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Synthesis of the dysiherbaine tetrahydropyran core utilizing improved tethered aminohydroxylation conditions

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ABSTRACT

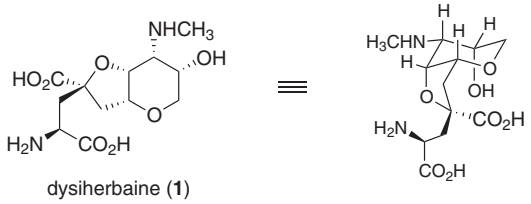
A concise stereoselective route to the dysiherbaine tetrahydropyran core was achieved in nine steps and 39% overall yield. Donohoe's improved tethered aminohydroxylation conditions were employed to concurrently install the amino and alcohol groups and construct the tetrahydropyran ring, which features four contiguous *cis*-stereocenters.

Activation of glutamate receptors (GluRs) is essential to rapid excitatory synaptic transmission and higher order brain functions including memory formation, learning, and pain transmission. Prolonged activation, however, initiates excitotoxicity, which in turn can lead to neurodegenerative disorders, such as stroke, depression, Parkinson's disease, and schizophrenia. Structurally unique excitatory amino acids that are potent and selective GluR agonists are essential to studying specific receptor subtypes and elucidating their respective roles in neuronal signaling and neurodegenerative diseases.[1] Dysiherbaine (**1**) (DH) is a novel amino acid isolated from the Micronesian sea sponge, *Dysidea herbacea*, in 1997 by Sakai et al. (Fig. 1).[2] A potent and selective non-NMDA type ionotropic glutamate receptor (*i*GluR) agonist, DH is approximately 50-fold selective for KA over AMPA receptors, while also exhibiting agonist activity on a subtype of metabotropic glutamate receptors (*m*GluRs). DH is also the most potent epileptogenic agent known.[1c] The unique structure of DH consists of a *cis*-fused hexahydrofuro[3,2-*b*]pyran ring substituted with a glutamic acid appendage. Contained in the bicyclic core is a densely functionalized tetrahydropyran (THP) ring that features four contiguous *cis*-stereocenters, including a methylamino group. The intriguing structure and favorable biological profile coupled with a low natural abundance has made DH a molecule of wide interest, as characterized by several total syntheses including one by our lab.[3,4]

The total synthesis accomplished in our lab was highly convergent and stereocontrolled; however, the overall efficiency suffered due to a low yielding late stage introduction of the methylamino group, therefore, our second-generation approach sought to install this moiety at a preliminary stage of the synthesis.[3d] This was accomplished in the retrosynthetic analysis by utilizing the key ring-contraction transformation from our first-generation synthesis to reveal lactone **2** (Scheme 1). Dismantling the lactone and removal of the amino acid appendage provides the elaborated THP core, which contains the methyl amino group masked as the oxazolidinone **3**. It appeared that a tethered aminohydroxylation of the allylic alcohol **4** would be an ideal strategy for obtaining the desired THP intermediate **3**.

The initial attempt to install the hydroxy carbamate functionality employed Donohoe's TAH reaction,[5] utilizing conditions originally reported by Sharpless[6] (Scheme 2). This unexpectedly resulted in a 1:1 mixture of the carbamates **6** and **7**. When the isomers were independently re-subjected to basic reaction conditions a 1:1 mixture was again obtained, confirming that a facile thermodynamic equilibration is occurring under the reaction conditions. The mixture was successfully converged to a single isomer over a six-step sequence.[7] While employing a TAH reaction to stereoselectively install the amino group and the hydroxyl group concurrently remained an attractive strategy, it was desirable to avoid the observed mixture of isomers.

Improved TAH conditions were recently reported by Donohoe et al., which featured base free reaction conditions that appeared to be amenable to our synthetic strategy (Scheme 3).[8] The allylic alcohol **4**, which was previously reported by our lab, is readily obtained in a high yielding three step sequence from tri-*O*-acetyl-D-galactal.[7] Subjecting alcohol **4** to CDI in pyridine, with the ensuing addition of hydroxylamine, produced the hydroxy carbamate **8** in 60% yield (27% recovered alcohol **4**). The resultant hydroxy carbamate was then treated with PFBCl, in the presence of Et_3N, to ob-



dysiherbaine (**1**)

Figure 1. Dysiherbaine.

