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Enantioselective Synthesis of (−)-Dysiherbaine

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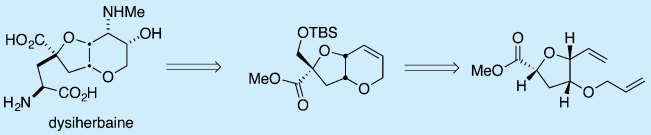
Supporting Information

ABSTRACT: Dysiherbaine, a natural product isolated from the Marine sponge *Dysidea herbacea*, has been shown to be a selective agonist of non-NMDA type glutamate receptors, kainate receptors. An enantioselective synthesis of dysiherbaine is reported. Metathesis of the diene followed by conversion of the resulting alkene to the amino alcohol and addition of the amino acid provides the natural product. This synthesis differs from previous approaches to the molecule in that the functionality on the tetrahydropyran ring is installed late in the route.



The use of molecules that selectively interact with central nervous system (CNS) receptors is one of the fundamental approaches that has been used to elucidate the role of various receptors. Kainate receptors (KAR) may be among the least understood of the ionotropic receptors, in part because of the lack of molecules that selectively interact with the different types of KARs. A series of neurotoxic amino acids, dysiherbaine and neodysiherbaine, have been isolated from the marine sponge *Dysidea herbacea* by Sakai and co-workers (Figure 1).[1−4] A study of these molecules revealed that they

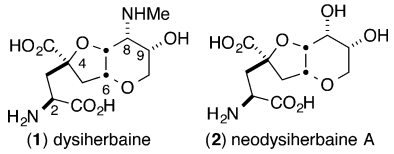
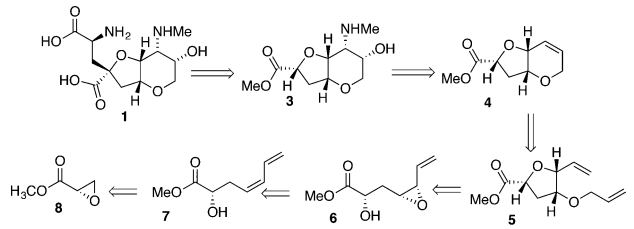


Figure 1. Dysiherbaine and neodysiherbaine A.

possess unique agonist activity with the non-NMDA type glutamate receptors, kainate receptors.[5−10] Initial studies examining simple analogues of dysiherbaine and neodysiherbaine have found that the glutamate section of the molecule is responsible for much of the binding to the receptor, while the conformation and functionality of the tetrahydropyran ring are key in determining the activity profile (agonist vs antagonist) of these molecules.[9] Since the functionality of the tetrahydropyran ring appears to be important in controlling the receptor response of these molecules, an approach to dysiherbaine and neodysiherbaine analogues was embarked on that would pass through an intermediate that allows the modification the tetrahydropyran ring at a late stage in the synthesis.

The previous routes to these molecules have generally utilized starting materials that have the amino alcohol or the diol at C-8 and C-9 in place.[10−17] Starting with such tetrahydropyran-containing starting materials limits the ability to make molecules where the functionality at C-8 and C-9 is varied. The approach described here forms the pyran ring at a late stage, as dihydropyran **4** (Scheme 1), and is designed to

Scheme 1. Retrosynthetic Analysis



allow for introduction of functionality at C-8 and C-9 toward the end of the synthetic sequence. After introduction of the amine and hydroxyl groups the amino acid is added.[3,10,12,14−16]

Dihydropyran **4** is derived from a metathesis reaction on diene **5** which is synthesized by epoxide opening of **6**. The epoxide is formed by directed epoxidation of homoallylic alcohol **7**. Asymmetry of the system is set by the use of optically active commerically available methyl glycidate **8**.[18]

The opening of glycidic methyl ester was attempted with a number of acetylides with the aluminum acetylide proceeding in good yield (Scheme 2). Following the removal of the trimethylsilyl group, the acetylene **9** was converted to enyne **10** by Sonogashira coupling. The reduction of the enyne to the required *cis*-diene required considerable optimization. Lindlar conditions generally failed to provide the desired product in good yield. The major product using a variety of different "Lindlar" conditions either resulted in over reduction or no reaction. Reaction with zinc/copper/silver amalgam in methanol/water provided the desired *cis*-diene **7** in good yield.[19,20] The stereogenic center α to the ester was then used to perform a regio- and diastereoselective epoxidation (12:1 ratio of diastereomers) of the diene **7**. The selective opening of epoxide **6** with formation of the desired tetrahydrofuran was first performed using $BF_3{\cdot}Et_2O$; however, after extensive optimization the yield was only 53%. The approach reported by Hirama, using palladium-catalyzed opening of the epoxide,

