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A Highly Stereocontrolled Total Synthesis of (−)-Neodysiherbaine A

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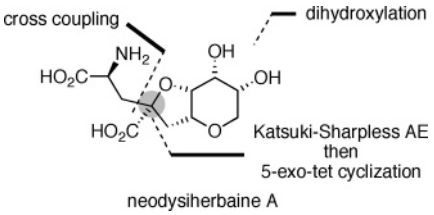
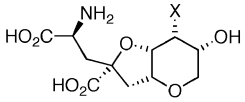


Neodysiherbaine A, a neuroexitotoxin occurring in a Micronesian marine sponge *Dysidea herbacea*, was synthesized from tri-*O*-acetyl-D-glucal with excellent stereocontrol. The method established enables us to obtain gram quantities of neodysiherbaine A and its related compounds.

Introduction

Dysiherbaine (**1**) and neodysiherbaine A (**2**) are novel amino acids isolated from the Micronesian sponge *Dysidea herbacea* by Sakai et al.[1,2] These amino acids are known to be highly selective agonists of AMPA-KA-type glutamate receptors and exhibit the most potent convulsant activity among the excitatory amino acids known to date such as kainic acid and domoic acid.[3] Due to the low availability from natural sources as well as the intriguing biological activity and characteristic structures involving a *cis*-fused hexahydrofuro[3,2-*b*]pyran ring system containing a glutamic acid appendage, this family of natural amino acids are good targets for synthesis. Thus, there have been a number of synthetic studies including four total syntheses of dysiherbaine (**1**)[4,5] and two total syntheses of neodysiherbaine A (**2**) (Figure 1).[2,6,7] However, all methods are not efficient enough to obtain gram quantities of these amino acids as well as their derivatives, except for the one just recently reported by Lygo et al.[6] In addition, the stereocontrolled construction of the C4 quaternary stereogenic center has remained an unsolved problem despite the significance of the C4 configuration for the biological activity.[2,4ab] For this stereocontrol issue, Lygo et al.[6] successfuly provided one solution using RuO_4-mediated oxidative cyclization of a 1,5-diene. We herein report a novel synthesis of (−)-neodysiherbfaine A (**2**) where all stereogenic centers including the C4 quaternary center were constructed in highly stereocontrolled manner over 98% de.



dysiherbaine (**1**): X = NHMe
neodysiherbaine A (**2**): X = OH

FIGURE 1. Neuroexcitatory amino acids of *Dysidea herbacea*.

Results and Discussion

Our synthetic plan is illustrated in Scheme 1. Based on the methodology we have demonstrated in the total synthesis of

(1) Sakai, R.; Kamiya, H.; Murata, M.; Shimamoto, K. *J. Am. Chem. Soc.* **1997**, *119*, 4112−4116.

(2) Sakai, R.; Koike, T.; Sasaki, M.; Shimamoto, K.; Oiwa, C.; Yano, A.; Suzuki, K.; Tachibana, K.; Kamiya, H. *Org. Lett.* **2001**, *3*, 1479−1482.

(3) (a) Sasaki, M.; Maruyama, T. Sakai, R.; Tachibana, K. *Tetrahedron Lett.* **1999**, *40*, 3195−3198. (b) Sakai, R.; Swanson, G. T.; Shimamoto, K.; Green, T.; Contractor, A.; Ghetti, A.; Tamura-Horikawa, Y.; Oiwa, C.; Kamiya, H. *J. Pharm. Exp. Ther.* **2001**, *296*, 650−658. (c) Swanson, G. T.; Green, T.; Sakai, R.; Contractor, A.; Che, W.; Kamiya, H.; Heinemann, S. F. *Neuron* **2002**, *34*, 589−598. (d) Sanders, J. M.; Ito, K.; Settimo, L.; Pentikäinen, O. T.; Shoji, M.; Sasaki, M.; Johnson, M. S.; Sakai, R.; Swanson, G. T. *J. Pharm. Exp. Ther.* **2005**, *314*, 1068−1078.

(4) (a) Masaki, H.; Maeyama, J.; Kamada, K.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *J. Am. Chem. Soc.* **2000**, *122*, 5216−5217. (b) Sasaki, M.; Koike, T.; Sakai, R.; Tachibana, K. *Tetrahedron Lett.* **2000**, *41*, 3923−3926. (c) Snider, B. B.; Hawryluk, N. A. *Org. Lett.* **2000**, *2*, 635−638. (d) Phillips, D.; Chamberlin, A. R.; *J. Org. Chem.* **2002**, *67*, 3194−3201.

(5) For synthetic studies on dyshiherbaine, see: (a) Miyata, O.; Iba, R.; Hashimoto, J.; Naito, T. *Org. Biomol. Chem.* **2003**, *1*, 772−774. (b) Kang, S. H.; Lee, Y. M. *Synlett* **2003**, *7*, 993−994. (c) Huang, J.-M.; Xu, K.-C.; Loh, T.-P. *Synthesis* **2003**, *5*, 755−764. (d) Naito, T.; Nair, J. S.; Nishiki, A.; Yamashita, K.; Kiguchi, T. *Heterocycles* **2000**, *53*, 2611−2615.

(6) Lygo, B.; Slack, D.; Wilson, C. *Tetrahedron Lett.* **2005**, *46*, 6629−6632.

(7) For the synthesis of 8,9-diepineodysiherbaine A, see: Shoji, M.; Shiohara, K.; Oikawa, M.; Sakai, R.; Sasaki, M.; *Tetrahedron Lett.* **2005**, *46*, 5559−5562.

