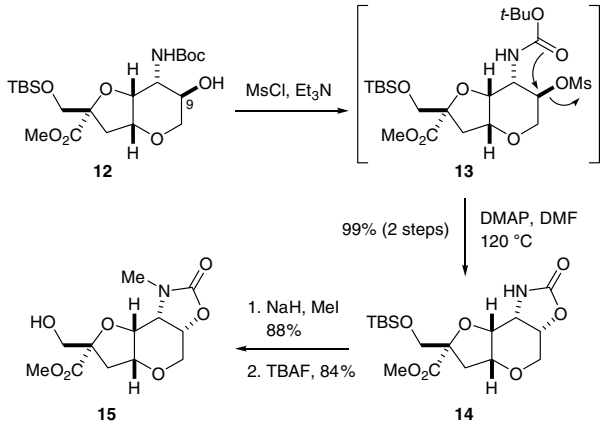
Scheme 2. Synthesis of neodysiherbaine A and analogues.



Scheme 3. Introduction of C8 amino group.

CH_2Cl_2, −20 °C), which was subsequently treated with tetramethylguanidium azide (DMF, 35 °C). Smooth displacement took place to provide the desired azide **10** in 71% yield over the two steps. Hydrogenation of **10** in the presence of di-*tert*-butyl dicarbonate proceeded cleanly to afford *N*-*tert*-butoxycarbonyl (Boc) derivative **11** in quantitative yield. Subsequently, removal of the pivaloyl group (NaOMe, MeOH) led to alcohol **12** in 91% yield.

Having successfully introduced an amino group at C8, we were now in a position to invert the C9 hydroxy group. We first attempted to perform this transformation by an oxidation–reduction sequence or Mitsunobu reaction, but all of these attempts were unsuccessful. We then opted for the inversion by an intramolecular cyclization according to the procedure of Benedetti and Norbedo.[13] Thus, treatment of **12** with methanesulfonyl chloride and triethylamine (CH_2Cl_2, 0 °C) afforded the corresponding mesylate **13**, which, without purification, was immediately treated with dimethylaminopyridine in DMF at 120 °C (Scheme 4). The expected



Scheme 4. Introduction of cis-oriented amino alcohol functionality on the tetrahydropyran ring.

oxazolidinone **14** was obtained in excellent yield over the two steps. Following N-methylation (NaH, MeI, DMF, 88%), the *tert*-butyldimethylsilyl (TBS) group was removed (TBAF, THF, 84%) to afford primary alcohol **15**. At this stage, the stereochemistry of the C8 and C9 positions was established by NOEs as shown in Figure 2.

Oxidation of **15** under Parikh–Doering conditions (SO_3·pyridine, Et_3N, DMSO, CH_2Cl_2)[14] followed by Horner–Wadsworth–Emmons olefination using phosphonate **16**[15] and tetramethylguanidine generated enamide ester **17** in 73% yield over the two steps (E:Z = ca. 1:14) (Scheme 5). Hydrogenation of **17** in the presence of 5 mol % of [Rh(I)(COD)-(*S*,*S*)-Et-DuPHOS]$^+$OTf$^-$ catalyst[16,17] in THF under pressurized hydrogen (0.9 MPa) at room temperature proceeded smoothly to give the desired amino acid derivative **18** in 83% yield. The corresponding diastereomer could not be detected in the 500 MHz ^{1}H NMR spectra. The stereochemistry at C2 was tentatively assigned based on Burk's empirical rule[16] and our previous results.[10d] Finally, global deprotection of **18** under alkaline hydrolysis conditions (40% NaOH, MeOH, 45 °C) furnished dysiherbaine (**1**) in 84% yield.[18] The synthetic dysiherbaine was identical to the natural material as judged by the ^{1}H and ^{13}C NMR spectra. Moreover, the in vivo toxicity of the synthetic compound against mice by intracerebroventricular injection was similar to that of the natural specimen.

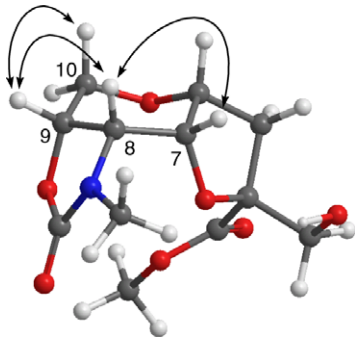
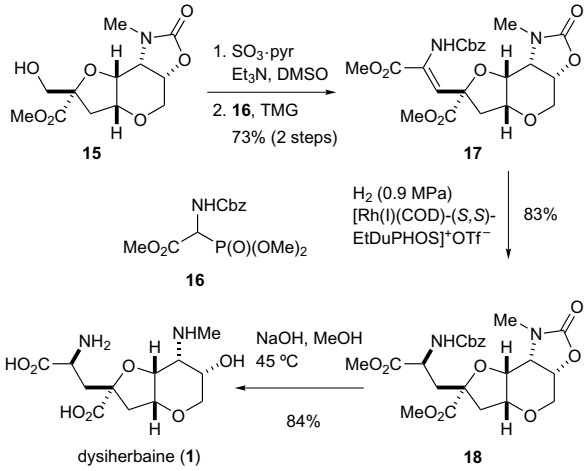


Figure 2. Key NOEs observed for compound **15**.



Scheme 5. Completion of total synthesis of dysiherbaine.

In summary, an efficient synthesis of dysiherbaine (**1**) was achieved in 24 steps and 4.3% overall yield from di-*O*-acetyl-L-arabinal. The present synthesis would allow for the synthesis of various dysiherbaine analogues to clarify the structure–activity relationship profiles. Further studies along this line are under way in our laboratory and will be reported in due course.

Acknowledgment

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18. *Selected spectral data for* **1**: $[\alpha]_D^{21}$ −9.2 (*c* 0.72, H_2O); IR (KBr) 3419, 3400–2500 (br), 1604, 1506, 1111 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 4.27 (s, 1H), 4.12 (s, 1H), 3.84 (d, $J = 14.5$ Hz, 1H), 3.81 (s, 1H), 3.51 (s, 1H), 3.50 (d, $J = 12.5$ Hz, 1H), 3.45 (d, $J = 10.0$ Hz, 1H), 2.71 (s, 3 H), 2.56 (d, $J = 13.0$ Hz, 1H), 2.54 (d, $J = 13.5$ Hz, 1H), 2.12 (dd, $J = 13.5$, 3.0 Hz, 1H), 1.88 (dd, $J = 15.0$, 11.5 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) δ 181.4, 175.0, 89.8, 77.4, 76.1, 69.9, 63.4, 57.7, 54.8, 45.7, 40.5, 30.8; HRMS (ESI) *m*/*z* calcd for $C_{12}H_{19}N_2O_7$ [$(M-H)^-$] 303.1192, found 303.1174.