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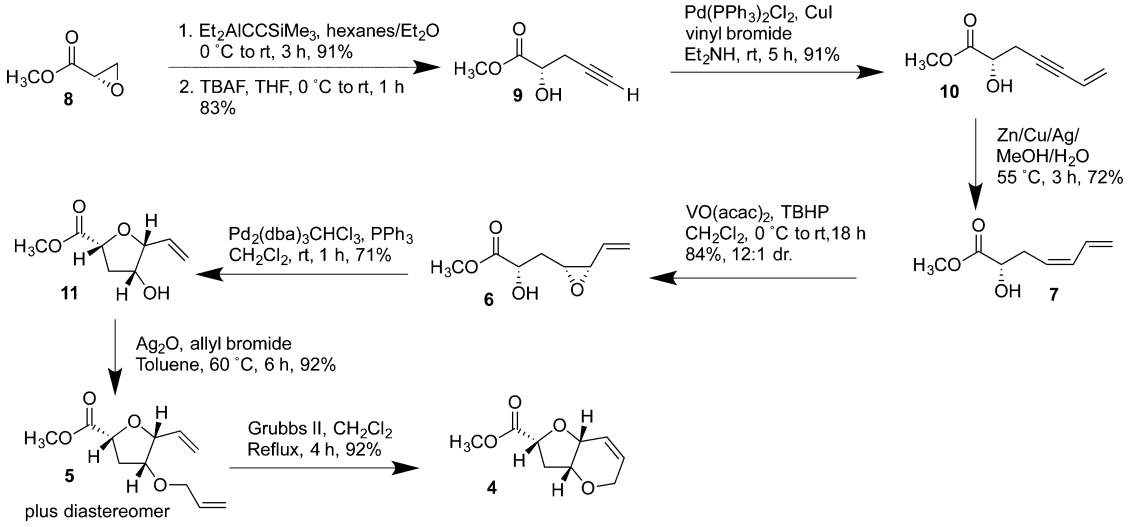
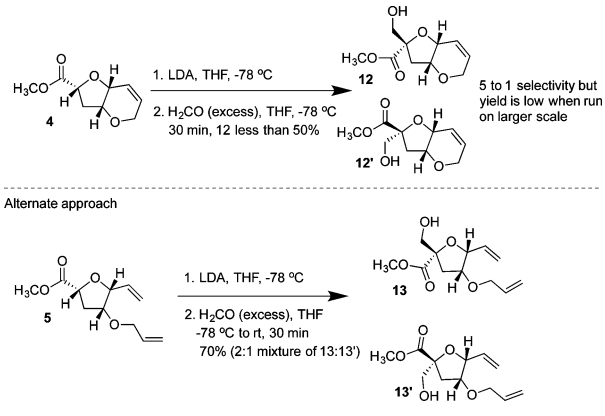
Scheme 2. Synthesis of the Furopyran Ring Skeleton



followed by addition of the α-hydroxyl group to the allyl palladium intermediate provided the desired furan ring with the inverted stereochemistry (**11**), consistent with the reported literature for similar substrates.[21,22] Allylation of the free alcohol with allyl bromide and silver oxide provided the diene metathesis substrate (**5**). Reaction with Grubbs II catalyst provided the 1,5-dioxaoctahydroindene (**4**) system in excellent yield.

The next step in the planned approach was to install the amino acid using one of the methods reported in the literature or by a new approach developed by us. The approach taken possesses elements of both (Scheme 3). Addition of formaldehyde provided a primary alcohol that would ultimately be oxidized and then converted to the amino acid by asymmetric hydrogenation. Reaction of **4** with LDA followed by quenching with formaldehyde proved the desired alcohol in limited yield but 5:1 selectivity.[23] When the scale of this reaction was increased the yield decreased significantly. Consequently, an alternate approach was taken where the formaldehyde addition was carried out before the metathesis ring closure. This results in significantly better yield but poorer selectivity (2:1); however, the two diastereomeric alcohols (**13**) are easily separated by column chromatography. Following separation, the metathesis reaction proceeds in high yield with both diastereomers. Both diastereomers were converted to a 4-bromobenzenesulfonic ester with the wrong diastereomer for dysiherbaine providing crystals that were used for an X-ray crystal structure to confirm the stereochemistry (data provided in the Supporting Information).

