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Total Synthesis of Neodysiherbaine A via 1,3-Dipolar Cycloaddition of a Chiral Nitrone Template

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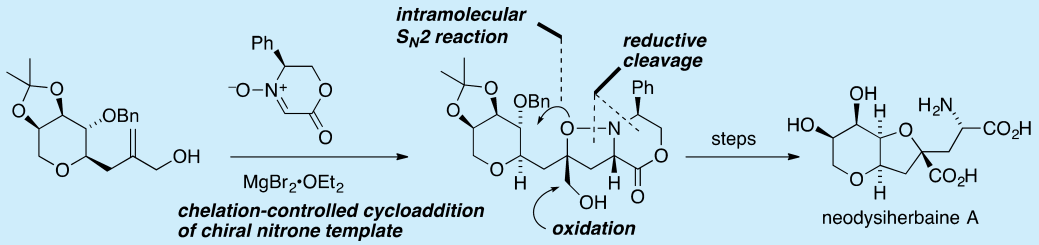
Supporting Information



ABSTRACT: The total synthesis of neodysiherbaine A was achieved via 1,3-dipolar cycloaddition of a chiral nitrone template with a sugar-derived allyl alcohol in the presence of $MgBr_2 \cdot OEt_2$. This cycloaddition constructed the C2 and C4 asymmetric centers in a single step. Then reductive cleavage, intramolecular S_N2 reaction of the tertiary alcohol, and oxidation of the primary alcohol afforded neodysiherbaine A.

Dysiherbaine (**1**)[1] and neodysiherbaine A (**2**)[2] were isolated from the Micronesian sponge *Dysidea herbacea* as excitatory amino acids that are selective agonists of non-NMDA-type glutamate receptors in the central nervous system (Figure 1). The structural characteristics of these compounds include a highly functionalized pyranofuran moiety (C4−C10), a glutamic acid moiety (C1−C4, C11), and an oxygen-substituted quaternary center (C4) that connects those two parts. Intensive efforts to synthesize these compounds have been made[2−5] because of their interesting structural characteristics and biological activities.

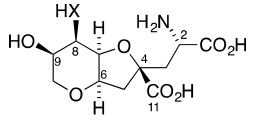


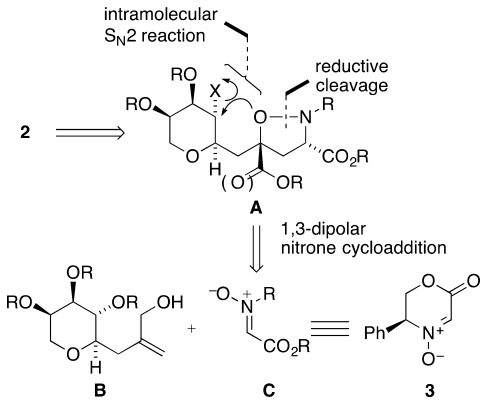
Figure 1. Dysiherbaine and neodysiherbaine A.

For example, these amino acids exhibit high affinities for kainate receptors Gluk1 and Gluk2.[6,7] Among various synthetic intermediates for these amino acids[8] and their analogues,[9] compound **2** and its analogues have proven to be useful tools for studying the structure and functions of kainate receptors.[7c]

In this communication, we report a total synthesis of **2** featuring a chelation-controlled cycloaddition of a nitrone with an allyl alcohol in the presence of magnesium bromide and tetrahydrofuran ring construction by means of intramolecular S_N2 reaction. The former reaction can construct the stereochemistries at both the 2- and 4-positions (glutamic acid numbering) in a single operation, and the latter reaction is challenging because a highly functionalized tertiary alcohol is used as the nucleophile.

Our retrosynthetic analysis of **2** is shown in Scheme 1. Inclusion of an additional bond from the C2-amino nitrogen to the C4-oxygen in **2** affords isoxazolidine **A**, which can be obtained by cycloaddition of a nitrone. Accordingly, we planned to utilize a stereocontrolled 1,3-dipolar cycloaddition in the synthesis of **2**. Thus, cycloaddition of fully functionalized allyl alcohol **B** with ester-substituted nitrone **C** would give isoxazolidine **A**, whose hydrogenolysis followed by intra-