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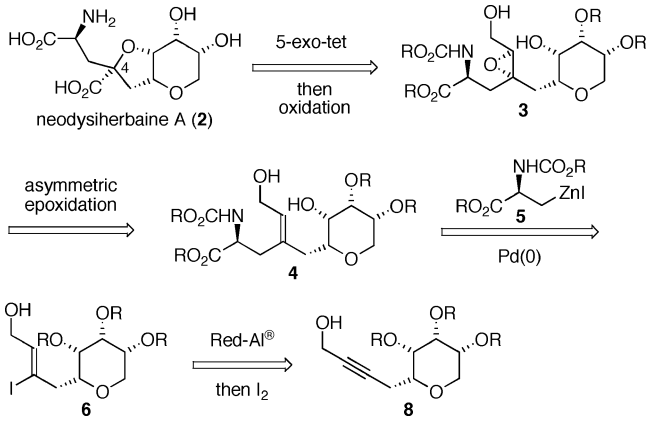
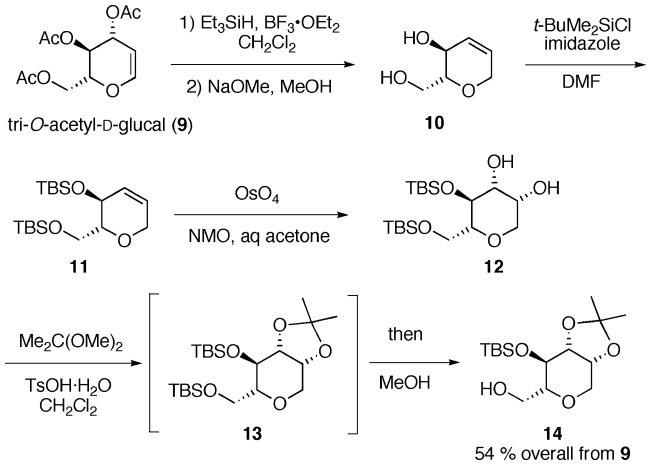
SCHEME 1. Retrosynthetic Analysis



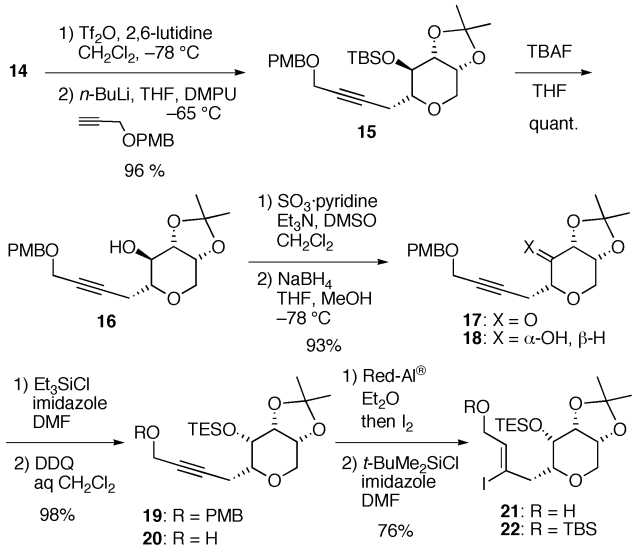
SCHEME 2. Preparation of the Pyran Ring Moiety



dysiherbaine[4a] and lycoperdic acid,[8] we envisaged allylic alcohol **4** as a precursor of neodysiherbaine A (**2**), which would be accessible via a cross-coupling reaction[9] of alkenyl iodide **6** and organozinc reagent **5**. We assumed that the C4 quaternary stereogenic center would be assembled in stereocontrolled manner via Katsuki−Sharpless asymmetric epoxidation[10] of **4** followed by 5-exo-tet cyclization of **3** with inversion of the configuration. Stereoselective construction of alkenyl iodide **6** could be achieved from **8** employing modified Corey's reductive iodination methodology.[11]

The required pyran ring moiety was first synthesized from tri-*O*-acetyl-D-glucal (**9**) in 54% overall yield (Scheme 2). Thus, according to the procedure established by Sasaki et al.,[2] **9** was first converted to diol **10** by triethylsilane-promoted reduction followed by methanolysis. After protection of **10** as its *tert*-butyldimethylsilyl ether, exposure of **11** to OsO_4−NMO conditions allowed highly diastereoselective dihydroxylation to afford diol **12** as the sole product. Since dihydroxylation of the corresponding benzylidene acetal was reported to exhibit lower diastereofacial selectivity (66% de),[2] the observed extremely high diastereoselectivity is assumed to be attributable to the stereoelectronic effect of the allylic silyloxy system.[12] After protection of **12** as its acetonide, addition of 1.3 equiv of methanol to the reaction mixture allowed selective removal of the primary *tert*-butyldimethylsilyl ether protecting group of **13** to give alcohol **14** cleanly. It is important to note that all reactions were carried out without purification during the transformation from **9** to **14**.

SCHEME 3. Synthesis of Alkenyl Iodide 22



According to the method established by Kotsuki et al.,[13] alcohol **14** was triflated and then the resulting triflate was directly reacted with the lithium acetylide derived from *p*-methoxybenzyl propargyl ether to give **15** in excellent yield (Scheme 3). After desilylation of **15**, the hydroxyl group of **16** was inverted via **17** in a completely steteoselective manner by an oxidation[14]−reduction[15] procedure to give **18** possessing four contiguous *all-cis* stereogenic centers. Protection of **18** as its triethylsilyl ether, followed by removal of the *p*-methoxybenzyl ether protecting group of **19**, gave propargyl alcohol **20**. Reaction[11b] of **20** with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al), followed by treatment of the resulting alkenylaluminate complex with iodine, allowed stereo- and regioselective formation of (*Z*)-iodoalkene **21** which was protected as its *tert*-butyldimethylsilyl ether to give alkenyl iodide **22**, the required precursor for the next crucial cross-coupling reaction.

Alkenyl iodide **22** thus prepared was subjected to cross-coupling reaction with organozinc reagent **24**, according to the procedure we have established in the previous syntheses of dysiherbaine[4a] and lycoperdic acid[7] (Scheme 4). Thus, iodoalanine **23**[16] was sonicated in the presence of Zn−Cu to generate **24**, which was reacted with **22** using 3 mol % of $(Ph_3P)_4Pd$ as catalyst. The coupling reaction completed within 2 h to furnish

(8) Masaki, H.; Mizozoe, T.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Tetrahedron Lett.* **2000**, *41*, 4801−4804.