Scheme 3. Functionalization of Ester 4



Introduction of the amino alcohol to the alkene was critical for the entire approach. Dihydroxylation of **14** gave diol **15**. Bis hydroxylation of the double bond functionalized carbons 8 and 9 but with the opposite configuration from dysiherbaine. Substitution at C-8 with a variety of nitrogen nucleophiles proved to be difficult due to the equatorial position of the hydroxyl group. It was necessary to introduce the amine nitrogen in an intramolecular fashion. This was accomplished by bis mesylation followed by selective substitution of with azide at C-9 (**16**). Treatment of **16** with PPh_3 and DIPEA successfully provided aziridine which was protected with Boc due to the ease of purification. Reaction of **17**, protected as the Boc carbamate, with copper(II) triflate provided the rearranged produce (**18**) which efficiently introduced both amine group at C-8 and hydroxyl group at C-9.[24−27] To the best of our knowledge this is the first example of a regioselective opening of a carbamate protected aziridine not directed by a carboxyl group somewhere in the molecule.[25−27] The regio- and stereochemistry of **18** was confirmed by COSY and NOESY NMR, respectively. Methylation of the nitrogen followed by oxidation of the primary alcohol set the stage for the introduction of amino acid by olefination of the newly formed aldehyde providing **21**. Asymmetric hydrogenation using rhodium DuPhos in ethanol provided the protected version of dysiherbaine. Hydrolysis of **22** with 40% NaOH in MeOH, followed by ion exchange and reverse phase chromatography provided dysiherbaine. The ^{1}H and ^{13}C NMR spectra of synthetic product matched well to those of the synthesized and natural product reported in literature.

In conclusion, we have completed the enantioselective synthesis of dysiherbaine by using the optically active readily available methyl glycidate. The approach of building a pyran ring at a late stage in the synthesis will allow for modification of functionality at C-8 and C-9 from a common intermediate in a late stage of the synthesis, thus providing a more efficient route to access to analogs of dysiherbaine.

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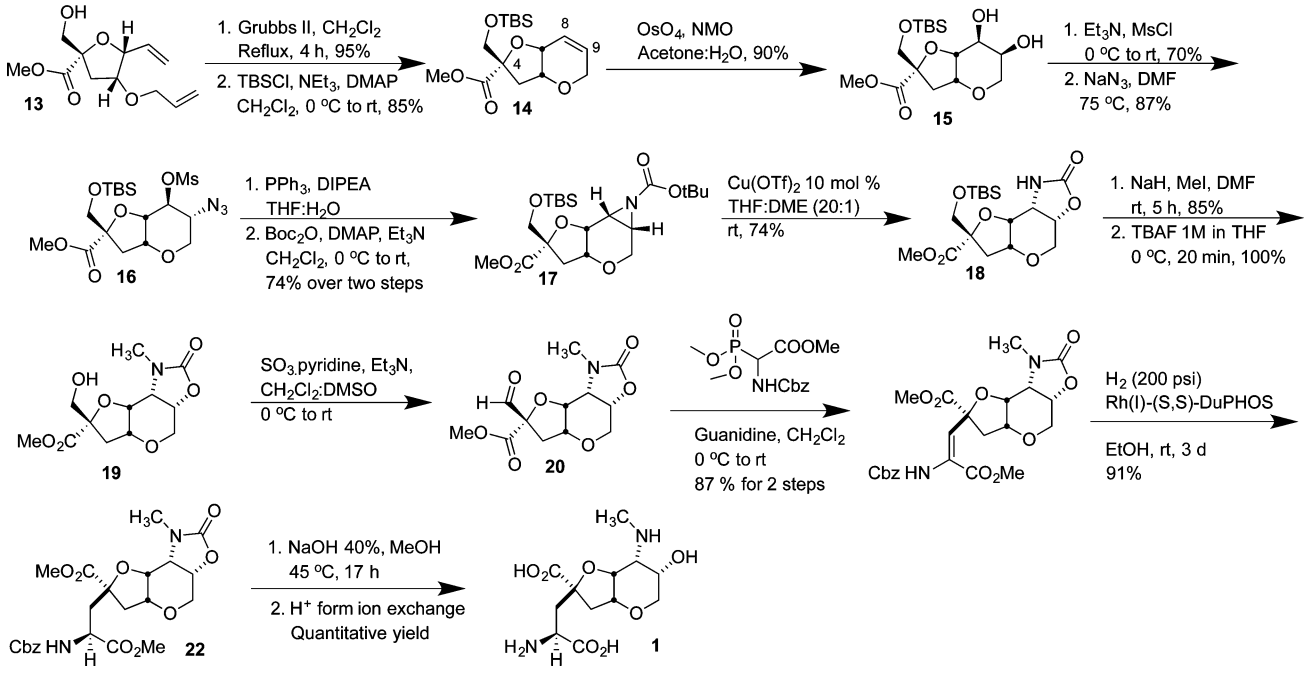
Scheme 4. Introduction of Amino Alcohol and Addition of Amino Acid



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01821.

General methods, experimental procedures, spectroscopic data, and ^{1}H and ^{13}C NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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