Scheme 1. Retrosynthetic Analysis of 2



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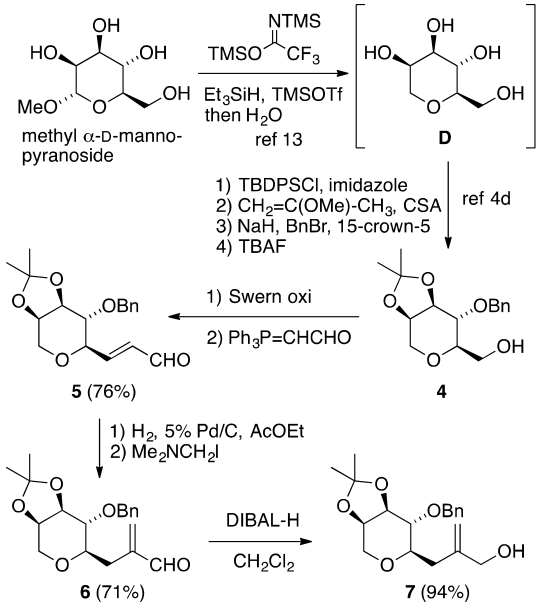
molecular S_N2 reaction should afford the target molecule **2**. We chose cyclic nitrone **3** as a chiral and geometry-fixed nitrone corresponding to **C**.[10−12] Thus, the first task was the synthesis of the fully functionalized allyl alcohol corresponding to **B**.

Allyl alcohol **7** was expected to be suitable, since one of the hydroxyl groups distinguished by the different protective group (benzyl group) can be transformed into a leaving group (Scheme 2). Considering the stereochemistry of **7**, we selected

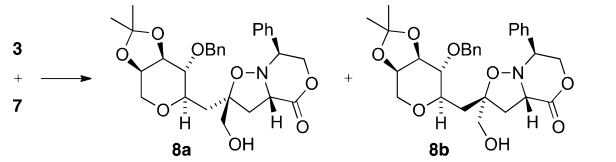
Scheme 2. Preparation of Allyl Alcohol 7



methyl α-D-mannopyranoside as the starting material. The pyranoside was converted to primary alcohol **4** by means of a known five-step procedure including silane reduction to afford **D**.[13,4d] Swern oxidation of **4** and Wittig reaction with a stable ylide afforded α,β-unsaturated aldehyde **5**. Hydrogenation of **5** followed by Mannich reaction with Eschenmoser's salt gave aldehyde **6**. Finally, reduction of **6** with DIBAL-H afforded the key allyl alcohol **7**.

Next, we examined the crucial cycloaddition (Table 1). First, a small excess amount of allyl alcohol **7** was used, as is usual.[12] Treatment of nitrone **3** (1 equiv) with alcohol **7** (1.5 equiv) in the presence of $MgBr_2{\cdot}OEt_2$ (1.5 equiv) at room temperature resulted in recovery of the starting materials (entry 1). Reaction in refluxing 1,2-dichloroethane gave a 1:1 mixture of **8a** and **8b** in 30% yield (entry 2). Taking into account possible coordination of $MgBr_2$ to the protected hydroxyl groups of the allyl alcohol, a larger amount of $MgBr_2{\cdot}OEt_2$ was used, and a higher ratio of **8a** was obtained (entry 3). After intensive experimentation, the use of an excess of nitrone **3** (1.5 equiv) over allyl alcohol **7** (1.0 equiv) and addition of 2-propanol[14c,e] were found to provide a high yield of **8a**, probably because of the improved solubility of $MgBr_2$ (entry 4). In contrast to these reactions, reaction of nitrone **3** with alcohol **7** in the absence of $MgBr_2$ afforded **8b** as the major isomer (entry 5). On the basis of these results, practical cycloaddition (multigram scale) was conducted using allyl alcohol **7** (1 equiv), nitrone **3** (2.6 equiv), and $MgBr_2{\cdot}OEt_2$ (7.4 equiv) in the presence of 2-propanol (7.4 equiv) in 1,2-dichloroethane to provide exclusively the desired cycloadduct **8a** in 85% yield along with recovery of unreacted nitrone **3** (see the Supporting Information). It is noteworthy that this cycloaddition enabled the incorporation of the amino

Table 1. Cycloaddition of Nitrone 3 with Allyl Alcohol 7



entry	conditions[a]	yield (%)	8a:8b
1[b]	$MgBr_2{\cdot}OEt_2$ (1.5 equiv), 3 h	–	–
2[c]	$MgBr_2{\cdot}OEt_2$ (1.5 equiv), 5 h	30	50:50
3	$MgBr_2{\cdot}OEt_2$ (4.5 equiv), 5 days	48	>95:<5
4[d]	$MgBr_2{\cdot}OEt_2$ (4.5 equiv), 2-propanol (4.5 equiv), 5 days	80	>95:<5
5	none, 50 °C, 3 days	89	12:88

[a]Unless otherwise specified, all reactions were carried out using **3** (50 mg) and **7** (130 mg, 1.5 equiv) in $ClCH_2CH_2Cl$ at room temperature. [b]CH_2Cl_2 was used as the solvent. [c]The reaction was conducted in refluxing $ClCH_2CH_2Cl$. [d]**7** (0.66 equiv) was used, and the yield is based on **7**.

acid moiety and construction of the oxygen-substituted quaternary center with the correct stereochemistries in a single step.