(9) For a review, see: Rilatt, I.; Caggiano, L.; Jackson, R. F. W. *Synlett* **2005**, 2701−2719.

(10) For a review, see: Johnson, R. A.; Sharpless, K. B. In *Comprehensive Organic Synthesis*; Trost B M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 7, pp 389−436.

(11) (a) Corey, E. J.; Katzenellenbogen, J. A.; Posner, G. H. *J. Am. Chem. Soc.* **1967**, *89*, 4245−4247. (b) Denmark, S. E.; Jones, T. K. *J. Org. Chem.* **1982**, *47*, 4595−4597.

(12) Arjona, O.; de Dios, A.; Plumet, J.; Saez, B. *J. Org. Chem.* **1995**, *60*, 4932−4935.

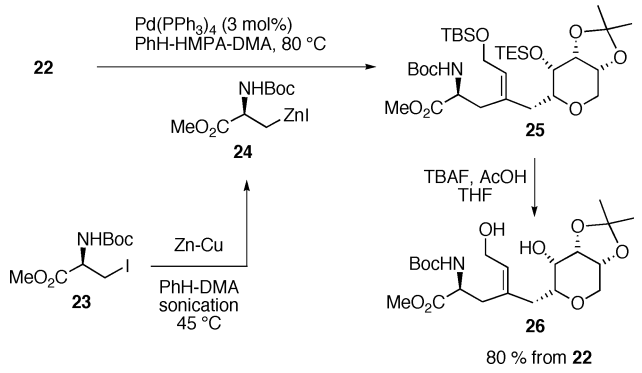
(13) Kotsuki, H.; Kadota, I.; Ochi, M. *Tetrahedron Lett.* **1990**, *31*, 4609−4612.

(14) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505−5507.

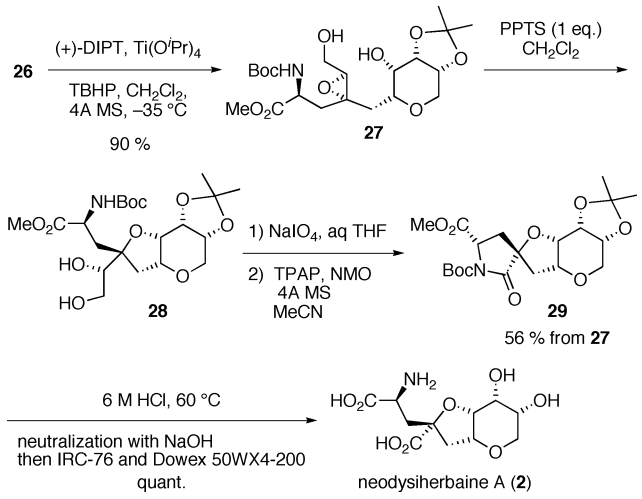
(15) The use of Dess−Martin periodinane (DMPI) instead of SO_3•pyridine/DMSO/Et_3N resulted in the quantitative conversion of **16** to **17** in less than one gram scale. However, DMPI turned out to be less effective in large scale due to lack of reproducibility and difficulty in purification.

(16) Jackson, R. F. W.; Perez-Gonzalez, M. *Org. Synth.* **2005**, *81*, 77−88.

SCHEME 4. Cross-Coupling Reaction



SCHEME 5. Completion of the Total Synthesis



25, and after desilylation using tetra-*n*-butylammonium fluoride (TBAF) together with acetic acid, diol **26** was obtained in good yield. In this desilylation step, the use of either TBAF without acetic acid or HF−pyridine turned out to cause decomposition of coupling product **25**.

Having obtained key intermediate **26** possessing the entire carbon framework of neodysiherbaine A (**2**), we then proceeded to the final stage involving stereoselective construction of the C4 quaternary stereogenic center, one of the most difficult issues in this synthesis (Scheme 5).

To introduce a scaffold for the construction of the C4 center in desirable fashion, we undertook Katsuki−Sharpless asymmetric epoxidation of **26**. Upon exposure of **26** to the conditions using a catalytic amount of $Ti(O^iPr)_4$ (9 mol %) and (+)-diisopropyl L-tartrate (10 mol %),[17] the epoxidation proceeded with excellent diastereoselectiviy (>98% de)[18] to give epoxide **27** in good yield. In this particular case, when stoichiometric amounts of $Ti(O^iPr)_4$ and (+)-diisopropyl L-tartrate were employed, the reaction became dirty due to the instability of **27** under the conditions.

The crucial 5-exo-tet cyclization of epoxide **27** was investigated using various Lewis acids and Brønsted acids. As a result, when epoxide **27** was treated with 1 equiv of PPTS in dichloromethane at room temperature, the cyclization took place cleanly to give diol **28**. In the cases of the stronger acids (e.g., CSA, Et_2AlCl, $BF_3{\cdot}Et_2O$, $Sc(OTf)_3$), the reaction became rather complex, possibly due to the competitive attack of the carbamate group to the polarized C4 center. Since purification of **28** was found to be difficult because of its polar nature, crude **28** was successively subjected to $NaIO_4$ oxidation and TPAP oxidation[19] to afford **29**[20] in 56% overall yield. In this case, the corresponding C4 epimer was not obtained at all, suggesting that the cyclization occurred with complete inversion of stereochemistry at the quaternary center. Finally, upon acidic hydrolysis, neutralization, and demineralization using ion-exchange chromatography, **29** furnished (−)-neodysiherbaine A (**2**), $[\alpha]^{23}_D$ −6.5 (*c* 0.75, H_2O),[21] quantitatively. The spectral data (^1H and ^{13}C NMR, CD, and FAB-Mass) exhibited good agreement with those reported for the natural specimen.

In conclusion, we have achieved a highly stereocontrolled total synthesis of (−)-neodysiherbaine A (**2**) from tri-*O*-acetyl-D-glucal (**9**) in 14% overall yield. This synthesis enables us to obtain even gram quantities of neodysiherbaine A (**2**). The synthetic method is of general value in approaches to related neuroexcitatory amino acids.