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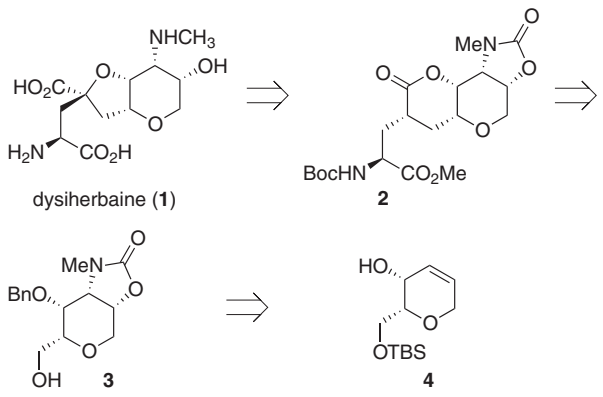
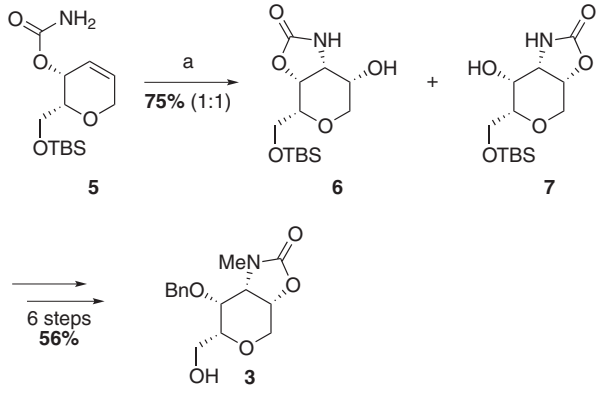
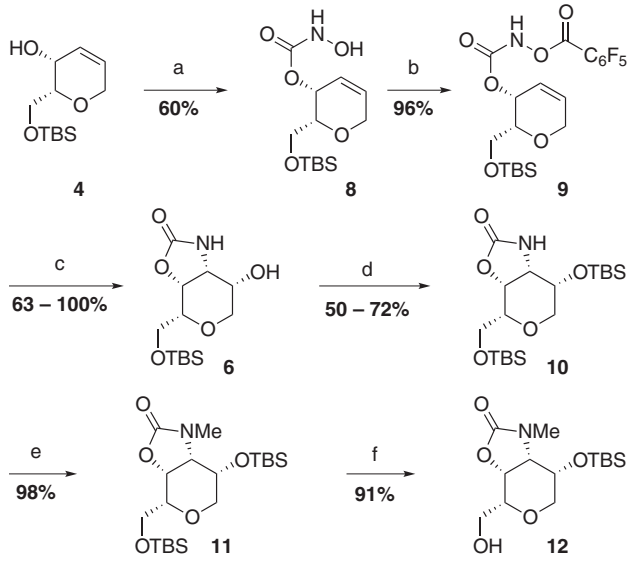


Scheme 1. Retrosynthetic strategy.



Scheme 2. Initial tethered aminohydroxylation: (a) *t*-BuOCl, NaOH, $K_2[OsO_2(OH)_4]$, $(DHQ)_2PHAL$, *n*-PrOH/H_2O.



Scheme 3. Synthesis of alcohol **12**: (a) (i) CDI, pyridine, 40 °C; (ii) $NH_2OH{\cdot}HCl$; (b) Et_3N, F_5C_6COCl, CH_2Cl_2, −8 °C; (c) $K_2[OsO_2(OH)_4]$ (1 mol%), *t*-BuOH/H_2O; (d) TBSCl, imidazole, DMF; (e) *t*-BuOK, MeI, THF; (f) DOWEX, MeOH.

tain the requisite O-substituted hydroxy carbamate **9** in 96% yield. Upon mixing carbamate **9** with potassium osmate, clean conversion to the oxazolidinone **6** was effected in 63–100% yield. While the amino hydroxylation gave complete conversion by TLC, oxazolidinone **6** proved difficult to purify due to high polarity and low solubility, which may account for the moderate 63% isolated yield when column chromatography was applied. Oxazolidinone **6** was also insoluble in both acetonitrile and water, including mixtures thereof, which precluded HPLC reverse phase purification. Favorably, the improved NaOH free conditions provided the oxazolidinone **6** as a single isomer, without any observed migration of the cyclic carbamate that proved detrimental when employing the original TAH conditions. The hydroxyl group was then protected as the TBS ether to give oxazolidinone **10** in 50–72% yield with the remainder of the mass balance accounted for by the recovered alcohol **6**. The yield was comparable whether purified or crude oxazolidinone was subjected to silyl protection conditions. Silylation of the secondary alcohol proved surprisingly tricky; employment of TBSOTf as the silylation reagent only lead to *N*-TBS formation and not the desired *O*-TBS product, while using *N*-TBS-*N*-methylacetamide showed no significant improvement in yield.[9] Treatment of carbamate **10** with methyl iodide in the presence of *t*-BuOK afforded *N*-methyl oxazolidione **11** in 98% yield, with subsequent chemoselective cleavage of the primary TBS to complete construction of the advanced THP core **12.**

A concise and stereoselective route to the dysiherbaine THP core employing Donohoe's improved TAH conditions was successfully completed. Alcohol **12** was synthesized in 39% yield over nine steps from commercially available material, featuring four contiguous stereocenters including the methyl amino group. The improved conditions avoided the mixture of alcohol isomers previously observed, and obviated the need for a chiral amine additive in the TAH reaction. The THP intermediate could potentially be applied to a concise total synthesis of dysiherbaine.

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Supplementary data

Supplementary data (complete experimental procedures, product characterization, and spectral data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.05.106.

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