The details of the stereoselection remain unclear, but **8a** may be formed by $MgBr_2$-promoted cycloaddition.[12,14] Reactions of 1,1-disubstituted alkenes with nitrone **3** always give only the products derived from cycloaddition from the less hindered *si* face because of severe steric interaction with the phenyl group in the *re* face (Figure 2, **E**).[11c,12b] Since the reaction of nitrone **3**

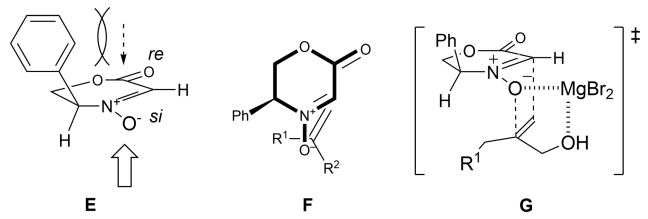


Figure 2. Stereoselection of cycloaddition of **3** with **7**.

and alkene **7** simultaneously forms two bonds, the reaction proceeds via geometry **F**. The endo-oriented R^1 group apparently occupies a closer position to the nitrone ring than does the R^2 group. When the hydroxymethyl group lies in the endo position ($R^1 = CH_2OH$) in the presence of $MgBr_2$, the R^1 group plays the role of a very bulky substituent by wearing $MgBr_2$ that also coordinates with nitrone oxygen, which generates stereorepulsion of the nitrone ring. Accordingly, the hydroxymethyl group occupies the exo position ($R^2 = CH_2OH$), and $MgBr_2$ forms chelation between the hydroxyl group and nitrone oxygen (**G**), providing **8a**.[12b] In the case of the thermal reaction (Table 1, entry 5), the bulky sugar-derived substituent occupies the exo position (R^2) in **F** to give **8b** predominantly.[12b]

With the cycloadduct **8a** in hand, we next focused on the ring-closure precursor (Scheme 3). When cycloadduct **8a** was stirred with 20% $Pd(OH)_2$ on charcoal in THF under an atmosphere of hydrogen at room temperature, hydrogenolysis of the *O*-benzyl bond, N−O bond, and *N*-benzyl bond occurred simultaneously to generate aminotriol **H**, which cyclized to form the γ-lactone. The amino group was protected with a Boc group, giving *N*-Boc lactone **9** in 80% yield. After protection of

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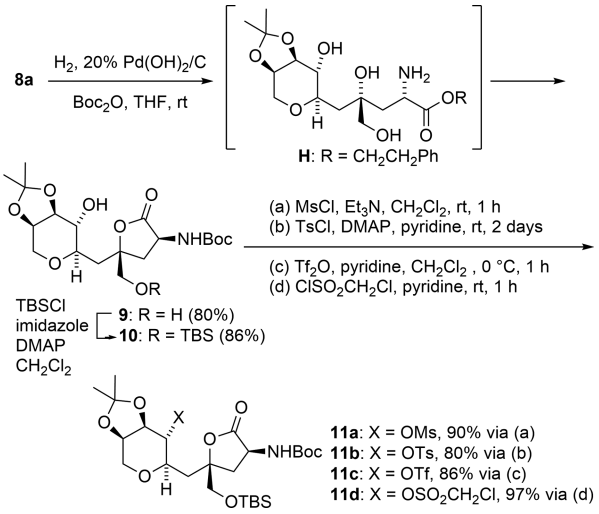
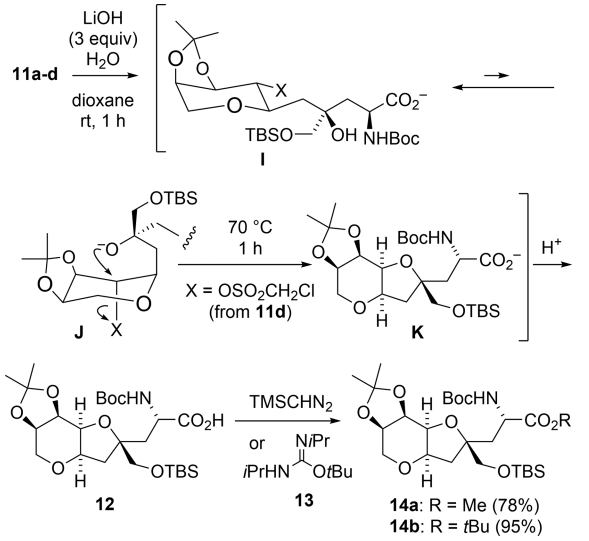
Scheme 3. Elaboration of Cycloadduct 8a