Experimental Section

(3a*R*,6*R*,7*R*,7a*R*)-6-(4-(*p*-Methoxybenzyloxy)but-2-ynyl)-7-(*tert*-butyldimethylsilyl)oxy-tetrahydro-2,2-dimethyl-3a*H*-[1,3]-dioxolo[4,5-*c*]pyran (15). To a stirred solution of **14** (25.0 g, 78.6 mmol) in CH_2Cl_2 (250 mL) at −65 °C were added 2,6-lutidine (12.6 g, 117.9 mmol) and trifluoromethanesulfonic anhydride (28.8 g, 102.1 mmol). After being stirred at −65 °C for 2 h, the reaction mixture was diluted with Et_2O and washed with saturated $NaHCO_3$. The organic layer was washed with 1 M HCl to remove 2,6-lutidine, saturated $NaHCO_3$, and brine, dried, and evaporated to give the corresponding triflate (36.0 g) as a brown oil, which was used for the next reaction without purification.

To a stirred solution of *p*-methoxybenzyl propargyl ether (27.7 g, 157.2 mmol) in THF (300 mL) at −65 °C was added *n*-butyllithium (2.55 M in hexane, 61 mL, 157.2 mmol), and the mixture was stirred at −65 °C for 2 h. *N*,*N*-Dimethylpropylene urea (DMPU) (60 mL) was added, and then a solution of crude triflate (36.0 g) in THF (30 mL) was added via a cannula over 10 min. After being stirred at −65 °C for 2.5 h, the reaction mixture was diluted with Et_2O and washed with saturated $NaHCO_3$ and brine, dried, and evaporated. Purification of the residue by column chromatography (SiO_2 600 g, hexane/AcOEt = 10/1−4/1) gave **15** (36.0 g, 96%) as a colorless oil: $[\alpha]^{24}_D$ −21.8 (*c* 1.00, $CHCl_3$); FTIR (neat) 2937, 2854, 1511, 1375, 1247, 1133, 1079 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 4.52 (s, 2H), 4.26 (d, J = 13.5 Hz, 1H), 4.17 (dd, J = 2.2, 6.0 Hz, 1H), 4.14 (t, J = 2.2 Hz, 2H), 3.96 (t, J = 6.1 Hz, 1H), 3.80 (s, 3H), 3.74 (dd, J = 2.2, 13.5 Hz, 1H), 3.63 (dd, J = 6.6, 9.3 Hz, 1H), 3.16 (ddd, J = 3.6, 6.6, 9.3 Hz, 1H), 2.75 (ddt, J = 3.68, 16.8, 2.2 Hz, 1H), 2.50 (ddt, J = 4.2, 16.8, 2.2 Hz, 1H), 1.52 (s, 3H), 1.36 (s, 3H), 0.90 (s, 9H), 0.17 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 129.6, 113.7, 109.2, 83.1, 79.6, 77.6, 77.5, 74.0, 73.2, 70.8, 66.7, 57.3, 55.2, 28.1, 26.4, 25.9, 25.8, 22.4, 18.1, −4.0, −5.0; HRMS (FAB) calcd for $C_{26}H_{40}O_6Si$ (M^+) 476.2594, found 476.2581.

(3a*R*,6*R*,7*R*,7a*S*)-6-(4-(*p*-Methoxybenzyloxy)but-2-ynyl)-tetrahydro-2,2-dimethyl-3a*H*-[1,3]dioxolo[4,5-*c*]pyran-7-ol (16). To an ice-cooled solution of **15** (21.3 g, 44.7 mmol) in THF (100 mL)

(17) Gao, Y.; Klunder, J. M.; Hanson, R. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765−5780.

(18) Determined by comparison of the ^1H NMR spectrum with that of the corresponding isomeric epoxide prepared by Katsuki−Sharpless asymmetric epoxidation of **26** using (−)-diisopropyl D-tartrate.

(19) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625−1627.

(20) Compound **29** was found to be stable enough to be purified by silica gel chromatography (hexane/AcOEt), although Chamberlin et al.[4d] reported that **29** was decomposed during silica gel chromatography.

(21) The specific rotation of natural neodyshiherbaine A was not reported previously.

was added tetra-*n*-butylammonium fluoride (TBAF) (1 M in THF, 53.7 mL, 53.7 mmol). After being stirred at 0 °C for 5 h, the reaction mixture was diluted with Et_2O, washed with water and brine, dried, and concentrated. Purification of the residue by column chromatography (SiO_2 500 g, hexane/AcOEt = 3/1−2/1) gave **16** (16.0 g, quant) as a colorless oil: $[\alpha]^{24}_D$ −35.5 (*c* 1.05, $CHCl_3$); FTIR (neat) 3448, 2985, 2933, 1722, 1612, 1514, 1381, 1250, 1078 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.6 Hz, 2 H), 6.87 (d, *J* = 8.6 Hz, 2H), 4.52 (s, 2H), 4.30 (d, *J* = 13.2 Hz, 1H), 4.20 (dd, *J* = 2.0, 6.0 Hz, 1H), 4.13 (t, *J* = 2.0 Hz, 2H), 4.02 (t, *J* = 6.0 Hz, 1H), 3.80 (s, 3H), 3.77 (dd, *J* = 2.1, 14.0 Hz, 1H), 3.67 (ddd, *J* = 3.6, 7.2, 10.4 Hz, 1H), 3.19 (ddd, *J* = 4.0, 6.4, 10.4 Hz, 1H), 2.77 (tdd, *J* = 2.0, 4.0, 16.8 Hz, 1H), 2.60 (tdd, *J* = 2.0, 6.4, 16.8 Hz, 1H), 2.52−2.50 (br, 1H), 1.53 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 129.7, 129.5, 113.7, 109.7, 82.7, 79.4, 77.9, 76.4, 73.9, 72.9, 71.0, 66.6, 57.3, 55.3, 28.2, 26.3, 22.3; HRMS (EI) calcd for $C_{20}H_{26}O_6$ (M^+) 362.1729, found 362.1709.

(3a*R*,6*R*,7*S*,7a*S*)-6-(4-(*p*-Methoxybenzyloxy)but-2-ynyl)-tetrahydro-2,2-dimethyl-3a*H*-[1,3]dioxolo[4,5-*c*]pyran-7-ol (18). To an ice-cooled solution of **16** (27.3 g, 75.6 mmol) in CH_2Cl_2 (150 mL) and DMSO (150 mL) were added triethylamine (69 g, 680 mmol) and SO_3·pyridine (36 g, 227 mmol). After being stirred at 0 °C for 4 h, the reaction mixture was diluted with Et_2O, washed with saturated $NaHCO_3$, water, and brine, dried, and concentrated to give **17** (31 g) as a yellow oil, which was used for the next reaction without purification. Pure **17**, a colorless oil, obtained by preparative TLC (hexane/AcOEt = 1/1) showed the following spectral and analytical data: $[\alpha]^{24}_D$ +7.6 (*c* 1.34, $CHCl_3$); FTIR (neat) 2987, 2935, 2235, 1743, 1612, 1513, 1382, 1253, 1130, 1072 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 4.58 (dd, *J* = 2.0, 6.0 Hz, 1H), 4.48 (s, 2H), 4.43 (d, *J* = 6.0 Hz, 1H), 4.27 (d, *J* = 12.6 Hz, 1H), 4.09 (t, *J* = 2.0 Hz, 2H), 3.95 (dd, *J* = 4.4, 7.8 Hz, 1H), 3.91 (dd, *J* = 2.0, 12.6 Hz, 1H), 3.78 (s, 3H), 2.82 (tdd, *J* = 2.0, 7.8, 16.8 Hz, 1H), 2.61 (tdd, *J* = 2.0, 7.8, 16.8 Hz, 1H), 1.44 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.1, 158.8, 129.3, 129.1, 113.3, 110.7, 81.8, 80.0, 77.0, 76.5, 76.4, 70.6, 66.5, 56.9, 54.9, 26.7, 25.5, 19.7; HRMS (EI) calcd for $C_{20}H_{24}O_6$ (M^+) 360.1573, found 360.1584.

Crude ketone **17** (31 g) thus obtained was dissolved into a mixture of MeOH (150 mL) and THF (150 mL). To this solution $NaBH_4$ (3.7 g, 98.2 mmol) was added at −78 °C, and the mixture was stirred at −78 °C for 2 h. The reaction was quenched with saturated NH_4Cl (150 mL), and the reaction mixture was extracted with Et_2O. The extract was washed with water, saturated $NaHCO_3$, and brine, dried, and concentrated. Purification of the residue by column chromatography (SiO_2 300 g, hexane/AcOEt = 4/1−2/1) gave **18** (25.0 g, 93%) as a colorless oil: $[\alpha]^{24}_D$ −67.2 (*c* 1.05, $CHCl_3$); FTIR (neat) 3498, 2937, 2840, 1612, 1513, 1380, 1249, 1068 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.0 Hz, 2H), 6.87 (d, *J* = 8.0 Hz, 2H), 4.50 (s, 2H), 4.32 (d, *J* = 14.4 Hz, 1H), 4.16−4.11 (m, 2H), 4.11 (t, *J* = 2.2 Hz, 2H), 3.85−3.80 (m, 1H), 3.81 (s, 3H), 3.80 (dd, *J* = 3.0, 14.4 Hz), 3.34 (t, *J* = 7.1 Hz, 1H), 2.69 (tt, *J* = 2.2, 7.1 Hz, 2H), 2.25 (d, *J* = 7.1 Hz, 1H), 1.61 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 129.5, 129.4, 113.6, 109.2, 82.5, 77.7, 76.7, 75.7, 73.1, 71.0, 71.0, 66.6, 65.2, 57.2, 55.1, 25.8, 25.3, 21.5; HRMS (EI) calcd for $C_{20}H_{26}O_6$ (M^+) 362.1729, found 362.1717.

4-((3a*R*,6*R*,7*R*,7a*R*)-7-Triethylsilyloxy-tetrahydro-2,2-dimethyl-3a*H*-[1,3]dioxolo[4,5-*c*]pyran-6-yl)but-2-yn-1-ol (20). To a stirred solution of **18** (560 mg, 1.55 mmol) in DMF (3 mL) at room temperature were added imidazole (421 mg, 6.19 mmol) and triethylsilyl chloride (465 mg, 3.1 mmol). After being stirred at room temperature for 50 min, the reaction was quenched by the addition of MeOH (2 mL). The reaction mixture was diluted with Et_2O, washed with water and brine, dried, and concentrated to give **19** (793 mg) as a pale yellow oil, which was used for the next reaction without purification.

To an ice-cooled solution of crude **19** (793 mg) in CH_2Cl_2 (17 mL) were added water (0.8 mL) and DDQ (982 mg, 4.33 mmol), and the mixture was stirred at 0 °C for 2 h. The reaction mixture was diluted with CH_2Cl_2, filtered through Celite, washed with saturated $NaHCO_3$, water, and brine, dried, and concentrated. Purification of the residue by column chromatography (SiO_2 30 g, hexane/AcOEt = 3/1−2/1) gave **20** (542 mg, 98%) as a colorless oil: $[\alpha]^{26}_D$ +38.4 (*c* 0.96, $CHCl_3$); FTIR (neat) 3424, 2954, 2877, 1380, 1213, 1135, 1058, 1002 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.27 (t, *J* = 2.2 Hz, 2H), 4.20−4.29 (m, 2H), 4.06 (dd, *J* = 3.9, 4.6 Hz, 1H), 3.84 (dt, *J* = 9.8, 4.6 Hz, 1H), 3.69 (dd, *J* = 5.6, 11.9 Hz, 1H), 3.63 (dd, *J* = 7.3, 11.9 Hz, 1 H), 2.93 (ddt, *J* = 9.8, 17.6, 2.2 Hz, 1H), 2.69 (ddt, *J* = 17.6, 4.6, 2.2 Hz, 1H), 1.55 (s, 3H), 1.35 (s, 3H), 0.98 (t, *J* = 8.0 Hz, 9H), 0.66 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.0, 83.6, 79.4, 75.1, 74.1, 72.0, 67.0, 61.9, 51.4, 27.6, 25.4, 18.9, 6.9, 4.9; HRMS (EI) calcd for $C_{18}H_{32}O_5Si$ (M^+) 356.2019, found 356.2002.