the primary alcohol of **9** to give **10**, the secondary hydroxyl group was sulfonylated to give four kinds of cyclization precursors: mesylate **11a**, tosylate **11b**, triflate **11c**, and chloromesylate **11d**.

With the four types of sulfonate in hand, the next task was tetrahydrofuran (THF) formation (Scheme 4). Sulfonates

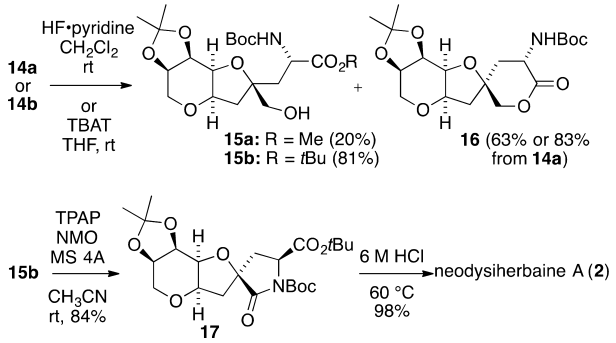
Scheme 4. Tetrahydrofuran Formation from 11



11a–d were treated with LiOH (3 equiv) at room temperature to generate carboxylate **I**, and then the mixture was heated at 70 °C. In the case of **11a** or **11b**, no THF formation took place, although hydrolysis of the lactone proceeded smoothly to give carboxylate **I**. Use of triflate **11c** led to a complex mixture, probably because of instability under aqueous basic conditions. In contrast to these sulfonates, **I** derived from chloromesylate **11d** underwent intramolecular S_N2 ring closure to generate carboxylate **K** via triaxial conformation **J**. After acidification of the mixture with dilute HCl, the organic extract containing acid **12** was treated with trimethylsilyldiazomethane to provide methyl ester **14a** in 78% yield from lactone **11d**. When *O-tert*-butyl-*N*,*N*′-diisopropylisourea (**13**) was used after workup with phosphoric acid, *tert*-butyl ester **14b** was obtained in 95% yield from **11d**. Although a few examples of similar S_N2-type THF formation are known,[4a,g,5c] this is the first case of THF construction by employing a highly functionalized tertiary alcohol as the nucleophile. This success with chloromesylate **11d** may be due to the combination of sufficient stability under the basic conditions, low steric hindrance favoring axial conformation **J**, and the high leaving ability of the chloromesyloxy group.[15]

To accomplish the synthesis, oxidation of the side chain to obtain the carboxylic acid is essential. For this purpose, desilylation of methyl ester **14a** and *tert*-butyl ester **14b** was next examined (Scheme 5). Upon treatment of **14a** with HF·

Scheme 5. Synthesis of Neodysiherbaine A (2)



pyridine, the desired **15a** and lactone **16** derived from **15a** were obtained in 20% and 63% yield, respectively. The use of $Bu_4N^+Ph_3SiF_2^-$ (TBAT), with less basic F^- compared with TBAF, gave only undesired **16** in 83% yield. In contrast to **14a**, utilization of *tert*-butyl ester **14b** greatly suppressed lactone formation, probably as a result of steric factors. Thus, **14b** underwent desilylation with TBAT to afford primary alcohol **15b**, a key intermediate for **2**,[5d] in high yield. Finally, the synthesis of **2** was achieved via two known steps:[5d] oxidation of the primary alcohol followed by removal of all protective groups of **17** gave neodysiherbaine A (**2**).

In conclusion, we have accomplished a stereocontrolled total synthesis of neodysiherbaine A (**2**) featuring magnesium bromide-mediated cycloaddition of chiral nitrone template **3** with allyl alcohol **7** bearing a polyoxygenated tetrahydropyran moiety and tetrahydrofuran construction by an intramolecular S_N2 reaction of a highly stereodemanding tertiary alcohol.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03092.

Experimental procedures and full spectroscopic data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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