(*Z*)-4-((3a*R*,6*R*,7*S*,7a*R*)-7-Triethylsilyloxy-tetrahydro-2,2-dimethyl-3a*H*-[1,3]dioxolo[4,5-*c*]pyran-6-yl)-3-iodobut-2-en-1-ol (21). To an ice-cooled solution of **20** (200 mg, 0.56 mmol) in Et_2O (2.2 mL) was added sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) (3.2 M in toluene, 0.38 mL, 1.22 mmol), and the mixture was stirred at room temperature for 2 h. Additional Red-Al (3.2 M in tolulene, 0.20 mL, 0.64 mmol) was added at 0 °C, and the mixture was stirred at room temperature for 1 h. AcOEt (112 mg, 1.2 mmol) was added at 0 °C and the mixture was stirred at 0 °C for 10 mim. Then solid I_2 (213 mg, 0.84 mmol) was added to the mixture at −40 °C, and the mixture was allowed to warm to room temperature. After being stirred at room temperature for 12 h, the reaction was quenched with saturated $Na_2S_2O_3$ (5 mL) at 0 °C, and the reaction mixture was diluted with AcOEt, filtered through Celite, washed with brine, dried, and concentrated. Purification of the residue by column chromatography (SiO_2 5 g, hexane/AcOEt = 5/1−4/1) gave **21** (206 mg, 76%) as a colorless oil: $[\alpha]^{26}_D$ +23.5 (*c* 0.86, $CHCl_3$); FTIR (neat) 3438, 2954, 2877, 1457, 1380, 1216, 1134, 1008 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.95 (t, *J* = 5.6 Hz, 1H), 4.31 (m, 1H), 4.22−4.23 (m, 3H), 4.07 (m, 2H), 3.62 (dd, *J* = 5.0, 12.4 Hz, 1H), 3.56 (dd, *J* = 6.8, 12.4 Hz, 1H), 3.22−3.28 (m, 1H), 2.80 (d, *J* = 15.6 Hz, 1H), 1.57 (s, 3H), 1.36 (s, 3H), 1.00 (t, *J* = 8.0 Hz, 9H), 0.67 (q, *J* = 8.0, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 110.1, 107.0, 75.3, 73.4, 72.3, 67.3, 67.1, 61.8, 43.1, 27.8, 25.6, 6.9, 4.8; HRMS (EI) calcd for $C_{18}H_{33}IO_5Si$ (M^+) 484,1142, found 484.1134.

(3a*R*,6*R*,7*S*,7a*R*)-6-((*Z*)-4-*tert*-Butyldimethylsilyloxy-2-iodobut-2-enyl)-7-triethylsilyloxy-tetrahydro-2,2-dimethyl-3a*H*-[1,3]dioxolo[4,5-*c*]pyran (22). To an ice-cooled stirred solution of **21** (615 mg, 1.25 mmol) in CH_2Cl_2 (10 mL) were added triethylamine (315 mg, 3.12 mmol), *tert*-butyldimethylsilyl chloride (318 mg, 2.12 mmol), and DMAP (15 mg, 0.125 mmol). After the mixture was stirred at 0 °C for 5 h, the reaction was quenched by MeOH (2 mL), and the reaction mixture was extracted with Et_2O. The extract was washed with 10% $Na_2S_2O_3$, saturated $NaHCO_3$, water, and brine, dried, and concentrated. Purification of the residue by column chromatography (SiO_2 20 g, hexane/AcOEt = 10/1−4/1) gave **22** (747 mg, quant.) as a colorless oil: $[\alpha]^{26}_D$ +39.4 (*c* 1.60, $CHCl_3$); FTIR (neat) 2924, 2858, 1460, 1375, 1248, 1101, 1007 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.86 (t, *J* = 5.2 Hz, 1H), 4.31 (dd, *J* = 3.6, 5.6 Hz, 1H), 4.24 (dd, *J* = 1.2, 5.2 Hz, 2H), 4.24−4.18 (m, 1H), 4.07−4.00 (m, 2H), 3.61 (dd, *J* = 5.2, 12.8 Hz, 1H), 3.53 (dd, *J* = 5.2, 18.2 Hz, 1H), 3.22 (dd, *J* = 10.0, 16.0 Hz, 1H), 2.76 (d, *J* = 16.0, Hz, 1H), 1.57 (s, 3H), 1.36 (s, 3H), 0.99 (t, *J* = 8.0 Hz, 9H), 0.90 (s, 9H), 0.67 (q, *J* = 8.0 Hz, 6H), 0.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.0, 110.0, 103.8, 75.4, 73.6, 72.3, 68.5, 67.2, 61.6, 42.8, 27.9, 26.0, 25.9, 25.7, 18.3, 6.9, 6.6, 5.9, 4.9, −5.0; HRMS (EI) calcd for $C_{23}H_{44}IO_5Si$ [(M − Me)$^+$] 583.1772, found 583.1746.

***tert*-Butyl (*S*,*E*)-1-(Methoxycarbonyl)-3-(((3a*R*,6*R*,7*S*,7a*S*)-tetrahydro-7-hydroxy-2,2-dimethyl-3a*H*-[1,3]dioxolo[4,5-*c*]pyran-6-yl)methyl)-5-hydroxypent-3-enylcarbamate (26).** A mixture of *N*-Boc-β-iodoalanine methyl ester (**23**) (1.40 g, 4.26 mmol) and Zn−Cu couple (1.36 g) in benzene (8 mL) and *N*,*N*-dimethylacetamide (DMA) (0.8 mL) was sonicated at 45 °C until the starting

material disappeared on TLC. This mixture of the organozinc reagent was added to a degassed mixture of **22** (641 mg, 1.076 mmol) and $(Ph_3P)_4Pd$ (37 mg, 0.032 mmol) in benzene (8 mL) and HMPA (0.8 mL), and the mixture was heated at 80 °C for 1 h. After cooling, the reaction mixture was diluted with AcOEt, filtered through Celite, washed with saturated $NaHCO_3$ and brine, dried, concentrated, and chromatographed (SiO_2 40 g, hexane/AcOEt = 6/1, then SiO_2 20 g, toluene/AcOEt =1/0−7/1) gave **25** (845 mg) as a yellow oil, which contained compounds derived from **23**. Pure **25**, a colorless oil, obtained by 2× silica gel column chromatography (toluene/AcOEt = 1/0−10/1, H/A=8/1−4/1) followed by recycling preparative HPLC ($CHCl_3$) showed the following spectral and analytical data: $[\alpha]^{23}_D$ +19.5 (*c* 0.84, $CHCl_3$); FTIR (neat) 3354, 2954, 1716, 1506, 1365, 1249, 1164, 1058 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.64 (t, J = 6.4 Hz, 1H), 5.50 (d, J = 6.8 Hz, 1H), 4.29 (dd, J = 4.0, 5.6 Hz, 1H), 4.27−4.35 (m, 1H), 4.22 (dd, J = 6.8, 12.8 Hz, 1H), 4.18 (dd, J = 6.8, 12.8 Hz, 1H), 4.10 (dd, J = 6.8, 12.8 Hz, 1H), 3.99 (dd, J = 4.0, 5.6 Hz, 1H), 3.80 (ddd, J = 2.0, 5.6, 10.8 Hz, 1H), 3.71 (s, 3H), 3.66 (dd, J = 7.2, 12.4 Hz, 1H), 3.60 (dd, J = 6.0, 12.4 Hz, 1H), 2.73 (dd, J = 10.8, 16.0 Hz, 1 H), 2.54 (m, 2H), 2.38 (d, J = 16.0 Hz, 1H), 1.56 (s, 3H), 1.41 (s, 9H), 1.36 (s, 3H), 0.98 (t, J = 7.8 Hz, 9 H), 0.92 (s, 9H), 0.66 (q, J = 7.8 Hz, 6H), 0.10 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 155.3, 136.4, 129.1, 110.0, 79.5, 77.2, 75.5, 77.2, 75.5, 75.4, 72.2, 67.9, 61.6, 59.3, 52.1, 33.6, 33.2, 28.4, 27.8, 26.1, 25.6, 18.5, 6.9, 4.9, −5.0, −5.1; HRMS (EI) calcd for $C_{33}H_{63}NO_9Si_2$ (M^+) 673.4041, found 673.4034.

To a stirred solution of **25** (845 mg) thus obtained in THF (10 mL) were added AcOH (323 mg, 5.38 mmol) and TBAF (4.3 mmol) at room temperature, and stirring was continued at room temperature for 10 h. The reaction mixture was diluted with AcOEt, washed with water, saturated $NaHCO_3$, and brine, dried, and concentrated. Purification of the residue by column chromatography (SiO_2 15 g, hexane/AcOEt = 1/1−0/1) gave **26** (382 mg, 80%) as a colorless oil: $[\alpha]^{23}_D$ −29.1 (*c* 2.04, $CHCl_3$); FTIR (neat) 3369, 2979, 1749, 1712, 1519, 1367, 1251, 1214, 1169, 1024 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.73 (t, J = 7.0 Hz, 1H), 5.40 (d, J = 7.5 Hz, 1H), 4.42 (m, 1H), 4.26 (d, J = 13.7 Hz, 1H), 4.11 (m, 4H), 3.75 (d, J = 13.7 Hz, 1H), 3.74 (s, 3H), 3.59 (s, 1H), 3.27 (t, J = 5.4 Hz, 1 H), 2.53−2.60 (m, 3H), 2.31 (dd, J = 5.1, 14.6 Hz, 1H), 1.61 (s, 3H), 1.42 (s, 9H), 1.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 155.2, 134.8, 130.0, 109.1, 79.8, 76.0, 73.3, 71.0, 66.4, 66.3, 58.0, 52.1, 38.0, 33.3, 28.2, 25.7, 25.4; MS (EI) *m*/*z* 57, 345, 389, 430, 445 (M^+); HRMS (EI) calcd for $C_{21}H_{35}NO_9$ (M^+) 445.2312, found 445.2311.

***tert*-Butyl (*S*)-1-(Methoxycarbonyl)-2-((2*S*,3*S*)-2-(((3a*R*,6*R*,7*S*,7a*S*)-tetrahydro-7-hydroxy-2,2-dimethyl-3a*H*-[1,3]dioxolo[4,5-*c*]pyran-6-yl)methyl)-3-(hydroxymethyl)oxiran-2-yl)ethylcarbamate (27).** To a suspension of powdered 4 A molecular sieves (560 mg) in CH_2Cl_2 (15 mL) were added (+)-diisopropyl L-tartrate (DIPT) (30 mg, 0.126 mmol), and $Ti(O^iPr)_4$ (32 mg, 0.112 mmol) at −35 °C, and the mixture was stirred at −35 °C for 50 min. *tert*-Butyl hydroperoxide (TBHP) (2.76 M in CH_2Cl_2, 0.91 mL, 2.52 mmol) was added, and then, 70 min later, a solution of allyl alcohol **26** (562 mg, 1.26 mmol) in CH_2Cl_2 (10 mL) was added to the reaction mixture at −35 °C. After the mixture was stirred at −30 °C for 67 h, 17% aqueous acetone (20 mL) was added, and the mixture was stirred for 30 min at room temperature. The reaction mixture was filtered through Celite and concentrated. The residue was dissolved into toluene, evaporated to remove the remaining TBHP by azeotropic distillation, and chromatographed (SiO_2 20 g, hexane/AcOEt = 1/1−0/1) to give **27** (520 mg, 90%) as a colorless amorphous: $[\alpha]^{22}_D$ −27.9 (*c* 0.90, $CHCl_3$); FTIR (neat) 3342, 2977, 1702, 1511, 1444, 1373, 1162, 1031 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.31 (d, J = 7.2 Hz, 1H), 4.50 (m, 1H), 4.28 (d, J = 13.6 Hz, 1H), 4.13 (m, 2H), 3.75(s, 3H), 3.73−3.75 (m, 4H), 3.57 (m, 1H), 3.22 (m, 1H), 3.12 (t, J = 5.6 Hz, 1 H), 2.35 (dd, J = 8.0, 15.2 Hz, 1H), 2.27 (d, J = 7.2 Hz, 2H), 2.15 (dd, J = 5.2, 14.4 Hz, 1H), 1.98 (dd, J = 9.2, 14.4 Hz, 1H), 1.88 (dd, J = 3.2, 15.2 Hz, 1H), 1.67 (s, 3H), 1.45 (s, 9H), 1.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 155.2, 109.2, 80.2, 73.2, 73.1, 70.9, 67.1, 66.2, 61.2, 60.2, 59.6, 52.5, 51.1, 36.3, 33.9, 28.3, 25.8, 25.4; HRMS (EI) calcd for $C_{21}H_{35}NO_{10}$ (M^+) 461.2261, found 461.2249.

Lactam 29. To a stirred solution of **27** (520 mg, 1.12 mmol) in CH_2Cl_2 (10 mL) was added pyridinium *p*-toluenesulfonate (PPTS) (283 mg, 1.12 mmol), and the mixture was stirred for 2 h. The reaction was quenched with saturated $NaHCO_3$ (30 mL), and the reaction mixture was extracted with AcOEt. The extract was washed with water and brine, dried over Na_2SO_4, and concentrated to give **28** (540 mg), which was used for the next reaction without purification.

To a solution of crude **28** (540 mg) in 20% aqueous THF (12.5 mL) was added $NaIO_4$ (480 mg, 2.25 mmol) at room temperature. After being stirred at room temperature for 50 min, the reaction was quenched with 10% $Na_2S_2O_3$ (10 mL), and the reaction mixture was extracted with AcOEt. The extract was washed with saturated $NaHCO_3$ and brine, dried, and concentrated to give the corresponding aminal (500 mg) as a pale yellow oil, which was used for the next reaction without purification.

To a solution of crude aminal (500 mg) in MeCN (10 mL) were added 4 A molecular sieves (500 mg) and *N*-methylmorpholine oxide (NMO) (263 mg, 2.25 mmol) at room temperature. After 10 min, tetra-*n*-propylammonium perruthenate (TPAP) (79 mg, 0.23 mmol) was added to the mixture, and stirring was continued at room temperature for 80 min. The reaction mixture was filtered through Celite, concentrated, and chromatograped (SiO_2 20 g, hexane/AcOEt = 1/2−0/1) to give **29** (269 mg, 56%) as a colorless solid: $[\alpha]^{24}_D$ −10.8 (*c* 0.60, MeOH); FTIR (neat) 2981, 1791, 1752, 1442, 1369, 1307, 1211, 1149 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 4.44 (dd, J = 2.5, 9.0 Hz, 1H), 4.01 (dd, J = 4.5, 12.5 Hz, 1H), 3.95 (dd, J = 4.5, 7.5 Hz, 1H), 3.83 (dt, J = 7.5, 4.5 Hz, 1H), 3.76 (dt, J = 7.0, 6.0 Hz, 1H), 3.38 (s, 3H), 3.34 (dd, J = 4.5, 6.0 Hz, 1H), 3.25 (dd, J = 4.5, 12.5 Hz, 1H), 2.72 (dd, J = 6.0, 13.5 Hz, 1H), 1.93 (dd, J = 2.5, 13.5 Hz, 1H), 1.59 (s, 3H), 1.49 (dd, J = 7.0, 13.0 Hz, 1H), 1.41 (s, 9H), 1.21 (s, 3H), 1.12 (dd, J = 9.0, 13.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 169.8, 149.4, 110.4, 83.9, 83.1, 75.7, 75.5, 72.0, 71.2, 65.7, 55.6, 52.6, 41.5, 36.0, 27.9, 26.3 25.6; HRMS (EI) calcd for $C_{20}H_{29}NO_9$ (M^+) 427.1842, found 427.1831.

Neodysiherbaine A (2). A solution of **29** (283 mg, 0.662 mmol) in 6 M HCl (20 mL) was heated at 60 °C for 10 h. The reaction mixture was evaporated and the residue was treated with 1 N NaOH followed by IRC-76 and then evaporated. The residue (300 mg) was subjected to ion-exchange chromatography using Dowex 50WX4-200 (30 mL of resin, H_2O then 5% NH_4OH) and lyophilization to give neodysiherbaine A (**2**) (199 mg, quant) as a pale yellow solid: $[\alpha]^{23}_D$ −6.5 (*c* 0.75, H_2O); ^1H NMR (500 MHz, D_2O) δ 4.06 (dd, J = 1.5, 3.0 Hz, 1H), 3.98 (brs, 1H), 3.74 (m, 1H), 3.69 (dd, J = 2.5, 13.0 Hz, 1H), 3.53 (brs, 1H), 3.41 (d, J = 13.0 Hz, 1H), 3.38 (dd, J = 2.5, 12.0 Hz, 1H), 2.48 (dd, J = 2.5, 15.0 Hz, 1H), 2.41 (d, J = 14.0 Hz, 1H), 1.99 (dd, J = 3.0, 14.0 Hz, 1H), 1.78 (dd, J = 12.0, 15.0 Hz, 1H); ^{13}C NMR (100 MHz, D_2O + CD_3OD) δ 108.9, 174.5, 88.2, 81.1, 77.4, 70.3, 68.5, 67.9, 54.4, 45.3, 39.9; MS (FAB) *m*/*z* 292 [(M + H)$^+$], 314 [(M + Na)$^+$]; HRMS (FAB) calcd for $C_{11}H_{18}NO_8$ [(M + H)$^+$] 292.1032, found 292.1054; CD (H_2O) λ_{ext} 204 nm. These spectral data was in good agreement with those for natural neodyshiherbaine A.[2]

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Supporting Information Available: General experimental procedures, experimental details for compound **14** from **9**, and ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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